Improving radionuclide therapy in prostate cancer patients with metastatic bone pain

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Thesis, Utrecht University

ISBN: 978-90-393-5074-4
Cover: Manon Wigny
Lay-out: Roy Sanders
Printing: Ipskamp drukkers B.V., Enschede, The Netherlands

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Vorderingen in radionuclidentherapie bij pijnlijke ossale metastasen van prostaatkanker

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de universiteit Utrecht op gezag van de rector magnificus, prof. dr. J.C. Stoof, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 24 juni 2009 des middags te 2.30 uur

door

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Publication of this thesis was financially supported by:

CIS bio International
Philips Medical Systems Nederland
Genzyme Nederland
Novartis Pharma
Sanofi-aventis Nederland
Roche Nederland
AstraZeneca
IDB Holland
GE healthcare
Covidien Nederland
Bayer Schering Pharma
Veenstra Instruments

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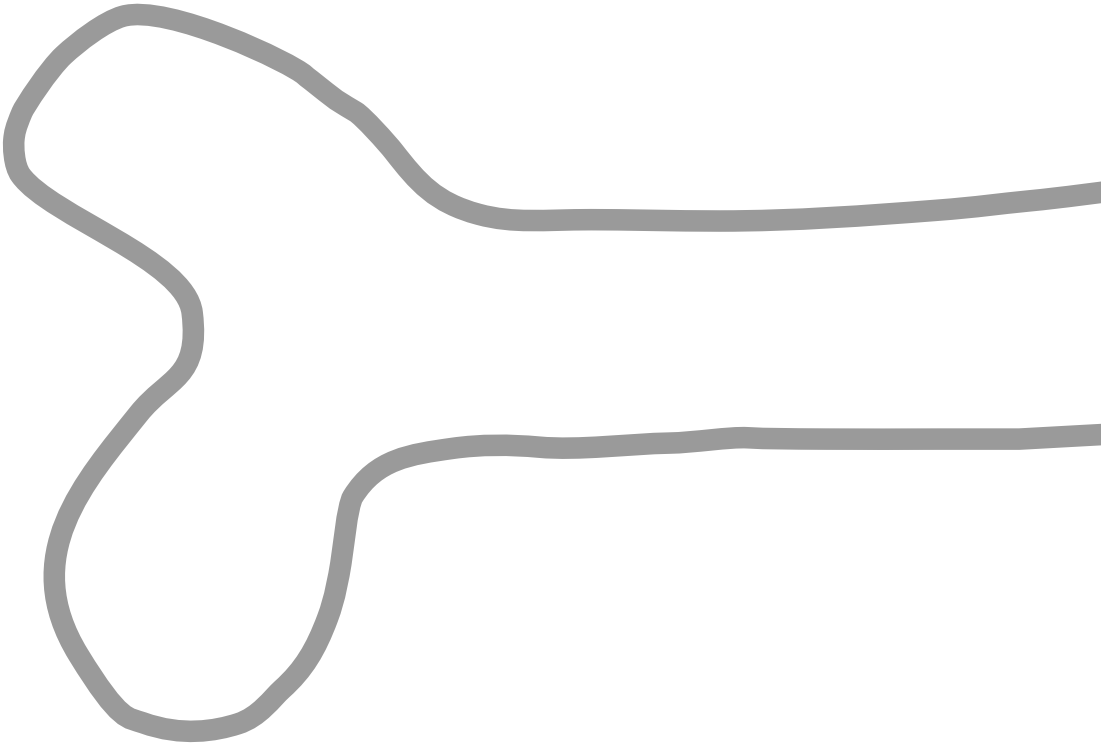
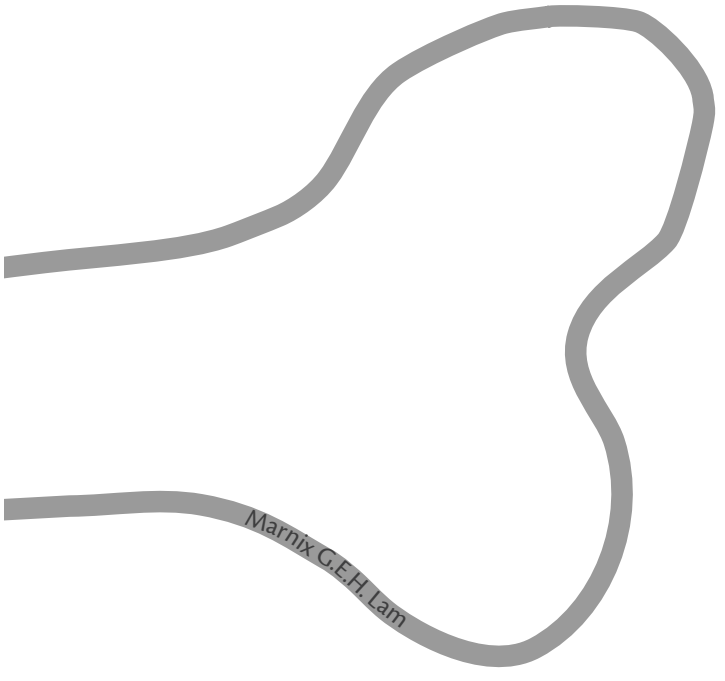


Chapter 1

General Introduction



Introduction

This thesis will discuss the treatment of metastatic bone pain in hormone-refractory prostate cancer patients with bone seeking radiopharmaceuticals. Two main issues will be discussed in the initial part of this introduction:

- Bone seeking radiopharmaceuticals in clinical practice. Issues regarding radiation safety and a protocol for routine use of bone seeking radiopharmaceuticals will be discussed in order to improve routine clinical care.
- Enhancement of efficacy of bone seeking radiopharmaceuticals.

But first a short introduction will be given on clinical relevance and bone seeking radiopharmaceuticals in general.

Prostate cancer and skeletal metastases

The incidence of malignancy in the Netherlands was 74.500 patients in 2005. This will increase to approximately 95.000 new cases in 2015. Because malignancy related death is decreasing and it is likely to decrease further the prevalence of cancer patients will increase to an estimated 692.000 patients in 2015, compared to 366.000 in 2000 (an estimated doubling time of 15 years) [1, 2]. One of the major causes of cancer related death in men is prostate cancer. These patients will be the focus of this thesis.

The incidence of prostate cancer is high worldwide. It is the most common malignancy in men in the Netherlands. Approximately 9000 men are being diagnosed with prostate cancer each year (***Figure 1***). The rising incidence may be attributed to the incremental use of screening methods using prostate specific antigen (PSA) to detect prostate cancer. This hypothesis is supported by the growing number of patients being diagnosed with early stages of prostate cancer. The incidence also increases with age. Consequently, with a growing number of old men in our society the incidence of prostate cancer will further increase. Fortunately mortality from prostate cancer is decreasing due to better diagnostic methods and treatments [3].

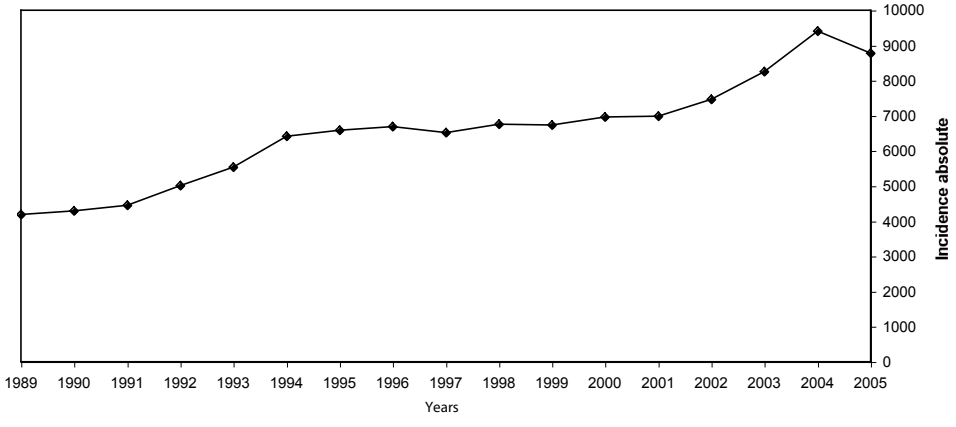


Figure 1 Prostate cancer incidence between 1989 – 2005 derived from data on www.ikcnet.nl

A hallmark of metastatic prostate cancer is the development of osteoblastic bone metastases. Almost all patients with advanced prostate cancer eventually develop osseous metastases. In a majority of patients with prostate cancer, bone is the only site of clinical metastases. Many of the established prognostic factors for advanced prostate cancer (eg, performance status, alkaline phosphatase level, and haemoglobin level) reflect the clinical consequences of bone metastases. Hence, patients who develop widespread, progressive, or early bone metastases tend to suffer more from their symptoms and fare worse. Conversely, patients who develop limited, stable, or delayed bone metastases tend to experience less morbidity and have a less dismal clinical outcome. Conceivably, targeting the relevant bone metastases–associated factors may improve therapeutic results [4]. These factors consist of the main cells involved in bone metastases (cancer cells, osteoblasts, osteoclasts, endothelial cells and stromal cells) and the numerous communicating substances (eg, interleukins, VEGF, RANKL, TNF-alfa, endothelins). They form a complex interaction and a microenvironment in which cancer cells may flourish [4].

Frequently these skeletal metastases cause pain. Less common complications include myelum compression and pathological fractures [3]. Besides hormonal treatment most other treatment modalities in advanced prostate cancer patients are intended to palliate bone pain. Metastatic bone pain is a nociceptive somatic pain, initiated and maintained through local tissue injury. It is well recognized that chronic pain (including cancer pain) is a multidimensional phenomenon consisting of five dimensions (pathophysiological, sensory, emotional, cognitive, and behavioural). These five dimensions together form a complex pattern of relations [5]. Stress is a well known stimulus for nociceptive pain. The impression that pain may be uncontrollable produces stress for patients, which may lead to increased suffering and despair, and decreases the patient's performance [6]. An effective pain management strategy requires breaking off this cycle using all available means. An effective pain control strategy, however, requires patients to take large quantities of opioids, often as much as 60 – 200 mg/day. This large dose may cause considerable side effects, including nausea, vomiting, constipation, and central sedation, all of which combine to a decrease in quality of life. Patients will have to take large doses of anti-emetics and laxatives to counteract nausea and constipation, respectively. Central sedation increases drowsiness, resulting in frequent falls, bone fractures, and driving accidents [7]. Supplemental therapy with local radiation, wide-field radiation, bisphosphonates, or bone seeking radiopharmaceuticals can significantly reduce the dose of opioids for most patients or may even completely eliminate the need for medication in a few patients [8].

Metastatic disease in prostate cancer may be treated first with hormonal therapy such as bilateral orchidectomy or medical first line hormone treatment (luteinizing hormone-releasing hormone agonist therapy). This androgen-deprivation therapy may be extended to maximal androgen blockade by adding anti-androgens (bicalutamide, flutamide, nilutamide). High risk prostate cancer patients may benefit from such a regimen even in the early stages of the disease [9]. It is also recognized that discontinuation of an anti-androgen once hormone-refractory biochemical progression occurs is associated with a biochemical response in many patients [10, 11]. Anti-androgens may become agonistic due to a combination of androgen receptor over-expression and mutation [10, 11]. After a median of two years the prostate cancer cells generally become insensitive for hormonal treatment. In the case of hormone-

refractory disease the patient may be treated by chemotherapy, local radiotherapy, systemic radiopharmaceuticals, bisphosphonates and analgesics, depending on the clinical status [12].

The clinical benefit of chemotherapy in hormone-refractory prostate cancer patients is limited. Some drugs showed potential as first-line treatment in hormone-refractory prostate carcinoma but were not sufficiently tested in clinical trials [13]. Patients however may benefit from docetaxel chemotherapy in combination with prednisone. In a landmark study treatment with 75 mg/m^2 docetaxel i.v. every three weeks with 5 mg prednisone twice daily p.o. was compared with mitoxantrone 12 mg/m^2 every three weeks [14]. The median survival increased from 16.3 months in the mitoxantrone-group to 19.2 months in the docetaxel-group [15]. The group receiving docetaxel three weekly had a hazard ratio for death of 0.79 (95 percent confidence interval, 0.67 to 0.93; p=0.004) compared to the mitoxantrone-group [15]. Pain and quality of life improved significantly better in the docetaxel group and more patients (45% versus 32%; p<0.001) showed a 50% reduction of serum PSA levels [14]. However, docetaxel nor any other treatment will be curative in an advanced stage of prostate cancer.

Patients with hormone-refractory prostate cancer who have progressive disease after first-line chemotherapy may still benefit from several treatment options. At this stage of disease, patients can expect only a short duration of survival, and most patients become symptomatic. Most patients will cease docetaxel treatment because of progressive disease or unacceptable adverse events. To control symptoms after the cessation of chemotherapy one should rely on optimizing medical therapy for palliation. This may be combined with radiotherapy applied to dominant painful bone lesions. External beam radiotherapy for painful skeletal metastases leads to a decrease of pain in 60 – 65% of the patients. In 33% of the patients a total remission of pain symptoms is observed [16]. Patients may be treated in one fraction (8 Gray). No difference has been found between such a single-dose regimen and multiple fractions [17, 18, 19]. Furthermore, when needed, patients may be treated a second time with a reported response rate between 66% and 84% [20, 21].

Besides chemotherapy further hormonal manipulation with a prednisone or dexamethasone may have some benefit as well. Glucocorticoids may lead to PSA response and/or a relief of symptoms in patients with late-stage prostate cancer [22]. Some investigators have suggested that the superior results of regimens with taxanes may be due in part to the dexamethasone that is administered to avoid toxic reactions to these drugs. However, most patients have already received substantial treatment with glucocorticoids concurrent with first-line chemotherapy, so their potential benefit in later stages is probably minimal.

Other treatment options in the advanced stage of prostatic cancer include ketoconazole and estrogens. Inhibition of steroid synthesis by ketoconazole may increase the probability of an anti-androgen withdrawal response, although this did not translate into improved survival [23]. Estrogens may improve symptoms but caution must be used because of their ability to stimulate thrombosis and cardiovascular events. Estrogens were found to be equivalent to estramustine (which contains estrogen), probably as its activity is largely due to the estrogen component [24]. Transdermal administration of oestrogens through a patch avoids the entero-hepatic circulation and therefore it should not be associated with the same level of

cardiovascular toxicity. Early data confirm the safety and efficacy of oestrogen patches as hormonal treatment in prostate cancer patients [25].
Currently new non chemotherapeutic options are studied such as endotheline antagonists [26] and abiraterone acetate, a potent, selective, small-molecule inhibitor of cytochrome P (CYP) 17, a key enzyme in androgen synthesis [27]. Many other agents are being developed [4].

Bone seeking radiopharmaceuticals

Bone seeking radiopharmaceuticals have proven to be useful for treatment of more generalized bone pain. All patients will finally progress to end stage disease with multiple skeletal metastases. These patients may receive bone seeking radiopharmaceuticals for generalized painful disease [13]. The association of integrated cancer centres in the Netherlands (VIKC) recently developed an evidence based guideline on the diagnosis and treatment of pain in cancer patients. Radionuclide treatment of cancer patients with metastatic bone pain (so called bone seeking radiopharmaceuticals) was evaluated using all available literature [28]. The conclusions are stated together with their level of evidence in ***Table 1***.
Most of the patients who have participated in the mentioned trials were heavily pre-treated patients with previous radiotherapy, chemotherapy and/or hormone therapy. It was recommended that radionuclide treatment with bone seeking radiopharmaceuticals is indicated in patients with multifocal pain originating from osteoblastic skeletal metastases. Repeated treatments are indicated after an initial response to treatment. The committee had the opinion that combined multimodality treatment should be performed in a trial setting. Further research in that field is warranted [28].
Radionuclide therapy with bone seeking radiopharmaceutical agents has been long used. It evolved from agents like ^{32}P-phosphate to newer agents like ^{188}Re-HEDP or ^{223}Ra (***Table 2***). Bone seeking radiopharmaceuticals consist of a radionuclide for the therapeutic effect and a carrier to reach the target site at the bone matrix level. Sometimes the carrier and the radionuclide are one and the same. This is the case for ^{32}P-phosphate, ^{223}Ra and ^{89}Sr. These radiopharmaceuticals behave as physiologic phosphate (^{32}P-phosphate) or Ca^{2+}-analogues (^{223}Ra and ^{89}Sr). They do not need a non-radioactive substance as a carrier to reach the target. Carriers like hydroxyethylenediphosphonic acid (HEDP in ^{186}Re-HEDP) and ethylenediaminetetramethylenephosphonic acid (EDTMP in ^{153}Sm-EDTMP) are being used in other bone seeking radiopharmaceuticals. They behave as bisphosphonates. These differences influence the biodistribution and pharmacokinetics of the pharmaceutical. Other differences between these agents include the radiation type, the radiation energy and the radionuclide half-life.
One thing that never changed during the last decades and stimulated the search for new agents was the conflict between efficacy and toxicity. The latter consisting of bone marrow suppression in particular. This has even led to a change of indication for the use of ^{32}P-phosphate. It is not used anymore for the palliation of metastatic bone pain but instead for the treatment of myeloproliferative diseases, making use of its bone marrow suppressive potential [47, 48]. Fortunately newer agents have proved to be feasible and relatively safe for

Table 1 Evidence based conclusions on treatment with bone seeking radiopharmaceuticals [28]

Conclusion	Evidence [a]	Study type [b]
It has been proven that treatment with bone seeking radiopharmaceuticals yields a better pain response than treatment with placebo in patients with painful osseous metastases from diverse cancers including prostate, breast and lung cancer.	Level 1	A1 [29, 30, 16, 31] A2 [32, 33, 34, 35, 36]
It has been proven that no difference exists with regard to local pain response between treatment with ^{89}Sr-Chloride or external beam radiotherapy in patients with painful osseous metastases from a prostate carcinoma.	Level 1	A2 [37, 38]
It is likely that no difference exists with regard to pain response between treatment with ^{89}Sr-Chloride and ^{186}Re-HEDP in patients with painful osseous metastases.	Level 2	A2 [39] B [40]
It is likely that the onset of the pain response of ^{186}Re-HEDP is faster than the onset of the pain response of ^{89}Sr-Chloride in patients with painful osseous metastases from a breast carcinoma.	Level 2	A2 [39]
It is likely that combined treatment with ^{89}Sr-Chloride and chemotherapy (platinum based) yields a better pain response than treatment without chemotherapy in patients with painful osseous metastases from a prostate carcinoma.	Level 2	A2 [41] C [42]
It has been suggested that adding ^{89}Sr-Chloride to chemotherapy may lead to improved survival and a longer duration of the pain response compared to treatment with chemotherapy alone.	Level 3	B [43]
It has been suggested that no difference exists with regard to the pain response after treatment with chemotherapy or ^{89}Sr-Chloride in patients with painful osseous metastases from a prostate carcinoma.	Level 3	B [44]
No conclusions can be drawn on the value of adding ^{89}Sr-Chloride to external beam radiotherapy in patients with painful osseous metastases from a prostate carcinoma because of conflicting results.		A2 [45, 46]

a Level of evidence: 1) A1 or at least two independent and consistent A2 studies; 2) One A2 study or at least two independent and consistent B studies; 3) One B or C study; 4) Professional opinion

b Quality and methodology of studies: A1) Systemic review of at least two independent A2 trials; A2) Double-blind randomized trial of sufficient size and quality (comparison with a reference test ('gold standard'), defined endpoints, independent evaluation of both tests, no confounding); B) Comparative trial not meeting A2 criteria; C) Non-comparative trial; D) Professional opinion

Table 2 Bone seeking radiopharmaceuticals categorized by half-life

Radiopharmaceutical	Half-life (days)	ß-emission MeV max (mean)	γ-emission keV (%)
^{188}Re-HEDP	0.7	2.12 (0.76)	155 (15%)
^{153}Sm-EDTMP	1.93	0.81 (0.23)	103 (29%)
^{186}Re-HEDP	3.7	1.07 (0.35)	137 (9%)
^{177}Lu-EDTMP	6.7	0.497 (0.15)	208 (11%)
^{223}Ra	11.4	Emits alfa-particles of circa 5.7 MeV	
^{117m}Sn-DTPA	13.6	Emits conversion electrons 127 – 152 keV	
^{32}P-Phosphate	14.3	1.71 (0.70)	None
^{89}Sr	50.5	1.46 (0.58)	910 (0.01%)

the palliative treatment of osseous metastases with acceptable and reversible bone marrow toxicity.

All patients with proven osteoblastic (or mixed type) skeletal metastases that accumulate ^{99m}Tc-HDP on skeletal scintigraphy may be candidates for treatment with bone seeking radiopharmaceuticals. They may be cancer patients with advanced disease originating from prostate cancer, breast cancer, lung cancer, medullary thyroid carcinoma, or other tumors (i.e. bronchial carcinoid tumors, medulloblastoma). In routine clinical practice the vast majority of patients are prostate cancer patients. In these patients the incidence of skeletal metastases is very high. They cause high morbidity and mortality [49, 50]. Metastases originating from prostate cancer are pure osteoblastic with relatively high radionuclide uptake, resulting in high tumor to non-tumor ratio's. And last but not least other treatment options are limited in advanced stages of this disease.

In the growing field of radionuclide therapy many new radiopharmaceuticals are being developed. At the moment $^{89}SrCl_2$ (Metastron®) and ^{153}Sm-EDTMP (Quadramet®) are both FDA approved. Together with ^{186}Re-HEDP (registered in some countries, not in the Netherlands) these bone seeking radiopharmaceuticals are mostly used today. They will be thoroughly discussed in chapter 2 of this thesis.

Bone seeking radiopharmaceuticals in clinical practice

Patients treated with any kind of radionuclide treatment must be regarded as a potential risk for public health because of a potential radiation hazard. Good understanding of the radionuclide used, its physical characteristics, its biodistribution and its pharmacokinetics, will allow us to draw proper guidelines for this kind of treatment. Does the patient need to be confined after treatment? Are we able to identify the radiation hazard from a qualitative and quantitative perspective? What does that mean for an individual patient in relation to its environment? These issues will be dealt with in chapter 3.

This knowledge of radiation safety considerations after treatment with bone seeking radiopharmaceuticals was used to draw a proper guideline. First and foremost this guideline should be used for high quality routine patient management. In other words: indications, contra-indications, dosage adjustments and toxicity profile with sufficient follow up. One of the major concerns is the patient's bone marrow reserve. Most patients have a limited bone marrow reserve due to progressive disease and previous myelotoxic treatments. In prostate cancer patients the most important development in the last years was the wide spread introduction of docetaxel chemotherapy in the treatment of hormone-refractory prostate cancer patients. Most patients have been treated with docetaxel before treatment with bone seeking radiopharmaceuticals. This is an important factor with an impact on the patient's bone marrow reserve before treatment with bone seeking radiopharmaceuticals. The same is true for renal function. Chapter 4 of this thesis will describe the procedure guideline for treatment of refractory metastatic bone pain, put forward by the European Association of Nuclear Medicine (EANM). It describes the indications, contra-indications and necessary precautions before treatment in this heavily pre-treated population.

Enhancement of efficacy

A major concern in the treatment of prostate cancer patients in the more advanced stage of the disease is the delicate balance between efficacy and toxicity. Treatment of metastatic bone pain with analgesics or localized external beam radiotherapy is relatively safe and easy. Treatment with bone seeking radiopharmaceuticals may be more appropriate in selected cases but efficacy is sometimes disappointing and bone marrow toxicity may be high in individual patients. Enhancement of overall efficacy without increasing toxicity could push the clinical decision algorithm in a positive direction with regard to the use of bone seeking radiopharmaceuticals.

One way of improving overall efficacy is combined treatment. Combined treatment regimens may deliver the beneficial effect of two different treatment modalities. These combinations may not only be additive but possibly synergistic to each other, leading to enhancement of overall efficacy (Chapter 5). But these combinations might also interfere or lead to additional toxicity.

Two combinations will be prospectively tested in clinical phase I studies. ^{153}Sm-EDTMP (Quadramet®) will be combined with the bisphosphonate zoledronic acid to study interaction between both pharmaceuticals and the safety of this combined treatment regimen (Chapter 6). This trial is not only designed as a classical single dose phase I escalation study but also as a feasibility study combining both pharmaceuticals with repeated treatments over a longer treatment period of six months (Chapter 7).

Secondly the combination of the relatively new and attractive homemade bone seeking radiopharmaceutical ^{188}Re-HEDP and capecitabine (Xeloda®) will be tested in a phase I dose-escalation study. Capecitabine may act as a radiation sensitizer for ^{188}Re-HEDP. Toxicity of this combined treatment regimen will be tested with incremental doses of capecitabine up to a maximum dose of 2500 mg/m^2/day. Interaction of these pharmaceuticals on biodistribution and pharmacokinetics will be evaluated as a secondary endpoint (Chapter 9).

The determination of the efficacy of any analgesic therapy is hampered by the highly subjective character of chronic pain. Assessing pain in patients gives rise to several methodological problems that need to be addressed to adequately understand pain. First, a major discrepancy may consist between the patient's pain experience and the physician's impression. Second, the reliability of pain assessment will be influenced by the setting in which the patient is questioned (whether in the hospital environment or at home). Third, daily assessment will improve the reliability compared to weekly scores due to the well-known problems of human memory [5]. More objective parameters like survival, PSA or bone markers may be more useful. The feasibility of bone markers for response monitoring after treatment with bone seeking radiopharmaceuticals was studied in the aforementioned study. The efficacy data of this population may be regarded as pilot data. They will be presented in chapter 8. It may offer an insight in the efficacy of this combined treatment regimen and new ideas regarding treatment response monitoring using specific markers of bone metabolism.

Discussion and conclusions

The final part of this thesis will discuss the findings of the presented trials. The implications on routine clinical use of bone seeking radiopharmaceuticals and future prospects will be discussed.

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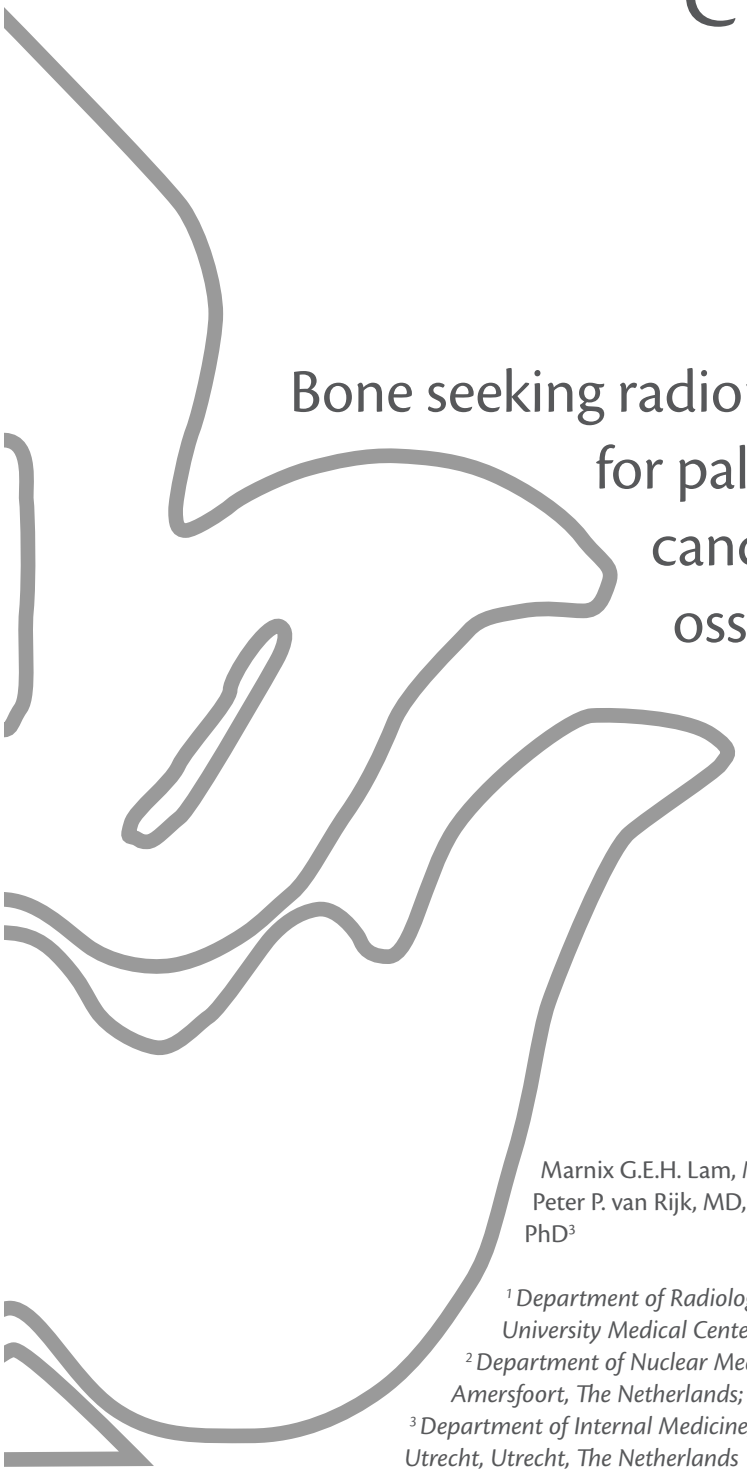
Chapter 2



Bone seeking radiopharmaceuticals for palliation of pain in cancer patients with osseous metastases

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Abstract

Many patients with cancer develop symptomatic skeletal metastases at an advanced stage of their disease. Skeletal metastases are often complicated by pain. They cause considerable morbidity and mortality. Besides analgesics, treatment options include external beam radiotherapy, bisphosphonates, chemotherapy, surgery and bone seeking radiopharmaceuticals. Pain palliation with bone seeking radiopharmaceuticals has proved to be an effective treatment modality in patients with metastatic bone pain. Radiopharmaceuticals bind to the bone matrix in areas of increased bone turnover, due to a metastatic response. Beta radiation from the specific radionuclide, bound to its carrier ligand, result in the therapeutic effect. Various radiopharmaceuticals have been developed for this purpose. All have their own characteristics. The radiopharmaceuticals Samarium-153-ethylenediaminetetramethylenephosphonic acid (^{153}Sm-EDTMP) and Strontium-89-Chloride (^{89}Sr-Chloride), which are approved in the USA and Europe, as well as the not universally approved Rhenium-186-hydroxyethylidenediphosphonic acid (^{186}Re-HEDP), will be discussed in greater detail. Depending on the half-life and radiation energy of the specific radionuclide, they exert a different effect and toxicity profile. In most cases, bone marrow toxicity is limited and reversible, which makes repetitive treatment relatively safe. Several studies have shown encouraging clinical results of palliative therapy using bone seeking radiopharmaceuticals, with an overall reported pain response rate in the order of ± 70 – 80% of patients. This systemic form of radionuclide therapy is simple to administer and complements other treatment options. It has been associated with marked pain reduction, improved mobility in many patients, reduced dependence on analgesics, and improved performance status and quality of life. Additionally, new therapeutic strategies hold the promise of enhancement of the palliative and anticancer effects of this form of therapy.

Introduction

Incidence of cancer is increasing. Every year more people suffer from a malignancy. This is mainly caused by an aging population. It is estimated that both incidence and prevalence will double between 2000 and 2015. Most common malignancies in the Western world include lung cancer, breast cancer, and prostate cancer. It is estimated that the incidence of these tumors worldwide (in 2002) was approximately 680.000 for prostate cancer (22 per 100.000), 1.355.000 for lung cancer (44 per 100.000) and 1.150.000 for breast cancer (37 per 100.000). In The Netherlands, as in the rest of the Western world, data for 2002 are even worse, with an incidence of 90 per 100.000 for prostate cancer, 121 per 100.000 for lung cancer, and 130 per 100.000 for breast cancer [1].

A considerable number of these cancer patients will develop bone metastases. In an advanced stage of their disease two-thirds of the patients with prostate cancer or breast cancer and one-third of the patients with lung cancer will have symptomatic skeletal metastases. Prostate and breast carcinoma together probably account for more than 80% of cases of metastatic bone disease. The pathophysiology of skeletal metastases and related complications is complex [2].

In normal healthy bone, a multicellular unit formed by two cell types, osteoclasts and osteoblasts, is responsible for bone remodelling. Osteoclasts resorb the bone matrix and osteoblasts replace bone. Continuous remodelling is necessary in order to maintain function. Systemic factors, such as the parathyroid hormone, and local factors such as cytokines, activate the osteoclasts. Throughout the process of remodelling numerous growth factors and mineral ions are released from the bone matrix. These factors stimulate the osteoblasts to form new bone [2-4].

Bone provides a very fertile soil for the growth of tumor cells and it is clear that many tumors grow very well in this microenvironment. Rather than being a simple random process determined solely by blood flow, metastasis of tumor cells to specific sites is a directed multistep series of events, that is dependent on specific properties of the tumor cells and supportive factors in the area of the metastatic site. Spread of a tumor cell from the primary site begins with detachment from the tumor, the attachment to the basement membrane of the endothelium lining the intra-tumor capillaries, and subsequent destruction of this membrane. Down regulation of cell adhesion molecules (laminin, E-cadherin), and production of proteolytic enzymes play a crucial role. They enable the tumor cell to migrate into the capillary system. Once inside the vascular system, cell adhesion molecules (integrins) also enable tumor cells to attach themselves to the endothelial cells at the metastatic site. This is a key initial step in tumor colonization. After disruption of the basement membrane by the proteolytic enzymes (type IV collagenase), tumor cells migrate across the basement membrane by a process of directed migrational chemotaxis. However, increased random movement (chemokinesis) may also be involved. The bone matrix contains multiple factors with chemotactic potential (fragments of type-1 collagen and osteocalcin, and several growth factors), released during bone resorption. These attract monocytes, as well as tumor cells. This is further enhanced by motility factors produced by the tumor cell. They increase their locomotive capacity. The overall propensity of a tumor cell to metastasize depends on multiple

factors. Selection inside a tumor by survival advantage, or acquired genetic variability by effects of anti-cancer treatment, may direct future metastasis. Genetic factors have been widely recognized as predictors for aggressive behaviour and metastasis [2-4].
Tumor cells that have metastasized to the bone marrow near the bone matrix induce either an osteolytic response, an osteoblastic response or a mixed type response. Osteolysis is increased due to tumor cell induced activation of the osteoclasts. The osteoclasts line adjacent endosteal bone surfaces, with distinctive osteoclast resorption lacunae. Growth factors, released when bone resorbs further enhance the production of osteoclast activators. By these means a proliferative circle is formed favouring the tumor cell. The other possibility is destruction of bone directly by the tumor cells themselves. Osteoclastic bone resorption is likely to be the predominant mechanism. Treatment of malignancy induced hypercalcemia by drugs such as bisphosphonates, which inhibit osteoclastic activity, supports this view. On the other hand, osteoblastic metastases are occasionally formed, characterized by the formation of new bone around the tumor cell deposits. This may occur without prior osteoclastic bone resorption. Newly formed bone may be laid down directly onto trabecular bone surfaces, without a preceding resorptive episode. Prostate cancer is the most common tumor that forms osteoblastic skeletal metastases. The mechanism by which these osteoblastic metastases are caused is not fully understood, but a number of factors (TGF-β, fibroblast growth factors, endothelin-1) have been suggested as activators of this osteoblastic response. Endothelin-1 for example, is a powerful mitogenic factor for osteoblasts and is produced in large amounts by the prostatic epithelium. In most cases both osteolytic and osteoblastic metastases occur, one of the two being most dominant [2-4].

Complications of skeletal metastases

Skeletal metastases cause considerable morbidity and mortality. It is an indicator of progressive disease and bad prognosis [5]. Patients frequently develop bone pain. Bone pain is the most common type of pain caused by cancer. It can be focal or multifocal, localized or diffuse, light or severely disabling. It has daily and even hourly changes in severity, often being worse at night, and not being relieved by sleep or lying down. Bone pain can be aching, burning, deep boring, or stabbing of nature. In most cases metastatic bone pain is a nociceptor somatic pain and maintained through local tissue injury. Peripheral nerve endings are triggered by various substances produced by cells (immune cells, osteoclasts, osteoblasts, platelets) in the vicinity of the tumor cell (e.g., Interleukins, Pg-E, GABA, Substance P, TGF), and by the tumor cell itself (TNF) [6]. When the periosteum is affected, bone pain may have neurogenic qualities. Additionally, pain may occur around joints due to mechanical, chemical or osseous change. All these varieties of pain cause considerable morbidity and worsen a patients' quality of life. However, analgesics given to treat this pain may cause side effects that are even worse than the pain itself. They often cause nausea, constipation and disturbances of alertness and sleep, further decreasing the patients' quality of life [2, 6, 7].
The load-bearing capabilities of the bone are reduced by the continuous metastatic destruction of the bone matrix. Eventually this may lead to bone fractures, of which rib fractures and vertebral collapse are the most common. In cancer patients these fractures

cause considerable morbidity and even mortality. They are more prone to occur in patients with metastatic disease which is confined to the bone. In order to prevent skeletal-related events, administration of bisphosphonates may be useful [8-13]. Surgical or percutaneous vertebroplasty may be another option [14].
Another possible complication of skeletal metastases is spinal cord compression. When a patient with known skeletal malignancy has pain in combination with neurological signs and symptoms, epidural disease should be suspected, and MRI should be performed. In the case of epidural tumor spread with spinal cord compression, treatment should start as soon as possible. Early diagnosis, high dose corticosteroids, and decompression by spinal stabilization and/or radiotherapy are crucial elements for successful rehabilitation [5].
Last but not least, hypercalcemia may occur as a complication of skeletal metastases. It is probably the most common metabolic complication of malignant disease and may cause numerous associated complaints, depending on the severity of the disturbance. Levels of calcium are increased due to the destruction of bone by activated osteoclasts. An additional mechanism may be a generalized process of bone resorption, caused by humoral factors produced by the tumor. An argument in favour of the former mechanism may be the potential of bisphosphonates to inhibit bone resorption by oseteoclasts, and to treat hypercalcemia successfully [8, 9, 11-13, 15].

Treatment of skeletal metastases

Curative options for multiple skeletal metastases do not exist. All treatment has a palliative setting. In this regard, pain is the most important complication of skeletal metastases. Other complications (spinal cord compression, pathological fractures) are closely related to pain, except possibly hypercalcemia. Various therapies specifically targeted to the treatment of painful bone metastases are currently available. These can be either in the form of local or systemic therapy and include analgesics, chemotherapy, hormonal therapy, surgery, bisphosphonates, external beam radiation, and systemically administered radiopharmaceuticals. A multidisciplinary approach to the treatment of cancer pain has been advocated. For the treatment of hypercalcemia, bisphosphonates are the treatment of choice [15].
Analgesics are the first step in the treatment of malignant bone pain. Depending on the nature of this pain (nociceptive or neuropathic pain, or a combination) and the severity, several drug types may be used. In the case of nociceptive pain these include paracetamol and non-steroidal anti-inflammatory drugs (step 1), followed by oral (step 2) or intravenous opioids (step 3). Neuropathic pain is first treated as nociceptive pain and can be supplemented by tricyclic antidepressants (step 2), and anti-epileptic drugs (step 3). Adjuvant drugs may include corticosteroids and benzodiazepines [16]. All these drugs aim for an alleviation of pain, but may result in many severe side effects. In particular opioids cause side effects such as nausea, confusion, hallucinations, profound sweating and dry mouth. These complaints can be severe and may be even worse than the pain itself.
Other systemic treatment options are hormones, anti-hormones and chemotherapy. Breast cancer and prostate cancer are common cancers with proven response to (anti-)hormones. As

long as these cancers are hormone sensitive (anti-)hormones may induce a palliative response and/or prolonged survival [17, 18]. In an advanced stage of cancer with multiple metastases and skeletal involvement, chemotherapy may be the next step for hormone resistant tumors, or the first step for hormone insensitive tumors. In common cancers such as lung cancer and breast cancer, chemotherapy has proven effects on palliation and survival. In prostate cancer, some papers have recently been published on the efficacy (palliation and prolonged survival) of chemotherapy (docetaxel) on hormone resistant prostate cancer [19, 20]. Side effects of chemotherapy may range from mild nausea to severe nefrotoxicity or myelotoxicity.

To prevent skeletal-related events in patients with advanced malignancies involving bone, bisphophonates may be used. These malignancies include multiple myeloma, prostate cancer, breast cancer, lung cancer, renal cancer and other solid tumors. Zoledronic acid is a new-generation bisphosphonate which exhibits a more potent inhibitory activity of osteoclasts, compared to other bisphosphonates [10, 11, 21, 22]. Chronic administration of zoledronic acid ≥ 4 mg every 3 to 4 weeks has been shown to be effective in reducing skeletal-related events in patients with prostate cancer. Patients with hormone-refractory prostate cancer and a history of bone metastases were randomly assigned to a double-blind treatment regimen of intravenous zoledronic acid at 4 mg (N=214), 8 mg (N=221) or placebo (N=208) every 3 weeks for 15 months. A greater proportion of patients who received placebo had skeletal-related events, when compared with those who received zoledronic acid at 4 mg (p=0.021). When compared with urinary markers in patients who received placebo, urinary markers of bone resorption were statistically significantly decreased in patients who received zoledronic acid at either dose (p=0.001) [9].

Instead of the systemic treatment modalities mentioned above, local treatment is the treatment of choice for severe local complaints unresponsive to systemic treatment (analgesics, chemotherapy), but it may also be first choice as well, when, for example, one painful site is present, without any further multifocal or systemic complaints. In the case of painful focal metastases or epidural metastatic spread with spinal cord compression, external beam radiotherapy is the optimal treatment [5]. In the case of pathological fractures or osteoporotic/pathological vertebral collapse, surgery or vertebroplasty may be necessary [14].

Depending on various parameters, concerning the patients' physical condition and stage of disease, the patients' complaints and the patients' wishes, a choice has to be made between all treatment modalities. One has to keep in mind that, besides prolongation of survival, the aim of treatment in patients with osseous metastases must be the patients' quality of life. The place of bone seeking radiopharmaceuticals in the treatment algorithm will be discussed in detail in the remainder of this paper.

Bone seeking radiopharmaceuticals

An additional approach for the relief of multifocal bone pain is the systemic administration of a radionuclide which concentrates at sites of increased bone turnover. Bone metastases from most tumors will excite some osteoblastic response in bone, leading to an increased uptake of bone seeking radiopharmaceuticals. In this way therapeutic doses of radionuclides may be

localized close to the tumor by utilizing uptake mechanisms in adjacent non-tumor tissue. Bone seeking radiopharmaceuticals have traditionally been used to image tumors in bone, but, depending on the carrier ligand and energy of the radioactive label, these agents can also be used to treat primary or metastatic tumors in bone (***Table 1***). They are indicated for the alleviation of pain from osseous metastases at multiple localisations, which do not respond to analgesics, or bone pain at sites where former external beam radiotherapy has been carried out.

Table 1 Bone seeking radiopharmaceuticals

Radiopharmaceutical	Half-life (days)	β-emission MeV max (mean)	γ-emission keV (%)
^{188}Re-HEDP	0.7	2.12 (0.76)	155 (15%)
^{153}Sm-EDTMP	1.93	0.81 (0.23)	103 (29%)
^{186}Re-HEDP	3.7	1.07 (0.35)	137 (9%)
^{177}Lu-EDTMP	6.7	0.497	208 (11)
^{117m}Sn-DTPA	13.6	Emits conversion electrons 127 – 152 keV	
^{32}P-Phosphate	14.3	1.71 (0.70)	None
^{89}Sr-Chloride	50.5	1.46 (0.58)	910 (0.01%)

External beam radiotherapy is preferred at single sites with severe bone pain and at sites with spinal cord compression [5, 23]. Metastases must be osteoblastic of nature in order to ensure high uptake of the radiopharmaceutical. This must be verified by recently (within 8 weeks) performed skeletal scintigraphy (^{99m}Tc-HDP). The palliative effect commences in days or weeks and usually sustains for months. Patients are treated in the outpatient clinic or in day-care, where the pharmaceutical is injected through an intravenous running line. After injection rapid uptake in places of increased bone turnover occurs and the non-bound fraction is cleared from the blood through the kidneys. Patients, who are incontinent of urine, are therefore advised to have their urine collected through a catheter, in order to avoid radioactive contamination. When the administered radiopharmaceutical has gamma-emission, post-treatment scintigraphy will be possible, using the therapeutic dosage. This may be used for follow up and dosimetry. Toxicity is mainly limited to myelosuppression, and thrombocytopenia in particular. Depending on the radiopharmaceuticals' energy and half-life, myelosuppression is most profound after four to eight weeks, followed by a recovery phase of approximately the same period. Recovery however, also depends on the amount of radioactivity administered and the patients' bone marrow reserve [24-26]. By calculating the percentage of the skeleton involved with metastases, combined with the dosage and the patients' bone marrow reserve, haematological toxicity can be predicted [27]. Contraindications for the use of bone seeking radiopharmaceuticals are thrombocytopenia ($< 100 \times 10^9$/L) or leukopenia ($< 3 \times 10^9$/L), spinal cord compression (acute external beam radiotherapy is indicated), acute renal insufficiency and pregnancy. The aim of the treatment is palliation of pain, improvement of the patients' quality of life, less intake of analgesics, less use of chemotherapy and external beam radiotherapy, and improvement of disease free survival. Efficacy and cost effectiveness are high.

As all currently used bone seeking radiopharmaceuticals have ligands (usually phosphonic acids) that bind to the bone matrix, the actual activity accumulates near, but not necessarily at the tumor site. The energetic beta-radiation emitted by the isotope must travel a distance of at least several millimetres to reach the tumor cells, as well as the other cells surrounding the bone matrix. Beta-radiation with greater energy has a higher range in tissue, and therefore a higher anti-tumor potential. It is hypothesized that the palliative effect will also be increased. However, bone marrow toxicity will increase proportionately to the energy of the beta-radiation. Unfortunately the ideal radiopharmaceutical does not exist. A compromise must be found between efficacy and toxicity, with the right balance for each individual patient. Further on in this paper, differences between several bone seeking radiopharmaceuticals will be discussed, but we will first discuss the most commonly used bone seeking radiopharmaceuticals in detail.

^{153}Sm-EDTMP

In the search for new therapeutic bone agents, ^{153}Sm was considered a promising beta-emitting radionuclide, because of its desirable physical characteristics and ready availability [28, 29]. It has beta-particle emissions of 810 (20%), 710 (50%), and 640 (30%) keV, a 103 keV gamma-ray emission (28%), 55 keV conversion electrons (41%), and a half-life of 46.8 hr. At the University of Missouri-Columbia it was demonstrated by Goeckeler *et al* that stable ^{153}Sm chelates could be readily produced, using phosphonate ligands [28, 29]. The biological characteristics of several of these chelates were investigated. ^{153}Sm was prepared by neutron irradiation of enriched $^{152}Sm_2O_3$, and chelates formed using different ligands (i.e. diethylenetriaminetetraacetic acid [EDTA], diethylenetriaminepentaacetic acid [DTPA], ethylenediaminetetramethylene phosphonic acid [EDTMP], methylene diphosphonic acid [MDP], and hydroxymethane diphosphonic acid [HDP]). Biodistribution studies were carried out on rats and rabbits. In these studies, both in rats as in rabbits, ^{153}Sm-EDTMP (***Figure 1***) proved to have the optimal characteristics.

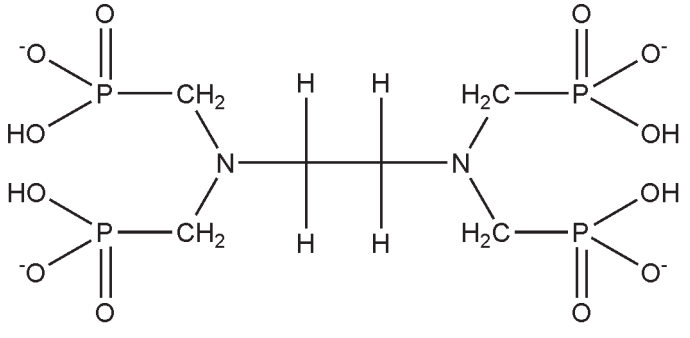

Figure 1 Structure of the EDTMP compound which complexes with ^{153}Sm to form ^{153}Sm-EDTMP

^{153}Sm-EDTMP had good selective skeletal localization, low blood levels, and low soft tissue retention, including the liver. Accumulation in non-osseous tissue other than the bladder/urine was low. This was confirmed by scintigraphy. The images demonstrated a pattern of localization that was consistent with the quantitative organ distribution studies, and revealed high selective skeletal uptake. No significant non-osseous tissue accumulation was observed. Lesion to normal bone ratios were calculated from a 'drill hole' model in rabbits using ^{153}Sm-EDTMP and ^{99m}Tc-MDP. The lesion/normal bone uptake ratio for ^{153}Sm-EDTMP did not significantly differ from ^{99m}Tc-MDP [28, 29]. The high lesion concentration of ^{153}Sm-EDTMP, and its low blood and bone marrow activity suggest that this complex should be therapeutically effective in treating metastatic bone disease. The mean energy emitted by the beta-particles of 225 keV is sufficient to deposit a high radiation dose in the tumor, with less damage to the bone marrow, due to its short range in tissue (penetration depth of 2-3 mm) [28]. Its gamma-ray emission of 103 keV permits scintigraphy, which can be used for biodistribution and dosimetric assessment of the radiopharmaceutical in the individual patient (***Figure 2***) [30].

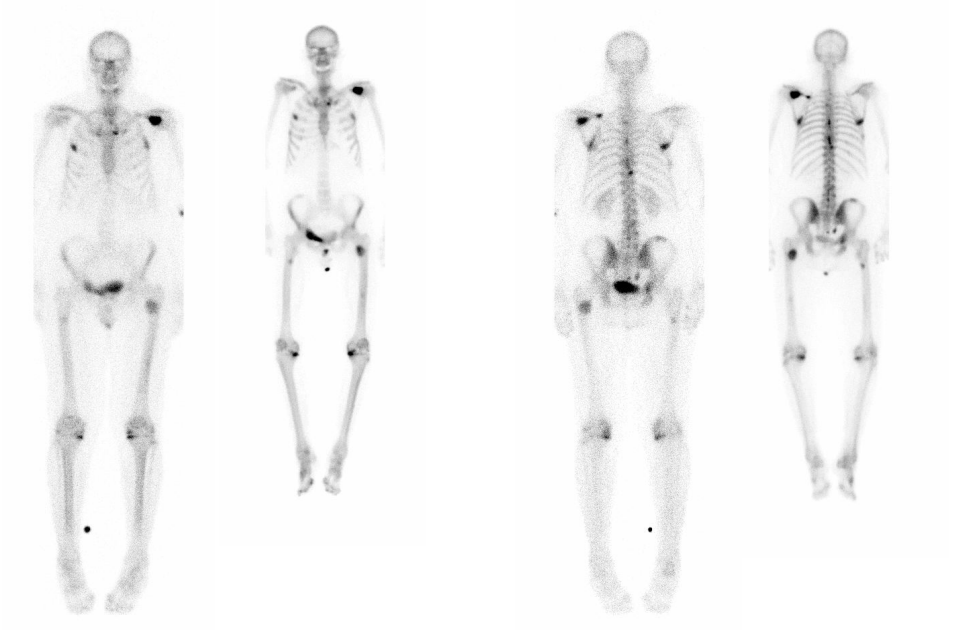

Figure 2 Skeletal scintigraphy in a patient with hormone refractory prostate carcinoma. 3 hours after injection of 600 MBq (16.2 mCi) ^{99m}Tc-HDP (Large images); or 6 hours after injection of 37 MBq/kg (1 mCi/kg) ^{153}Sm-EDTMP (Small images)

^{153}Sm-EDTMP: Pharmacokinetics

After the development of ^{153}Sm-EDTMP, a pharmacokinetic trial was undertaken in 5 patients with histopathologically proven primary cancer and radiographic and/or scintigraphic skeletal metastases [31]. Biodistribution of the study agent was investigated, using skeletal scintigraphy 2 hours after injection of 74 MBq ^{153}Sm-EDTMP. Quantified indices included: lesion-to-normal bone ratios (L/B), lesion to soft-tissue ratios (L/S); and normal bone to soft-tissue ratios (B/S). The mean ratios ± 1 standard deviation from 23 lesions in these 5 patients were 4.04 ± 2.62 for L/B, 5.98 ± 3.18 for L/S and 2.47 ± 1.01 for B/S. This did not significantly differ from the same calculations performed using ^{99m}Tc-MDP, thus suggesting the same mechanism of localization with minimal soft-tissue retention. The blood clearance curve of ^{153}Sm-EDTMP showed a rapid decline, with only 5.17% ± 1.05% and 2.09% ± 0.52% of the activity remaining in whole blood at 2 and 4 hours post injection. The complex clears through the kidneys with excretion of approximately half of the administered dose (53.4% ± 10.4%) into the urine during the first 8 hours, and 56.1% ± 10.5% at 24 hours. The remaining dose is deposited in the skeleton with little soft-tissue uptake [31].

An expanded version of this pharmacokinetic study reported the data of 22 patients treated with variable amounts of activity (0.37 – 37 MBq/kg ^{153}Sm-EDTMP) [32]. Rapid plasma clearance of the radioactivity occurred in all patients, and at 30 minutes post injection only 9.6% ± 2.8% of the administered amount remained in the plasma. At the end of 4 and 24 hours, plasma radioactivity had dropped to 1.3% ± 0.7% and 0.05% ± 0.03% respectively. Urinary excretion at 24 hours was 35.9% ± 13.55, with a range of 9.7% – 62.4% in the 22 patients. This wide range was attributed to the variation in metastatic load. A significant correlation was found between skeletal uptake and the number of metastatic sites ($r = 0.65$; $p = 0.001$). This was unaffected by the amount of ^{153}Sm-EDTMP administered [32].

The pharmacokinetic results of these studies correlate well with the results of a more recent study performed by Brenner *et al* [33]. They introduced a new quantification method to separately measure bone uptake and soft-tissue retention, using scintigrafic images at different times post injection. A mean bone uptake of 47.7% ± 11.2% at 24 hours after injection of 37 MBq/kg ^{153}Sm-EDTMP in 18 patients, was found. Soft-tissue retention at 24 hours was 12.7% ± 4.7%, and urinary excretion 39.5% ± 13.8% of the administered activity [33].

^{153}Sm-EDTMP does not undergo measurable in-vivo degradation. This lack of complex dissociation is evident since no liver or other soft-tissue uptake was seen on the scintigrams taken after treatment [32]. Analysis of urine samples from metastatic bone cancer patients treated with ^{153}Sm-EDTMP showed 96.9% ± 1.7% of the radioactivity in the urine to be present as the intact ^{153}Sm-EDTMP chelate [34].

^{153}Sm-EDTMP: Dosage and toxicity

A phase-I study, conducted by Turner *et al*, performed individual beta-radiation dosimetry, based on pharmacokinetic studies of a 740 MBq (20 mCi) tracer dose of ^{153}Sm-EDTMP [35]. At frequent time intervals after administration blood and urine activity was quantified and scintigrams performed. The radiation absorbed dose to the bone compartments was calculated. The final therapy dose was injected 7 hours after the test dose. Groups of at least three successive patients were treated at each bone marrow radiation exposure level, starting

at 100 cGy and increasing to 280 cGy total bone marrow absorbed dose. As previously mentioned, retained skeletal activity demonstrated considerable patient variation, mostly dependent on the extent of metastatic bone involvement. The major dose-limiting toxicity was thrombocytopenia. Platelet counts of less than 100 x 109/L occurred in 42% of courses with bone marrow doses over 200 cGy (> 21.5 MBq/kg [> 0.58 mCi/kg]) 4 – 6 weeks post treatment [35].

Radiation dose to the bone marrow may vary significantly regardless of the administered dose. Even with individualized dosimetry as described above, toxicity may vary considerably. Toxicity depends on multiple factors such as previous myelotoxic treatment, clinical condition and disease progression. Although less accurate, fixed dosages could therefore be a less complex alternative.

In a phase I/II study, 52 patients with prostate cancer were treated with doses ranging from 37 MBq/kg (1.0 mCi/kg) to 111 MBq/kg (3.0 mCi/kg), with increments of 18.5 MBq/kg (0.5 mCi/kg) [36]. 2/4 patients at the 93 MBq/kg (2.5 mCi/kg) dosage level and 2/4 patients at the 111 MBq/kg (mCi/kg) dosage level developed grade 3 or 4 hematologic toxicity (neutrophils < 900/mm^3 and/or platelets < 50,000/mm^3). The maximum tolerated dosage in this trial was determined to be 93 MBq/kg (2.5 mCi/kg). Sixteen more patients were treated in both the 37 MBq/kg (1.0 mCi/kg) and 93 MBq/kg (2.5 mCi/kg) dosage groups. In the 37 MBq/kg (1.0 mCi/kg) group 2/20, and in the 93 MBq/kg (2.5 mCi/kg) group 8/20 patients experienced grade 3 or 4 hematologic toxicity [36].

Using an escalating dose schedule (22 patients; dosages from 3.7 - 37 MBq/kg [0.1 – 1.0 mCi], Farhanghi *et al* found a decline in platelet count in patients receiving ≥ 13 MBq/kg (≥ 0.35 mCi/kg), and decline in white blood cell (WBC) count ≥ 28 MBq/kg (≥ 0.75 mCi/kg), without any significant difference between dosing groups [32]. The platelet count fell below 140 x 10^9/L (86 – 140 x 10^9/L) in 34.5% of the treatment courses (mean nadir of 4 weeks; recovery after 6-8 weeks), and leucopenia of less than 3.5 x 10^9/L occurred in only 2 instances (recovery after 6-8 weeks). Non-hematological toxicity was limited to a transient exacerbation of preexisting pain (flare reaction; 4 patients), beginning 2-3 days after therapy and lasting 3-4 days [32].

Alberts *et al* attempted to establish a dose response relationship by treating patients with 3 different dosages (28 MBq/kg [0.75 mCi/kg], 56 MBq/kg [1.5 mCi/kg], and 112 MBq/kg [3.0 mCi/kg]) [37]. They found a grade 3 or 4 platelet count decline in 7%, 12% and 20%, and white blood cell count decline in 4%, 11% and 20% respectively in the lowest, intermediate and the highest dosage group. Moreover, they did not find a dose response relationship [37].

These and other (efficacy) studies led to the currently approved dosage of 37 MBq/kg (1.0 mCi/kg). Serafini combined the toxicity results of three controlled studies, in which patients were treated with 37 MBq/kg (1.0 mCi/kg) ^{153}Sm-EDTMP [38]. Hematologic toxicity grades were based on the National Cancer Institute Common Toxicity Criteria. Approximately 10% of the patients experienced transient grade 3 or 4 hematologic toxicity, with a nadir between 3-5 weeks after treatment, and recovery after 8 weeks [38]. Retreatment is possible with an interval of 2-3 months. Toxicity after retreatment is comparable with that after single dosage treatment [37, 39, 40].

^{153}Sm-EDTMP: Dosimetry

One of the first dosimetric studies on ^{153}Sm-EDTMP was performed on rats [41]. The data revealed that the highest absorbed doses were present in the skeleton and the urinary bladder wall. The estimated organ dose per MBq injected activity of ^{153}Sm-EDTMP was 1.23 mGy/MBq for the bladder, 3.05 mGy/MBq for the trabecular bone of the skeleton, 2.84 mGy/MBq for the cortical bone of the skeleton, and 1.03 mGy/MBq for the red marrow [41]. Heggie, using a different model, found a substantially lower absorbed dose for mineral bone, but the absorbed dose to the red marrow was perfectly in agreement [42]. A dosimetry study on humans by Eary *et al* reported dose estimates for soft tissue that were similar to those estimated by Logan *et al* and Heggie, which were human doses scaled from rat data [41, 42, 43]. In the study by Eary *et al*, skeletal doses ranged from 5.3 – 8.8 mGy/MBq, marrow doses ranged from 1.2 – 2.0 mGy/MBq, and bladder doses ranged from 0.36 – 1.3 mGy/MBq. Non-skeletal sites received negligible doses [43]. Dosimetric calculations in another study resulted in an estimated absorbed bone marrow dose of 0.89 mGy/MBq ± 0.27 mGy/MBq. In 19 patients, receiving either 18.5 MBq/kg (0.5 mCi/kg) or 37 MBq/kg (1.0 mCi/kg), calculated marrow doses ranged from 0.27 Gy to 3.38 Gy [44]. Turner *et al* indicated that it is prudent to limit the red marrow radiation absorbed dose to 2 Gy, since doses in excess of 2 Gy caused significant myelosuppression in all patients [35]. In a more recent study they introduced an individualized prospective dosimetry method, in order to calculate the therapeutic dosage, with a maximum bone marrow radiation absorbed dose of 2 Gy [30]. Pre-treatment, 740 MBq (20 mCi) was injected in order to perform scintigraphy and take urine samples. With these parameters the therapeutic dosage was calculated which would result in a bone marrow absorbed dose of 2 Gy. In 10 patients the total administered activity of ^{153}Sm-EDTMP varied between 35 and 63% of the standard recommended regimen of 37 MBq/kg (1 mCi/kg). Administration of 37 MBq/kg (1 mCi/kg) would have resulted in delivered bone marrow doses of 3.27-5.90 Gy [30].

^{153}Sm-EDTMP: Efficacy

Beginning in the late eighties, several studies have been made of the efficacy of ^{153}Sm-EDTMP [32, 36, 37, 39, 40, 45-53]. Most of these studies are retrospective, open-label or encompass only small groups of patients, which renders them as less valid for the evaluation of efficacy. However, they do contribute to the discussion and further development of this drug. ***Table 2*** gives an overview of all performed efficacy studies available in the literature. Results from single dosage treatment are given. Some papers also studied the efficacy of repeated treatment with ^{153}Sm-EDTMP [39, 40]. Some of these results are discussed later in this paper. Since most studies found no difference in efficacy between different dosing groups, overall response rates for the total study population are included. Where differences between dosing groups were significant, the best response rate is recorded. This applied to two studies, in which the study group with the recommended dosage of 37 MBq/kg did best [46, 47]. The mean response rate for all studies is 73% (range 61-95%). Three of these studies will be discussed in further detail. They include a well-designed randomized dose-controlled study and also the only two published double-blind placebo-controlled studies [46, 47, 49].

Table 2 Efficacy studies on single dosage treatment with ^{153}Sm-EDTMP

References	Year	No. of patients	Diagnosis	Dosage (MBq/kg)	Response rate*
Turner et al [35].	1989	19	Prostate, breast, miscellaneous	Individual case dosimetry: dose of 1-2.75 Gray***	79%
Turner et al [40].	1991	23	Prostate, breast, miscellaneous	Individual case dosimetry: dose of 2 Gray	61%
Farhanghi et al [32].	1992	22	Prostate, lung, miscellaneous	Dosage range: 3.7 - 37	65%
Collins et al [36].	1993	46	Prostate	Dosage range : 18.5 - 111	76%
Alberts et al [37].	1997	82	Prostate, breast, miscellaneous	28 (28 pts) or 56 (35 pts) or 112 (19 pts)	78-95%
Resche et al [47].	1997	114	Prostate, breast, miscellaneous	18.5 (55 pts) or 37 (59 pts)	70% ($)
Serafini et al [46].**	1998	118	Prostate, breast, miscellaneous	Placebo (39 pts) or 18.5 (40 pts) or 37 (39 pts)	62-72% ($)
Tian et al [48].	1999	105	Prostate, breast, miscellaneous	18.5 (35 pts) or 37 (70 pts)	84%
Dolezal et al [50].	2000	33	Prostate, breast, miscellaneous	39	70%
Wang et al [45].	2003	9	Prostate, breast, miscellaneous	37	78%
Sapienza et al [53].	2004	73	Prostate, breast	37	76%
Etchebehere et al [52].	2004	58	Prostate, breast, miscellaneous	37	78%
Sartor et al [49].**	2004	152	Prostate	Placebo (51 pts) or 37 (101 pts)	65%

* Response rate is defined as percentage of patients with either complete pain disappearance or significant pain reduction (usually >50%). Overall response rates are mentioned when no significant differences between groups exist. Otherwise, the response rate for the 37 MBq/kg group is mentioned ($)

** Double-blind placebo-controlled clinical trial

*** Bone marrow dose: 100 cGy (4 pts), 150 cGy (3 pts), 200 cGy (3 pts), 250 cGy (4 pts), 275 cGy (5 pts)

($) A significant difference between dosing groups was found

Pts patients

One of the first reported studies on the efficacy of ^{153}Sm-EDTMP compared two different dosages in a randomized controlled study [47]. Fifty-five patients received single doses of 18.5 MBq/kg and fifty-nine patients received single doses of 37 MBq/kg. The study population consisted mostly of patients with prostate or breast carcinoma, and some other tumors (lung, miscellaneous). Multi-modality assessment of pain was used in this study. Level of pain, sleep characteristics, and analgesic use were recorded in a diary that each patient completed once a day from the week before dose administration (baseline) until the end of week 4, and then once a week from week 5 to week 16. The physician evaluated the clinical condition of the patient by global assessment. During the first 4 weeks after treatment both study groups experienced alleviation of their bone pain, measured by a visual analogue scale (VAS). For

the 18.5 MBq/kg dosing group this did not register significant differences from baseline. The 37 MBq/kg dosing group, however, had a significant reduction of pain in week 3 and 4, with a significant difference between dosing groups in week 4. For the other characteristics all the results were in favour of the 37 MBq/kg with significant improvement compared to baseline. The physicians judged that 70% of the patients in the 37 MBq/kg dosing group had a clinical response to therapy, compared with 55% of the patients in the lower dosing group. After 16 weeks, 39% of the patients of the higher dosing group were still experiencing some degree of pain relief. With regard to toxicity, a decrease in haematological parameters was the only toxicity noted. The changes from baseline were greater for the 37 MBq/kg dosing group than for the 18.5 MBq/kg dosing group, for both platelets and white blood cells, but were acceptable for both groups. Toxicity grade 3 or 4 was reached in 10% of the cases (National Cancer Institute Common Toxicity Criteria). In most of these cases patients received either external beam radiotherapy or chemotherapy, after receiving the study agent [47].

The first published double-blind placebo-controlled study reported results on 118 patients with painful metastases, treated with either 18.5 MBq/kg (40 patients), 37 MBq/kg (39 patients), or placebo (39 patients) [46]. Most of the primary tumors were either prostate (68%) or breast carcinomas (18%). Response to therapy was assessed by pain diary scores (visual analogue scales), physician's global assessment, and opioid analgesic use. These parameters were recorded every week until week 4, and every month thereafter until week 16. Whereas the mean pain scores for the placebo group remained relatively unchanged, the scores for both active groups decreased during each of the 4 weeks after administration, with larger decreases observed at each week for the 37 MBq/kg dosing group. Decreases for the higher dosing group were significant at each of the first 4 weeks, but only at the first week for the lower dosing group. These findings correlated well with the physician's global assessment. In the 37 MBq/kg group, two-third of those judged to be responders at week 4 were still responding at week 16. The significant improvements in pain scores in this group were correlated with an ability to decrease their use of opioid analgesics. As in previous studies, a mild transient, dose-related myelosuppression was the only undesirable pharmacological effect seen [46].

Another double-blind placebo controlled study compared the efficacy of the radioactive (^{153}Sm) versus de non radioactive (^{152}Sm) lexidronam complexe [49]. This ensured that the chelating agent (ethylenediaminetetramethylenephosphonic acid [EDTMP]) would not explain the treatment effects. This placebo was administered to 51 patients, while 101 patients received 37 MBq/kg ^{153}Sm-EDTMP. All patients had hormone-refractory prostate carcinoma. Statistically significant improvement occurred in analgesic consumption and pain in patients treated with radioactive ^{153}Sm-EDTMP. In week 3 and 4 after treatment analgesic consumption was significantly reduced in the 'treated' group when compared with the 'placebo' group. The same result was found for reduction in the visual analogue scale of pain (VAS), a linear model to scale pain complaints, and the 'nonlinear' Pain Descriptor Scale (PDS), in which patients described their pain in words. The differences between the proportion of complete responders favoured the experimental arm, compared with the placebo group (38% versus 18%). Overall response rate for the 'treated' group was 65%, compared to 45% in the 'placebo' group. During a follow-up period of 16 weeks, 7 patients in the 'treated' group showed a decrease in prostate-specific antigen of more than 50%, compared with 2 patients in the 'placebo' group. No differences in survival were noted between treatment arms. In the study,

the only significant toxicity was mild transient myelosuppression [49].
All studies indicate the efficacy of single dosage treatment with ^{153}Sm-EDTMP in an optimal dosage of 37 MBq/kg. It is both effective and safe. In the case of a good response, repeated treatment may be desirable. As previously mentioned this was studied in a phase II study by Turner *et al* [40]. Both single and repeated dosage treatment were studied in 34 patients. A single dosage was given to 23 patients and 15 patients received an additional treatment. Among these 15 patients were 4 patients from the 'single-dosage-group'. These 4 patients did not respond to a single dosage. Good control of pain after retreatment was obtained in 13/15 patients (87%). Both median duration of pain relief and survival of patients in the re-treated group were significantly better than that for patients treated with a single administration of ^{153}Sm-EDTMP [40]. In 2/4 cases who did not respond to the first treatment, did experience pain relief after re-treatment within 3 months. In a period of 28 months, a patient with advanced hormone-refractory prostate cancer was given 11 treatments of 37 MBq/kg ^{153}Sm-EDTMP. He experienced improvement in pain, quality of life and his ability to perform activities of daily living [39]. Toxicity was mostly confined to transient myelosuppression, with a nadir at week 3-5 after treatment, and recovery after approximately 8 weeks. Repeated dosage treatment is not only safe but effective, as was the case with single dosage treatment.

^{186}Re-HEDP

Rhenium-186-hydroxyethylidene diphosphonate (^{186}Re-HEDP) was developed at the University of Cincinnati. HEDP (***Figure 3***) is strongly adsorbed on hydroxy-apatite in vitro. In vivo, HEDP is markedly concentrated by primary and metastatic bone lesions. In 1979 Mathieu *et al* first suggested the possible use of ^{186}Re-HEDP in the treatment of osseous metastases [54]. However, it was not until 1986 that therapeutically useful boneseeking compounds were generated, when Deutsch and Maxon were able to purify the ineffective mixture originally reported by Mathieu [55].

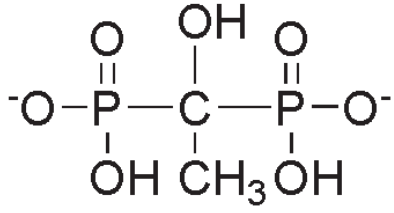

Figure 3 Structure of the HEDP compound which combines with ^{186}Re to form ^{186}Re-HEDP

^{186}Re is produced by irradiating enriched ^{185}Re and is chemically similar to ^{99m}Tc. It can be readily complexed with HEDP with a high radiochemical purity (>97%). ^{186}Re is a beta-emitting radionuclide with a maximum beta-emission of 1.07 MeV. It has a 9% abundant gamma emission of 137 KeV, which makes it suitable for diagnostic imaging. The physical half-life of 89.3 hours is short when compared to some other isotopes.

^{186}Re-HEDP: Pharmacokinetics

The pharmacokinetics of ^{186}Re-HEDP was previously investigated by our group, in 11 patients (17 studies) with bone metastases from breast or prostate cancer [56]. Half-life times of ^{186}Re-HEDP in three blood fractions (whole blood, plasma and plasma water) were 40.1 ± 5.0, 41.0 ± 6.0 and 29.5 ± 6.4 hours, respectively. This implies that repeated doses may be administered after a theoretical interval of 200 hours (elimination of a drug is over 9% after five half-lives). However, the optimal interval time between two doses will also depend on the overall clinical condition of the patient. With respect to the plasma water (free) half-life time, this value differs significantly from whole blood and plasma half-life times. This phenomenon is explained by non-constant protein binding. A time-dependent increase in plasma protein binding was observed, probably caused by in vivo decomposition of ^{186}Re-HEDP. Total urinary ^{186}Re-HEDP excretion was 69 ± 15%, of which 71 ± 6% was excreted in the first 24 hours after injection. Post-therapy ^{186}Re-HEDP scintigraphy showed no uptake in organs other than the skeleton and kidneys. The ^{186}Re-HEDP images were identical to the technetium-99m-hydroxymethylene diphosphonate (^{99m}Tc-HDP) images, showing the same number and localization of the metastases (***Figure 4***). The Bone Scan Index (BSI) (i.e. fraction of the skeleton showing scintigraphic evidence of metastatic disease) correlated closely with the fraction of dose non-renally cleared (R=0.98).

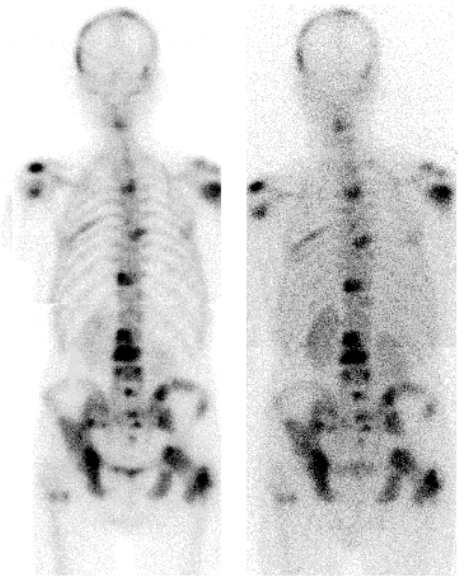

Figure 4 Skeletal scintigraphy 3 hours after injection of 600 MBq (16.2 mCi) ^{99m}Tc-HDP (Left); or 24 hours after injection of 1295 MBq (35 mCi) ^{186}Re-HEDP (Right). Biodistribution of the radiopharmaceutical and localisation of the metastases correlates perfectly between the 2 images in this patient, with hormone-refractory prostate carcinoma

^{186}Re-HEDP: Dosage and toxicity

Our dose-escalation study found a maximum tolerated dose (MTD) of 2405 MBq (65 mCi) ^{186}Re-HEDP for breast cancer patients and 2960 MBq (80 mCi) for prostate cancer patients with symptomatic bone metastases [25, 57]. Thrombocytopenia proved to be the dose-limiting

factor, with a nadir in platelet count at four weeks post-treatment. Leucopenia played a minor role. In patients with skull metastases, transient cranial neuropathy was noticed shortly after treatment with ^{186}Re-HEDP, as a rare side effect [58]. This transient neuropathy of cranial nerves needs to be distinguished from neurological abnormalities caused by progression of the disease. A transient increase in pain, also called "flare reaction", was often noted within 24 hours of injection, and lasted for one to three days in up to 20% of all cases.
The administered dose does not by itself always determines the grade of toxicity. However in prostate cancer patients, using the bone scan index (BSI) as an index of the extent of bone involvement, individual dosage adjustment (using dosages ranging from 1251 - 4336 MBq [33.8 – 117.2 mCi]) can avoid unacceptable hematological toxicity [27]. Our results were similar to Graham *et al*, who reported that in patients with prostate carcinoma, the determination of total activity remaining at 24 hours, as well as an estimate of the bone marrow dose, correlated well with the amount of myelosuppression observed [59]. Furthermore, they found post-therapy decreases of prostate specific antigen (PSA) of 50% or more in the highest treatment levels. The results suggest that a single 24-hour measurement of retained activity would allow individualized dosing and an improved therapeutic index, relative to fixing a dosing schema. Repetitive dosing is required in order to increase palliation. The recommended treatment dosage for routine use is currently 1295 MBq (35 mCi) ^{186}Re-HEDP.

^{186}Re-HEDP: Dosimetry

Dosimetric studies with an injected dose of 1295 MBq (35 mCi) showed a high tumor absorbed dose, with a mean dose to the tumor lesions of 35.3 Gy and a mean bone marrow dose of 0.92 mGy/MBq [61]. We calculated bone marrow absorbed doses using a noninvasive (based on urine collection) and a pharmacokinetic (based on urine and blood data) approach, after 19 treatments. The mean bone marrow absorbed doses were 1.137 ± 0.243 mGy/MBq and 1.092 ± 0.247 mGy/MBq, respectively [24]. The tumor-to-non tumor ratios have a high therapeutic index, with a mean value of 34:1 and a median value of 20:1 [61]. Israel *et al* found a good predictive value by measuring the radiation dose using quantitative bone single photon emission computed tomography (SPECT) for the prediction of pain relief. Furthermore, bone SPECT using ^{99m}Tc-MDP predicts radiation doses delivered by ^{186}Re-HEDP [62].

^{186}Re-HEDP: Efficacy

Using a computer-aided search of the literature, 21 clinical studies evaluating ^{186}Re-HEDP for the treatment of painful osseous metastases, predominantly prostate and breast cancer, were identified (***Table* 3**). The 21 studies included a total of 562 patients (338 prostate, 199 breast, 25 miscellaneous). Seven studies comprised patients with osseous metastases from prostate cancer only, seven studies comprised breast cancer only and seven studies comprised patients with a mixture of prostate, breast and a variety of other cancers. The overall response rate in these 21 studies was 73% (range 50-92%). Unfortunately, most studies currently available involve small numbers of patients. The largest study, conducted by Sciuto *et al* with 60 patients (45 prostate, 10 breast, 5 miscellaneous) reported an overall response rate of 80% [64]. In a more recently published study by Sciuto *et al*, concerning 25 patients with breast cancer they reported an even higher response rate of 92%, the highest response rate

Table 3 Efficacy studies on single dosage treatment with ^{186}Re-HEDP

References	Year	No. of patients	Diagnosis	Dosage (MBq)	Response rate*
Maxon et al [63].	1990	20	Prostate	1225 ± 152	80%
Maxon et al [61].**	1992	44	Prostate, breast, miscellaneous	1258	77%
Quirijnen et al [67].	1996	37	Prostate	1295 - 3515	54%
Guerra et al [142].	1997	5	Breast	1406	80%
Schoeneich et al [143].	1997	44	Prostate, breast, miscellaneous	1295	60%
Limouris et al [144].	1997	16	Prostate	1400 ± 100	81%
Limouris et al [145].	1997	14	Breast	1400 ± 100	71%
Virotta et al [146].	1997	14	Breast	1300	80%
Holle et al [147].	1997	15	Prostate	1810 - 2590	87%
Hauswirth et al [148].	1998	17	Breast	1295	59%
Han et al [71].	1999	24	Breast	1295 - 2960	58%
Palmedo et al [149].	1999	30	Breast	1295	60%
Giannakenas et al [150].	2000	25	Prostate, breast, miscellaneous	1300	80%
Liepe et al [110].	2000	13	Prostate, breast	1336 ± 166	77%
Kolesnikov-Gauthier et al [66].	2000	26	Prostate, breast	1295	50%
Tennvall et al [70].	2000	14	Prostate	2590	79%
Kucuk et al [69].	2000	31	Prostate, breast, miscellaneous	1295	68%
Sciuto et al [64].	2000	60	Prostate, breast, miscellaneous	1406	80%
Sciuto et al [65].	2001	25	Breast	1406	92%
Dafermou et al [109].	2001	58	Prostate	1295	86%
Han et al [60].**	2002	43	Prostate	1295	65%

* Response rate is defined as percentage of patients with either complete pain disappearance or partial pain reduction (usually >50%)

** Double-blind placebo-controlled clinical trial

found in the literature [65]. In contrast, Kolesnikov-Gauthier *et al* (26 patients: 12 breast, 14 prostate), as well as Quirijnen *et al* (37 patients: prostate only) found a low response rate of 50% and 54% respectively [66, 67]. Only two randomized double-blind placebo-controlled studies have been published so far. Maxon *et al* conducted a trial with 13 evaluable patients, which resulted in a significantly greater decrease in pain after treatment with ^{186}Re-HEDP than after treatment, which used ^{99m}Tc-methylene diphosphonate (MDP) as a radioactive placebo [68]. At our hospital, we conducted the 'Placorhen' study, which confirmed, in a double-blind, placebo-controlled, randomized study (131 patients), that ^{186}Re-HEDP resulted in a significantly longer pain response in the treatment of bone pain from metastasized prostate cancer [60]. This is illustrated in ***Figure* 5**, which shows a significant difference between

^{186}Re-HEDP and placebo for the visual analogue scale for pain (VAS) and the assessment of daily activity. No significant difference was found in the medication index score [60].
Instead of asking patients at predetermined intervals about their pain relief, we assessed pain relief using an electronic diary containing questions reflecting the multidimensional character of chronic pain during a 84-day follow-up period. By using this method it was confirmed that pain is never constant and that it fluctuates day by day, which makes daily pain assessment mandatory. We evaluated whether each registered day was a response day or a non-response day, according to standardized criteria. The finally reported proportional-response days during the 84-day follow-up cannot be compared with the results from any other publication. If we had decided that a responder was any patient who reported more than 5 days of improved pain index, we would have found a 65% response rate [60]. This number is fully comparable with the response rates reported in the literature.

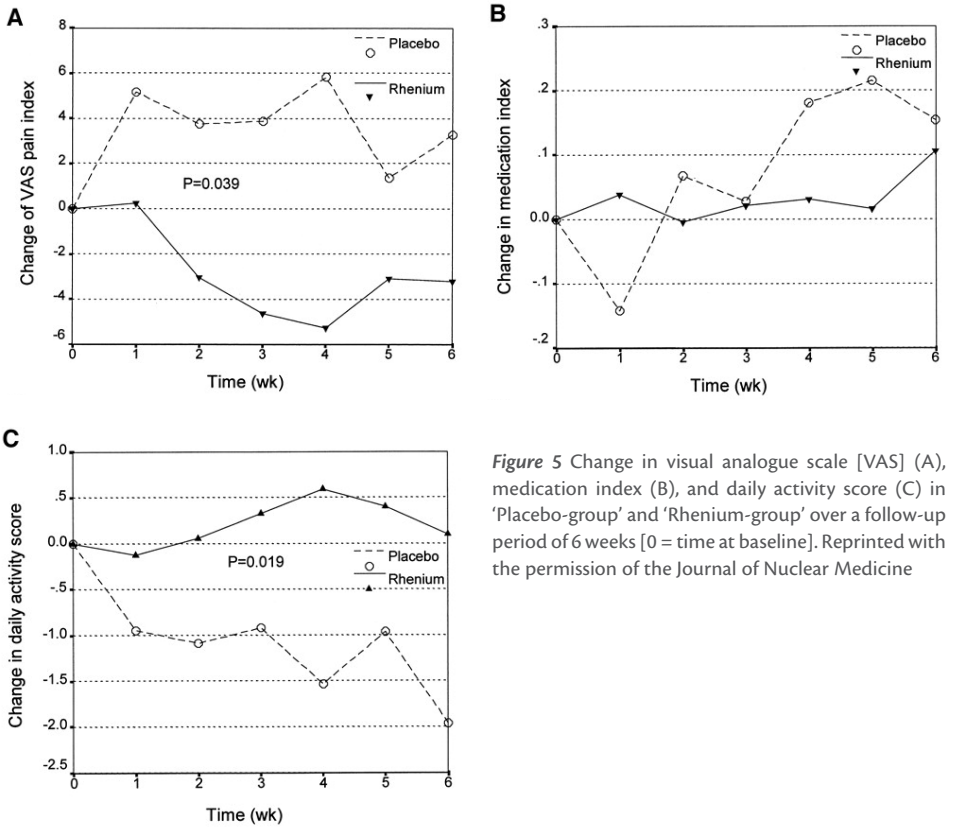

Figure 5 Change in visual analogue scale [VAS] (A), medication index (B), and daily activity score (C) in 'Placebo-group' and 'Rhenium-group' over a follow-up period of 6 weeks [0 = time at baseline]. Reprinted with the permission of the Journal of Nuclear Medicine

Some studies specifically concentrated on the difference between response rates of breast and prostate cancer. Kolesnikov-Gauthier *et a*l evaluated the efficacy of ^{186}Re-HEDP in treatment of patients with painful osseous metastases of prostate or breast cancer [66]. In a study group of 26 evaluable patients (12 men with prostate cancer, 14 women with breast cancer) they found a difference between the response rates of breast (36%) and prostate (67%) cancer.

Breast carcinoma typically produces mixed but predominantly lytic lesions in bone, whereas metastases from prostate carcinoma are predominantly osteoblastic. In contrast, Kucuk *et al* found the same response rate (87,5%) for breast and prostate cancer [69]. Overall no difference was found in response rate between the prostate and breast cancer group.
The activity used was approximately 1295 MBq (35 mCi) in the majority of all studies. Although in a study from our group escalating doses from 1295 MBq (35 mCi) to 1850 MBq (50 mCi) to 2405 MBq (65 mCi) of ^{186}Re-HEDP were used, a clear dose-response relationship could not be demonstrated either by us nor in any other study. Tennvall *et al* used 2590 MBq (70 mCi) ^{186}Re-HEDP (i.e. twice the activity normally used) to evaluate the safety of intravenously administered ^{186}Re-HEDP, and to investigate whether the response rates would markedly improve [70]. In their study, pain relief was observed in 11 out of 14 evaluable patients (79%), 4 of who became completely free from pain.
One of the most striking differences between the studies was the wide variety of methods used to assess clinical response. Most investigators measured response using a questionnaire or a visual analogue scale (VAS), or both. Qualitative responses such as very good or moderate pain relief, were also used as levels of clinical success, but these could not be used in comparison with other series. The Utrecht group, Kolesnikov-Gauthier *et al* and Sciuto *et al* have used a multi-dimensional schema integrating pain reduction, activities of daily life, and medication index, in order to outline strict criteria for response [60, 64-67, 71]. Thus, a reduction of pain would not be considered a response if the patient was spending more time in bed. If pain reduction was considered to be the only parameter of response, our group would have scored a much higher 71% response rate instead of the 58% reported, in accordance with the strict inclusion criteria of response. Kolesnikov-Gauthier *et al* used the same strict criteria for response and found a 67% response rate for patients with prostate carcinoma and 36% response rate for patients with breast carcinoma [66]. Analogously, the overall high response rate of 80% in the study by Sciuto *et al* [64] would have dropped to 68%, if they had used the strict criteria of the Utrecht workers. The same could be said from their more recently published data showing a 92% response rate, in which they also included the minimal responders [65]. The minimum percentage of improvement in pain relief or medication index was also different in the studies analyzed, and varied from 15% to 25%. As mentioned above our so-called 'Placorhen' study used another approach by using an electronic diary with daily questions, assessing pain relief for an 84-day follow-up period. We finally reported proportional-response days during this follow-up period, instead of an overall response rate.
Repetitive treatments with ^{186}Re-HEDP were used in several studies, in order to prolong the duration of response, and there was a general agreement that further pain relief could be expected if the patient had responded previously to treatment with ^{186}Re-HEDP. Length of response differed in most studies, with a wide range of up to several months in this difficult patient group in advanced stages of disease.

^{89}Sr-Chloride

The therapeutic possibilities of ^{89}Sr-Chloride (Metastron®) for the palliation of bone pain had already been suggested in the early forties, but were further explored from the early seventies

onwards. It was the first radionuclide to receive US Food and Drug Administration approval for bone palliation in many years. ^{89}Sr-Chloride has a half-life of 50.5 days. It decays to stable ^{89}Y, emitting predominantly high energy beta-particles (E_{max} = 1.46 MeV) and a very small proportion of gamma rays (910 keV). ^{89}Sr-Chloride has a ^{85}Sr impurity ranging from 0.03% to 0.2%, and ^{90}Sr impurity less than 1.5%. The radiopharmaceutical may be readily administered through intravenous injection. Strontium, like calcium, is member of the family IIA of the periodic table and, as a divalent cation, is incorporated into hydroxyapatite. After injection it migrates to the bone and is actively incorporated in the bone matrix. Beta-particles are responsible for the therapeutic effect. These electrons deposit their energy within 6-7 mm in soft tissue and 3-4 mm in bone. Because of the negligible amount of gamma rays and a small amount of 'bremsstrahlung', treated patients cause no radiation risk to others and may therefore be treated on an outpatient basis. Post-therapy scintigraphy is possible, because of 'bremsstrahlung' [72], but qualitatively it is not as good as ^{186}Re-HEDP or ^{153}Sm-EDTMP.

^{89}Sr-Chloride: Pharmacokinetics

The pharmacokinetics of ^{89}Sr-Chloride were investigated in a group of 14 patients, receiving ^{89}Sr-Chloride for palliation of bone pain, secondary to prostate carcinoma [73]. Patients received either 1.48 MBq/kg or 2.22 MBq/kg ^{89}Sr-Chloride, together with a tracer dose of 10-40 MBq ^{85}Sr-Chloride (half-life = 64.85 days; gamma rays: 514 keV), in order to permit a more comprehensive study of strontium metabolism than would otherwise have been possible. The total body strontium retention in a healthy population 3 months after injection is around 20%. In the study population it varied from 11% to 88%, strongly dependent on the degree of metastatic involvement of the skeleton. This also had a positive correlation with plasma clearance, being much faster in patients with superscans, presumably because of rapid early loss of strontium to an extensive metastatic bone compartment. Strontium renal plasma clearance varied between 1.6 L/day and 11.6 L/day. In addition to the degree of metastatic involvement of the skeleton, the wide range in whole body retention of strontium, is also caused by the range in renal plasma clearance. The low values of renal plasma clearance found in this study may be caused by changes in calcium homeostasis sometimes associated with disseminated prostate malignancy. The retention curves of individual osseous metastases showed some variation in pattern (increase/decrease) during the first days, dependent on overlying soft-tissue retention, but plateaued at 10 days and thereafter were very flat. Retention in skeletal metastases is higher (up to five times greater than in comparable areas of normal bone), and has a prolonged retention when compared to normal bone. Together with a malignancy induced low renal plasma clearance these factors favour the objective of ^{89}Sr-Chloride of achieving a clinically effective radiation dose to tumor cells [73].

^{89}Sr-Chloride: Dosage and toxicity

In an early phase I/II study, 38 patients were treated with doses ranging from 1.0-4.5 mCi (16-70 µCi/kg). After treatment with these doses no haematological toxicity occurred. Some pain relief, as measured by analgesic reduction and/or improved performance status, occurred in 23/45 (51%) of injections. A dose response relation could not be detected. Failures were as likely as responses at all dose levels and for all tumor types. Median time to response was 9

days (range 3-25 days). The duration of response averaged 1.6 months, ranging from 1 – 4 months. It was concluded that the dosage should be increased to aim for more effective pain relief [74].
After this study, case reports stated the importance of close haematological monitoring, since marked bone marrow depression was shown after treatment with ^{89}Sr-Chloride [75, 76]. Other studies confirmed these findings. Currently, haematological toxicity is recognized as the most common side effect after ^{89}Sr-Chloride therapy, with a mild to moderate bone marrow suppression. It generally consist of a transient mild thrombocytopenia of around 30%, with a nadir after 6 weeks and recovery at 12 weeks [77- 81].

^{89}Sr-Chloride: Dosimetry

One of the first studies on dosimetry was performed on 10 patients referred for ^{89}Sr-Chloride for disseminated prostate carcinoma [82]. A tracer dose of ^{85}Sr was used together with scintigraphic follow-up for 6 months. The mean absorbed dose was 850 cGy/mCi (23 cGy/MBq) with a wide range from 220 – 2269 cGy/mCi (6 – 61 cGy/MBq). This can be explained by the differences in renal plasma clearance (range 0.1 – 11.8 L/day) and the extent of skeletal metastatic disease, varying from two small metastases to a superscan. The doses calculated in this report are mean doses averaged over the total mass of bone and soft tissue in the metastases [82]. It was found that in metastases, most accumulation of ^{89}Sr-Chloride occurred in areas adjacent to metastatic deposits, where most of the osteoblastic activity resides, and it occurred far less in areas of normal bone and within the marrow [83]. Additionally, by direct measurement of ^{89}Sr-Chloride activity in bone metastases, they found a mean absorbed dose in metastatic bone of 12.2 cGy/MBq. The average total dose to normal bone sites was 0.74 cGy/MBq, which resulted in a metastatic to normal bone ratio ranging from 8 to 40 [84]. Breen *et al* found a somewhat higher median absorbed dose of 68 cGy/MBq (4 patients; range 21 – 231 cGy/MBq) [85]. All of these doses are thought to be sufficiently large to produce a therapeutic effect.
Calculated doses to the red marrow in different studies varied widely from 0.3 – 1.2 cGy/MBq [84], 1 cGy/MBq [82], to 4.5 – 33 cGy/MBq [85]. This is probably caused by the different methods used and the small number of patients included in each study. As described previously this may cause considerable bone marrow depression. Doses for other tissue were found to be 0.036 cGy/MBq for blood, 0.046 cGy/MBq for soft tissue, 1.45 cGy/MBq for bone surface, 0.13 cGy/MBq for upper large intestine, 0.38 cGy/MBq for lower large intestine, and 0.38 cGy/MBq for the bladder [86].

^{89}Sr-Chloride: Efficacy

The efficacy of ^{89}Sr-Chloride has been studied in great detail (***Table 4***). Most of the early work comprised ill-defined studies with only small groups of patients [87]. Most of these studies showed a positive effect of ^{89}Sr-Chloride for pain palliation. In contrast, Buchali et al included 47 patients with prostate carcinoma in a double blind study, examining the efficacy of ^{89}Sr-Chloride. They received either 3 x 75 MBq ^{89}Sr-Chloride at monthly intervals, or saline as placebo. They found no significant differences between the treatment group and the placebo group for relief of pain. However, no distinction was made in being hormone refractory or

not. This factor, together with the unusual fractionated dosing schedule, could well have influenced the results. Remarkable in these circumstances, was their finding of a significantly improved survival rate in the ^{89}Sr-Chloride treatment group [81]. After this publication the same research group presented a paper with the results on another 179 patients with skeletal metastases from hormone refractory prostate carcinoma, combined with 21 patients from the placebo-group of their first published study. These patients were also treated with a fractionated dosing schedule, with doses ranging from 3 x 0 MBq to 3 x 150 MBq at monthly intervals. They now found a response of 34% in the placebo group compared to 59% in the overall treatment group, correlating with the activity administered. In this study group no survival benefit was found [88]. Another prospective randomised double-blind study evaluated 26 patients, treated with a dose of 150 MBq ^{89}Sr-Chloride. Statistical comparison between placebo and ^{89}Sr-Chloride showed clear evidence of a therapeutic response to ^{89}Sr-Chloride, compared with only a limited placebo effect. All patients had prostate carcinoma metastatic to the bone which had escaped control by conventional treatments (analgesics, hormone manipulation). After first treatment with 150 MBq ^{89}Sr-Chloride, 8/12 patients showed some to dramatic improvement, as compared to 3/14 in the placebo-group. Complete pain relief was only reported following ^{89}Sr-Chloride injection.

Table 4 Efficacy studies on single dosage treatment with ^{89}Sr-Chloride

References	Year	No. of patients	Diagnosis	Dosage	Response rate*
Buchali et al [81].**	1988	41	Prostate	3 x 75 MBq (19 pts) or placebo (22 pts)	37%
Robinson et al [151].	1989	128	Prostate, breast	40 microCi/kg (1.5 MBq/kg)	80-89%
Lewington et al [80].**	1991	26	Prostate	150 MBq (12 pts) or placebo (14 pts)	67%
Laing et al [79].	1991	83	Prostate	1.5 – 3.0 MBq/kg	75%
Haesner et al [88].	1992	200	Prostate	3 x 37 MBq (65 pts), 3 x 75 MBq (72 pts), 3 x 100 MBq (25 pts), 3 x 150 MBq (17 pts), or placebo (21 pts)	59% ($)
Quilty et al [77].	1994	123	Prostate	200 MBq	65-70%
Pons et al [152].	1997	76	Prostate, breast	148 MBq	89-92%
Baziotis et al [153].	1998	64	Breast	2 MBq/kg	81%
Kasalicky et al [89].	1998	118	Prostate, breast, miscellaneous	148 MBq	96%
Fuster et al [154].	2000	40	Breast	148 MBq	92%
Kraeber-Bodere et al [138].	2000	94	Prostate	150 MBq	78%
Dafermou et al [109].	2001	527	Prostate	148 MBq	60%
Turner et al [155].	2001	93	Prostate	150 MBq	63%

* Response rate is defined as percentage of patients with either complete pain disappearance or partial pain reduction. Overall response rates are mentioned for all dosing groups

** Double-blind placebo-controlled clinical trial

($) A significant difference between dosing groups exists

Pts Patients

Toxicity was confined to transient myelosuppression [80]. A later report by the same research group compared the palliative effect of ^{89}Sr-Chloride (200 MBq) with external beam radiotherapy (284 patients). All treatments provided effective pain relief. After 3 months improvement sustained in 63.6% after hemibody radiotherapy compared with 66.1% after ^{89}Sr-Chloride, and in 61% after local radiotherapy compared with 65.9% in the comparable ^{89}Sr-Chloride-group. Fewer patients reported new pain sites after ^{89}Sr-Chloride than after local or hemibody radiotherapy. No significant differences in survival were found [77].
A multi-centre study by Laing *et al* showed ^{89}Sr-Chloride to be effective for pain palliation in hormone refractory prostate carcinoma in 75% of the cases (22% complete response). 83 patients were treated with at least 1.5 MBq/kg (1.5 – 3.0 MBq/kg). Response occurred within 6 weeks with a mean duration of 6 months (range of 4 – 15 months). A flare response was seen in some patients; this lasted 2 – 4 days and was generally an indicator of a good response. 24 patients were retreated for recurrence of pain. The response to the additional treatments was comparable with that seen in the first treatment for an individual patient. Toxicity was generally mild and transient, with no differences between first dosing and re-treatment, as long as peripheral blood count had returned to acceptable levels, usually after at least 3 months interval. No dose-response relationship could be established. Based on dose estimations they recommended a fixed dose of 150 MBq [79].
Robinson *et al* evaluated studies on single dose treatment with ^{89}Sr-Chloride up to 1994. For study eligibility, evaluation of clinical response as assessed by the Karnofsky index, need for pain medication, or changes in mobility or sleep patterns was required. A minimum of 10 cases, and sufficient hemotoxicity data were needed. Doses ranged from 0.6 MBq/kg (16 microCi/kg) to 400 MBq (10.8 mCi) per patient. Overall more than 500 patients were evaluated. Improvement occurred in as many as approximately 80% of patients. Duration of response may average 3 to 6 months [78]. Repeated therapy is effective and safe [89, 78].

Other bone seeking radiopharmaceuticals

The high-energy bone seeking radiopharmaceutical ^{32}P-phosphate has been employed for palliation of bone pain for many years. It has a half-life of 14.3 days and emits purely beta-particles of maximum 1.71 MeV. ^{32}P-phosphate is incorporated into the hydroxyapatite molecule present in large amounts in most osseous metastases. Until the 1980s it was the most commonly used radiopharmaceutical for the palliation of painful osseous metastases. For prostate cancer the overall response rate was 77%, and 84% for breast cancer, with an average onset of response of 14 days and duration of response of several months [90]. As in other bone seeking radiopharmaceuticals no dose-response relationship could be found [91]. Because of its maximum range of 8 mm, significant bone marrow suppression occurs, with pancytopenia around 4-5 weeks after injection and recovery after 7-8 weeks. Most studies did not find this toxicity to be clinically significant [90- 92]. However, because of its toxicity profile and better alternatives, it is not used for this purpose anymore. Nowadays, ^{32}P-phosphate is mostly used as a radionuclide therapy for myeloproliferative disorders [93], and, bound to colloid, for peritoneal instillations in patients with malignant ascites [94].
One of the new radiopharmaceuticals for bone palliation is ^{188}Re-HEDP. ^{188}Re is inexpensively

produced from a ^{188}W (Tungsten)/^{188}Re generator, and a kit is available for easy radiolabeling of the bone seeking HEDP. This 'on demand' and inexpensive production is a major advantage over other radiopharmaceuticals. The chemical characteristics of ^{188}Re-HEDP are the same as ^{186}Re-HEDP. ^{188}Re has a high-energy beta-particle emission with a maximum energy of 2.1 MeV (half-life 17 hours). A dose escalation study in 22 patients with prostate carcinoma (doses ranging from 1.2 GBq [35 mCi] to 4.4 GBq [120 mCi]) resulted in a maximum tolerated dose of 3.3 GBq (90 mCi). Thrombo- and leukopenia were the most important side-effects, with a maximum percentage decrease in thrombocytes in the 3.3 GBq dose group of 60%. Pain palliation was reported by 64% of the patients and tended to increase with higher doses [95]. The therapeutic effect of ^{188}Re-HEDP was further established by Liepe *et al*. In a group of 27 patients with hormone refractory prostate carcinoma, treated with doses of 2700 – 3459 MBq, they found a response rate of 76%. Karnofsky performance scale increased, and analgesic intake and pain intensity decreased significantly [96]. The response rate further improved to 92% after repeated treatment, with an interval of two months, as randomly compared to a group of patients treated with a single dose (64 patients in total; 70 – 90 mCi ^{188}Re-HEDP per dose). Repeated treatment even resulted in a significant improvement in progression-free and overall survival. In both groups toxicity was low, with reversible myelosuppression and return to baseline within 8 weeks [97].

^{117m}Sn(4+)-DTPA (diethylenetriaminepentaacetic acid), another bone seeking radiopharmaceutical, has unique physical characteristics. It decays by isomeric transition with emission of the dominant gamma-ray at 156 keV. The gamma-ray undergoes conversion and it is the conversion electrons that have the therapeutic potential. The energetic conversion electrons have a very short range in soft tissue of 0.2 – 0.3 mm. This may explain the low incidence of myelosuppression. Pilot studies have shown bone palliation without any significant toxicity to bone marrow [98, 99]. After injection, the radiopharmaceutical preferentially accumulates at sites with high bone turnover, comparable to the uptake pattern of ^{99m}Tc-MDP. Approximately 78% of the administered dose is taken up by bone. The remaining 22% resides in the soft tissue and is excreted by the kidneys with an average biologic clearance half-time of 1.45 days [100]. Post mortem research on a human body showed a retention of 81% of the administered dose 47 days after injection. Of the whole body retained activity at 47 days, 82.4% was in bone, 7.8% in the muscle and 1.5% in the liver. The rest was distributed among other tissues [101]. This high skeletal retention results in high efficacy. In 47 patients with painful bone metastases from various malignancies, an overall response rate of 75% (range 60 – 83%) was found (dose levels ranging from 2.64 to 10.58 MBq per kg of body weight. Myelotoxicity was minimal [102]. A large scale trial is warranted in order to evaluate this compound in comparison with other similar agents.

The last mentioned isotope is ^{177}Lu. ^{177}Lu is produced by thermal neutron bombardment of a target prepared from natural Lu. It has a half-life of 6.71 days and decays by emission of beta radiation (E_{max} = 497 keV [78.6%]; 384 keV [9.1%]; 176 keV [12.2%]) to stable ^{177}Hf. It also emits gamma photons of 113 keV (6.4%) and 208 kev (11%) which are quite suitable for imaging the in vivo distribution. The relatively low radiation energy will result in less penetration into the marrow, hence less bone marrow toxicity, while a relatively short half-life offers a faster rate of dose delivery for therapeutic purposes. The isotope can be bound to several ligands. The chelation of the isotope ^{177}Lu to EDTMP (ethylenediaminetetramethylene phosphonic acid) is

obtained by heating for 30 minutes in boiling water at pH 8.8, resulting in a radiochemical yield of over 99%. It has selective bone accumulation, with fast blood clearance, high bone uptake and high bone-to-soft tissue ratios [103]. Other polyaminomethylene phosphonate ligands may also be used, which show more or less the same excellent characteristics as EDTMP [104, 105]. All the ^{177}Lu phosphonates complexes need to be further explored in clinical trials as promising alternatives to ^{153}Sm-EDTMP.

Treatment recommendations

It may seem difficult to choose between all these bone seeking radiopharmaceuticals for the treatment of painful osseous metastases. Long time experience with a certain radiopharmaceutical, as well as non-medical factors (financial factors, logistics), are often prominent arguments to choose between available radiopharmaceuticals. However, significant differences between the radiopharmaceuticals do exist, each having their own pro's and con's. In certain cases these differences may, and sometimes should, be decisive in a physician's choice for a certain treatment. Moreover, the specific characteristics of each radiopharmaceutical, are of eminent importance in further research and development.
Important differences between the radiopharmaceuticals are radiation half-life, energy of gamma-emission and beta-emission (***Table 1***). These differences determine both the clinical benefit and the side-effects. Other differences include chemical properties, clearing, and the mechanism of uptake in the bone matrix.
Short-lived isotopes in bone seeking radiopharmaceuticals may have potential advantages in comparison with longer-lived isotopes. Radionuclides with long half-lives will produce a lower dose rate than those with short lifetimes**.** At low dose rates (long-lived radionuclides), there is presumably more opportunity to repair radiation-induced damage, unless the repair system itself was inactivated. Fairly rapid delivery of therapeutic radiation is a potential method for obviating DNA repair mechanisms. Secondly, short-lived radionuclides provide opportunities for multi-dose deliveries, and for bone marrow ablation, by allowing earlier reinfusion of the transplant marrow [106-108].
Few studies have concentrated on the difference between the efficacy of different radionuclides in the treatment of painful osseous metastases. Dafermou *et al* reported a multicentre study, in which from 510 evaluable patients with painful bone metastases of prostate cancer, 453 patients were treated with ^{89}Sr and 58 patients were treated with ^{186}Re-HEDP (one patient was first treated with ^{89}Sr and later with ^{186}Re-HEDP). They found no statistically significant difference in palliative efficacy of the two radiopharmaceuticals [109]. Sciuto *et al* studied the difference in pain palliation of ^{186}Re-HEDP and ^{89}Sr, treating 50 patients with painful osseous metastases of breast cancer with either ^{89}Sr (25 patients) or ^{186}Re-HEDP (25 patients). They found a response rate of 84% for ^{89}Sr and 92% for ^{186}Re-HEDP, which also shows no significant difference (p-value of 0.66) [65]. In a group of 44 patients (38 prostate, 6 breast) Liepe *et al* treated 15 patients (11 prostate, 4 breast) with ^{89}Sr, 13 patients (12 prostate, 1 breast) with ^{186}Re-HEDP and 16 patients (15 prostate, 1 breast) with ^{188}Re-HEDP. They found response rates of 80%, 77% and 81% for the ^{89}Sr, ^{186}Re-HEDP and ^{188}Re-HEDP group respectively, which is also no significant difference [110].

Although no difference could be found in treatment response, differences in onset of response, duration of response and toxicity do exist. The onset of response is rapid after treatment with short-lived isotopes (i.e. ^{153}Sm-EDTMP, ^{186}Re-HEDP) usually after 2-3 days. After treatment with long-lived isotopes (^{89}Sr), the onset is prolonged to a few weeks. The duration of response, on the other hand, is longer for long-lived radioisotopes, than for short-lived isotopes. This is an important advantage. A disadvantage of long-lived isotopes, however, is the considerable toxicity. The maximum energy of the beta-radiation of ^{89}Sr is 1460 keV, compared to 860 keV for ^{153}Sm-EDTMP. The range in bone is greater for ^{89}Sr, and therefore the radiation dose to the bone marrow is increased. Combined with the long half-life of ^{89}Sr, this results in considerable myelosuppression for a longer period.

Although the ideal radiopharmaceutical does not exist, the best balance between efficacy and toxicity (in patients with advanced disease), seems to be a radiopharmaceutical with a relatively short half-life [111]. Patients with progressive disease and pain, for whom rapid relief is warranted, are best treated with short-lived isotopes. Relief will be quick and toxicity acceptable. If needed, patients can be treated multiple times with an interval of 2-3 months. Patients with a somewhat better prognosis and better clinical condition, for whom treatment of pain with radioisotopes is indicated, may be treated with long-lived isotopes. The duration of response will be longer. However, care must be taken for toxicity. In most cases, treatment of painful osseous metastases with radionuclide therapy is indicated at an advanced stage of the disease in heavily pre-treated patients with minimal bone marrow reserve, for whom rapid relief of pain with minimal toxicity is warranted. In these cases, short-lived isotopes are preferred over long-lived isotopes.

Last but not least, the gamma radiation of radiopharmaceuticals such as ^{153}Sm-EDTMP (103 keV) and ^{186}Re-HEDP (137 keV) give the opportunity to perform skeletal scintigraphy. ^{153}Sm-EDTMP has an extra advantage, due to its high uptake in bone, low uptake in soft-tissue and rapid renal clearing. This will result in high quality images for staging, therapy monitoring, and dosimetry (***Figure 2 and 4***).

Radiopharmaceuticals combined with chemotherapy

In the field of external beam radiotherapy, chemosensitization is a well recognized, accepted, and widely used method for improving the overall efficacy of treatment. The cytotoxic effects of chemotherapy make cancer cells more susceptible to radiation damage. In the field of bone seeking radiopharmaceuticals, chemosensitization may also lead to an overall improved efficacy. Early studies already suggested a synergistic effect [112]. This synergism was shown in vitro by Geldof *et al*, who studied the combined effect of ^{186}Re-HEDP and cisplatin in prostate cancer cells [113].

The more than additive effect of the combined treatment was also shown in human patients [114-120]. Most promising in this respect was a report by Tu *et al*. They treated 103 patients with androgen-independent carcinoma of the prostate with induction chemotherapy (ketoconazole and doxorubicin alternating with estramustine and vinblastine). Patients with stable disease or a response to induction chemotherapy (73 patients) were randomly assigned to receive weekly doxorubicine for 6 weeks with or without one dose of ^{89}Sr-Chloride (2.0 MBq/

kg) in week one. In addition to a very good clinical and biochemical response, median survival time for the 36 patients, randomly assigned to receive ^{89}Sr-Chloride and doxorubicin, was 27.7 months, compared with 16.8 months for the patients who received doxorubicin alone (p = 0.0014). Moreover, 43/103 (42%) patients had a more than 80% decline in prostate specific antigen concentration and 49/103 (52%) patients had complete resolution of pain [120]. It has recently been reported that a single dose of ^{89}Sr-Chloride combined with chemotherapy did not affect the delivery of subsequent courses of chemotherapy [121]. It demonstrates that this form of therapy is not only effective, but safe and well tolerated.
Most, if not all, clinical studies were performed using ^{89}Sr-Chloride as the radiopharmaceutical. More studies, using different radiopharmaceuticals, different chemotherapeuticals and different schemes are warranted to explore this promising field.

Radiopharmaceuticals combined with other treatments

Chemotherapy is an effective anti-tumor agent. Even in the field of hormone resistant prostate carcinoma, recent advances have been made [122]. However, many patients do become chemotherapy resistant, and need alternative treatment. Investigation for new agents and / or combinations of existing agents in chemotherapy resistant patients is underway. These agents could be directed against the tumor cells themselves, like chemotherapy, or they could be directed against the environment of the tumor cells, inhibiting their proliferation and induce cell death. The latter is warranting much attention in the field of anti-cancer research. It is likely that a combination of several modalities is potentially the most efficacious. This needs further evaluation. Due to their tolerability, efficacy and ease of use, bone seeking radiopharmaceuticals may be administered in combination with these agents.
External beam radiotherapy is directed against both the tumor cells and their environment. All tissue in the radiation field is affected. This includes tumor cells, bone marrow, osteoclasts,

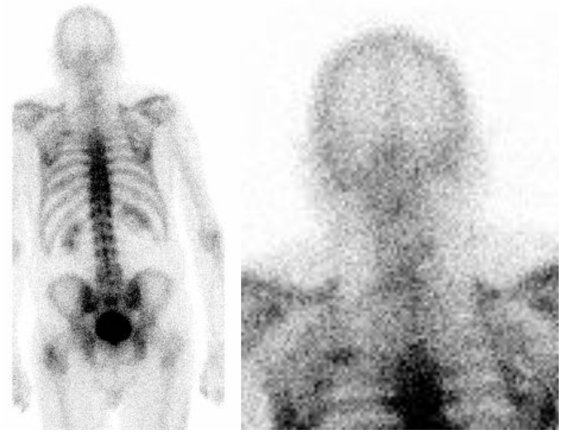

Figure 6 Eighty year old patient with laryngeal cancer, who was irradiated in 1989 (66 Gray in 33 fractions) in the laryngeal region, including the cervical spine and part of the thoracic spine. In March 2002 he was re-irradiated in the same region (50 Gray in 25 fractions), due to residual disease. A photopenic area is clearly visible in the post-irradiated region. The uptake of the radiopharmaceutical (^{99m}Tc-HDP) in the spine is reduced in this region, because of diminished activity of osteoclasts and osteoblasts, and reduced blood supply

osteoblasts, and the vasculature. This is demonstrated by skeletal scintigraphy, which shows no uptake of ^{99m}Tc-HDP in the post-irradiated field (***Figure 6***). It prevents to some extent the formation of new osseous metastases in post-irradiated bone, although it is not excluded and sometimes metastases reoccur when regeneration of the tissue occurs. A combination of external beam radiotherapy and bone seeking radiopharmaceuticals could lead to synergy, with higher efficacy in the radiation field and prevention of new pain sites [123, 124].

Bisphosphonates exhibit potent inhibitory activity of osteoclasts. They produce significant declines in bone metabolism markers. This decrease suggests that these drugs may preferentially target and down regulate active sites of bone resorption [21, 22]. Secondly, and possibly more importantly, bisphosphonates have a proven anti-tumor effect in several tumor cell lines, including carcinomas of the breast and prostate [125-128]. Although they are currently indicated for the prevention of skeletal-related events, their anti-tumor efficacy needs to be further evaluated. Concomitant administration of bone seeking radiopharmaceuticals and bisphosphonates in patients with painful osseous metastases may lead to an increased clinical benefit. Patients would have a relief of pain, together with prevention of pathological fractures. Moreover, possible synergy between both agents could lead to an improved clinical outcome. It has already been shown in vitro, using prostate cancer and myeloma cell lines, that concomitant use of zoledronic acid and radiation, led to synergy and an increased cytotoxic effect, when compared with either treatment alone [129].

Last but not least, it is of interest to note that several new anti-cancer agents are under investigation, that might have potential as monotherapy, but may also be used in combination with bone seeking radiopharmaceuticals. The process of osseous metastasis offers a broad range of potential intervention [130]. Endothelin-1-antagonists are an example of new promising drugs. The production of endothelin-1 is increased in many tumor types, where it plays crucial roles in proliferation and angiogenesis. Endothelin-1-antagonists block the endothelin-1-receptor. This causes an inhibition of tumor proliferation [131, 132]. Secondly, it was found that basal production of endothelin-1 in tumors leads to the development of a myogenic tone in the tumor vasculature which represents an important reserve for vasorelaxation. The use of endothelin-1-antagonists can selectively promote tumor perfusion and oxygenation, and consecutively increase the effectiveness of tumor radiotherapy by an increased tumor oxygenation [133]. Combinations with bone seeking radiopharmaceuticals might thus increase overall efficacy.

Discussion

Efficacy

Treatment of metastatic disease to the bone is complex and multi-dimensional. Curative options are non-existent. By using bone seeking radiopharmaceuticals for metastatic bone pain, pain relief will occur in a high percentage of patients (70-80%). Although efficacy is high, as well as cost-effective [134], it is of paramount importance to explore the possibilities of improving efficacy even further. Unfortunately, numbers of patients achieve incomplete pain resolution, and some patients obtain no pain relief at all. In addition, there is little evidence that this therapy results in improved survival, and relatively few patients exhibit evidence of

significant anti-tumor effect. Recently McCready and O'Sullivan suggested possibilities for improvement of the therapeutic efficacy [135]. These included: *1. Local dose escalation*; In a phase I study with dosages of 5000 MBq (135 mCi) ^{186}Re-HEDP, using autologous peripheral blood stem cell rescue, O'Sullivan *et al* reported a PSA responses > 50% lasting at least 4 weeks [136]. Although most studies could not determine a dose-response relationship, this might clear the way for improved efficacy. *2. Enhancement of radionuclide uptak*e; An increased uptake of bone seeking radiopharmaceuticals occurs 4 weeks to 3 months following the start of hormonal therapy. Administering the bone seeking radiopharmaceutical at the time of this flare-up reaction may increase the tumor-absorbed dose. This is illustrated by the study of Bushnell *et al*, who reported an enhanced uptake of ^{99m}Tc-MDP in skeletal metastases from prostate cancer, following initiation of hormone treatment. They found that approximately 3 weeks following initiation of hormone blockade, most skeletal metastases from prostate cancer will show significantly enhanced ^{99m}Tc-MDP uptake relative to normal bone [137]. *3. Chemosensitization*; As mentioned above, chemotherapeuticals may be used in combination with bone seeking radiopharmaceuticals to enhance the effect of the therapy. *4. Repeated administrations*; Repeated administrations with a relatively short interval may lead to an enhanced effect compared to single treatments alone [89, 97]. It is recognized that the therapeutic effect of radionuclide therapy is increased in patients with a less advanced stage of their disease [138, 64]. Repeated dosing may have a better effect on larger metastatic lesions in patients with a more advanced stage. *5. Radionuclide "cocktails"*; The combination of short-lived radionuclides, like ^{186}Re (or ^{188}Re) and ^{153}Sm-EDTMP in combination with longer lived radionuclides (^{89}Sr) and alpha emitters may enhance this effect on larger metastatic lesions. Henriksen *et al* reported the use of the alpha-particle-emitting ^{223}Ra in nude rats with skeletal metastases. A significant antitumor effect was found, while sparing the bone marrow [139]. A combination of different radionuclides with different radiation energies, half-lives and range, may be more effective for patients with osseous metastases, that are generally of all sizes. Toxicity may be kept low while offering high dose treatment. Besides these suggestions we would like to add, *6. Combined modality treatment*; As mentioned previously, all sorts of combinations are possible and may potentially lead to a synergistic effect and improved efficacy.

The efficacy of single or combined treatment with bone seeking radiopharmaceuticals may be improved but response is never guaranteed. The ability to predict response to treatment in the individual patient would be important for day to day patient care. As well as the recognition that response is increased in patients with early stage disease, some reports have attempted to further unravel this dilemma, but have had little success so far. Resche *et al* examined factors that may have differed in treatment responders and non-responders in a dose-controlled study comparing two dosing groups (18.5 MBq/kg ^{153}Sm-EDTMP and 37 MBq/kg ^{153}Sm-EDTMP) [47]. In their study, females, and in particular females with breast cancer, responded better with regard to physicians' global assessment as to reduction in pain, measured on a visual analogue scale. The fact that these women were heavily pre-treated might be the cause for this difference, but the mechanism behind this is so far unexplained [47]. Exactly the same phenomena was found in a double-blind placebo-controlled study by Serafini *et al* investigating the efficacy of different doses of ^{153}Sm-EDTMP compared to placebo [46]. A paper from China also suggests a negative effect on response from male

sex, and certain types of tumors, and distribution of metastases to lower parts of the body [140]. Further exploration of a better way to determine dosage and predict response for each individual case is needed.

Toxicity

In addition to efficacy, toxicity is of major importance. One of the main indications for bone seeking radionuclide therapy is pain originating from osseous metastases, that react poorly to external irradiation, chemotherapy or analgesics. Frequently, these patients have been heavily pre-treated, resulting in limited bone marrow reserve. Focusing on patients with hormone-refractory prostate carcinoma, recent progress has been made on chemotherapy. Docetaxel (with prednisone) treatment every three weeks led to superior survival and improved rates of response in terms of pain, serum PSA level, and quality of life, when compared with mitoxantrone plus prednisone [19]. Together with the patients' progressive bone disease, this treatment will result in a marginal bone marrow reserve before the start of treatment with radiopharmaceuticals. It further emphasizes the need to carefully evaluate toxicity and bone marrow reserve, when considering these patients for secondary treatment with bone seeking radiopharmaceuticals. In this regard, individual dosing schemes may be useful to limit toxicity. Thrombocytopenia is found to be the dose limiting factor in treatment of painful bone metastases with bone seeking radiopharmaceuticals. De Klerk *et al* evaluated thrombocytopenia in patients with hormone refractory prostate carcinoma, treated with ^{186}Re-HEDP. As an index of the extent of bone involvement, the bone scan index (BSI) was determined from the pre-therapy ^{99m}Tc--HDP scintigram. They described a functional relation ($r = 0.78$; $p < 0.001$) of the percentage of platelet decrease after treatment with the extent and distribution of skeletal metastases (BSI) and administered activity, normalized to standard body surface area. Using this relation, it is possible to predict thrombocytopenia by pre-treatment bone scintigraphy and to adjust the dosage to each patient to avoid unacceptable toxicity. The formula of De Klerk may also be used to calculate an individually based optimized dose [27].

Radiation safety considerations

After the administration of bone seeking radiopharmaceuticals patients need to stay in the department for several hours, or they may be sent home immediately, depending on the radionuclide used. All radionuclides emit beta-radiation to cause therapeutic effect. Because of their high energy and short range in tissue, it is generally thought that all beta-radiation is absorbed inside the patients' body and will cause no harm to the environment of the patient. However, all used radionuclides also emit gamma-radiation and / or x-rays, which are not completely absorbed by the patients body. They do cause a small but not negligible radiation hazard to the environment. In addition to this radiation field, a large amount of the administered activity (see *pharmacokinetics* sections) is rapidly cleared and will cause urine contamination. Although, the overall radiation hazard is low and none of the patients need to stay overnight, some questions do remain. It is known that the total radiation field is low, but is all beta-radiation indeed absorbed? The combination of bone seeking radiopharmaceuticals with other treatment modalities may alter the pharmacokinetics. Altered pharmacokinetics

may lead to altered urine contamination and retained activity, consequently resulting in an altered radiation hazard. A precise understanding of the environmental hazard of this treatment is therefore essential for good clinical practice.
Last but not least, nuclear physicians need to gain trust in the treatments they offer by delivering high quality. This is reached by a good understanding of all the characteristics of the used radiopharmaceuticals, including both clinical properties (efficacy and toxicity) and radiation properties (environmental hazards). Guidance of patients and a proper communication with the referring clinicians is very important. Although the literature supports its effectiveness and cost efficiency, today the routine clinical use of bone seeking radiopharmaceuticals remains limited. It was found on investigation that medical oncologists usually prefer other modalities for palliation [141]. This under-utilization is in part due to a poor understanding of their appropriateness, efficacy and toxicity. Bone marrow depression after treatment for example, often causes great concern to the referring physician. The full potential of this form of therapy, on the other hand, is yet to be realized. Where treatment with bone seeking radiopharmaceuticals will mostly be indicated in heavily pre-treated patients at the end of the line, as secondary or tertiary treatment, it may well move forward and be given upfront, if efficacy improves. In particular the combined treatment with chemotherapy seems promising in this aspect. However, a good understanding of the toxicity profile of these substances, and the ability to provide individualized dosing recommendations by means of calculation, are required to achieve these goals.

Conclusion

Bone seeking radiopharmaceuticals for the palliation of metastastic bone pain are both effective and safe. Approximately 80% of the treated patients showed a clinical response, with a consequent decrease in morbidity and an improvement in quality of life. Toxicity is usually mild and transient. Furthermore, bone seeking radiopharmaceuticals are cost-effective, and may be repeated when indicated. In clinical practice it should be actively considered, especially in patients with widespread metastasis. Ongoing research aims for an optimized efficacy and individualized dosing schemes, to bring response beyond palliation, towards improved survival.

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Chapter 3

Radiation safety considerations for the bone seeking radiopharmaceuticals $^{89}SrCl2$, ^{186}Re-HEDP and ^{153}Sm-EDTMP

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Abstract

Purpose

The radiation exposure to bystanders from $^{89}SrCl_2$, ^{186}Re-HEDP and ^{153}Sm-EDTMP, is generally thought to be caused by "bremsstrahlung" and gamma-radiation, with negligible contribution from beta-radiation. The latter assumption may be erroneous. The aim of this prospective study was the investigation of radiation safety after treatment with these radiopharmaceuticals. The radiation field around treated patients was characterized and the magnitude estimated.

Methods

Thirty-three patients (30 prostate carcinoma; 3 breast carcinoma) were treated with 150 MBq $^{89}SrCl_2$ (9 patients), 1295 MBq ^{186}Re-HEDP (12 patients) or 37 MBq/kg ^{153}Sm-EDTMP (12 patients). External exposure rates at 30 cm from the patient were measured at times 0 to 72 hr post-injection. To evaluate the respective contribution of "bremsstrahlung", beta-radiation and gamma-radiation, a calibrated survey meter was used, equipped with a shutter. For each patient, the measured exposure rate-versus-time data were fit to a curve and the curve integrated (area under the curve) to estimate the total exposure.

Results

For 29/33 patients the total ambient equivalent doses (mean ± 1 standard deviation [SD]) based on the integral of the fitted curve were 2.1 ± 1.2 mSv for $^{89}SrCl_2$, 3.3 ± 0.6 mSv for ^{186}Re-HEDP and 2.8 ± 0.6 mSv for ^{153}Sm-EDTMP. Beta-radiation contributes significantly to these doses (>99% for $^{89}SrCl_2$, 87% for ^{186}Re-HEDP and 27% for ^{153}Sm-EDTMP). The effective doses (at 30 cm) are < 0.1 mSv for $^{89}SrCl_2$, 0.3 mSv for ^{186}Re-HEDP and 1.6 mSv for ^{153}Sm-EDTMP.

Conclusion

Patients treated with $^{89}SrCl_2$, ^{186}Re-HEDP or ^{153}Sm-EDTMP emit a spectrum of radiation, including non-negligible beta-radiation. With specific instructions effective doses to bystanders are small and acceptable.

Introduction

Almost two-thirds of cancer patients will develop osseous metastases in an advanced stage of their disease. Often, this is accompanied by intractable bone pain; a complex and difficult-to-treat effect of malignant disease. During the last decades several bone seeking radiopharmaceuticals have been successfully used in the management of metastatic bone pain, with an overall response rate of approximately 70-80% [1-7]. Today, the bone seeking radiopharmaceuticals $^{89}SrCl_2$ (Metastron®), ^{186}Re-HEDP and ^{153}Sm-EDTMP (Quadramet®) are most often used (***Table 1***). $^{89}SrCl_2$ and ^{153}Sm-EDTMP have received FDA approval for therapeutic use in patients with painful osseous metastases.

Table 1 Radiopharmaceutical characteristics

Radiopharmaceutical	Half-life (in days)	Beta-radiation (MeV)		Gamma-radiation		Range in soft tissue (max)
		max	mean	keV	%	mm
^{153}Sm-EDTMP	1.93	0.81	0.23	103	29	3.1
^{186}Re-HEDP	3.7	1.07	0.35	137	9	4.5
^{89}Sr-Chloride	50.5	1.46	0.58	910	0.01	6.6

Beta-emitting radiopharmaceuticals are preferred for this treatment modality, because of the suitable range of the beta-particles in tissue [8]. Besides beta-radiation, some radionuclides may additionally emit gamma-radiation and/or x-ray radiation. The gamma-radiation emitted by ^{153}Sm (29%) and ^{186}Re (9%) is a substantial part of the total radiation. Because gamma-radiation can be detected outside the body after administration of the radiopharmaceutical, it may be used for post-treatment scintigraphy and dosimetric studies. Furthermore, x-ray radiation will be produced by deceleration of beta-radiation passing through matter. Such "bremsstrahlung" ("brake radiation"), together with any gamma-radiation, make patients treated with bone seeking radiopharmaceuticals an environmental source of radiation.

It is generally thought that patients treated with beta-emitting radiopharmaceuticals cause radiation exposure to bystanders by "bremsstrahlung" (and gamma-radiation), without any contribution of beta-radiation. Given the short ranges of the beta-particles in soft tissue (3.1 mm – 6.6 mm (***Table 1***)) it is assumed that all beta-radiation will be absorbed completely by the patient. Furthermore, Zanzonico *et al* stated that the "bremsstrahlung" from pure beta-emitting radiopharmaceuticals, produced in vivo, is low. They calculated that for pure beta-emitting radiopharmaceuticals, the activities requiring medical confinement are very high ("on the order of hundreds of thousands to millions of megabecquerels") [9].

However, a substantial part of the beta-radiation may theoretically be emitted by the patient when the radiopharmaceutical passes through superficial blood vessels or accumulates in tissue close to the body surface. After administration of 150 MBq $^{89}SrCl_2$ to patients, the dose rate around these patients (dose rates of 50 – 80 μSv/h at 30 cm distance) is unexplainable by "bremsstrahlung" alone. The question arises whether the radiation field originating from

these patients was caused by "bremsstrahlung" (x-rays) alone or by "bremsstrahlung" *and* some beta-radiation. If the radiation field is indeed a combination of both, it is important to know the contribution of the beta-radiation to the total exposure.
The theoretical assumptions of radiation safety were never validated in clinical practice. In order to devise proper guidelines for radiation safety and a good understanding of both the quality and the quantity of the radiation field emitted by patients treated with beta-emitting radiopharmaceuticals, radiation exposure was evaluated from patients with painful bone metastases originating from hormone-resistant prostate carcinoma and breast carcinoma treated with $^{89}SrCl_2$, ^{186}Re-HEDP or ^{153}Sm-EDTMP.

Materials and methods

Subjects

Thirty-three patients entered the study. Thirty patients had been diagnosed with painful osseous metastases originating from hormone-resistant prostate carcinoma; three patients had breast cancer. Four patients were excluded from evaluation because some of the measurements were missing. Twenty-nine patients were evaluable [26 prostate cancer patients (mean age ± 1 SD: 67 ± 7.2 years) and 3 breast cancer patients (age: 40, 50 and 72 years)]. Patients were treated with 150 MBq (4 mCi) $^{89}SrCl_2$ (GE Health, Den Bosch, The Netherlands)(8 patients), 1295 MBq (35 mCi) ^{186}Re-HEDP (Tyco, Petten, The Netherlands)(10 patients, including all 3 breast cancer patients), or 37 MBq/kg (1 mCi/kg) ^{153}Sm-EDTMP (CIS Bio International, Saclay, France)(11 patients). All patients who were treated with $^{89}SrCl_2$ were hospitalized for three days, during which urine was collected and serial dose rate measurements were performed. Patients who received treatment with ^{186}Re-HEDP were treated in an outpatient setting. They were hospitalized for approximately 8-10 hours. Serial dose rate measurements were performed during their hospital stay as well as at home after discharge, but no urine was collected. All patients treated with ^{153}Sm-EDTMP were hospitalized for 48 hours. Urine was collected and serial dose rate measurements were performed during this period. The study was approved by the local ethics committee and informed consent was signed by all patients.

Dose rate measurements

Dose rate measurements were performed using a portable survey meter with an analog scale (Model PDM1; Nuclear Enterprises Limited, England). The ambient equivalent dose rate was measured [H*(d)]. The scale accuracy of this type of survey meter is ± 3% of the full scale display (FSD). The dose rate measurement ranges are: 0 – 30 µSv/h or 0 – 300 µSv/h, and 0 – 3 mSv/h, 0 – 30 mSv/h or 0 – 300 mSv/h. The detector consists of an air-filled ionization chamber vented to atmosphere. The chamber volume is 450 cm^3 with a window area of 100 cm^2 and a window thickness of 8 mg/cm^2. The window is protected by a sliding shutter of 0.6 cm thickness (700 mg/cm^2). The PDM1 is calibrated in units of roentgen (R) against an exposure standard, and scaled in sieverts (Sv) on the basis of 1 sievert (Sv) = 100 roentgen (R), as recommended by the British Committee on Radiation Units and Measurements (BCRU). When the sliding shutter is closed only x-rays and gamma-radiation can be detected. The

thickness of the sliding shutter is sufficient to block all beta-radiation. We can use this feature when measuring patients treated with either $^{89}SrCl_2$, ^{186}Re-HEDP, or ^{153}Sm-EDTMP. With the shutter open the survey meter is sensitive to x-rays, gamma-radiation and beta-radiation; with the shutter closed it is sensitive only to x-rays and gamma-radiation.
Before dose rate measurements, the background dose rate was determined in the patient room, and proved to be less than 0.1 μSv/h in all cases. All patients were measured at regular time intervals while sitting in a chair. The dose rate was determined at a distance of 30 cm in front of the umbilicus, both with open and closed sliding shutter. Patients were asked to urinate before measurements. Dose rate measurements were performed at different time points, up to 72 hours after injection of the radiopharmaceutical, but more frequently during the first day (hourly to once every 4 hours). Measurements were performed at a distance of 30 cm from the patient (instead of 1 meter) for better count statistics.

Analysis

For every patient, the measured dose rates were plotted as a function of time, and a curve was drawn through the resulting plot (curve of best fit). This curve represents the dose rate decline over time. The area under the curve (AUC) represents the total ambient equivalent dose at 30 cm of the patient. The shape of the curve will be influenced by pharmacokinetic processes like renal clearance, retention in the extra-vascular space, and decay. Most likely, more than one process will occur at the same time with one dominant process during each time frame. Only the dominant process for each time frame is taken into account. The shape of the curve will thus be defined by a combination of one or more dominant processes, depending on the characteristics of the radiopharmaceutical and the period in which the measurements took place. In a simplified model we may assume that the decline in dose rate is dominated by renal clearance during the first period after injection, and by decay and/or clearance thereafter, depending on excretion rate and half-life of the administered radiopharmaceutical. During 48 – 72 hours after injection this may result in either a 'mono-exponential' model (dominated by renal clearance only), or a 'bi-exponential' model (dominated first by renal clearance, and decay thereafter). A 'bi-exponential' model is defined as two straight lines on a semi-logarithmic scale.
From the urinary excretion data of the different radiopharmaceuticals renal clearance was studied. The most suitable model for dose rate decline was chosen on the basis of renal clearance and physical decay. The AUC may be calculated in a 'mono-exponential' or a 'bi-exponential' model, resulting in an estimation of the total ambient equivalent dose at a certain distance from the patient (30 cm).
The dose rate measured by the survey meter represents the ambient equivalent dose H*(d). For penetrating radiation the relationship between H*(10) and the effective dose E is dependent on the photon-energy. For energies above 100 keV the relationship is: $E / H^*(10) \approx 0.8$ [10]. After calculation of the contributions of both penetrating radiation and non-penetrating beta-radiation to the dose rate this relationship was used to calculate the contribution of penetrating radiation to the effective dose. The contribution of beta-radiation to the effective dose was calculated using the weighting factor of 0.01 for skin. The effective dose of photon-radiation and beta-radiation combined is an estimate for the total effective dose delivered to

bystanders by external radiation.

Urine collection

The cumulative activity excreted in urine was analyzed to find the turning point between dose rate decline caused by renal excretion and dose rate decline caused by decay alone. This knowledge was used to draw a bi-exponential graph for dose rate decline over time.
All urine of the patients treated with $^{89}SrCl_2$ was collected at 4-hour intervals up to 72 hours after injection. Patients treated with ^{153}Sm-EDTMP collected urine from 0 – 4, 4 – 8, 8 – 12, 12 – 24 and 24 – 48 hours after injection. Activity in 15-ml aliquots of urine was assayed in a liquid scintillation counter (Packard Instruments: type 2425 sample changer). Cumulative renal excretion of administered activity during the first 48 – 72 hours after injection was calculated from these data, corrected for decay. For the evaluation of patients treated with ^{186}Re-HEDP, excretion data were used from a previous study [11].

Dose rate measurements on a $^{89}SrCl_2$ phantom

Before dose rate measurements were performed on patients, an experiment was performed using a point source of $^{89}SrCl_2$ (15 MBq) and the PDM1 detector. The aim of this experiment was to identify different types of emitted radiation, emitted by one radionuclide, using a survey meter. As previously mentioned, "bremsstrahlung" (x-rays) may originate in patients treated with $^{89}SrCl_2$, ^{186}Re-HEDP, or ^{153}Sm-EDTMP, together with gamma-radiation and beta-radiation. To calculate the intensity of the total radiation field and its different contributors we carried out an experiment with $^{89}SrCl_2$ with two contributors: beta-radiation and "bremsstrahlung". Different amounts of tissue-equivalent material (acrylate) were interposed between a point source of $^{89}SrCl_2$ and the PDM1 detector. The distance between the point source and the PDM1 detector was exactly 30 cm (fixed). While the distance between point source and detector remained constant, the thickness of the interposed material varied from no material to 16 mm acrylate. The area of the material was large (3600 cm^2) compared with the window area of the detector (100 cm^2), so all detected radiation had passed the material. Dose rate measurements were performed with open shutter at a distance of 30 cm (with different amounts of interposed material). To study the penetration of gamma-radiation through the shutter, the dose rate was also measured at 30 cm with closed shutter, with the maximum amount of interposed material (16 mm).

Results

$^{89}SrCl_2$ phantom

The measured dose rate from a point source of ^{89}Sr, with open shutter, was plotted on a semi-logarithmic scale against the thickness of tissue-equivalent material interposed between the survey meter and the point source (***Figure 1***). Initially, an exponential decline of the dose rate is seen after each increment of the thickness of the interposed material between the point source and the survey meter. With increased thickness of the interposed material the curve follows a near straight line. This straight line is caused by the contribution of the dose rate

from the x-rays or so called "bremsstrahlung". The initial exponential decline of the curve is caused by the contribution of beta-radiation to the dose rate, which is rapidly declining after increasing the interposed material. By extrapolating the straight line towards the y-axis (***Figure 1***: straight line) it is possible to subtract the "bremsstrahlung" contribution' from the original curve ('"bremsstrahlung" plus beta-radiation contributions'). A corrected curve is created (***Figure 1***: dotted line), depicting the presumed beta-radiation contribution. From this curve the beta-spectrum range of ^{89}Sr in the interposed tissue-like material can be estimated, after extrapolating the curve towards the x-axis. A value of about 6 mm is found. This is roughly in agreement with the theoretically predicted value of 6.6 mm.

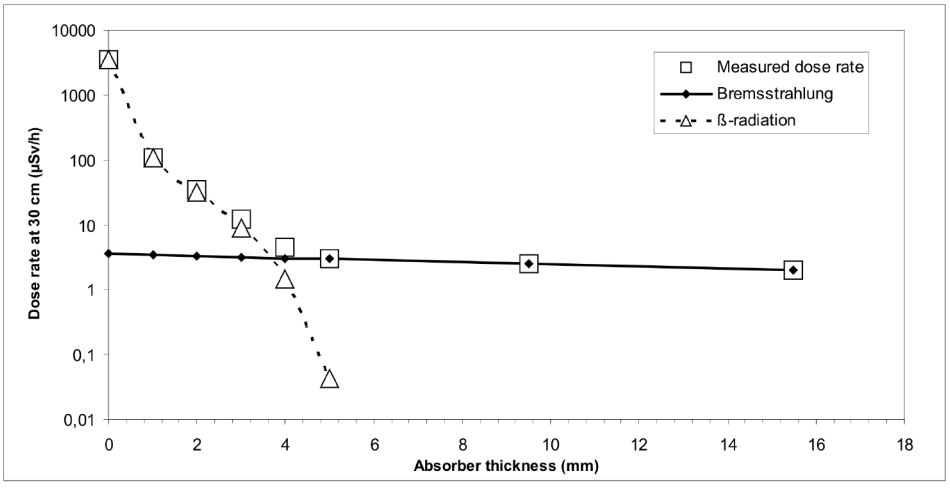

Figure 1 Dose rate of a ^{89}Sr-Chloride point source (15 MBq), measured with a survey meter at 30 cm distance (fixed) and different absorber thickness interposed between the point source and the survey meter. The measured dose rate represents both beta-radiation and bremsstrahlung. Extrapolating the dose rates at the end of the curve represents the contribution of the bremsstrahlung (straight line). The total dose rate minus the bremsstrahlung represents the beta-radiation (dotted line). In this simplified model the maximum range of the beta-radiation will be around 6 mm

The survey meter response at the tail of the original curve was verified with the shutter closed (together with 16 mm interposed material). A slightly lower value was found due to some attenuation of the x-rays. From the latter it can also be concluded that the survey meter measures beta-radiation, gamma-radiation and x-rays with open shutter and gamma-radiation and x-rays with a closed shutter (beta-radiation is blocked), with only little attenuation of gamma-radiation and x-rays by the closed shutter. This is in agreement with theoretical calculations from the literature: the spectrum of "bremsstrahlung" of these three radiopharmaceuticals will be minimally attenuated by this kind of shutter for most of the spectrum.

Clinical patients

Retained activity was calculated in patients treated with ^{153}Sm-EDTMP or ^{89}Sr-Chloride and corrected for decay (***Figure 2***).

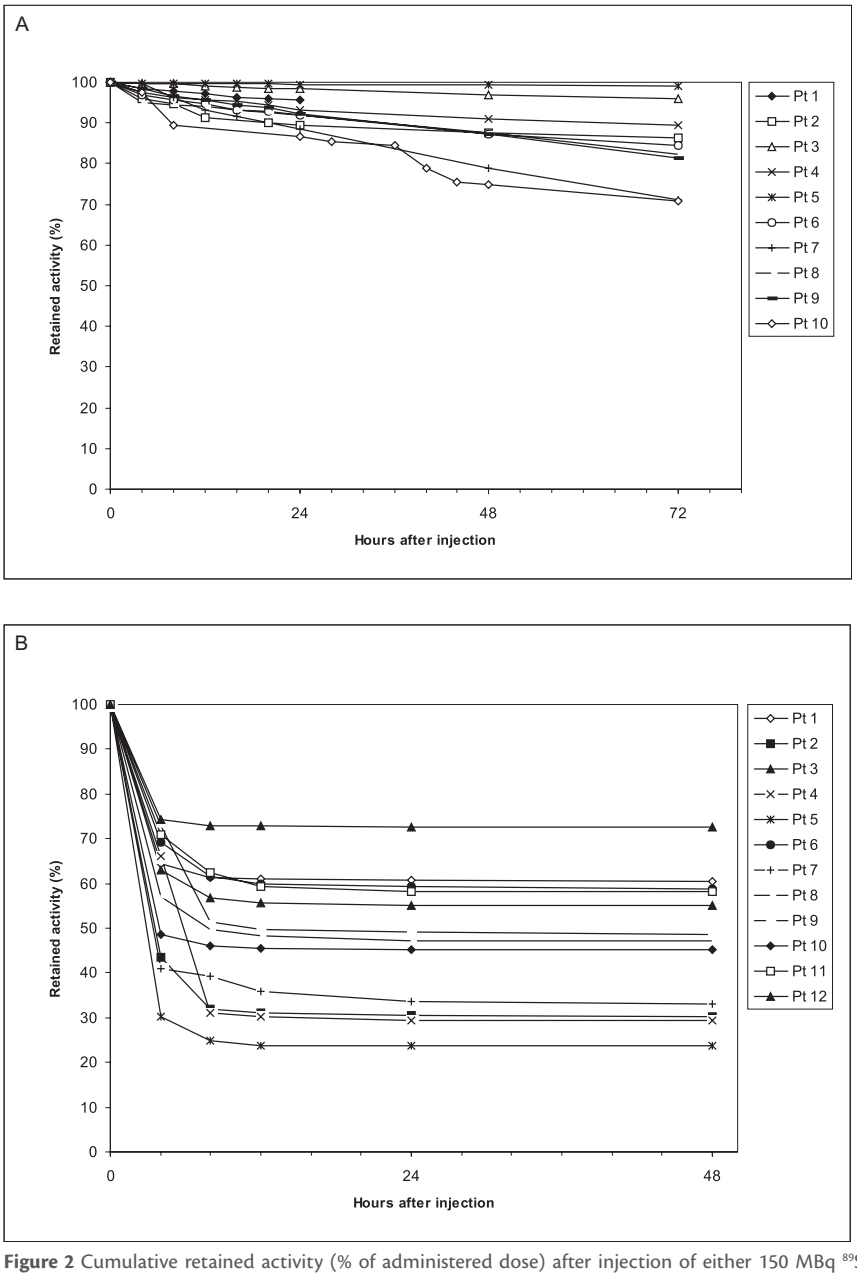

Figure 2 Cumulative retained activity (% of administered dose) after injection of either 150 MBq ^{89}Sr-Chloride (A) or 37 MBq/kg ^{153}Sm-EDTMP (B). Retained activity of ^{89}Sr-Chloride declines during the first three days after injection, due to continuous renal excretion. Renal excretion is complete 12 hours after injection of ^{153}Sm-EDTMP (plateau phase). Cumulative retained activity was corrected for decay

After injection of ^{153}Sm-EDTMP, all activity that did not bind to bone was rapidly excreted. Excretion was nearly complete within 12 hours after injection. A 'second phase' started after 12 hours, during which decay of the radionuclide was the dominant factor in the process of dose rate decline (instead of renal clearance). Forty-eight hours after injection a mean (± 1 SD) of 53.3 ± 15.8% of the administered dose was excreted. Therefore, during the first 48 hours after injection of ^{153}Sm-EDTMP a 'bi-exponential' model for this process seemed most applicable. This is illustrated in Figure 3, in which the data for all patients treated with ^{153}Sm-EDTMP are plotted in one graph. It clearly demonstrates a 'first' phase of rapid dose rate decline, followed by a slow 'second' phase. Urinary excretion data and the cumulative retained activity graph confirm this.

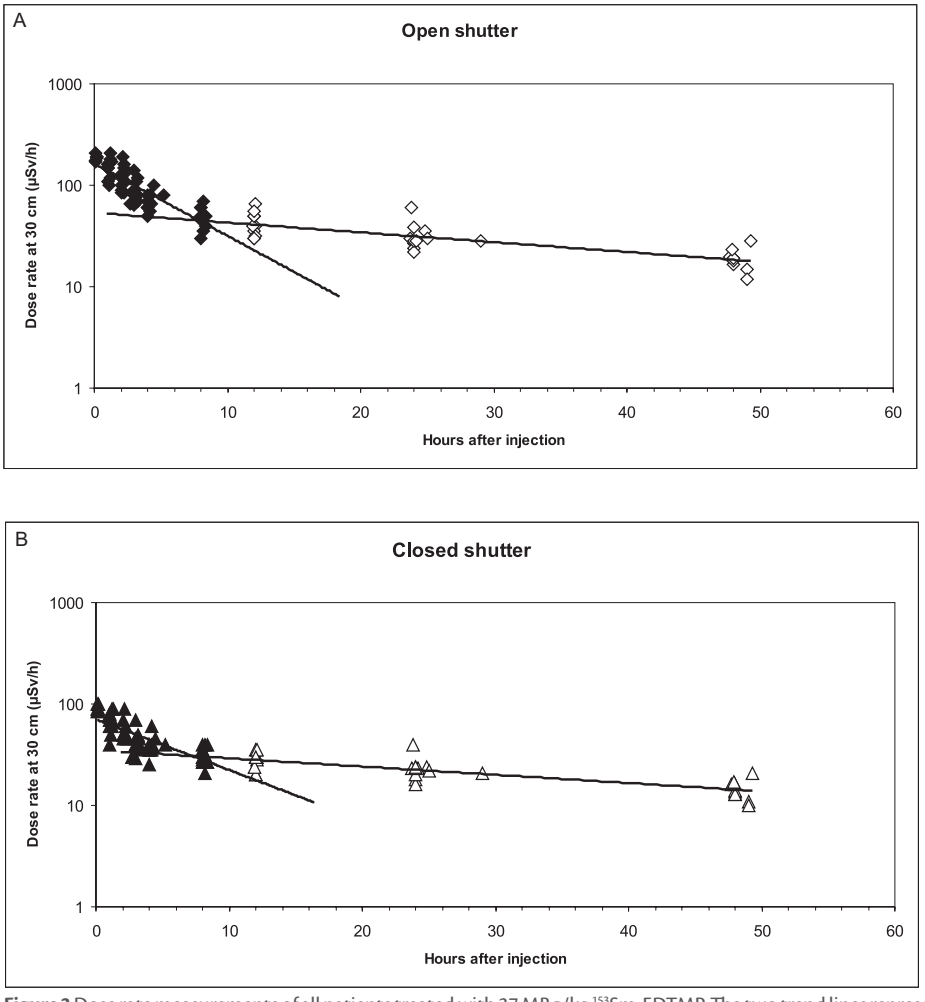

Figure 3 Dose rate measurements of all patients treated with 37 MBq/kg ^{153}Sm-EDTMP. The two trend lines represent two different pharmacokinetic phases (dominantly renal excretion: black diamonds/triangles; dominantly decay: white diamonds/triangles). The AUC with open survey meter shutter (A) represents the total radiation field, the AUC with closed shutter (B) represents the total radiation field minus the beta-radiation. The difference between the AUC's of both curves represents the contribution of beta-radiation to the total radiation field

After injection of ^{89}Sr-Chloride a continuous excretion of activity in urine is seen (***Figure 2***). The mean percentage ^{89}Sr excretion in urine (mean ± 1 SD) at day 1, day 2 and day 3 was 7.5 ± 6.1%, 4.2 ± 3.5% and 2.9 ± 2.1%, respectively. After 3 days 15.8 ± 10.5% had been excreted. Because the half-life of ^{89}Sr is 50.5 days, decay is not a dominant factor during the first 3 days after injection. A 'mono-exponential' model for ^{89}Sr-Chloride seemed most applicable.
Like ^{153}Sm-EDTMP, ^{186}Re-HEDP is rapidly cleared during the first 8 hours after injection, after which renal excretion is almost complete and the remaining activity is predominantly retained in the skeleton [11]. The dose rate decline after injection of ^{186}Re-HEDP is comparable to that of ^{153}Sm-EDTMP. It is best described in a 'bi-exponential model'.
From this point the ambient equivalent dose was calculated (***Table 2***). By calculating the AUC of the fitted line in the point graph (dose rate related to time), an estimation can by made of the total ambient equivalent dose at 30 cm from the patient. Because survey meter measurements were performed with both an open and a closed shutter, discrimination could be made between the dose rate of all radiation (open shutter) and the dose rate of all radiation minus the contribution of beta-radiation (closed shutter). By subtraction of these two, the contribution of beta-radiation to the dose rate was calculated.

Table 2 Ambient equivalent dose H*(d)

	Shutter	^{153}Sm-EDTMP	^{186}Re-HEDP	^{89}Sr-Chloride
Total dose at 30 cm (mean ± 1 SD)	Open	2.8 ± 0.6 mSv	3.3 ± 0.6 mSv	2.1 ± 1.2 mSv
	Closed	2.1 ± 0.5 mSv	0.4 ± 0.1 mSv	Not done [a]
Percentage beta-radiation (mean ± 1 SD)		27 ± 7%	87 ± 2%	> 99%

a Dose rate with closed shutter was too low to be measurable in the current setting

The beta-radiation dose rate contributions at 30 cm for $^{89}SrCl_2$, ^{186}Re-HEDP, and ^{153}Sm-EDTMP are >99%, 87%, and 27% respectively. Patients treated with $^{89}SrCl_2$ emit almost solely beta-radiation (>99%), apart from a little contribution from "bremsstrahlung". After treatment with ^{186}Re-HEDP beta-radiation accounts for 87 ± 2% of the dose rate measured at 30 cm from the patient. Due to a greater contribution of gamma-radiation (29%), and a lower energy of the beta-radiation with shorter range, the beta-radiation accounts for only 27 ± 7% of the dose rate measured from patients treated with ^{153}Sm-EDTMP. In all cases the contribution of beta-radiation to the total radiation hazard is not negligible. At 30 cm from the patient, the total ambient equivalent dose is approximately 2.1 ± 1.2 mSv for $^{89}SrCl_2$, 3.3 ± 0.6 mSv for ^{186}Re-HEDP and 2.8 ± 0.6 mSv for ^{153}Sm-EDTMP. The latter is mainly caused by gamma-radiation (Tables 2 and 3).
From the total ambient equivalent dose at a certain distance from the patient, as measured by the survey meter, it is possible to calculate the effective dose absorbed by bystanders at a certain distance, assuming that they will stay at this distance for an indefinite time. A conversion factor of 0.8 (from ambient equivalent dose to effective dose) was used for penetrating radiation with an energy of around 100 keV. This conversion factor may solely be used for penetrating radiation, so the contribution of different radiation must be taken into

account [10]. Beta-radiation will be absorbed by the skin with a weighting factor of 0.01 to come to an effective dose. The mean total effective doses absorbed by bystanders at 30 cm distance from a patient was roughly 0.02 mSv for $^{89}SrCl_2$, 0.3 mSv for ^{186}Re-HEDP, and 1.6 mSv for ^{153}Sm-EDTMP (***Table 3***).

Table 3 Exposure to bystanders

	^{153}Sm-EDTMP	^{186}Re-HEDP	^{89}Sr-Chloride
Ambient equivalent dose H*(d) at 30 cm [a]	2.8 mSv	3.3 mSv	2.1 mSv
Beta-radiation percentage (Table 2)	27%	87%	> 99%
Equivalent dose (skin) beta-radiation [b]	0.8 mGy	2.9 mGy	2.1 mGy
Effective dose beta-radiation [c]	0.008 mSv	0.03 mSv	0.02 mSv
Penetrating radiation percentage (Table 2)	73%	13%	< 1%
Penetrating radiation H*(10) [d]	2.0 mSv	0.4 mSv	0 mSv
Effective dose penetrating radiation [e]	1.6 mSv	0.3 mSv	0 mSv
Effective dose (total) at 30 cm [f]	1.6 mSv	0.3 mSv	0.02 mSv

a Measured by the ionization chamber at 30 cm from the patient
b [Ambient equivalent dose H*(d) at 30 cm] * [Beta-radiation percentage]
c [Equivalent skin dose] * [Weighting factor for skin, i.e. 0.01]
d [Ambient equivalent dose H*(d) at 30 cm] * [Percentage penetrating radiation]
e [Penetrating radiation H*(10)] * [Correction factor in AP radiation geometry, i.e. 0.8]
f Effective dose beta- and penetrating-radiation

Discussion

The theoretical assumptions of radiation safety after treatment with bone seeking radiopharmaceuticals were never validated in clinical practice. In order to provide proper guidelines it is necessary to identify the composition of the radiation field around a patient and to estimate the magnitude of that field. It is important to realize that the variation in magnitude of that field varies greatly among patients. This is mostly caused by variations in metastatic load and retained activity. Other variations include actual residence times and distances in relation to relatives and variations in renal clearance. These uncertainties cannot be overcome. The used measuring technique may be less accurate for quantitative analysis. A small part of the "bremsstrahlung" spectrum (low energy photons) will be attenuated by the shutter together with the beta-radiation. This will lead to a small overestimation of the beta-radiation contribution. This is however neglected because of other more important intra-patient en inter-patient variations, as mentioned above. One has to realize that numbers given in this paper are estimations of the magnitude of the radiation field around patients. The used technique is adequate to characterize the radiation field (i.e. show the existence of beta-radiation outside the patient's body) and to estimate the magnitude of that field. These are estimations of the radiation hazard to bystanders. This validation of theoretical safety considerations in routine patient care gives a useful insight in daily practice. It shows the, theoretically ignored, contribution of beta-radiation and it may be used to draw proper guidelines.

Beta-radiation produces "bremsstrahlung" with a spectrum dependent upon the maximum beta-energy and the atomic number of the involved medium. It is assumed that beta-radiation will be completely absorbed in the patient's body. This is incorrect.
If indeed "bremsstrahlung" is the only radiation emitted by patients after administration of pure beta-emitting radiopharmaceuticals, two apparent inconsistencies have to be resolved:
Following administration of 150 MBq $^{89}SrCl_2$, the measured dose rates at 30 cm from the patient (50 – 80 μSv/h) are too high to be explainable by "bremsstrahlung" alone.
The reduction (> 99%) in the measured $^{89}SrCl_2$ dose rate with versus without the shutter in place is too large to be explained on the basis of "bremsstrahlung" alone unless the "bremsstrahlung" energies were uniformly less than 10 keV, which is certainly not the case for ^{89}Sr. The "bremsstrahlung" spectrum of ^{89}Sr is very little attenuated by the used shutter.
As a result, it must be concluded that after administration of $^{89}SrCl_2$ patients emit beta-radiation as well as "bremsstrahlung" and that exposure to bystanders is therefore a result of both beta-radiation and "bremsstrahlung" contributions. The beta-radiation dose rate contributions at 30 cm for $^{89}SrCl_2$, ^{186}Re-HEDP, and ^{153}Sm-EDTMP are >99%, 87%, and 27% respectively.
^{89}Sr has a beta-spectrum with E_{max}= 1.46 MeV, and therefore a range of 6.6 mm in soft tissue. The range of the ^{186}Re beta-spectrum (E_{max} = 1.07 MeV) is 4.5 mm in soft tissue. For ^{153}Sm the range of the beta-spectrum (E_{max} = 0.81 MeV) is 3.1 mm in soft tissue.
Electrons in the lower-energy portion of the beta-radiation energy spectrum are easily absorbed, whereas high-energy electrons have sufficient energy to pass through the superficial tissue (superficial blood vessels, bone). This hypothesis is further supported by the fact that the contribution of beta-radiation to the radiation dose augments when beta-emitting radiopharmaceuticals are administered that emit beta-radiation with higher energy and higher range in tissue.
The (ambient equivalent) dose at 30 cm distance from the patient is lower for $^{89}SrCl_2$ (2.1 mSv) than for ^{186}Re-HEDP (3.3 mSv) and ^{153}Sm-EDTMP (2.8 mSv)(***Table 2***). These differences are mainly caused by the differences in administered activities. The dose per MBq administered is highest for $^{89}SrCl_2$ (approximately 14 μSv/MBq), followed by ^{186}Re-HEDP (approximately 3 μSv/MBq) and ^{153}Sm-EDTMP (approximately 1 μSv/MBq). ^{153}Sm-EDTMP has a 29% yield of gamma-radiation and $^{89}SrCl_2$ none, but the total ambient equivalent dose per MBq of $^{89}SrCl_2$ at 30 cm distance from the patient is a factor 10 higher than ^{153}Sm-EDTMP. This is caused by the higher retention and half-life for $^{89}SrCl_2$, as well as the contribution of beta-radiation.
The total effective dose absorbed by bystanders at 30 cm distance from a patient (0.02 mSv for $^{89}SrCl_2$, 0.3 mSv for ^{186}Re-HEDP, and 1.6 mSv for ^{153}Sm-EDTMP) is highest for ^{153}Sm-EDTMP. This is caused by the much higher contribution of gamma-radiation (circa 73%) to the total ambient equivalent dose. Because beta-radiation is absorbed by the superficial tissues with a weighting factor of 0.01 (skin) the contribution of beta-radiation may be significant for the measured ambient equivalent dose, but much less so for estimations of the effective dose. That is why $^{89}SrCl_2$ produces a low effective dose to bystanders.
The total effective dose, as given above, is estimated for bystanders who reside at exactly 30 cm from the patient for an indefinite time. Because this is never the case, these estimations must be corrected for variations in time and distance between bystanders and patients. The effective dose may be reduced by instructing the patients and their families to keep

distance as much as reasonably possible (e.g. watching TV and during sleeping). With proper instructions to family, residence times may be reduced and distances increased, lowering the radiation burden to bystanders. In all instances effective doses will be < 1 mSv and with proper instructions they will be < 0.1 mSv or even < 0.01 mSv.
In general we recommend hospitalizing patients treated with ^{186}Re-HEDP and ^{153}Sm-EDTMP for at least 8 hours. This is mostly based on urinary excretion and the risk of internal contamination, because the radiation exposure to bystanders is < 20 μSv/hour (1 meter from the patients) directly or within a few hours after administration in all cases. Patients treated with $^{89}SrCl_2$ may therefore be released without hospitalization. The risk of significant internal contamination for bystanders is much lower, and acceptable, for this radiopharmaceutical. After discharge it is advisable to keep distance where possible, following the ALARA ('as low as reasonably achievable') principle. The ICRP has proposed an effective dose limit of 1 mSv per year for individuals. In clinical practice, the therapeutic use of bone seeking radiopharmaceuticals will give rise to radiation exposure to all those in contact with patients, albeit in very low doses (< 0.1 mSv). Our results further confirm the safety of treatment with bone seeking radiopharmaceuticals.
Although the total effective dose for bystanders is low, especially when proper instructions are given, the significant contribution of beta-radiation to the radiation field emitted by patients treated with beta-emitting radiopharmaceuticals is a phenomenon to consider for radiation protection. However, for $^{89}SrCl_2$, ^{186}Re-HEDP and ^{153}Sm-EDTMP it is unlikely to become important for effective doses for bystanders, even when high dosages are being used.

Conclusion

Patients treated with $^{89}SrCl_2$, ^{186}Re-HEDP or ^{153}Sm-EDTMP emit a spectrum of radiation, including beta-radiation measurable outside the patient. Beta-particles in superficial tissue cross the skin and contribute to the ambient equivalent dose. This must be considered when using beta-emitting radiopharmaceuticals. The calculated effective doses for bystanders are well below the recommended values and do not lead to unacceptable additional radiation burden to health care workers and patients' families.

Acknowledgements

We are grateful to Alice van Dongen for her limitless surveillance and coordinating activities.

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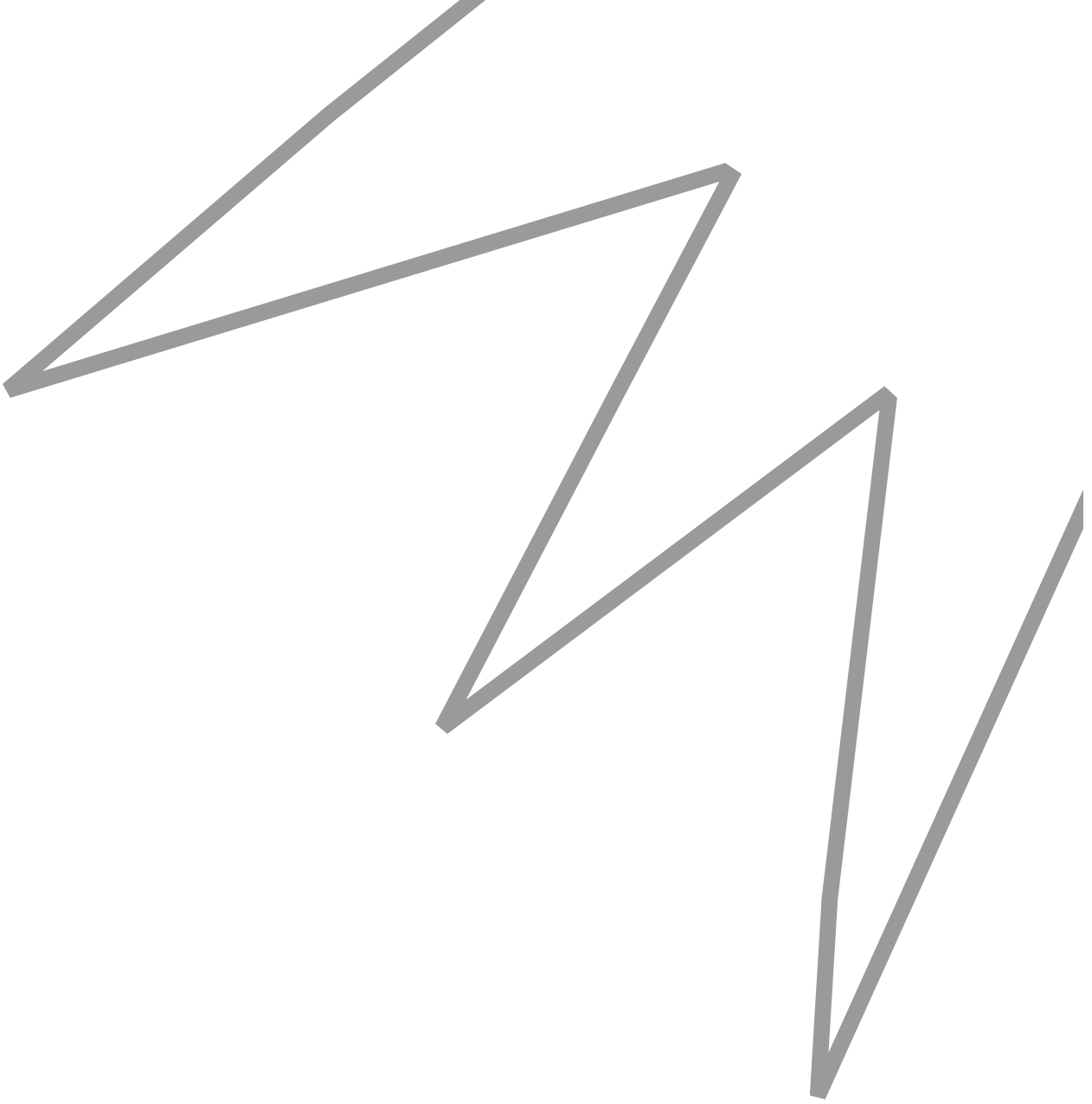

Chapter 4

EANM procedure guideline for treatment of refractory metastatic bone pain

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Abstract

Introduction

Bone pain is a common symptom of metastatic disease in cancer, experienced with various intensities by about 30% of cancer patients, during the development of their disease, up to 60–90% in the latest phases.

Discussion

In addition to other therapies, such as analgesics, bisphosphonates, chemotherapy, hormonal therapy and external beam radiotherapy, bone seeking radiopharmaceuticals are also used for the palliation of pain from bone metastases. Substantial advantages of bone palliation with radionuclide therapy include the ability to simultaneously treat multiple sites of disease with a more probable therapeutic effect in earlier phases of metastatic disease, the ease of administration, the repeatability and the potential integration with the other treatments.

Conclusion

The Therapy, Oncology and Dosimetry Committees have worked together to revise the EANM guidelines on the use of bone seeking radiopharmaceuticals. The purpose of this guideline is to assist the nuclear medicine physician in treating and managing patients undergoing such treatment.

Purpose

The purpose of this guideline is to assist nuclear medicine practitioners in:

1. Evaluating patients who might be candidates for treatment to palliate refractory, metastatic bone pain using ^{89}Sr (approved in Europe for prostate cancer), ^{153}Sm-lexidronam (^{153}Sm-EDTMP; approved in Europe for osteoblastic metastases) or ^{186}Re-etidronate (^{186}Re-HEDP; approved in some European countries).
2. Providing information for performing these treatments.
3. Understanding and evaluating the consequences of therapy.

Background information and definitions

Bone pain is a common symptom of metastatic disease in cancer, experienced with various intensities by about 30% of cancer patients, during the development of their disease, up to 60–90% in the latest phases [1]. In addition to other therapies, such as analgesics, bisphosphonates, chemotherapy, hormonal therapy and external beam radiotherapy, bone seeking radiopharmaceuticals are also used for the palliation of pain from bone metastases. Substantial advantages of bone palliation radionuclide therapy include the ability to simultaneously treat multiple sites of disease with a more probable therapeutic effect in earlier phases of metastatic disease, the ease of administration, the repeatability, and the potential integration with the other treatments.

Definitions

1. Metastatic bone pain in this context means bone pain arising from secondary skeletal malignancy.
2. Bone palliation means conventionally the treatment of metastatic bone pain resistant or intolerant to conventional treatments such as analgesics, bisphosphonates, antitumour therapy (chemotherapy or hormone manipulation) or arising from multiple sites not easily controlled by external beam radiotherapy or surgery.
3. Radionuclide therapy in this context means the intravenous administration of ^{89}Sr-chloride in aqueous solution, or ^{153}Sm-lexidronam (^{153}Sm-ethylene-diamine-tetramethylene-phosphonate [^{153}Sm-EDTMP]), or ^{186}Re-etidronate (^{186}Re-hyroxyethylidine-diphosphonate] [^{186}Re-HEDP]).
4. Bone seeking radiopharmaceutical efficacy relies on their selective uptake and prolonged retention at sites of increased osteoblastic activity. The exact mechanism of action is not fully understood, but involves the reduction of cytokines and growth factors released by tumour and inflammatory cells at the interface between tumour and normal bone and radiation-induced mechanical factors, such as reduction of periosteal swelling [2].
5. Osteoblastic means focal increased skeletal metabolic activity, namely, sclerosis, caused by osseous reaction to bone metastases, as evidenced by increased activity on bone scintigraphy. Osteolytic means focal areas of bone destruction caused by the action of osteoclasts. A mixed pattern, however, is common in many lesions [3]. Bone seeking

radiopharmaceuticals may be also used for the treatment of primary and metastatic bone tumours, such as osteosarcoma, inducing an osteoblastic reaction.

Background

Bone seeking radiopharmaceuticals are one of the therapeutic tools available for palliation of bone pain and should be used within a multidisciplinary approach to choose the best option for each patient in a correct sequence. A careful patient selection should be performed before treatment with bone seeking radiopharmaceuticals, which should be preferably administered early in the metastatic phase, to increase the rate of therapeutic responses. Haematological function at peripheral blood cell count, bone (marrow) involvement at pre-therapy bone scintigraphy, performance status, recent use of myelosuppressive therapies, and expectancy of life should be considered before indicating radionuclide therapy [4, 5].

1. ^{89}Sr emits a beta particle with a maximum energy of 1.46 MeV, mean energy of 0.58 MeV, average soft tissue range of 2.4 mm and 0.01% abundant gamma emission with a 0.91-MeV photo peak. The physical half-life is 50.5 days [6].
2. ^{153}Sm emits a beta particle with a maximum energy of 0.81 MeV, mean energy of 0.23 MeV, average soft tissue range of 0.6 mm and a 28% abundant gamma emission with a 0.103-MeV photo peak. The physical half-life is 1.9 days [7].
3. ^{186}Re emits a beta particle with a maximum energy of 1.07 MeV, mean energy of 0.349 MeV, average soft tissue range of 1.1 mm and a 9% abundant gamma emission with a 0.137-MeV photo peak. The physical half-life is 3.7 days [8].

Indications

Intravenous injection of ^{89}Sr-chloride, ^{153}Sm-lexidronam or ^{186}Re-etidronate is used for the treatment of bone pain due to osteoblastic metastases or mixed osteoblastic lesions from prostate or breast carcinomas (established indications) or any other tumour presenting osteoblastic lesions seen as areas of intense uptake at bone scan. Approval for the clinical use of radiopharmaceuticals may vary in different countries. The choice of the radiopharmaceutical is based on the physic characteristics of the radionuclide in relation to the extent of metastatic disease, the bone marrow reserve and the availability of the radiopharmaceutical in single countries.

Contraindications

Absolute

Pregnancy; breastfeeding.

Relative

Low blood cell count, within certain limits, may represent a relative contraindication to the use of bone seeking radiopharmaceuticals for the possible myelotoxicity. Nevertheless, the precise lower limit is not well-defined in literature. Routinely, the following values may be considered [4, 7-9]:

1. Haemoglobin < 90 gl^{-1},
2. Total white blood cell count (WBC) < 3.5×10^9 l^{-1},
3. Platelet count (PLT) < 100×10^9 l^{-1}.

In selected situations, however, lower values may be considered: values of WBC ≥2.4×10^9 l^{-1} may be used; values of PLT, such as ≥60×10^9 l^{-1}, may be considered, provided that chronic disseminated intravascular coagulation (DIC) can be excluded by means of coagulation tests. The presence of bone marrow involvement does not represent per se a contraindication, provided that blood figures remain within the cited parameters and the extent of substitution does not trespass a threshold beyond which severe myelotoxicity is expected. Bone scintigraphy may help to describe the extent of bone marrow involvement. Usually a superscan appearance on bone scintigraphy corresponds to an important bone marrow involvement and this represents a contraindication, except for selected situation in which bone marrow figures are within limits. Blood cell figures should be stable before undertaking bone palliation therapy. If there are any doubts to perform the therapy due to low blood cell counts, it might be worthwhile to repeat a new blood sample within a short time frame to exclude a rapid deterioration in blood cell counts before the decision. Poor renal function reduces the plasma clearance of bone seeking radiopharmaceuticals, thus leading to a higher whole-body dose and risk of myelotoxicity. Therefore, patients with severely reduced renal function: creatinine >180 µmol/l and/or GFR <30 ml/min should be excluded. The safety and toxicity of treatment in patients with renal insufficiency has not been thoroughly investigated. However, an increase of myelosuppressive toxicity is expected because of the impairment of renal excretion. It is, therefore advised to lower the administered dose by 50% in patients with creatinine clearance <50 ml/min (according to the Cockroft and Gault formula for creatinine clearance in ml/min: [(140 – age) x weight (kg) x C] / (plasma creatinine x 0.814) in which C=1 if male, C=0.85 if female; plasma creatinine in µmol/l). In this case, ^{153}Sm-lexidronam and ^{186}Re-etidronate are the treatments of choice. Repeated treatment in the case of acceptable toxicity must be considered after 8 weeks [5, 10]. ^{89}Sr, ^{153}Sm-lexidronam and ^{186}Re-etidronate have no place in the management of acute spinal cord compression or in treating pathological fractures. Metastases at risk of such complications should be appropriately evaluated on the basis of clinical and neurological symptoms, examination and, if necessary, radiology. In particularly selected cases, "chronic" spinal cord compression can be evaluated for radionuclide therapy, together with high-dose corticosteroid administration and a careful clinical observation [11, 5, 12]. Therapy with ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate is inappropriate for patients with a life expectancy less than 4 weeks and, considering the latency in the onset of the palliative effect, is more beneficial in patients with a relatively long life expectancy [4].

Procedure

Facility and personnel

The facilities required will depend on the national legislation for the emission of pure beta- or beta–gamma-emitting therapy agents. If in-patient treatment is required by national legislation, this should take place in an approved facility with appropriately shielded rooms and en-suite bathroom facilities. The facilty in which treatment is administered must have appropriate personnel, radiation safety equipment, procedures available for waste handling and disposal, handling of contamination, monitoring personnel for accidental contamination and controlling contamination spread [4].

The administration of ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate should be undertaken by appropriately trained medical staff with supporting physics and nursing staff.

Physicians responsible for treating patients should have an understanding of the clinical pathophysiology and natural history of the disease processes, should be familiar with other forms of therapy and should be able to liaise closely with other physicians involved in managing the patient.

Clinicians involved in unsealed source therapy must be knowledgeable about and compliant with all applicable national and local legislation and regulations.

Patient preparation and data required

Patients considered for ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate therapy will have pain that limits normal activities and/or is not easily controlled by regular analgesics. Patients may have failed conventional analgesics, bisphosphonates and anti-tumour therapy (chemotherapy, hormone manipulation), but better candidates to bone seeking radiopharmaceuticals, to obtain a better response, are those in earlier phases of bone metastatisation [5, 13].

Patients will have undergone recent (within 4 weeks or less) bone scintigraphy documenting increased osteoblastic activity at painful sites. Radiographs demonstrating osteosclerotic lesions are inadequate, as increased bone density does not always result in increased uptake on radionuclide imaging. Abnormalities on bone scintigraphy must be correlated with appropriate physical examination to exclude other causes of chronic pain, which would be unlikely to respond to treatment using bone seeking radiopharmaceuticals. Neurogenic pain and pathological fractures should be specifically excluded.

Clinical practice and experimental studies demonstrated that treatment can be safely performed after local field external beam radiotherapy. The use of wide field (hemi-body) radiotherapy within 3 months of ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate administration is likely to result in increased myelosuppression and is relatively contraindicated [14, 15]. Except for experimental clinical trials exploring the antitumour potential of combined chemotherapy and bone seeking radiopharmaceuticals, long-acting myelosuppressive chemotherapy should be discontinued at least 4 weeks before the administration of ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate and withheld for 6–12 weeks post-therapy to avoid concomitant myelosuppression [4, 5].

A full haematological and biochemical profile should be obtained within 7 days of the proposed treatment. Recommended reference levels are listed. DIC may be a risk factor for severe thrombocytopenia post-therapy. Pre-treatment clotting studies to identify patients with subclinical DIC should be performed [16].
There are conflicting data as to whether bisphosphonates inhibit the uptake of radiolabelled phosphonates in bone metastases. This discussion is based on the hypothesis that as both drugs interact at the hydroxyapatite crystal surface of the skeleton, competition might exist for uptake by bone. At present, there is no evidence of competition between bisphosphonates and ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate. Therefore, they may be used concomitantly [17, 18].

Patient information and instruction

Patients should receive both written and verbal information about the procedure before receiving therapy. Informed written consent must be obtained from the patient, if required by local legislation. Patients should be told that 60–80% of patients benefit from ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate therapy. Patients should be warned of the risk of temporary increase in bone pain (pain flare). The patient should be told that pain reduction is unlikely within the first week, more probable in the second week and could occur as late as 4 weeks or longer after injection, particularly for long-lived isotopes. Patients should continue prescribed analgesics until bone pain decreases and receive advice regarding subsequent analgesic dose reduction where appropriate. Patients should also be informed on the duration of the analgesic effect, generally of 2–6 months and that retreatment is possible. The patient should understand that ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate are palliative treatments especially designed for treating bone pain and are unlikely to cure metastatic cancer [19].

Administration

^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate are supplied in solution to be used at room temperature. ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate should be administered by slow infusion via an indwelling intravenous butterfly or cannula followed by 0.9% saline flush. Care should be taken to avoid extravasation of the radiopharmaceutical.
Recommended administered activities are as follows:

^{89}Sr = 150 MBq,
^{153}Sm-lexidronam = 37 MBq/kg,
^{186}Re-etidronate = 1,295 MBq.

The use of bone seeking radiopharmaceuticals is associated with improved pain control and decreased analgesic consumption. To evaluate the therapeutic effect, patients should be monitored by means of objective parameters, such as the visual analogue scale or quality of life assessment forms or the course of analgesic intake.
Important differences between the radiopharmaceuticals are physical half-life, energy of gamma emission and beta emission. These differences determine both the clinical benefit

and the side effects. Although no clear difference in treatment response between ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate was reported, differences in onset of response, duration of response and toxicity do exist. The onset of response is rapid after treatment with short-lived isotopes (i.e. ^{153}Sm-lexidronam or ^{186}Re-etidronate). After treatment with long-lived isotopes (^{89}Sr), the onset is prolonged for a few weeks. The duration of response, on the other hand, is longer for long-lived radioisotopes than for short-lived isotopes [4, 5]. Patients with progressive disease and pain, for whom rapid relief is warranted, are best treated with short-lived isotopes. Relief will be quick and toxicity acceptable [5]. If needed, patients can be re-treated. Patients with a somewhat better prognosis and better clinical condition may be treated with long-lived isotopes. The duration of response will be longer. However, care must be taken for myelosuppressive toxicity, as stated before.

In responding patients, in case of recurrent pain, retreatment can be effective and safe, provided that haematological parameters are fully recovered, although the quality of response may decrease with treatments. The minimum should be 8 weeks for ^{153}Sm-lexidronam, 6–8 weeks for ^{186}Re-etidronate or 12 weeks for ^{89}Sr [20, 21].

Starting from the observation of biochemical response reported on tumour and bone resorption markers, presently, multiple phase I/II studies are focussing on the tumouricidal effect of the combination of radiosensitizing chemotherapeutic agents and bone seeking radiopharmaceuticals [22, 23]. In this case, the different physical properties of each radiopharmaceutical will influence the toxicity profile of the particular combination [4, 24, 25]. At the moment, signals from literature indicate that, despite the fact that a conclusive statement is not possible to date, the use of bone seeking radiopharmaceuticals may improve survival especially when used in earlier phases of metastatic disease or in combination with chemotherapy or radiotherapy [26-29].

Precautions, follow-up and side effects

The treating clinician must advise the patient on reducing unnecessary radiation exposure to family members and the public.

Following treatment, patients should thoroughly avoid pregnancy for at least 6 months after ^{153}Sm-lexidronam and ^{186}Re-etidronate, and even longer for ^{89}Sr. In reality, it is unlikely that women of childbearing age will be eligible for this therapy.

Patients should be appropriately hydrated before and after therapy. If the treatment is performed on an out-patient basis, patients should remain in the nuclear medicine facility for the first 4–6 h after administration.

Urinary radiopharmaceutical excretion is of particular concern during the first 2–3 days post-administration, particularly for ^{89}Sr. Urinary excretion of ^{186}Re-etidronate takes place mostly during the first 24 h after administration. For ^{153}Sm-lexidronam, it is nearly completed after the first 8–12 h after administration. Patients should be advised to observe rigorous hygiene to avoid contaminating groups at risk using the same toilet facility. Patients should be warned to avoid soiling underclothing or areas around toilet bowls for 1 week post-injection and that significantly soiled clothing should be washed separately. A double toilet flush is recommended after urination. Patients should wash their hands after urination. If contaminated with urine, patients should wash their hands abundantly with cold water without scrubbing [4].

Because urinary excretion of ^{153}Sm-lexidronam and ^{186}Re-etidronate is fast and takes place predominantly during the first 8–12 h after injection, special caution for urinary contamination should be taken during this first period.
Incontinent patients should be catheterised before radiopharmaceutical administration for radioprotection of relatives and/or caring personnel. The catheter should remain in place for an appropriate period of time (^{89}Sr = 4 days, ^{186}Re-etidronate = 2–3 days, ^{153}Sm-lexidronam = 24 h). Catheter bags should be emptied frequently. Gloves should be worn by staff caring for catheterised patients.
If in-patient treatment is required, nursing personnel must be instructed in radiation safety. Any significant medical conditions should be noted and contingency plans made in case radiation precautions must be breached for a medical emergency. Concern about radiation exposure should not interfere with the prompt appropriate medical treatment of the patient.
Haematological toxicity is the main side effect of bone seeking radiopharmaceuticals. Therefore, periodical haematological monitoring may be useful up to 6 weeks post-therapy (^{153}Sm-lexidronam, ^{186}Re-etidronate) to exclude significant myelosuppression in high-risk patients. After treatment with ^{89}Sr, longer follow-up is necessary because of prolonged myelosuppressive toxicity (12–16 weeks) [30].
Post-therapy scintigraphy, when feasible, may be of value to check tumour extent and radiopharmaceutical distribution and to perform dosimetry calculations.

Side effects

"Flare" phenomena: increase of pain symptoms, in about 10% of the patients, usually within 72 h, typically transient, usually mild and self-limiting and usually responding to standard analgesics. Generally, flare phenomena are associated with good clinical response [4, 5, 6, 31]. When cervicodorsal spinal metastases are present, an increased rate of spinal cord compression is possible. Prophylactic corticosteroids may be considered according to local protocols.
A decrease of thrombocytes and leucocytes in peripheral blood, as a result of myelosuppression, is frequently observed and has a nadir of 3–5 weeks (^{153}Smlexidronam, ^{186}Re-etidronate) or 12–16 weeks (^{89}Sr). The occurrence of grade 3 or 4 toxicity is dependent on previous (myelosuppressive) therapy and bone marrow disease. Haematological toxicity is usually temporary with complete or partial recover over the next 3 months. The rate of recovery depends on the administered activity and the bone marrow reserve.
Calcium-like flushing sensation, described with the use of ^{89}Sr, should not occur if the compound is infused slowly, as recommended.

Radiopharmaceutical

1. Pharmaceutical name: ^{89}Sr-strontium-chloride. Labelling:
   The radiopharmaceutical is supplied in aqueous solution. Radiation dosimetry: ***Table 1*** [32].
2. Pharmaceutical name: ^{153}Sm-samarium-lexidronam (EDTMP). Labelling:
   The radiopharmaceutical is supplied in aqueous solution. Radiation dosimetry: ***Table 2*** [33].
3. Pharmaceutical name: ^{186}Re-rhenium-etidronate (HEDP). Labelling:
   The radiopharmaceutical is supplied in aqueous solution. Radiation dosimetry: ***Table 3*** [34].

Quality control

The amount of activity to be administered should be checked using an isotope calibrator. Either of the following two methods can be used to measure the amount of ^{89}Sr to be administered:

1. Follow the "Guidelines for the Calibration of Metastron (^{89}Strontium-chloride injection)," available from Amersham Corporation (800/554-0157) or
2. Use a dose calibrator specially configured to quantify beta emissions.

Table 1 Radiation dosimetry ^{89}Sr [32]

Organ	mGy/MBq	rad/mCi
Bone surface	17	63
Red Bone Marrow	11.0	41
Lower Bowel Wall	4.7	17
Bladder Wall	1.3	4.8
Testes	0.80	3.0
Ovaries	0.80	3.0
Uterine Wall	0.80	3.0
Kidneys	0.80	3.0

Table 2 Radiation dosimetry ^{153}Sm-EDTMP [32]

Organ	mGy/MBq	rad/mCi
Bone surface	6.8	25
Red Bone Marrow	1.5	5.6
Lower Bowel Wall	0.010	0.037
Bladder Wall	1.0	3.7
Testes	0.0050	0.019
Ovaries	0.0090	0.033
Kidneys	0.020	0.074

Table 3 Radiation dosimetry ^{186}Re-HEDP [32]

Organ	mGy/MBq	rad/mCi
Bone surface	1.4	5.19
Red Bone Marrow	1.3	4.95
Lower Bowel Wall	0.57	2.12
Bladder	0.54	1.98
Testes	0.8	3
Ovaries	0.019	0.07
Kidneys	0.16	0.59

Issues requiring further clarification

1. Beneficial effect of combined treatment, such as chemotherapy with bone seeking radiopharmaceuticals, on the survival of patients.
2. Beneficial effects of bone seeking radiopharmaceuticals in patients receiving bisphosphonates concomitantly.
3. Safety of bone seeking radiopharmaceuticals in patients with extensive bone marrow substitution ("superscan" appearance at bone scintigraphy).

Disclaimer

The European Association of Nuclear Medicine has written and approved guidelines to promote the cost-effective use of high-quality nuclear medicine therapeutic procedures. These generic recommendations cannot be rigidly applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability. Conflict of interest statement: None of the authors have any conflict or duality of interests.

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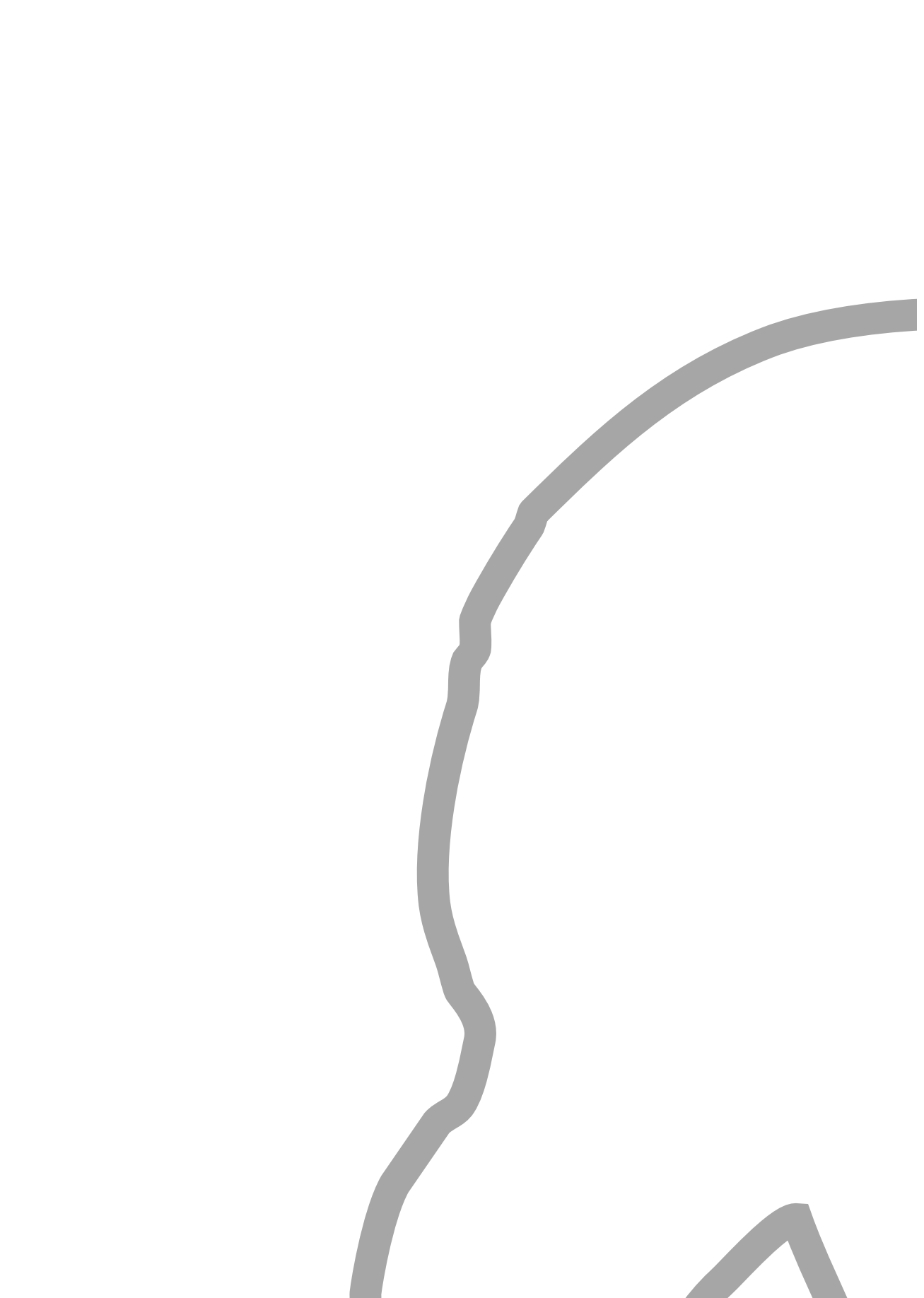

Chapter 5

Multimodality treatment in hormone-refractory prostate cancer patients with bone metastases

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Bone seeking radiopharmaceuticals are indicated for the relief of bone pain in patients with multiple painful osteoblastic metastases. Several new approaches are being studied not only to improve treatment efficacy, related to pain response, but also to extend efficacy by improving overall survival. As a single treatment modality, treatment at short intervals has shown to be beneficial with regard to pain palliation and survival [1]. However, most progress has been made with combinations of treatment modalities, for example bone seeking radiopharmaceuticals and chemotherapy [2].

In a recent publication we showed the feasibility of ^{153}Sm-EDTMP combined with zoledronic acid in hormone-refractory prostate cancer patients [3]. The combination of these two phosphate based pharmaceuticals does not lead to competition in uptake at the level of the calcified bone matrix, nor does it lead to unacceptable toxicity. As a phase I study, it was not designed to study efficacy. However, as an illustration of potentially increased efficacy, 2 patients showed a complete remission of pain and a remarkable decline in PSA levels over pretreatment values (-71% and -43%), and markers of bone metabolism (-65% and -90%) over a period of almost 6 months. These results suggest a clinical benefit. But, further research is needed to explore the possible benefit of bone seeking radiopharmaceuticals in combination with bisphosphonates, preferably in phase II and phase III randomized controlled settings.

In the past our center performed a double-blind, placebo-controlled, randomized trial to study the efficacy of ^{186}Re-HEDP compared to placebo [4]. Pain relief was assessed using an electronic diary containing questions reflecting the multidimensional character of pain. Daily pain assessment was mandatory because it fluctuated day by day. Besides a visual analogue scale (VAS) for pain and the assessment of daily activities, a medication index score was also registered. This complex method of evaluation showed a significant decrease of pain in the treated population. Besides this, the study illustrated the difficulty of pain response as an endpoint and the necessity of a well designed method for pain evaluation. Although a survival benefit could not be detected in this study using ^{186}Re-HEDP as a single modality treatment, survival should be studied in future trials focusing on the efficacy of bone seeking radiopharmaceuticals in combination with bisphosphonates.

Several clinicians have postulated the multimodality approach for the treatment of hormone-refractory prostate cancer patients with painful osseous metastases. Combinations of multiple single treatment modalities may lead to an improvement of clinical benefit beyond an additive effect alone. From all available single agent modalities, docetaxel is currently the first choice because of its proven efficacy on patients' survival [5]. Its toxicity is considerable but responders show a clear benefit with regard to quality of life and survival. A combination of radiopharmaceuticals and chemotherapy might be an interesting therapeutical option. Besides the clinical benefit of each pharmaceutical separately, the radiation sensitizing effect of chemotherapy may lead to synergy and a further improvement of clinical benefit. The combined use of chemotherapy as a radiosensitizer is well known in the field of external beam radiotherapy but must still be explored in the field of radionuclide therapy. Potential radiation modifiers may be docetaxel or other chemotherapeutics (such as platinum compounds or 5-FU). In hormone-refractory prostate cancer patients continuous treatment with hormones and bisphosphonates in combination with periodical administrations of a bone seeking radiopharmaceutical, modified by chemotherapy, may prove to be an effective regimen (***Figure 1***). Such a regimen benefits from 1) the effects of repeated treatment with radiopharmaceuticals, bisphosphonates and chemotherapy as single agent modalities, and

2) the radiation sensitizing effects of chemotherapy. Different possible strategies should be studied in the future.

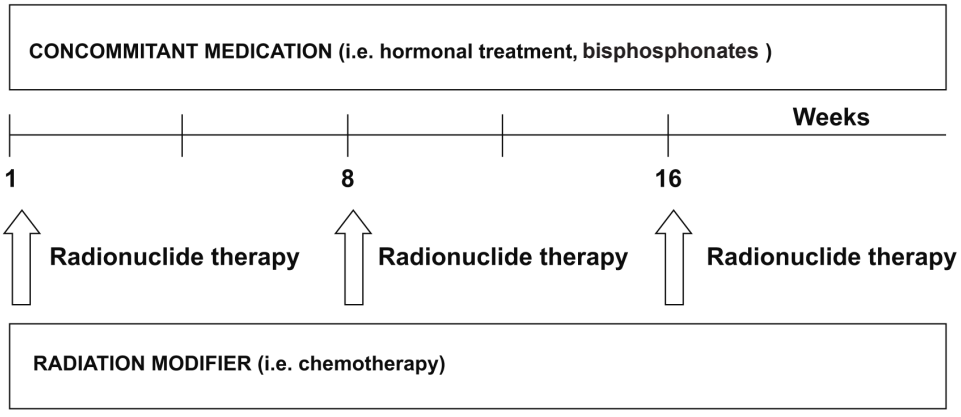

Figure 1 Proposed treatment regimen in hormone-refractory prostate cancer patients

in general will be the selection of responders and non-responders. Especially in hormone-refractory prostate cancer a minority of treated patients show clinical benefit. It will prove to be beneficial to patients, as well as cost-effective, to recognize those who respond to the proposed treatment regimen. Molecular imaging may play a crucial role in identifying these subjects. In hormone-refractory prostate cancer patients several tracers are being developed and studied for PET-imaging [6]. Stratification of patients and the development of new treatment strategies will lead to improvement of efficacy with improved overall survival.

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Chapter 6

Combined use of zoledronic acid and ^{153}Sm-EDTMP in hormone-refractory prostate cancer patients with bone metastases

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Abstract

Purpose

^{153}Sm-EDTMP (Quadramet®) is indicated for the treatment of painful bone metastases, whereas zoledronic acid (Zometa®) is indicated for the prevention of skeletal complications. Because of the different therapeutic effects combining the treatments may be beneficial. Both however accumulate in areas with increased osteoblastic activity. Possible drug interactions were investigated.

Methods

Patients with hormone-refractory prostate cancer were treated with 18.5 MBq/kg ^{153}Sm-EDTMP in weeks 1 and 3 and with 37 MBq/kg in week 15. Treatment with 4 mg zoledronic acid began in week 3 and continued every 4 weeks through week 23. In weeks 3 and 15, zoledronic acid was administered 2 days before ^{153}Sm-EDTMP treatment. Urine was collected 48 h after injection of ^{153}Sm-EDTMP, and whole body images were obtained 6, 24, and 48 h post-injection. The effect of zoledronic acid on total bone uptake of ^{153}Sm-EDTMP, was measured indirectly by the cumulative activity excreted in the urine in weeks 1, 3 and 15. Biodistribution, safety, tolerability and effect on PSA level were also studied.

Results

The urinary excretion in week 3 divided by the urinary excretion in week 1 (baseline), times 100% was mean 98.4% ±11.6% (median 96.2%). From week 1 to 15, after four zoledronic acid treatments, the mean ratio was 101.9% ±10.7% (median 101.8%). Bioequivalence could be concluded by using a two-sample *t*-test for both per-protocol (n=13) and full-analysis sets (n=18). Toxicity was comparable to that of monotherapy with ^{153}Sm-EDTMP.

Conclusion

Zoledronic acid treatment does not influence ^{153}Sm-EDTMP skeletal uptake. Combined treatment is feasible and safe.

Introduction

Prostate cancer is one of the most common malignancies worldwide. Approximately 50-70% of patients present at a locally advanced stage, and ~15-30% have bone metastases at the time of diagnosis [1]. Metastatic disease may be found upon presentation or may develop after treatment for localized disease.

In advanced prostate cancer, spread of the disease to the skeleton occurs in the majority of patients, with skeletal metastases being predominantly osteoblastic in nature. The clinical course of metastatic bone disease in prostate cancer is relatively long, with patients experiencing complications over a period of several years. These complications include bone pain, fractures, hypercalcemia, and spinal cord compression, all of which may profoundly impair a patient's quality of life. Careful attention to pain management by care providers is crucial.

External radiotherapy is the best treatment for localized metastatic bone pain [2]. Nevertheless, external beam radiotherapy is less favorable when the disease has metastasized globally because the effective radiation dose is limited by toxicity in adjacent or overlapping critical structures and organs. Radionuclide therapy has been proposed as an alternative modality for the management of bone pain. These radiopharmaceuticals localize preferentially in active bone and mainly at metastatic lesions, allowing site-directed radiotherapy [3].

Samarium-153-ethylenediaminetetramethylphosphonic acid (^{153}Sm-EDTMP or ^{153}Sm-lexidronam; Quadramet®) is a radiopharmaceutical compound that has an affinity for skeletal tissue and concentrates in areas of increased bone turnover [4]. ^{153}Sm-EDTMP is indicated for the relief of pain in patients with osteoblastic metastatic bone lesions at a dose of 37 MBq/kg (1.0 mCi/kg). With a half-life of 46.3 h, the radioisotope emits a 103-keV gamma ray (29%) for external imaging and beta-particles (average energy 233 keV) for localized radiotherapy. The average range of emission of ^{153}Sm-electrons is only 1.7 mm in bone, limiting the exposure of bone marrow and other adjacent tissues to radiation. The combination of radiopharmaceuticals with other treatment options (systemic or local) needs to be investigated to further improve efficacy [5, 6].

To minimize the incidence of skeletal-related events, bisphosphonates may be indicated as a systemic treatment for patients with osseous metastases. Bisphosphonates are characterized by a central phosphorus-carbon-phosphorus structure. They bind tightly to the calcified bone matrix and are powerful inhibitors of osteoclast-mediated bone resorption. Zoledronic acid, a new-generation bisphosphonate, exhibits a more potent inhibitory activity of osteoclasts compared with other bisphosphonates [7]. In July 2002, the European Agency for the Evaluation of Medicinal Products (EMEA) granted marketing authorization in the European Union (EU) for Zometa® (zoledronic acid) for the prevention of skeletal-related events in patients with advanced malignancies involving bone. These malignancies include multiple myeloma, prostate cancer, breast cancer, lung cancer, renal cancer, and other solid tumors.

To manage potential complications related to bone metastasis in prostate cancer (pain, pathological fractures, etc.), several approaches are being developed, including radiopharmaceuticals and bisphosphonates. With regard to pain relief, radiopharmaceuticals are indicated in prostate cancer. In contrast, the efficacy of bisphosphonates for pain

management has not been clearly demonstrated [8]. Combined treatment with both pharmaceuticals may improve palliative care and enhance overall efficacy [9].
However, there are conflicting data as to whether bisphosphonates inhibit the uptake of radiolabeled phosphonates in bone metastases. Some studies reported that bone uptake of ^{99m}Tc-labeled bone scanning agents was decreased in patients receiving etidronate intravenously or orally [10-12]. On the other hand, other studies reported the feasibility of the combined use of bisphosphonates with radiolabeled phosphonates [13-15]. With regard to bone seeking radiopharmaceuticals, proper studies evaluating the influence of bisphosphonates on bone uptake are non-existent.
Patients with an indication for ^{153}Sm-EDTMP therapy often receive monthly infusions of bisphosphonates such as zoledronic acid, and these related compounds are both taken up by the bone. Thus, the purpose of the present clinical trial was to investigate the effects of zoledronic acid on the bone uptake of ^{153}Sm-EDTMP and on bone metabolism and to assess the safety of the combined use of both products.

Materials and methods

Study population

Patients with histologically documented adenocarcinoma of the prostate, progressive hormone-refractory disease, and more than one bone metastasis were included in this open-label prospective study. Other inclusion criteria were a Karnofsky performance status of at least 70%, life expectancy of at least 8 months, age of at least 18 years, and the ability to understand and willingness to sign an informed consent document. Patients receiving bisphosphonate therapy had to discontinue their treatment for at least 3 months prior to study entry, and patients under LH-RH agonists had to continue their treatment. Patients with pathologic long-bone fractures or metastatic involvement of >75% of the ribs, vertebrae, and pelvic bones and patients with known malignancies other than prostate cancer (not including basal cell carcinoma of the skin) were excluded. Other exclusion criteria were chemotherapy (including Estracyt®) within the past 5 years; prior treatment with systemic radiotherapeutic bone agents; receipt of any other investigational drug within 4 weeks of study entry; previous hemi-body external radiation therapy (for >25% of the bone marrow within 90 days); concomitant treatment with aminoglycosides; clinically significant bleeding disorders; hypersensitivity to phosphonate compounds, mannitol, or zoledronic acid; concurrent illnesses or treatments that might preclude study completion; active CNS or epidural brain metastasis; absolute neutrophil count <2 x 10^9/L; platelet count <150 x 10^9/L; hemoglobin <6.2 mmol/L; serum creatinine >177 µmol/L; or total PSA <5 ng/mL. The study was approved by the local ethics committee, and written informed consent was obtained from all patients.

Treatment

Included patients were treated with 18.5 MBq/kg (0.5 mCi/kg) ^{153}Sm-ethylenediaminetetramethylphosphonic acid (EDTMP) (Quadramet®; CIS bio International, Saclay, France) in week 1 (mean ± 1 SD: 1606 ± 252 MBq) and week 3 (mean ± 1 SD: 1672 ± 293 MBq) and with 37

MBq/kg (1.0 mCi/kg) ^{153}Sm-EDTMP in week 15 (mean ± 1 SD: 3319 ± 609 MBq). The three intravenous injections contained the same absolute amount of EDTMP.

To avoid an effect of progressive disease with significant changes in skeletal metastatic load, a short interval of 2 weeks was chosen between the first two treatments. Half the usual dose of ^{153}Sm-EDTMP was administered to avoid unacceptable toxicity. Although this regimen is unusual, it seems acceptable from a therapeutic standpoint. A dose response relation for ^{153}Sm-EDTMP was not clearly found in all studies [16]. Furthermore, repeated treatments at short intervals have shown favorable responses [17]. The interval between the second and third treatment with ^{153}Sm-EDTMP (12 weeks) was chosen to allow a) bone marrow recovery from the first two treatments and b) four consecutive administrations of zoledronic acid before the third ^{153}Sm-EDTMP treatment. Another 12-week interval between the third treatment and the final visit in week 27 was chosen to allow bone marrow recovery.

Treatment with 4 mg zoledronic acid (Zometa®; Novartis, Stein, Switzerland) every 4 weeks started in week 3 and continued through week 23 (six treatments total). In weeks 3 and 15, zoledronic acid was administered 2 days (48 h) before ^{153}Sm-EDTMP treatment. Zoledronic acid treatments were injected as single 15-min intravenous infusions in a daycare setting. After infusion, vital signs were recorded every 30 min for the first 2 h, after which patients were discharged. In weeks 1, 3, and 15, patients were hospitalized for 48 h after ^{153}Sm-EDTMP administration. Urine was collected during the 48 h following injection of ^{153}Sm-EDTMP in five portions (0–4, 4–8, 8–12, 12–24, and 24–48 h). Whole-body images were captured with a dual-head gamma camera at 6, 24, and 48 h post-injection (anterior and posterior). Patients with lower urinary tract obstruction or incontinence had to consent to catheterization of the bladder for up to 48 h.

Analysis

After intravenous injection of ^{153}Sm-EDTMP, most of the activity is rapidly cleared from the blood and excreted in urine. No appreciable extraskeletal uptake was observed on the scintigraphic images because the remaining activity in the body was almost completely localized to the skeletal mass. Previous animal studies confirm the minimal uptake of ^{153}Sm-EDTMP by extraskeletal tissues [4, 18]. Therefore, the uptake of ^{153}Sm-EDTMP by the whole skeleton was studied indirectly by measuring the urinary excretion of activity [19, 20].

After the initial injection of ^{153}Sm-EDTMP, urine was collected over the next 48 h. The amount of activity in these samples was determined by measurement of 15-mL, non-diluted samples with a dose calibrator. For comparison with the administered activity, the exact injected dose was determined by measurement of the syringe before and after administration. This procedure enabled determination of the amount of activity excreted and, as a corollary, the relative amount of activity retained within the body. The primary endpoint of the study was the effect of zoledronic acid on the urinary excretion of ^{153}Sm-EDTMP, which was measured in weeks 1 and 3, i.e., before and after the first zoledronic acid infusion. The effect of repeated zoledronic acid treatment on the urinary excretion of ^{153}Sm-EDTMP in weeks 1 and 15 was a secondary endpoint.

Secondary endpoints also included the effects of the combined use of zoledronic acid and ^{153}Sm-EDTMP on the uptake of ^{153}Sm-EDTMP in bone metastases, liver, and kidneys. The

scintigraphic images were evaluated by an independent certified nuclear physician with expertise in skeletal scintigraphy, blinded for patient data and the week the images were acquired. Images of each week (6 h, 24 h and 48 h after injection) were shown together for each patient, since the reader could anyhow identify the different points in time by the decrease in activity. The reader started with the '6 h' image and drew ROIs (at least 25 pixels) for three metastatic bone lesions, normal bone (femur), background (soft tissue of the thigh), the liver (ROIs without overlap of ribs. Anterior image: paravertebral space at height Th11 – Th12; posterior image: interribonspace 9 – 10 or 10 – 11) and kidneys (arithmetic mean of both kidneys was used). ROIs were copied to the other images of the same patient. From all ROIs 30% isocontour ROIs were automatically drawn. Geometric means of anterior and posterior images were calculated for these ROIs and corrected for background. Evaluation of biodistribution was based on a quantitative analysis of the pixel-normalized lesion-to-normal bone ratios and pixel-normalized organ-to-normal bone ratios. Blood sampling was not performed.
Other secondary endpoints were the following: safety and tolerability of the combined use of ^{153}Sm-EDTMP and zoledronic acid (vital signs, laboratory values, and adverse events according to the NCI Common Terminology Criteria for Adverse Events, version 3.0), the effect on markers of bone metabolism as measured in blood and urine samples (serum bone-specific alkaline phosphatase [BAP], serum procollagen type 1 N propeptide [PINP], and the urinary N-terminal type 1 collagen peptide [NTX]), and the effect on PSA levels.
The present study was not designed to investigate the efficacy of the combined treatment.

Statistical methods

Descriptive statistics (n, mean, standard deviation [SD], minimum, quartile 1 [Q1], median, quartile 3 [Q3], and maximum) were calculated for quantitative variables; frequency counts by category were determined for qualitative variables. A bioequivalence test was performed using the classical 90%-confidence interval method for the ratio of the cumulated activities excreted in urine within 48 h after administration in weeks 3 and 1 [(excreted urine week 3) / (excreted urine week 1) x 100%]. For a broad range of drugs, the FDA has chosen a limit of 80-125% for the confidence interval of a bioequivalence test. Generally, the limit of 80-125% is based on a clinical judgment that a test product with values outside this range should be denied market access. If the confidence interval lay completely within the equivalence interval of 80-125%, equivalence was concluded.
The primary target variable was analyzed with a two-sample t-test. It was assumed that this parameter was log-normally distributed; therefore, the logarithms (base e) were analyzed.

Results

A total of 20 patients were enrolled in this study. Two patients were not treated because of low platelet counts. Major protocol deviations leading to exclusion from analysis of the primary objective were found in five patients. One patient had not stopped anti-androgen medication; one patient received a dosage in week 3 higher than the required dose due to miscalculation of his weight, and this patient also started anti-androgen treatment; one

patient went off-study before treatment in week 3 due to progressive disease (lymphangitis carcinomatosa); and two patients had no or incomplete urine collection. Thus, 18 patients were included in the full-analysis set (FAS) and 13 in the per-protocol set (PPS). All patients in the FAS were Caucasian with a mean age of 67.3 years (range 61–74).

Among the 18 patients who entered the treatment period, 7 withdrew before the end of the treatment period (before week 23), and 11 completed both the treatment period and the study course (27 weeks). Two patients were withdrawn because of adverse events (increase in creatinine level, disseminated intravascular coagulation), four patients were recommended to start with radiotherapy or chemotherapy because of progressive disease, and one patient was withdrawn due to decreasing PSA level after the start of anti-androgen treatment.

Of the 18 included patients, 13 were evaluable for the primary endpoint (PPS). Urinary excretion data expressed as percentage of administered activity are shown in ***Table 1***. The mean ratio of urinary excretion of ^{153}Sm in week 3 to that at baseline (week 1) expressed as a percentage was 98.4% ± 11.6% (median 96.2%, range 81.1–118.9%) (***Table 2***). The point estimate and the 90% confidence interval for the assessment of bioequivalence were 97.83% (92.39 – 103.60%) for week 1 to 3, which was completely within the presumed equivalence range used by the FDA (80–125%). Hence, bioequivalence could be concluded.

Table 1 Urinary excretion of ^{153}Sm-EDTMP (percentage of administered activity)

Patient	Week 1	Week 3	Week 15
1	36.3	9.2*	39.3
2	48.5	57	55.9
3	Screening failure†		
4	37.6	44.7	42.8
5	43.7	46	44.3
6	55.6	48.8	50.2
7	43.8	46.7	50.1
8	---*	37.8	Off study
9	43.5	49.2	48.5
10	47.5	43.1	48.6
11	Screening failure†		
12	46.6	49.2	47
13	32	30	Off study
14	38.1	37	31.7
15	30.8	27.1	Off study
16	33.7	38.1	Off study
17	31.8	25.8	Off study
18	39.6	38.1	37.1
19	39.8	36.3	41.1
20	51.2	Off study	Off study

* Collection of urine was not complete / not performed

† Exclusion due to low trombocyte count

Table 2 Descriptive statistics of ratios (%) of urinary excretion of ^{153}Sm-EDTMP

	N	Mean (%)	SD	Min	Q1	Median (%)	Q3	Max
Week 3 / Week 1								
PPS	13	98.44	11.58	81.13	90.74	96.21	105.58	118.88
FAS	16	95.70	22.00	25.34	89.36	96.66	109.84	118.88
Week 15 / Week 1								
PPS	10	101.85	10.71	83.20	93.69	101.84	113.83	115.26
FAS	12	103.18	10.20	83.20	97.27	102.79	112.66	115.26
Week 15 / Week 3								
PPS	10	100.48	8.59	85.68	95.75	97.72	107.28	113.22
FAS	12	127.55	94.68	85.68	96.03	98.32	110.02	427.17

As shown in ***Figure 1***, there was no change in the fraction of ^{153}Sm-EDTMP excreted in urine after one administration of zoledronic acid (week 3) or after repeated administrations of zoledronic acid (week 15) compared with the urinary excretion at baseline (week 1). Descriptive statistics were similar in the PPS and the FAS except for the mean ratio of ^{153}Sm-EDTMP excretion between weeks 15 and 3, which was higher for FAS (127.55%) due to the low value of urinary excretion in one patient at week 3. This patient was excluded from the PPS because the collection of his urine at week 3 was not complete (Tables 1 and 2).

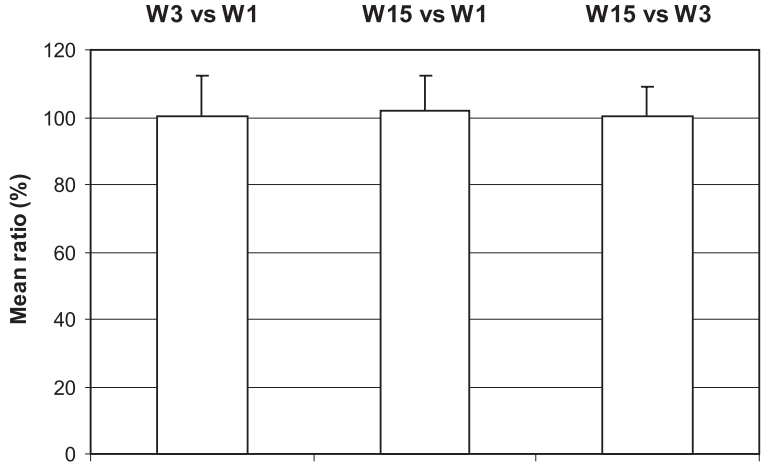

Figure 1 Urinary excretion of ^{153}Sm-EDTMP in week 3 (combined therapy with zoledronic acid) divided by urinary excretion of ^{153}Sm-EDTMP in week 1 (without zoledronic acid), times 100%. Also for week 15 (after repeated zoledronic acid administrations) versus week 1, and week 15 versus week 3. All data for the per-protocol set (PPS). Zoledronic acid does not change the excretion nor the uptake of ^{153}Sm-EDTMP because no changes between different weeks were observed (all ratios are close to 100%)

The uptake of ^{153}Sm-EDTMP in bone metastases or organs versus uptake in normal bone was determined by calculation of the lesion- or organ-to-normal bone ratios at each time point (skeletal scintigrams were obtained 6, 24, and 48 h post-injection). ***Figure 2*** shows the uptake of ^{153}Sm-EDTMP in normal bone 6 h, 24 h, and 48 h after each administration of ^{153}Sm-EDTMP. The uptake of activity in normal skeleton was dosage- and time-dependent because it decreased with increasing time after injection (from 6 to 48 h post-injection) and increased proportionally with increased injected dose (18.5 MBq/kg at weeks 1 and 3 versus 37 MBq/kg at week 15). ^{153}Sm-EDTMP was bound to the bone in a stable manner because the decrease in uptake between 6 and 48 h was due solely to the physical decay of ^{153}Sm. Importantly, the FAS results showed no effect of one dose (week 3) or repeated doses (week 15) of zoledronic acid on the uptake of ^{153}Sm-EDTMP by normal bone. Similar results were obtained for the PPS.

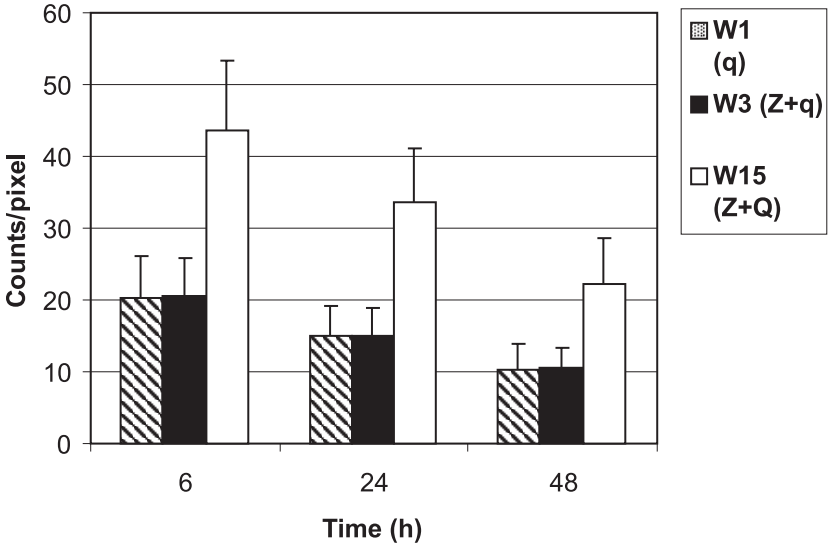

Figure 2 Mean (±1 SD) uptake (counts per pixel) of ^{153}Sm-EDTMP in normal bone in post-treatment skeletal scintigrams obtained 6, 24, and 48 h after administration for the full-analysis set (FAS). Weeks 1, 3, and 15 are compared. q = 18.5 MBq/kg ^{153}Sm-EDTMP, Q = 37 MBq/kg ^{153}Sm-EDTMP, Z = zoledronic acid

The ^{153}Sm-EDTMP uptake ratios of metastases/normal bone, kidneys/normal bone, and liver/normal bone were calculated at baseline (week 1), week 3, and week 15. ***Figure 3*** shows the differences between these time points given as ratios, e.g. ratio of metastases/normal bone at week 3 to metastases/normal bone at baseline x 100% (given numbers are thus ratios of ratios). The uptake of ^{153}Sm-EDTMP in bone metastases was relatively insensitive to variation in the injected dose of ^{153}Sm-EDTMP and to repeated administrations of zoledronic acid and ^{153}Sm-EDTMP. In addition, the uptake of ^{153}Sm-EDTMP in kidneys and liver was not affected by the activity of the injected dose of ^{153}Sm-EDTMP or by repeated administrations of zoledronic acid and ^{153}Sm-EDTMP. Similar results were obtained for the FAS and the PPS. No significant changes were found. None of the images showed liver uptake or any other extraskeletal uptake besides kidneys and bladder. Activity in the kidneys and bladder was only visualized on the early images.

Blood sampling was not performed. Blood plasma activity clearance was therefore not measured. Because uptake in normal bone, metastatic bone and organs, as well as urinary excretion of activity were stable it is reasonable to assume that the retention of activity in the blood pool compartment did not change either. Any change in the retention of activity in this compartment would lead to a secondary change in either urinary excretion of activity or uptake in the skeleton. This hypothesis is supported by stable and low background activity as measured in the thigh. Besides minimal visualization of activity in soft tissue, the measured soft tissue activity was approximately 30 – 40 times less than normal bone activity (0.6 ± 0.1 counts per pixel compared to 22.1 ± 5.7 counts per pixel 6 hours p.i. in week 1; 0.7 ± 0.1 counts per pixel compared to 22.3 ± 4.3 counts per pixel 6 hours p.i. in week 3 [PPS]).

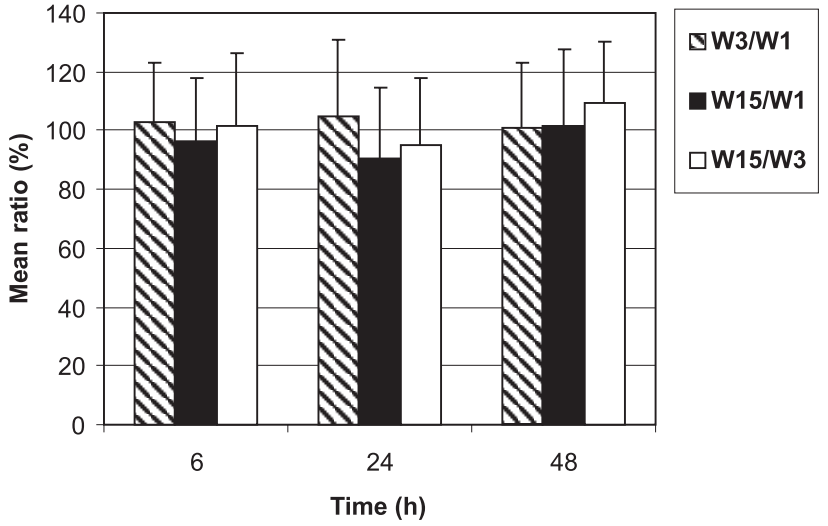

Figure 3 Per patient (FAS) a total of 9 scintigrams were performed at 3 different weeks (week 1, 3 and 15) and 3 different time-points post injection (6, 24 and 48 h p.i.). Lesion-to-normal bone ratios were calculated on every scintigram. Comparison between different weeks were made for every time-point post injection as follows: [Lesion-to-normal bone ratio] week 3, 6 h p.i. divided by [Lesion-to-normal bone ratio] week 1, 6 h p.i., times 100%. Zoledronic acid does not change the uptake of ^{153}Sm-EDTMP in lesions compared to normal bone (all ratios are close to 100%)

After onset of the study treatment, hematological parameters were measured on a weekly basis (***Figure 4***) and serum chemistry (including creatinine level) on a monthly basis. All patients experienced the expected temporary decline in platelet count in week 5 (mean ± 1 SD: 42.2 ± 18.8% decline, 4 weeks after the first ^{153}Sm-EDTMP administration) and in week 19 (64.3 ± 9.9% decline, 4 weeks after the third ^{153}Sm-EDTMP administration), with subsequent recovery. Also as expected, there was a temporary decline in white blood cell count in week 7 (36.5 ± 23.8% decline, 6 weeks after the first ^{153}Sm-EDTMP administration) and in week 20 (40.5 ± 15.2% decline, 5 weeks after the third ^{153}Sm-EDTMP administration), with recovery thereafter. Hemoglobin levels steadily declined throughout the study course with a mean decrease of 12.5 ± 8.0% at the end of the study compared with baseline. This is consistent with the disease progression (PSA increase) observed for most patients during the study course.
Grades 2, 3, and 4 hematological toxicity occurred in 12, 1, and 2 patients, respectively.

Creatinine levels were stable throughout the study period for all except one patient, who experienced a sudden increase in creatinine level (grade 2) in week 10 (after two doses of 18.5 MBq/kg ^{153}Sm-EDTMP and two infusions of 4 mg zoledronic acid) due to bilateral ureter obstruction caused by pathologically enlarged lymph nodes. This patient went off-study, and creatinine levels returned to normal after relief of the obstruction.

Other adverse events included pain and fatigue due to disease progression and 'influenza-like symptoms,' nausea, vomiting, and hypocalcemia related to zoledronic acid administration. One patient experienced a pathological hip fracture, and another patient had monoparesis as a result of epidural metastatic disease. A third patient had disseminated intravascular coagulation, causing him to develop grade 3 hematoma and grade 4 thrombopenia. These patients went off-study. No further unexpected toxicity occurred (***Table* 3**).

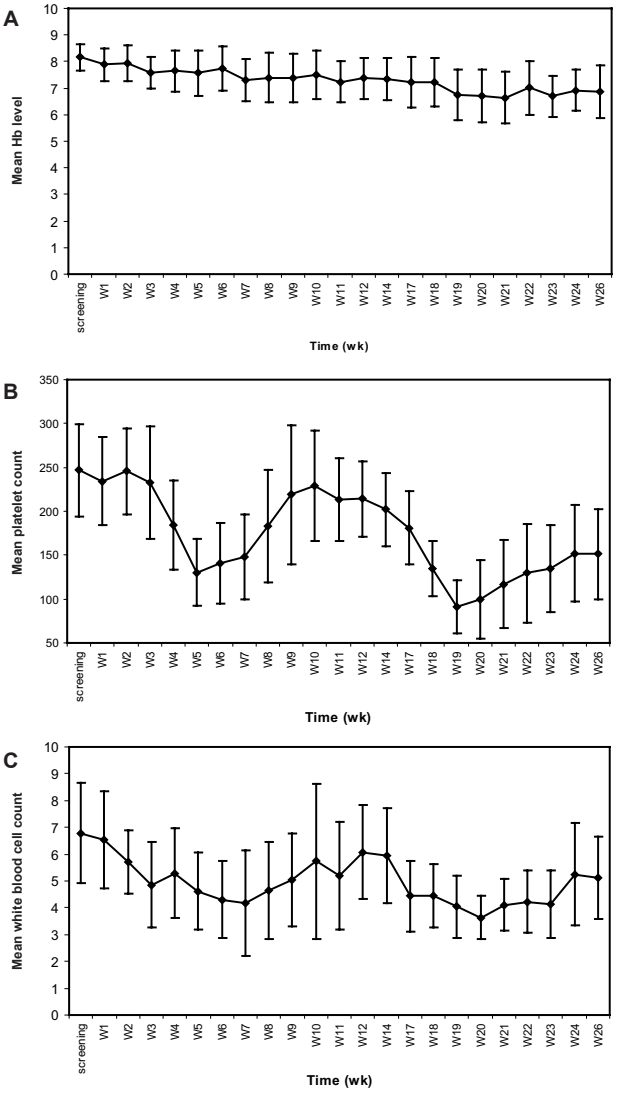

Figure 4 Mean hematological parameters (FAS) during the whole study period: hemoglobin (a), platelet count (b) and white blood cell count (c)

Table 3 Number of patients experiencing adverse events

	Grade 1	Grade 2	Grade 3	Grade 4
Disseminated intravascular coagulation	-	-	1	-
Abdominal pain	4	-	-	-
Constipation	4	-	-	-
Diarrhea	2	-	-	-
Nausea	6	1	1	-
Vomiting	1	-	2	-
Asthenia	2	1	-	-
Crepitations	-	1	-	-
Fatigue	1	1	1	-
Influenza like illness	13	-	-	-
Malaise	1	1	-	-
Pain	4	4	4	1
Pyrexia	3	-	-	-
Hip fracture	-	-	1	-
Anaemia	4	7	-	1
Leucopenia	4	8	0	-
Neutropenia	1	7	1	-
Thrombopenia	12	2	-	2
Hypocalcaemia	11	1	2	-
Creatinine increase	1	1	-	-
Urea increase	3	1		
Weight decreased	7	-	-	-
Dizziness	2	1	-	-
Headache	5	1	-	-
Monoparesis	-	-	-	1
Paraesthesia	2	-	-	-
Euphoric mood	-	1	-	-
Obstructive uropathy	-	1	-	-
Urinary retention	2	-	-	-
Cough	2	1	-	-
Dysnpoea	-	3	-	-
Epistaxis	2	-	-	-
Haemoptysis	2	-	-	-
Hypoxia	-	-	1	-
Hyperhidrosis	3	-	-	-
Night sweats	2	-	-	-
Haematoma	-	-	1	-
Hypertension	4	2	-	-
Lymphangitis	-	1	-	-

This table includes adverse events which are related or unrelated to study drugs, with either an intensity > grade 1 (according to NCI Common Terminology Criteria for Averse Events) or frequency > 1 patient

Secondary endpoints for efficacy were bone metabolism markers and PSA response. ***Figure 5*** shows the change from baseline of bone metabolism markers (FAS). Urinary NTX corrected to creatinine excretion, which reflects bone resorption, was reduced markedly, falling rapidly (median decrease ~70%) within 1 month after the first administration of zoledronic acid (week 3) and remaining suppressed during the entire study course. Serum BAP, reflecting bone formation by osteoblasts, decreased, with a mean reduction of ~25% at week 15. An additional 25% decrease in BAP was noticed after the administration of a full dose of ^{153}Sm-EDTMP at week 15, leading to a 50% total decrease from baseline. The increase in BAP at week 15 may reflect some disease progression before the ^{153}Sm-EDTMP treatment at week 15. Serum PINP decreased progressively over 15 weeks to a mean reduction of 50% after 4-5 repeated administrations of zoledronic acid.

Baseline levels of total PSA measured before administration of the study drugs ranged from 15 to 2400 ng/mL. Of the 18 treated patients, 14 had baseline levels <400 ng/mL, and 4 had baseline levels >1000 ng/mL. After the start of treatment, PSA levels of the 15 evaluable patients (2 patients did not stop or started anti-androgen treatment, 1 patient went off-study before week 3) were either increasing (9 patients), stabilized (3 patients), or decreasing (3 patients). Eight weeks after the final administration of ^{153}Sm-EDTMP in week 23, PSA levels in most patients had increased by >50%, reflecting prostate cancer progression. Two patients had remarkably decreased PSA levels (from 24 to 6.9 ng/mL [-71%] and from 30.7 to 17.6 ng/mL [-43%]) at week 23.

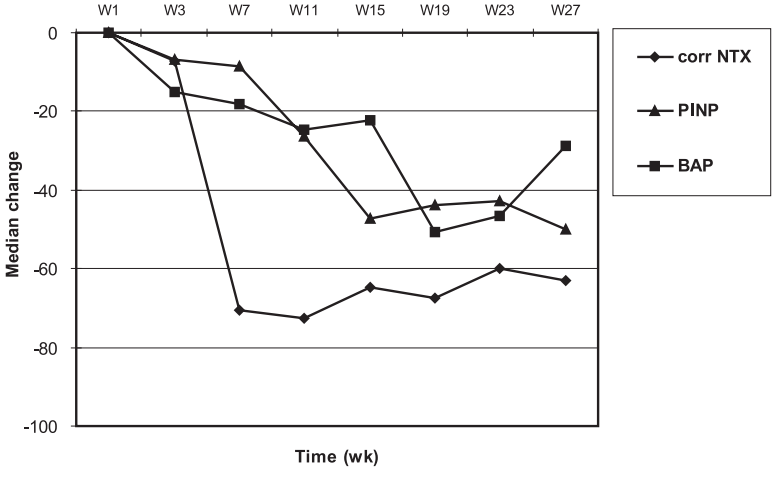

Figure 5 Median change (%) from baseline of bone markers during the study period of 27 weeks (FAS). AP, serum bone-specific alkaline phosphatase; PINP, serum procollagen type 1 N propeptide; corr NTX, urinary creatinine-corrected N-terminal type 1 collagen peptide

Discussion

Various therapies for the treatment of painful skeletal metastases are currently available. These can be in the form of local or systemic therapy and include analgesics, chemotherapy, hormonal therapy, surgery, bisphosphonates, external beam radiation, and systemically administered radiopharmaceuticals. A multidisciplinary approach to the treatment of cancer pain has been advocated [20]. Besides optimizing radiopharmaceutical dosing schemes and treatment regimens [21, 22], synergy between different pharmaceuticals could ultimately enhance efficacy to move beyond mere palliation [6].

The combined use of bisphosphonates and bone seeking radiopharmaceuticals could have clinical benefit [9]. The prevention of skeletal-related events could have an additive effect on the palliative treatment of bone seeking radiopharmaceuticals. Nevertheless, the European label of ^{153}Sm-EDTMP includes the contra-indication that "it should not be used concurrently with other bisphosponates if an interference is shown on the ^{99m}Tc-labeled bisphosphonate bone scan." This contra-indication is based on the hypothesis that as both drugs interact at the hydroxyapatite crystal surface of the skeleton, competition might exist for uptake by bone. However, the present study shows that the combined use of zoledronic acid has no effect on the uptake of ^{153}Sm-EDTMP in skeletal metastases of hormone-refractory prostate carcinoma. These results are consistent with the American label of ^{153}Sm-EDTMP, which does not include the contra-indication of the combined use of ^{153}Sm-EDTMP with other bisphosphonates. The present results show that combining ^{153}Sm-EDTMP and zoledronic acid is both feasible and safe. No competition for uptake by bone was observed, and only the known adverse drug reactions associated with ^{153}Sm-EDTMP and zoledronic acid were encountered.

Regarding the conflicting data on the effect of bisphosphonates on radiolabeled phosphonates, it should be noted that reduced uptake observed on ^{99m}Tc-labeled bone scans after initiating therapy with bisphosphonates does not necessarily indicate an interaction between these agents. The reduced uptake of radiolabeled phosphonates could also reflect a true decrease in metabolic bone activity due to the therapeutic effect of the bisphosphonates, especially when repeated bone scintigraphy takes place after a long interval of bisphosphonate treatment [23]. This was not the case in the present study.

Secondly, in studies that reported an adverse interaction between bisphosphonates and radiolabeled phosphates, bisphosphonates were administered because of malignancy-induced hypercalcemia [10, 12]. High serum calcium levels may lead to complex formation between calcium ions and radiolabeled phosphates, resulting in impaired imaging [24]. Furthermore, in patients with malignant hypercalcemia in association with renal failure, progressive soft tissue uptake of radiolabeled phosphates may occur due to metastatic microcalcification. This soft tissue uptake may occur at in vivo calcium-phosphate ion product concentrations of ≥ 5 mmol^2/l^2 [25, 26]. In patients with normal calcium levels, interactions between bisphosphonates and radiolabeled phosphates could not be confirmed. In patients with prostate cancer treated with alendronate (oral 40 mg daily) and in patients with breast cancer treated with clodronate (iv 300 mg daily), no effects of these bisphosphonates on repeated bone scintigraphy were observed [13, 15]. All patients in our study had either normal or below-normal serum calcium levels throughout the study course.

The recent identification of specific and sensitive biochemical markers reflecting the overall rate of bone formation and bone resorption has improved the non-invasive assessment of bone turnover abnormalities in patients with prostate cancer. Several studies have shown a rapid decrease in bone resorption markers in patients with prostate cancer and bone metastases after treatment with bisphosphonates. It has been reported that the magnitude of the decrease correlated with the efficacy of the treatment [27, 28]. Our results are consistent with data reported by Saad *et al*. for metastatic prostate cancer patients treated with zoledronic acid (4 mg every 3 weeks) [7]. In our study, urinary NTX corrected to creatinine excretion showed a 70% decrease and remained suppressed during the entire study course. Serum BAP decreased, with a mean reduction of ~25% at week 15. Similarly, Saad *et al*. reported a 25% decrease in serum BAP, which was stable for ~1 year, in hormone-refractory prostate cancer patients treated with zoledronic acid. However, in our study an additional 25% decrease in BAP was observed after administration of a full dose of ^{153}Sm-EDTMP at week 15, leading to a 50% total decrease from baseline. The additional decrease may be attributed to a BAP-reducing effect of ^{153}Sm-EDTMP. In support of this idea, the bone markers had already started to decrease after ^{153}Sm-EDTMP treatment alone. Bone marker responses may suggest an additive effect of the two treatments. Besides that it is interesting to note that, while bone markers declined, most patients showed a PSA increase. Presumably the decrease in bone metabolism was not enough to lead to an objective anti-tumor effect in this study population. However, the present study was not designed to investigate the efficacy of combined treatment because the number of treated patients is small. Although overall results on PSA decline do not seem to parallel the data on bone marker decline, two patients did respond very well. In addition to a remarkable and durable PSA decline (-71% and -43% at week 23), all bone markers decreased (-65% and -90% at week 23), and clinical responses were complete.

To enhance the efficacy of bone seeking radiopharmaceuticals, the search for effective combination therapies is crucial. Individual patients in our study responded very well to the combined treatment of bisphosphonates and bone seeking radiopharmaceuticals. In these patients significant bone marker decline paralleled a significant clinical and PSA response. Because the present study was not designed for evaluating treatment efficacy, the value of this particular combination therapy merits further investigation. Furthermore, it is of growing importance for the optimization of palliative treatment and enhancement of efficacy to characterize the bone marker responses of those patients that respond well to the proposed treatment regimen. This characterization may prove important for individualized therapy monitoring.

Conclusion

Combined treatment with the bisphosphonate zoledronic acid has no effect on the skeletal uptake of ^{153}Sm-EDTMP in patients with hormone-refractory prostate carcinoma and normal calcemia. Combined treatment is feasible and safe. The potential additive effect on efficacy of the two treatments should be studied in future trials.

Acknowledgements

We thank Alice van Dongen for her input. This study was financially supported by CIS bio International, Saclay, France. Zoledronic acid was kindly provided by Novartis, Stein, Switzerland.

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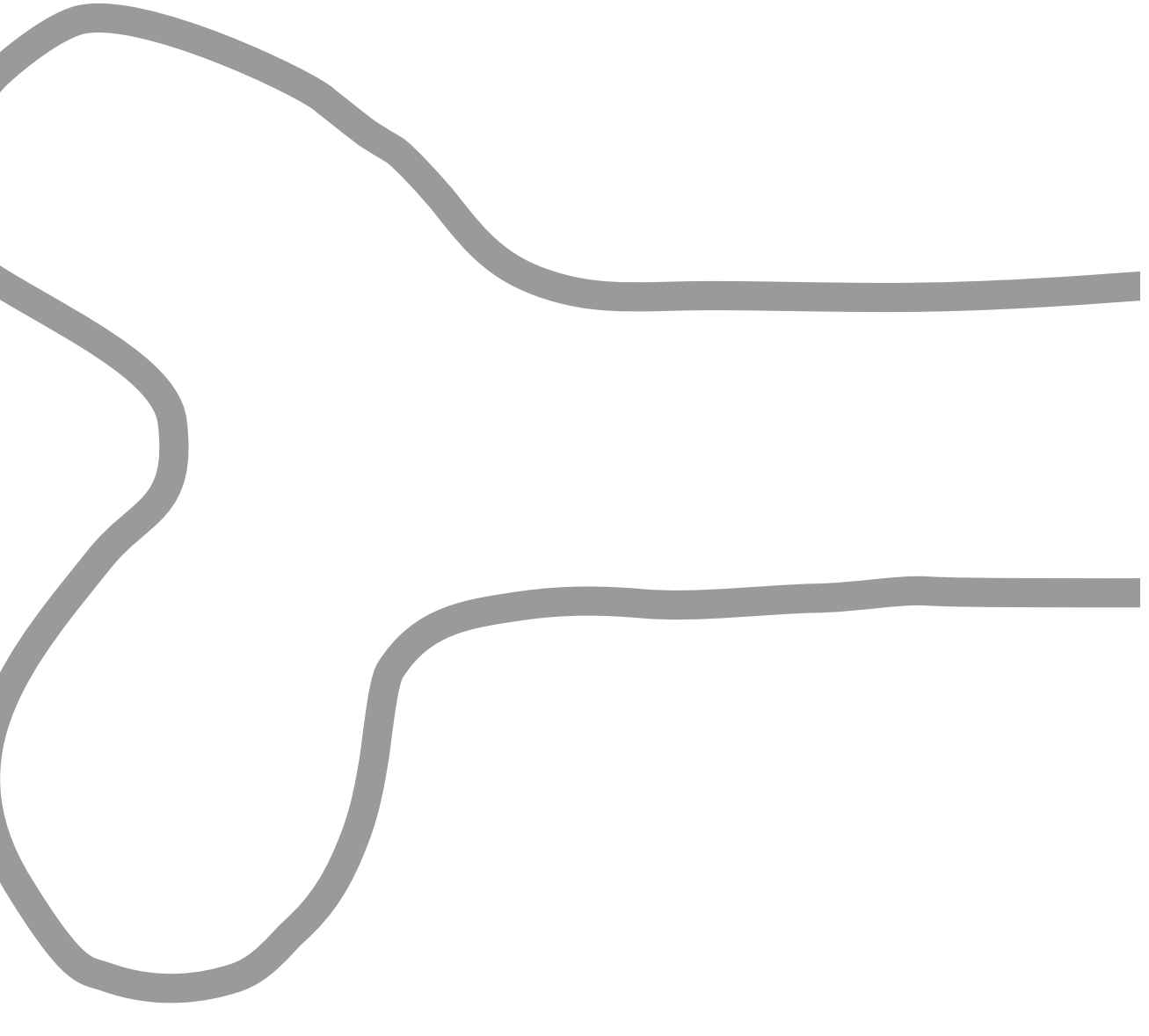

Chapter 7

Treatment of painful bone metastases in hormone-refractory prostate cancer with zoledronic acid and ^{153}Sm-EDTMP combined

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Abstract

Bone seeking radiopharmaceuticals and bisphosphonates may be indicated in cancer patients with painful osseous metastases to palliate pain symptoms or to prevent skeletal-related events. Both pharmaceuticals may have an additive or even synergistic palliative effect. The combined use of bone seeking radiopharmaceuticals and bisphosphonates is however controversial because of assumed competition between both phosphonate-compounds at the bone level. We report a case of hormone-refractory prostate cancer (HRPC) with multiple painful osseous metastases. The patient was treated with ^{153}Sm-EDTMP (Quadramet®) in combination with zoledronic acid (Zometa®). He was treated for 6 months with 4 weekly intervals of zoledronic acid in combination with 3 monthly intervals of ^{153}Sm-EDTMP. No negative interaction was found, toxicity was low and efficacy high. He experienced a total relief of pain, a significant decrease of PSA and, surprisingly, a significant decrease of tumor burden.

Introduction

Samarium-153-ethylenediaminetetramethylphosphonic acid (^{153}Sm-EDTMP or ^{153}Sm-lexidronam; Quadramet®) is a radiopharmaceutical that has an affinity for skeletal tissue and concentrates in areas of increased bone turnover [1]. ^{153}Sm-EDTMP is indicated for the relief of pain in patients with osteoblastic metastatic bone lesions at a dose of 37 MBq/kg (1.0 mCi/kg). With a half-life of 46.3 h, the radioisotope emits a 103-keV gamma ray (29%) for external imaging (***Figure 1***) and beta-particles (average energy 233 keV) for localized radiotherapy.
Zoledronic acid (Zometa®) is a potent bisphosphonate. It inhibits osteoclast mediated bone resorption and proved to be more potent than other bisphosphonates [2]. It is indicated for the prevention of skeletal-related events in advanced malignancies involving bone [3].
Treatment with ^{153}Sm-EDTMP in combination with zoledronic acid may improve palliative care. Improved overall survival has been suggested for both pharmaceuticals but clear evidence is lacking [4-6]. The synergy between these pharmaceuticals could ultimately enhance efficacy to move beyond palliation.

Case report

A 65-yr-old patient was referred to the department of Nuclear Medicine with HRPC and multiple painful osseous metastases. He had been diagnosed with prostate carcinoma 3 years earlier, after complaints of a painful right groin and left arm, and pollakisuria. His PSA blood level was 440 ng/L. A prostate biopsy revealed a pT4 prostate carcinoma. A CT-scan and skeletal scintigraphy showed besides pathological enlarged lymph nodes, multiple skeletal metastases, including the right proximal femur and the left clavicle. Treatment with the LHRH-agonist gosereline acetate (Zoladex®) was initiated. Approximately 2.5 years later, after a pathological increase of serum PSA level, the anti-androgen bicalutamide (Casodex®) was added. Unfortunately, the disease proved refractory to anti-hormone treatment within months.
the patient was referred to the department of Nuclear Medicine because of pain in the left femur and lower ribs on the right side. PSA was rising progressively with a doubling time of 3-4 weeks. The fracture risk of the left hip was high. He participated in a clinical phase I study on the feasibility of combined treatment with zoledronic acid and ^{153}Sm-EDTMP in HRPC (institutional review approval was obtained, all patients signed written informed consent). Over a period of 6 months he was treated with zoledronic acid (4 mg i.v. every 4 weeks) (Zometa®; Novartis, Stein, Switzerland) in combination with ^{153}Sm-EDTMP (37 MBq/kg) (Quadramet®; CIS bio International, Saclay, France) every 3 months. The first zoledronic acid treatment started two days prior to the first ^{153}Sm-EDTMP treatment. Patient finally received 7 treatments with zoledronic acid and 3 treatments with ^{153}Sm-EDTMP (37 MBq/kg) with a cumulative dosage of 13,173 MBq.
Post-treatment ^{153}Sm-EDTMP bone scintigraphy showed excellent uptake (***Figure 1 and 2***). Clinical side effects due to zoledronic acid treatment included shivering, cold-intolerance and minor headache. These complaints vanished within a day and became less intensive after repetitive treatments. After the first ^{153}Sm-EDTMP treatment patient experienced a transient

increase of pain in the lower ribs, the so called 'flare phenomenon'. These complaints lasted for only a few days. Bone marrow toxicity was acceptable with total recovery after each treatment with ^{153}Sm-EDTMP. Renal function and serum calcium remained normal. Two weeks after the first treatment with zoledronic acid in combination with ^{153}Sm-EDTMP all pain disappeared. The only remaining complaints consisted of fatigue. The patient remained clinically stable thereafter. Surprisingly, post-treatment ^{153}Sm-EDTMP bone scintigraphy showed a significant decrease of all skeletal lesions (and no new lesions), reflecting a decrease of metastatic burden of the skeleton (***Figure 1 and 2***). This was confirmed by markers of bone metabolism in blood and urine (serum bone-specific alkaline phosphatase [AP], serum procollagen type 1 N propeptide [PINP], and the urinary N-terminal type 1 collagen peptide [NTX]), which all normalized during treatment (***Figure 3***). PSA decreased steadily with a maximum decrease of 71% after initiation of treatment as compared to baseline (***Figure 4***). After approximately 6 months PSA started to increase. Further treatment with this combined treatment regimen was omitted thereafter.

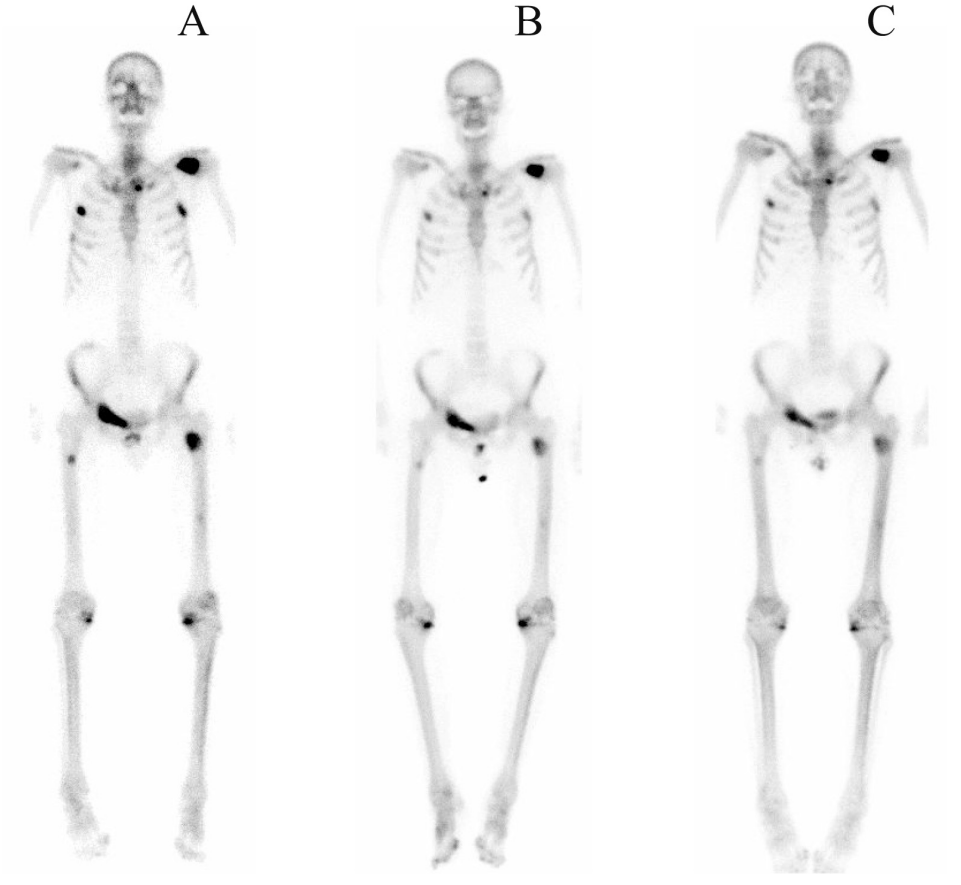

Figure 1 Anterior images (A) 6 h after first ^{153}Sm-EDTMP injection, (B) 6 h after second ^{153}Sm-EDTMP injection, and (C) 6 h after third ^{153}Sm-EDTMP injection. Note resolution of lesions, especially in the left proximal femur and right superior pubic bone

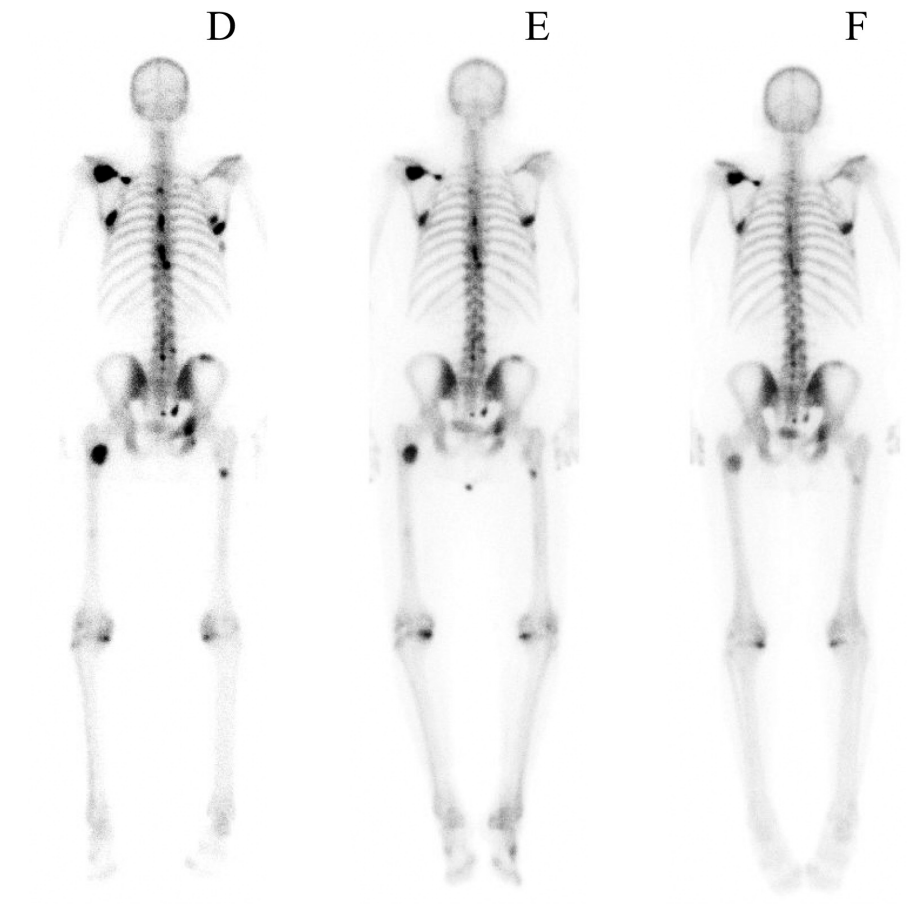

Figure 2 Posterior images (D) 6 h after first ^{153}Sm-EDTMP injection, (E) 6 h after second ^{153}Sm-EDTMP injection, (F) and 6 h after third ^{153}Sm-EDTMP injection. Note resolution of lesions, especially in the left proximal femur and thoracic spine

Discussion

The combined use of bisphosphonates and bone seeking radiopharmaceuticals is controversial because of a presumed competition of both phosphonate-compounds at the calcified bone matrix level. In the study in which this patient participated competition did not occur [7]. The regimen proved to be feasible and safe.

In the presented case a remission of pain symptoms was observed during the whole treatment period of more than 6 months; PSA blood levels declined significantly and a

decline of metastatic burden was observed by skeletal scintigraphy. The latter is occasionally observed after initiation of anti-androgen treatment but not in the hormone-refractory state. Furthermore a major decrease of bone markers in blood and urine was observed. These markers can be used to evaluate metastatic bone disease [8]. High levels are correlated with a worse prognosis, whereas a decline in bone markers after treatment predicts a favourable outcome [4, 5, 9]. The observed decline in bone markers was greater (all normalized for > 6 months) than what may be expected from treatment with zoledronic acid alone. In a randomized, placebo controlled trial of zoledronic acid as monotherapy (4 or 8 mg versus placebo), serum bone-specific alkaline phosphatase (AP) increased with a mean value of 0.7% compared to baseline (95% CI = -9.9% to 14.3%; maximum decrease -25%) at the end of the study in the 4 mg treatment group (214 patients) [2]. In the presented case AP decreased continuously until -65% compared to baseline at the end of the study. A decrease in AP level has been correlated with improved survival in HRPC [9].

Patients with end stage disease and painful osteoblastic metastases may benefit from combined treatment with bone seeking radiopharmaceuticals. Clinical benefit should be studied in phase II clinical studies. Markers of bone metabolism may prove to be important indicators of an individual response to this combined treatment regimen.

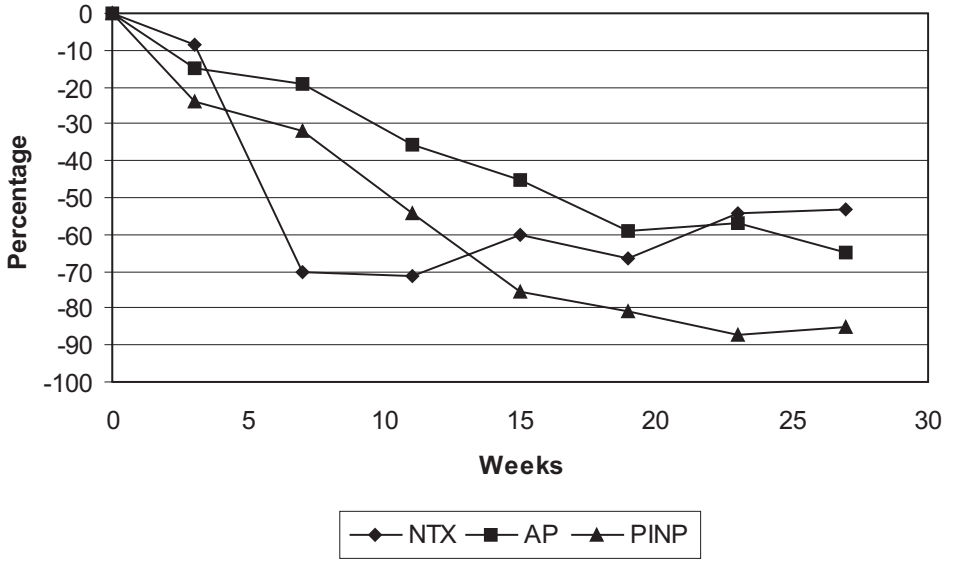

Figure 3 Markers of bone metabolism in blood and urine (serum bone-specific alkaline phosphatase [AP], serum procollagen type 1 N propeptide [PINP], and the urinary N-terminal type 1 collagen peptide [NTX])

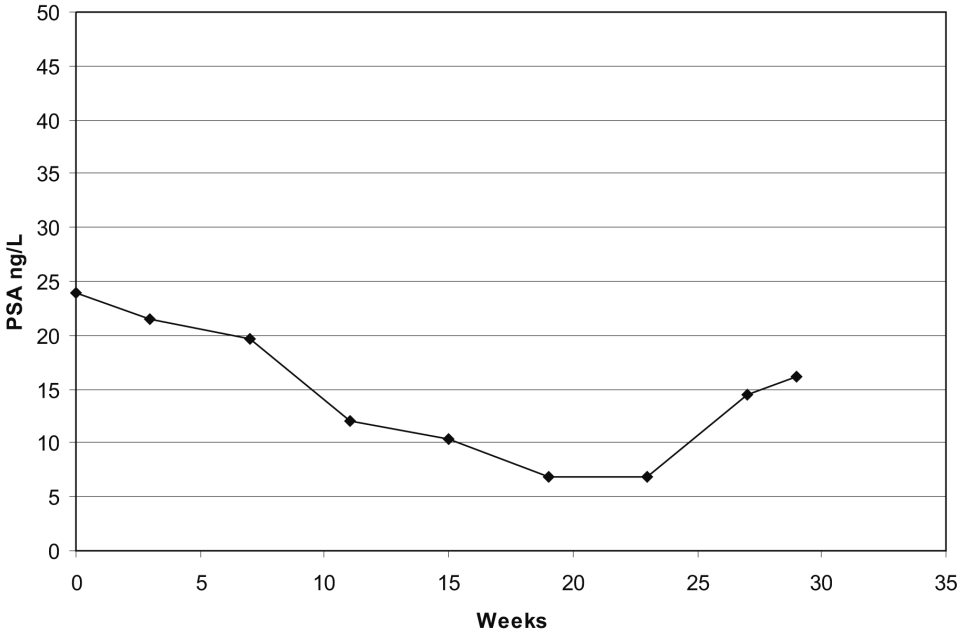

Figure 4 PSA blood levels during the treatment period in ng/L

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Chapter 8

Bone markers may predict response of hormone-refractory prostate cancer skeletal metastases to ^{153}Sm-EDTMP / zoledronic acid treatment

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Abstract

Purpose

The evaluation of the effect of bone seeking radiopharmaceuticals has relied mainly on more or less subjective endpoints such as the multidimensional pain model and quality of life questionnaires. In order to obtain more objective endpoints that correlate well with the subjective endpoints in the palliation of pain caused by skeletal metastases specific bone markers were investigated in a clinical phase 1 study combining ^{153}Sm-EDTMP (Quadramet®) and zoledronic acid (Zometa®) in hormone-refractory prostate cancer patients. Bone marker changes were compared with PSA changes and with clinical effect.

Methods

Patients with hormone-refractory prostate cancer were treated with 18.5 MBq/kg ^{153}Sm-EDTMP in weeks 1 and 3 and with 37 MBq/kg in week 15. Treatment with 4 mg zoledronic acid started at week 3 and continued every 4 weeks through week 23. Clinical response was recorded by EORTC questionnaires. PSA and bone marker levels (bone specific alkaline phosphatase [BAP], procollagen type I N propeptide [PINP], N-terminal type I collagen peptide [NTX]) were measured every 4 weeks. Bone marker changes, PSA changes and clinical effect were compared in week 11 (mid-treatment) and 23 (end-treatment).

Results

12/18 treated patients were evaluable. Median PSA change was +7% in week 11 and +109% in week 23. NTX (-72%; -63%), BAP (-25%; -46%) and PINP (-26%; -43%) values decreased. A significant agreement with clinical effect was found for BAP and PINP changes in week 23. BAP correlated very well with PINP changes, but less with NTX. Bone marker changes did not correlate with PSA changes. BAP decrease was more pronounced than may be expected from mono-therapy with zoledronic acid, further supporting the suitability of bone markers for response monitoring.

Conclusion

Markers of bone metabolism are feasible for response monitoring in radionuclide therapy for metastatic bone disease. A clinical response after treatment with ^{153}Sm-EDTMP and zoledronic acid correlated best with BAP and PINP changes.

Introduction

When solid tumors metastasize to the skeleton, they cause a variety of alterations in bone cell function that may lead to discrete osteolysis, diffuse osteopenia, osteoblastic lesions, or a combination of all of the above. All these effects are caused by the impact of tumor products on the normal bone remodelling sequence. The most common of these lesions is the destructive or osteolytic lesion. Osteolysis is characterized by a marked increase in osteoclast formation and osteoclast activity. There may be a subsequent osteoblastic response, but this is often blunted and sometimes absent. Less commonly, solid tumors cause an increase in osteoblast activity. This may occur without obvious previous resorption; although it may also be associated with prior resorption at the same site, the formation phase may be relatively exaggerated [1]. Depending on the primary malignancy skeletal metastases may be classified as osteolytic (e.g. multiple myeloma), mixed type (e.g. breast carcinoma) or osteoblastic (e.g. prostate carcinoma).

Many of the established prognostic factors for advanced prostate cancer (e.g. performance status, alkaline phosphatase level, and haemoglobin level) reflect the clinical consequences of skeletal metastases. Hence, patients who develop widespread, progressive, or early skeletal metastases tend to suffer more from their symptoms and fare worse [2, 3]. Conversely, patients who develop limited, stable, or delayed skeletal metastases tend to experience less morbidity and have an improved clinical outcome. Conceivably, targeting the relevant skeletal metastases–associated factors will improve therapeutic efficacy [4].

To monitor bone targeted therapy several bone markers were retrospectively tested in clinical studies. Most of these studies were done in hormone-refractory prostate cancer patients treated with the bisphosphonate zoledronic acid. Bone resorption and formation markers proved to be good predictors of skeletal complications and survival [5-10]. However, bone markers were never used as predictor of response in other bone targeted treatments like radionuclide therapy. Moreover, bone markers were never correlated to a clinical response, reflected by a reduction of pain symptoms and improvements in quality of life.

Samarium-153-ethylenediaminetetramethylphosphonic acid (^{153}Sm-EDTMP or ^{153}Sm-lexidronam; Quadramet®) is a radiopharmaceutical compound that has an affinity for skeletal tissue [11]. It targets skeletal metastases by preferential deposition at sites of increased osteoblastic activity and bone matrix synthesis. ^{153}Sm-EDTMP is indicated for the relief of pain in patients with osteoblastic metastatic bone lesions at a dose of 37 MBq/kg (1.0 mCi/kg) [12-14]. With a half-life of 46.3 h, the radioisotope emits a 103-keV gamma ray (29%) for external imaging and beta-radiation (average energy 233 keV) for localized radiotherapy. The average range of emission of the beta-radiation is 1.7 mm in bone, limiting the exposure of bone marrow and other adjacent tissues to radiation [15].

Bisphosphonates bind tightly to the calcified bone matrix and are powerful inhibitors of osteoclast-mediated bone resorption. Zoledronic acid, a relatively new-generation bisphosphonate, exhibits a more potent inhibitory activity of osteoclasts compared with other bisphosphonates [16, 17]. It is indicated for the prevention of skeletal-related Events (i.e. pathological fractures, myelum compression) in patients with advanced malignancies involving bone.

The feasibility and safety of treatment with the bone seeking radiopharmaceutical ^{153}Sm-EDTMP in combination with zoledronic acid was investigated in a clinical study [18]. In this study no competition in uptake at the bone matrix level was found between both phosphonate-based compounds. The combination was feasible and safe. Such combined treatment with ^{153}Sm-EDTMP and zoledronic acid may target osteoblasts and osteoclasts at the same time. The present study used the same combination. Efficacy parameters were recorded as secondary endpoints. These included validated questionnaires for clinical response and measurements of PSA, as well as several markers of bone metabolism.

Although skeletal metastases from prostate cancer are typically described as osteoblastic, these lesions might be more accurately described as mixed with both osteolytic and osteoblastic components from a histo-pathological point of view [1]. Therefore, studying the combined effect of zoledronic acid and ^{153}Sm-EDTMP amongst others by bone markers, this should be done using markers for both osteoblastic and osteolytic activity. Two markers which reflect different aspects of the osteoblastic activity were selected. Serum bone specific alkaline phosphatase (BAP) which is currently the most sensitive and established index of bone formation in patients with prostate cancer and skeletal metastases [19, 20]. And serum aminoterminal propeptide of type I collagen (PINP) which has been shown to be more sensitive than carboxiterminal propeptide of type I collagen (PICP) but with performances similar to BAP in the detection of increased bone turnover in patients with prostate cancer and skeletal metastases [21]. For bone resorption, the urinary aminoterminal telopeptide of type I collagen (NTX) was measured. It was corrected for creatinine excretion. This marker has been shown to be markedly increased in patients with prostate cancer and skeletal metastases and has been used as a primary bone resorption marker in the oncology program of zoledronic acid [17, 22].

The feasibility of these bone markers for response monitoring in the treatment with bone seeking radiopharmaceuticals was investigated in a phase I study. The changes in bone marker levels after combined treatment with zoledronic acid and ^{153}Sm-EDTMP were compared with changes in serum PSA levels and with clinical effects.

Materials and methods

Study population

Patients with histologically documented adenocarcinoma of the prostate, progressive hormone-refractory disease and more than one bone metastasis were included in this open-label prospective study. Other inclusion criteria were a Karnofsky performance status of at least 70%, life expectancy of at least 8 months, age of at least 18 years, and the ability to understand and willingness to sign an informed consent document. Patients receiving bisphosphonate therapy had to discontinue their treatment for at least 3 months prior to study entry. Patients under LH-RH agonists had to continue their treatment. Patients with pathologic long-bone fractures or metastatic involvement of >75% of the ribs, vertebrae, and pelvic bones and patients with known malignancies other than prostate cancer (not including basal cell carcinoma of the skin) were excluded. Other exclusion criteria were chemotherapy (including Estracyt®) within the past 5 years; prior treatment with systemic radiotherapeutic

bone agents; receipt of any other investigational drug within 4 weeks of study entry; previous external radiation therapy (of >25% of the bone marrow within the last 90 days); concomitant treatment with aminoglycosides; clinically significant bleeding disorders; hypersensitivity to phosphonate compounds, mannitol, or zoledronic acid; concurrent illnesses or treatments that might preclude study completion; active CNS or epidural brain metastasis; absolute neutrophil count <2 x 10^9/L; platelet count <150 x 10^9/L; hemoglobin <6.2 mmol/L; serum creatinine >177 µmol/L; or total PSA <5 ng/mL. The study was approved by the local ethical review board, and written informed consent was obtained from all patients.

Treatment

Included patients were treated with 18.5 MBq/kg (0.5 mCi/kg) ^{153}Sm-ethylenediaminetetramethylenephosphonic acid (EDTMP) (Quadramet®; CIS bio International, Saclay, France) in week 1 (mean ± 1 SD: 1606 ± 252 MBq) and week 3 (mean ± 1 SD: 1672 ± 293 MBq) and with 37 MBq/kg (1.0 mCi/kg) ^{153}Sm-EDTMP in week 15 (mean ± 1 SD: 3319 ± 609 MBq). The reason to split the first treatment with ^{153}Sm-EDTMP was to compare biodistribution and pharmacokinetics of ^{153}Sm-EDTMP without (week 1) and with (week 3) zoledronic acid in a phase I setting [4]. For efficacy evaluation the split dose treatments with ^{153}Sm-EDTMP in week 1 and 3 were regarded together as the 'first' treatment with ^{153}Sm-EDTMP and the treatment in week 15 as the 'second' treatment with ^{153}Sm-EDTMP (***Figure 1***).

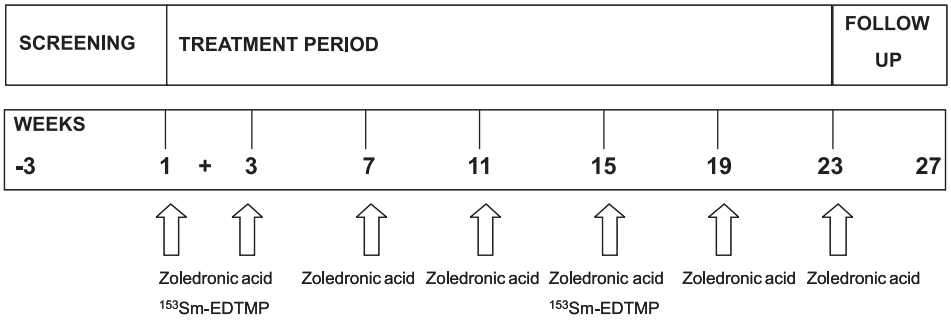

Figure 1 Study treatment regimen. 37 MBq ^{153}Sm-EDTMP in week 1+3 and in week 15. 4 mg zoledronic acid i.v. in week 3, 7, 11, 15, 19 and 23

Treatment with 4 mg zoledronic acid (Zometa®; Novartis, Stein, Switzerland) every 4 weeks started in week 3 and continued through week 23 (6 treatments total). In weeks 3 and 15, zoledronic acid was administered 2 days (48 h) before ^{153}Sm-EDTMP treatment.

Efficacy parameters

Patients filled out validated questionnaires (EORTC QLQ-C30 version 3.0) at baseline and in week 11, being 8 weeks after the first treatment with ^{153}Sm-EDTMP, and in week 23, being 8 weeks after the second treatment with ^{153}Sm-EDTMP. Weeks 11 and 23 were chosen for evaluation of clinical response mid-treatment and at the end of the treatment respectively. These questionnaires were developed by the European Organization for Research and

Treatment of Cancer (EORTC) and validated in many clinical trials [23]. They include questions on global health status / quality of life, functional scales and symptom scales. The functional scales are subdivided in physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning. The symptom scales are subdivided in fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties. Each domain was scored on a scale of 0 – 100, according to the EORTC scoring manual [24]. Changes of scores in time were defined as no clinical effect (-5 to +5), little (5 – 10), moderate (10 – 20) or large (20 – 30) clinical effect for better or for worse. The clinical relevance of the magnitude of these changes was validated in oncology patients. Not a statistical significant change but rather the proposed absolute changes correlated well with clinical status [25]. A clinical response for each separate domain was defined as stable or any clinical improvement. Serum bone specific alkaline phosphatase (BAP) and serum N-terminal propeptide of type I collagen (PINP) were measured as markers of bone formation. For bone resorption, the N-terminal telopeptide of type I collagen (NTX) was measured. It was corrected for creatinine excretion. These 3 markers were measured at baseline and in week 3, 7, 11, 15, 19, and 23. At the same time points total serum PSA levels were measured.
Serum BAP was measured by an immunochimiluminiscence assay using the Ostase reagent on an automatic analyzer (Beckman Coulter Inc., Fullerton, USA). Serum PINP was measured by a competitive immunoradiometric assay using the intact PINP (^{125}I) RIA kit (Orion Diagnostica, Espoo, Finland). Urinary creatinine corrected NTX was measured by ELISA using the Osteomark assay (Osrex Inc., Seattle, USA).

Analysis

The bone marker changes (in percentage from baseline) were correlated with the changes in PSA levels and with one another using Pearson's bivariate correlation-coefficient for continuous variables (R). The hypothesis 'no correlation' versus the alternative hypothesis 'significant correlation' was tested using the students' t-test (1-tailed). The clinical effect was correlated to changes in bone marker levels and PSA levels. Clinical effect was analysed for each separate domain of the EORTC questionnaires. Clinical response was defined as stable or any improvement (see above). PSA and bone marker responses were defined with a cut off level of > 50% decrease. The agreement between a clinical response and a PSA or bone marker response was defined as: the number of patients with no clinical response and no change in PSA / bone markers plus the number of patients with a clinical response and with a change in PSA / bone markers. This was done mid-treatment (week 11) and at the end of treatment (week 23). Kappa-coefficient was used as a measurement of agreement between two tests for response (95%-confidence interval). It was used as a chance-corrected proportional agreement between clinical effect and PSA / bone marker changes.

Results

A total of 20 patients were enrolled in this study. Two patients were not treated because of low platelet counts at baseline. One patient was withdrawn because of decreasing PSA level after the start of anti-androgen treatment. Among the 17 patients who entered the treatment

period, 12 completed both the treatment period and the study course up to 23 weeks after the start of treatment. Two patients were withdrawn because of adverse events (increase in creatinine level, disseminated intravascular coagulation), three patients were recommended to start with radiotherapy or chemotherapy because of progressive disease before week 23. After a total follow up of 54 months only 1 patient was still alive. All 12 evaluable patients were Caucasian with a mean age of 69 years (range 57–77). The median survival of these 12 patients was 25 months (range 13 – 54).

EORTC questionnaires were filled out up to week 23. The reported changes showed quite a variation from significant improvement to significant progression. ***Table 1*** shows the changes in scores and scales for the different domains. It shows the number of patients categorized to clinical effect in week 11 compared to baseline (being 8 weeks after the first treatments with ^{153}Sm-EDTMP).

Table 1 Number of patients with a clinical effect mid-treatment (week 11) compared to baseline [a]

	Improvement			Stable	Progressive disease		
Quality of Life Domain	**Very much [b]**	**Moderate**	**Little**	**Stable**	**Little**	**Moderate**	**Very much**
Global health status							
General health status / Quality of Life	3		3	3	1	1	1
Functional scales							
Physical functioning	1	1	3	2	1	2	2
Role functioning	2	1		5		3	1
Emotional functioning	2	2	1	3	2	1	1
Cognitive functioning		3		7		2	
Social functioning	1	1		9		1	
Symptom scales							
Pain	3	1		4		3	1
Fatigue				7		3	0
Nausea and vomiting				10		1	1
Single items	+3 [c]	+2	+1	0	-1	-2	-3
Dyspnoea		1		9	1	1	
Insomnia		1	1	9		1	
Appetite loss			1	11			
Constipation			1	10	1		
Diarrhoea			2	10			
Financial difficulties			1	10	1		

a EORTC QLQ-C30 version 3.0; 12 evaluable patients

b Clinical effect (improvement or progression) is classified as little (5-10), moderate (10-20) or very much (>20) [14]. These numbers are changes in EORTC questionnaires scores, graded from 0-100

c Single items were scored on a 4 point scale (not at all; little; quite a bit; very much). Changes are given

Table 2 shows the clinical effect in week 23 compared to baseline (being 8 weeks after the second treatment with 153Sm-EDTMP). Changes of response scores were defined as stable clinical effect (-5 to +5), little (5 – 10), moderate (10 – 20) or large (20 – 30) clinical effect.

These numbers give a good reflection of the clinical response during the treatment period of 23 weeks. The reported pain response (3 patients had very much improvement, 1 intermediate improvement and 4 were stable) correlated well with changes in the other domains, except for fatigue, nausea and vomiting. The latter domains showed some progression during the treatment period without any improvements. Most interesting however is the observation that most patients who showed a clinical response in week 11 still experienced a clinical response in week 23. With regard to the single items most patients remained stable or experienced little changes.

Table 2 Number of patients with a clinical effect end-treatment (week 23) compared to baseline [a]

	Improvement			Stable	Progressive disease		
Quality of Life Domain	**Very much [b]**	**Moderate**	**Little**	**Stable**	**Little**	**Moderate**	**Very much**
Global health status							
General health status / Quality of Life	2	1	1	4	1	2	1
Functional scales							
Physical functioning		2	2	1	3	2	2
Role functioning	3	1		4	1	3	1
Emotional functioning		3	1	4	1		3
Cognitive functioning		1	1	5		3	3
Social functioning		3		6		1	2
Symptom scales							
Pain	3	1		4		2	2
Fatigue				6		1	5
Nausea and vomiting				9		3	
Single items	+3 [c]	+2	+1	0	-1	-2	-3
Dyspnoea			2	8	2	2	
Insomnia		1	2	5	4		
Appetite loss				8	3	1	
Constipation				8	2	2	
Diarrhoea				11			1
Financial difficulties			1	9	2		

a EORTC QLQ-C30 version 3.0; 12 evaluable patients

b Clinical effect (improvement or progression) is classified as little (5-10), moderate (10-20) or very much (>20) [14]. These numbers are changes in EORTC questionnaires scores, graded from 0-100

c Single items were scored on a 4 point scale (not at all; little; quite a bit; very much). Changes are given

Baseline levels of total PSA measured before administration of the study drugs ranged from 15 to 2400 ng/mL. Of the 12 patients, 6 had baseline levels < 50 ng/mL, and 6 had baseline levels > 50 ng/mL. The median change in week 11 compared to baseline was +7% (range -50% to +157%), and in week 23 compared to baseline +109% (range -71% to +384%). Only three patients showed a durable PSA decline of > 25% during the whole treatment period and only 1 patient > 50% (***Figure 2***).

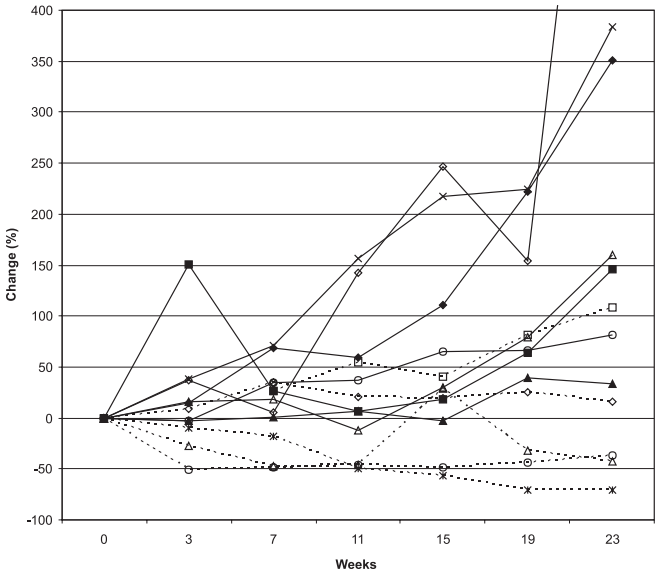

Figure 2 Changes in serum PSA levels for individual patients. Patients with a dotted line were patients with > 50% bone marker decrease

Baseline levels of urinary NTX ranged from 43 to 143 nmol/mmol creatinine (normal values 21 – 83 nmol/mmol creatinine). Of the 12 patients, 6 had normal baseline levels, and 6 had baseline levels > 83 nmol/mmol creatinine. Urinary NTX (corrected for creatinine excretion) showed a median decrease of -72% (range -84% to -48%) in week 11 compared to baseline, and a median decrease of -63% (range -90% to -39%) in week 23 compared to baseline (***Figure 3***).

Baseline levels of serum BAP ranged from 12 to 128 ng/mL (normal values 6.3 – 23.8 ng/mL). Of the 12 patients, 4 had normal baseline levels, and 8 had baseline levels > 23.8 ng/mL. Serum BAP showed a progressive decrease with a median decrease of -25% (range -80% to +22%) in week 11 compared to baseline, and a median decrease of -46% (range -84% to +199%) in week 23 compared to baseline (***Figure 4***).

Baseline levels of serum PINP ranged from 56 to 386 ng/mL (normal values 17.8 – 66.6 ng/mL). Of the 12 patients, 3 had normal baseline levels, and 9 had baseline levels > 66.6 ng/mL. Serum PINP also decreased progressively with a median decrease of -26% (range -88% to +84%) in week 11 compared to baseline, and a median decrease of -43% (range -94% to +163%) in week 23 compared to baseline (***Figure 5***).

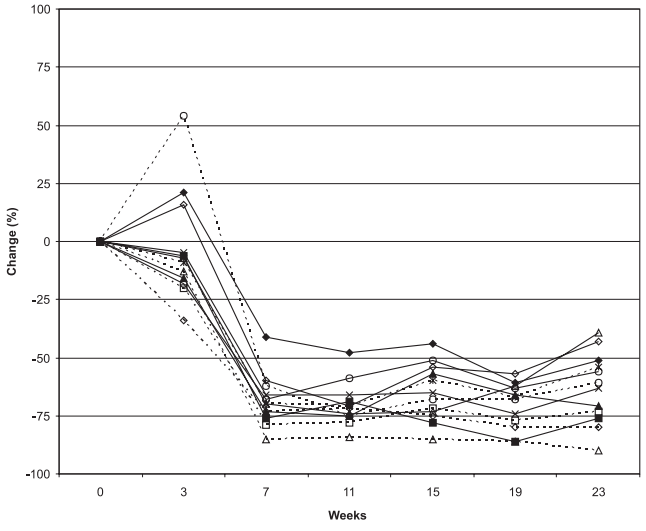

Figure 3 Changes in urinary N-terminal type I collagen peptide (NTX) corrected for creatinine excretion for individual patients. Patients with a dotted line were patients with > 50% bone marker decrease

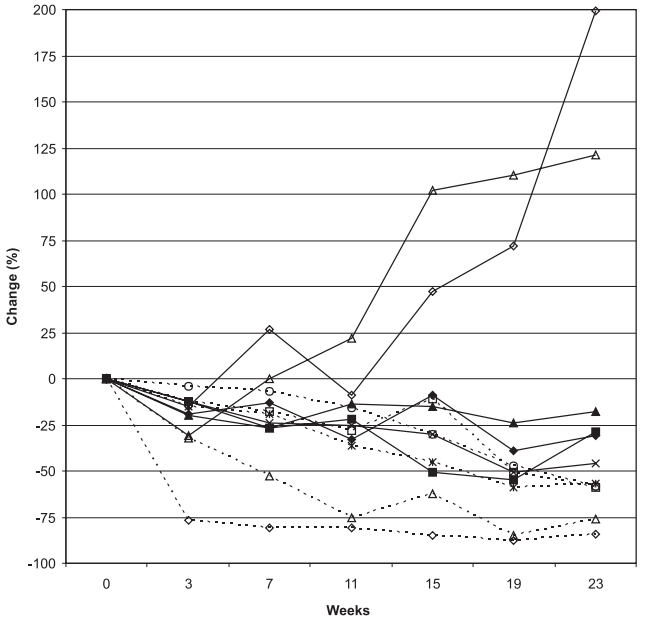

Figure 4 Changes in serum bone specific alkaline phosphatase (BAP) for individual patients. Patients with a dotted line were patients with > 50% bone marker decrease

The changes from baseline of PSA levels were correlated with the changes from baseline of the various bone markers. No correlation was found between PSA and bone marker changes in week 11 and 23. The changes from baseline of the bone resorption marker NTX did not correlate with those of the bone formation markers BAP nor PINP in week 11, but did correlate with BAP ($R = 0.72$; $p = 0.01$) and PINP ($R = 0.74$; $p = 0.01$) in week 23. The changes from baseline of BAP correlated very well with those of PINP in week 11 ($R = 0.83$; $p = 0.001$) and in week 23 ($R = 0.91$; $p < 0.001$). BAP and PINP are both bone formation markers.

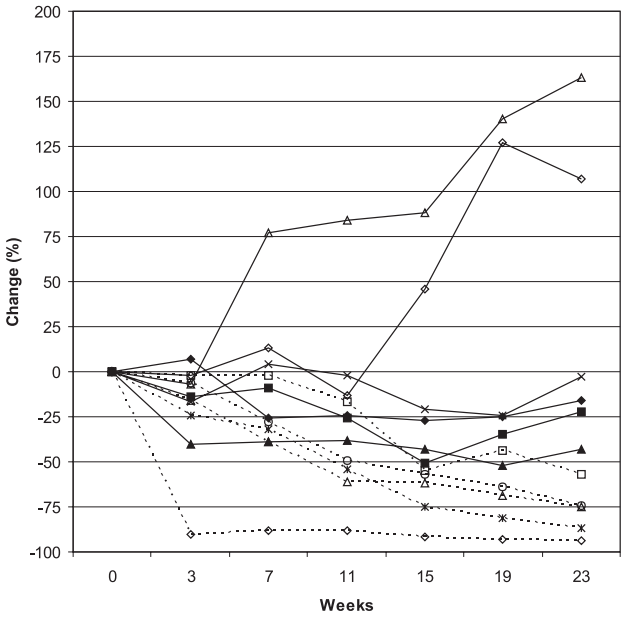

Figure 5 Changes in serum procollagen type I N propeptide (PINP) for individual patients. Patients with a dotted line were patients with > 50% bone marker decrease

The clinical effect reported by each patient was also correlated with PSA and bone marker changes. A decrease of > 50% in PSA or bone marker levels from baseline was used as a cut off value for the prediction of clinical response. The absolute number of patients for whom agreement was found (> 50% decrease together with a clinical response, plus < 50% decrease together with no clinical response) was reported. This was done mid-treatment (week 11: ***Table 3***) and at the end of treatment (week 23: ***Table 4***). Mid-treatment no significant agreement between bone marker / PSA changes and clinical effect was found (***Table 3***). However, at the end of treatment in week 23 a better agreement between clinical effect and changes in bone markers was found, especially for the bone formation markers serum BAP and serum PINP. Significant agreement was found between changes in BAP or PINP (cut off 50%) and clinical effects (EORTC questionnaires). Changes in PSA and NTX showed no agreement with clinical effects. Furthermore the agreement was only found in week 23. No agreement was found between clinical response and normal bone marker levels at baseline, nor relatively low PSA levels (< 50 ng/mL).

Table 3 Number of patients with agreement between PSA or bone markers and clinical effects: week 11 [a]

	PSA	BAP	PINP	NTX
Decrease from baseline [b]	**> 50%**	**> 50%**	**> 50%**	**> 50%**
Global health status response				
General health status / Quality of Life	5	5	6	9*
Functional scales response				
Physical functioning	7	7	6	7
Role functioning	7	7	8	7
Emotional functioning	6	6	7	8
Cognitive functioning	4	5	6	8
Social functioning	4	5	4	8
Symptom scales response				
Pain	6	7	8	6

a mid-treatment: 8 weeks after the first treatment with ^{153}Sm-EDTMP (week 11)

b > 50% decrease from baseline was used to discriminate clinical effect: yes or no. Clinical effect was defined as stable or any improvement according to ***Table 1***

***** P < 0.05, using Kappa co-efficient for chance corrected measurement of agreement between two tests

Table 4 Number of patients with agreement between PSA or bone markers and clinical effects: week 23 [a]

	PSA	BAP	PINP	NTX
Decrease from baseline [b]	**> 50%**	**> 50%**	**> 50%**	**> 50%**
Global health status response				
General health status / Quality of Life	6	9*	9*	7
Functional scales response				
Physical functioning	6	9*	9*	7
Role functioning	7	10*	10*	6
Emotional functioning	6	9*	9*	7
Cognitive functioning	7	10*	10*	6
Social functioning	7	10*	10*	6
Symptom scales response				
Pain	6	9*	9*	7

a end-treatment: 8 weeks after the second treatment with ^{153}Sm-EDTMP (week 23)

b > 50% decrease from baseline was used to discriminate clinical effect: yes or no. Clinical effect was defined as stable or any improvement according to ***Table 2***

***** P < 0.05, using Kappa co-efficient for chance corrected measurement of agreement between two tests

Discussion

A vast majority of patients with hormone-refractory prostate carcinoma suffer from skeletal metastases. In most patients pain is their major complain [26]. It causes high morbidity and is often difficult to treat. Many treatment modalities aim for an improvement of pain symptoms. In hormone-refractory prostate cancer patients with painful skeletal metastases a multimodality treatment approach has been advocated. Early studies show a beneficial effect of combined treatment regimens [27-29]. Combined multimodality treatment may lead to

improvements in palliative care [30]. Therefore, many new combinations are being tested [4].

Parameters for efficacy may be difficult to define as most treatment regimens are palliative in nature. Clinical benefit is best described as an improvement in pain symptoms. But pain is a soft endpoint. It is multidimensional, heterogeneous, fluctuates in time and it is subjective [31, 32]. In an effort to capture these different factors several techniques have been used including a physician's clinical assessment (based on anamnesis and physical examination), medication scores and visual analogue scales (VAS). Even daily pain diaries have been used to evaluate response [33]. Nevertheless, clinical validation of these techniques is mostly lacking. That is why the EORTC developed questionnaires for clinical response monitoring in oncology that were validated in large clinical series [23]. In the present study these questionnaires were used to monitor clinical effect mid-treatment and at the end of treatment.

PSA may be used in hormone-refractory prostate cancer for response monitoring. The majority of the clinical studies in this patient category uses a PSA response to monitor efficacy [34]. A 50% decline in PSA levels is most commonly used. This criterion seems to correlate with survival [35]. It does however not correlate very well with clinical benefit [34]. Better predictors of response are clearly warranted.

The recent identification of specific and sensitive biochemical markers reflecting the overall rate of bone formation and bone resorption has improved the non-invasive assessment of bone turnover abnormalities in patients with prostate cancer. Several studies have shown a rapid decrease in bone resorption markers in patients with prostate cancer and skeletal metastases after treatment with bisphosphonates. It has been reported that the magnitude of the decrease correlated with the efficacy of the treatment. High levels were correlated with a worse prognosis, whereas a decline in bone markers after treatment predicted a favourable outcome [5-7, 9, 10, 36]. In hormone-refractory prostate carcinoma bone markers were almost exclusively tested in the treatment with bisphosphonates.

The reported data on the efficacy of zoledronic acid combined with ^{153}Sm-EDTMP are the first efficacy data on this combined treatment regimen available in the literature. Multiple treatments with ^{153}Sm-EDTMP were combined with multiple treatments with zoledronic acid over a long treatment period of circa 6 months. Approximately 67% (8/12) of the patients showed a response with regard to pain and quality of life. The question is how to identify these patients? In this study we tested the diagnostic performance of bone markers for response monitoring in radionuclide therapy for metastatic bone pain. This has not been done before in radionuclide therapy. Clinical response was assessed with validated EORTC questionnaires and compared to changes in bone marker and PSA levels. The correlation between PSA and bone marker changes was also tested.

The bone formation markers serum BAP and serum PINP correlated very well with one another. They correlated to NTX to some extent (only in week 23) and not at all with PSA levels. It is well known that PSA does not correlate very well with clinical outcome [34]. In contrast to PSA and urinary NTX, changes in BAP and PINP were better in agreement with the clinical response of individual patients. Patients with a decrease in BAP and PINP levels of at least 50% showed a positive clinical effect with regard to pain and quality of life. This was only observed in week 23 at the end of treatment. Maybe the effect of treatment had to be durable over a longer period of time to be able to discriminate between a positive and

negative clinical effect. No agreement between PSA changes and clinical effect was found. This may be attributed to the fact that this treatment is targeted to skeletal metastases only. PSA producing soft tissue lesions will not be affected. Like PSA, no agreement between NTX and clinical effect was observed. Bone formation markers (BAP and PINP) may be better indicators of a post-treatment effect because they reflect the extent of osteoblastic skeletal disease in prostate cancer patients. The effect of treatment on osteoblastic metastases may be better evaluated with a bone formation marker. Changes in bone formation markers may therefore be better in agreement with clinical effect. Another factor that may explain the differences between NTX and BAP / PINP may be the variation between patients. All patients showed a strong decrease in urinary NTX corrected to creatinine. This lowers the discriminative potential. PINP and BAP showed larger inter-patient variability. They may therefore be better discriminators than creatinine corrected NTX (***Figure 3 – 5***). Bone markers as predictors of response after bone seeking radiopharmaceuticals are feasible and should be the subject of further research with larger patient numbers.

Markers of bone metabolism were also used in a randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory prostate carcinoma [17]. Patients were treated with 4 mg zoledronic acid (N=214), 8 mg zoledronic acid (N=221) or placebo (N=208) every 3 weeks. Urinary creatinine-corrected NTX and serum BAP were measured every 3 months. Urinary NTX, a measure of bone resorption, decreased approximately 70% within 1 month after treatment with zoledronic acid at 4 mg (95% confidence interval -72.6% to -66.3%) or at 8 mg (95% confidence interval -75.9% to -69.5%) and remained suppressed. Serum bone alkaline phosphatase, a measure of bone formation activity by osteoblasts, increased significantly more by the end of the study in patients who received the placebo (+33.7%, 95% confidence interval +21.1% to +56.3%) than in patients who received zoledronic acid at 4 mg (+0.7%, 95% confidence interval -9.9% to +14.3%; p = 0.001) or at 8 mg (+5.6%, 95% confidence interval -7.8% to +24.1%; p = 0.003). The observed decrease during the first 6 months was circa 25% [17]. In the present study serum BAP decreased, with a median reduction of 25% at week 11, comparable to the results of zoledronic acid as monotherapy [17]. However, an additional 25% decrease in BAP was observed after administration of the second dose of ^{153}Sm-EDTMP in week 15, leading to a median decrease of 46% from baseline in week 23. This was not observed in hormone-refractory prostate cancer patients treated with zoledronic acid as monotherapy [17]. The median 46% decrease, observed in the present study, may be attributed to an additive effect of ^{153}Sm-EDTMP. Besides that, all bone markers started to decrease after the start of treatment with ^{153}Sm-EDTMP (i.e. before treatment with zoledronic acid). The latter further supports the hypothesis of an additive effect of both pharmaceuticals. Urinary NTX excretion showed an expected 70% decrease after the start of treatment. This is consistent with the expected decrease after treatment with zoledronic acid (4 mg i.v.) as monotherapy [17]. No differences in NTX decrease were found between the present study and literature data. These observations, especially those on BAP, further support the feasibility of bone markers for response monitoring in radionuclide therapy combined with bisphosphonates.

Conclusion

Markers of bone metabolism are suitable for response monitoring in the treatment of hormone-refractory prostate cancer patients with zoledronic acid in combination with ^{153}Sm-EDTMP. They may prove to be good predictors of response, especially the bone formation markers BAP and PINP. They perform better than PSA and may be used to evaluate the additive effect of radionuclide therapy in multimodality treatments. They should be further tested in clinical trials on bone seeking radiopharmaceuticals.

Acknowledgements

We thank Tjitske B. Bosma for her input and Dr. Jos P.M. Wielders for critical reading of the manuscript.

Conflict of interest

This study was financially supported by CIS bio International, Saclay, France. Zoledronic acid was kindly provided by Novartis, Stein, Switzerland.

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Chapter 9

^{188}Re-HEDP combined with capecitabine in hormone-refractory prostate cancer patients with bone metastases; a phase 1 safety and toxicity study

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Abstract

Purpose

^{188}Re-HEDP is indicated for the treatment of pain in patients with painful osteoblastic bone metastases, including hormone-refractory prostate cancer patients. Efficacy may be improved by adding chemotherapy to the treatment regimen as a radiation sensitizer. The combination of ^{188}Re-HEDP and capecitabine (Xeloda®) was tested in a clinical phase I study.

Methods

Patients with hormone-refractory prostate cancer were treated with capecitabine for 14 days (oral twice daily in a dose-escalation regimen with steps of 1/3 of 2500 mg/m^2/day in cohorts of 3-6 patients, depending on toxicity). Two days later patients were treated with 37 MBq/kg ^{188}Re-HEDP as an intravenous injection. Six hours after treatment post-therapy scintigraphy was performed. Urine was collected for 8 hours post injection. Follow up was at least 8 weeks. The primary endpoint was to establish the maximum tolerable dose (MTD) of capecitabine when combined with ^{188}Re-HEDP. Secondary endpoints included the effect of capecitabine on the biodistribution and pharmacokinetics of ^{188}Re-HEDP.

Results

Three patients were treated in the first and second cohort, each without unacceptable toxicity. One out of six patients in the highest cohort experienced unacceptable toxicity (grade 4 trombopenia). The MTD proved to be the maximum dose of 2500 mg/m^2/day capecitabine. No unexpected toxicity occurred. Capecitabine had no effect on uptake nor excretion of ^{188}Re-HEDP.

Conclusion

Capecitabine may be safely used in combination with ^{188}Re-HEDP in a dose of 2500 mg/m^2/day and 37 MBq/kg respectively. Efficacy will be further studied in a phase II study using these dosages.

Introduction

The majority of patients with hormone-refractory prostate cancer have, or will have, osseous metastases in the course of their disease [1]. Treatment with bone seeking radiopharmaceuticals may be indicated when they experience refractory bone pain at multiple sites. Bone seeking radiopharmaceuticals decrease pain and improve the patients' quality of life [2]. This effect may be increased by concomitant use of chemotherapy, used as a radiation sensitizer. Some studies show promising results on the use of chemotherapy as a radiation sensitizer for bone seeking radiopharmaceuticals, but evidence is still low [3-5]. However, it is clear that multimodality treatment may enhance efficacy and may lead us beyond palliation alone towards improvement of survival [6]. In the present study the combination of the bone seeking radiopharmaceutical ^{188}Re-HEDP and capecitabine chemotherapy was studied in a phase I setting.

Rhenium-188-hydroxyethylidene-1,1-diphosphonic acid (^{188}Re-HEDP) is a relatively new and attractive radiopharmaceutical for the treatment of metastatic bone pain. It has an affinity for skeletal tissue and concentrates in areas of bone turnover secondary to invasion by tumor. As a product of a ^{188}W / ^{188}Re generator, it is convenient for clinical therapeutic use, because of on demand use at relatively low costs. The radioisotope, with a half-life of 16.9 hours, emits a 155 keV gamma ray (15%) for external imaging and a number of beta particles ($E_{ß\ max}$ 2.12 MeV; $E_{ß\ mean}$ 0.76 MeV) for localized radiotherapy [7, 8]. Therapy with ^{188}Re-HEDP results in symptomatic relief of bone pain in approximately 70 – 80% of treated patients. ^{188}Re-HEDP is an effective and well tolerated treatment in the management of metastatic bone pain [9-12].Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine which is converted to 5-fluorouracil (5-FU) inside the tumor cell by thymidine phosphorylase. 5-FU is metabolized to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N-5-10-methylenetetrahydrofolate, bind to thymidylate synthase to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis [13, 14].

5-FU has been long used as a radiation sensitizer. Within a few years of the discovery of 5-FU, radiation sensitization by 5-FU was used in clinical trials. Improved survival and local control with acceptable toxicity profiles was shown in cancers of the esophagus, anus and rectum [15, 16]. 5-FU chemoradiation schedules were optimized and oral 5-FU analogs that may be substituted for intravenous administration were developed. The sensitizing effects of 5-FU in vitro are maximal when exposure to 5-FU occurs for at least 24 hours and up to 48 hours after the radiation exposure, supporting the use of continuous infusion or oral 5-FU analogs instead of bolus intravenous administration [17]. Capecitabine (Xeloda®) can be administered orally, resulting in continuous high levels of active FU. In contrast to 5-FU, capecitabine has

an improved therapeutic to toxicity index, because it is metabolized to cytotoxic 5-FU in the target cell by way of thymidine phosphorylase. Measuring the activity of thymidine phosphorylase in normal and cancerous prostatic tissue has shown significantly higher levels in cancerous tissue, making capecitabine a potentially more active agent against prostate cancer than 5-FU [18, 19]. Compared to oral 5-FU prodrugs, protracted venous infusion is costly, inconvenient and has a risk of central line maintenance. Capecitabine is currently used as a radiation sensitizer in several cancer types, like advanced colorectal cancer patients and pancreatic cancer [16, 20].

Radiation sensitization by capecitabine in hormone-refractory prostate cancer patients has never been described. Like in other cancer types, it could lead to enhancement of the radiation effect in prostate cancer [14]. This radiation sensitizing effect of capecitabine could enhance the palliative effect of treatment with the bone seeking radiopharmaceutical ^{188}Re-HEDP. The primary aim of this phase I study was to establish the safety and toxicity profile and to determine the maximum tolerated dose of capecitabine combined with ^{188}Re-HEDP. Secondary endpoints included the effect of capecitabine on the biodistribution and pharmacokinetics of ^{188}Re-HEDP.

Materials and methods

Study population

Patients with histologically documented adenocarcinoma of the prostate, progressive hormone-refractory disease, and more than one painful bone metastasis (^{99m}Tc-HDP-scintigraphy within 8 weeks prior to screening) were included in this open-label prospective phase I study. Other inclusion criteria were a Karnofsky performance score of at least 60%, life expectancy of at least 3 months, age of at least 18 years, and the ability to understand and willingness to sign an informed consent document. Patients receiving bisphosphonate therapy had to discontinue their treatment for at least 2 weeks prior to study entry, and patients under LH-RH agonists (and/or anti-androgens) had to continue their treatment. Patients with pathologic long-bone fractures or clinical evident spinal cord compression and patients with known malignancies other than prostate cancer (not including basal cell carcinoma of the skin) were excluded. Other exclusion criteria were chemotherapy (including Estracyt®) within 6 weeks prior to screening; prior treatment with systemic radiotherapeutic bone agents within 3 months (6 months for ^{89}Sr); receipt of any other investigational drug within 4 weeks of study entry; previous hemi-body external radiation therapy (for >25% of the bone marrow within 6 months); concomitant treatment with interferon-alfa, allopurinol, sorivudine and folinic acid; clinically significant bleeding disorders; disseminated intravascular coagulation; hypersensitivity to phosphonate compounds or 5-FU; known deficiency of dihydropyrimidine dehydrogenase; concurrent illnesses or treatments that might preclude study completion; active CNS or epidural brain metastasis; absolute neutrophil count < 2 x 10^9/L; platelet count < 150 x 10^9/L; hemoglobin < 6.0 mmol/L; serum creatinine clearance < 50 mL/min (Cockroft and Gault); bilirubin > 1.5 upper limit of normal; AST/ALT > 2.5 upper limit of normal; or total PSA < 5 ng/mL. The study was approved by the local ethics committee, and written informed consent was obtained from all patients.

^{188}Re-HEDP

^{188}Re was obtained from an alumina-based ^{188}W / ^{188}Re-generator on site. The ^{188}W was produced by double-neutron capture of ^{186}W. Elution of the ^{188}W / ^{188}Re-generator with 3 mL normal saline provided solutions of carrier-free ^{188}Re sodium perrhenate ($NaReO_4$). High-performance liquid chromatographic (HPLC) analysis revealed that the ^{188}Re eluate was > 99% perrhenate [7]. ^{188}W / ^{188}Re-generators have demonstrated consistently high ^{188}Re yields and low parent breakthrough for periods of at least 2 months.
A HEDP (hydroxyethylidene-1,1-diphosphonic acid) vial contained exactly 15 mg of Na_2HEDP, 4.5 mg Sn_2Cl-$2H_2O$, 4.0 mg of gentisinic acid 98% and 0.1mg NH_4ReO_4. A second vial contained a sodium acetate trihydrate solution of 41 mg/ml in aqua distillate (0,3 M). After preparation the HEDP kit was immediately stored at –20 C°. To make ^{188}Re-HEDP, 1.0 ml NH_4ReO_4 solution (containing 0.01-0.1 mg of NH_4ReO_4) and 1ml $^{188}ReO_{4-}$ was added to the kit vial. The whole mixture was heated for 20 minutes in a heating block at 120 C°, and allowed to cool to room temperature for 10 minutes. Another 1 mL of 0.3 M sodium acetate trihydrate solution was added to adjust the pH range to 5 – 6. The radiochemical purity of ^{188}Re-HEDP was determined by the instant thin-layer chromatographic (ITLC) technique [7].

Treatment

Cohorts of three successive patients were treated with a combination of capecitabine (Xeloda®; Roche, Woerden, The Netherlands) and ^{188}Re-HEDP. Capecitabine treatment started 48 hours before ^{188}Re-HEDP administration. The first cohort was treated with 1/3 x 2500 mg/m^2 / day capecitabine, followed by a weight related dose of 37 MBq/kg body weight ^{188}Re-HEDP. Capecitabine was administered in twice daily doses for 14 days. Escalation of administered doses capecitabine were implemented in increments of 1/3 x 2500 mg/m^2 /day to a maximum dose of 2500 mg/m^2 /day capecitabine (the maximum recommended dose for metastatic breast and colorectal cancer). Follow up lasted for 8 weeks with weekly blood samples and 4 weekly history taken and physical exam.
Patients were hospitalized for 8 hours after ^{188}Re-HEDP administration. Urine was collected during the 8 hours following injection of ^{188}Re-HEDP. Whole-body images were captured with a dual-head gamma camera at 6 hours post-injection (anterior and posterior; 10% energy window around the peak of 155 keV, medium energy collimator, scan speed 6 cm per min.).

Analysis

If one dose limiting toxicity (DLT) would occur in the cohort of 3 patients then the cohort would increase to 6 patients. If a maximum of 1 out of 6 patients would have had a DLT then the next cohort would have been tested. If at least 2 out of 6 patients would have had a DLT then the maximum tolerated dose (MTD; i.e. the dosage level of the previous cohort) would have been reached. At least 6 patients were treated in the final MTD group.
Any of the following events which were considered possibly or probably related to the administration of capecitabine, ^{188}Re-HEDP or a combination of those were considered a DLT during the 8 weeks of follow-up (using National Cancer Institute (NCI), Common Terminology for Adverse Events version 3.0): grade 3 – 4 neutropenic infection (ANC < 1.0 x 10^9/L) with fever

> 38.3 °C; grade 4 neutropenia lasting > 7 days; grade 4 thrombocytopenia (platelet count < 25 x 10^9/L), grade 3 thrombocytopenia lasting for > 7 days; any non-hematologic grade 3 or 4 toxicity possibly related to study medication; grade 3 – 5 nausea, vomiting, mucositis, fatigue, tearing, nail disturbance, alopecia, or diarrhea; any life threatening event possibly related to the study drug. Disease progression was not considered a DLT event.
Secondary end-points were the evaluation of pharmacokinetics and biodistribution of ^{188}Re-HEDP when combined with capecitabine. Post-treatment scintigraphy was compared with pre-treatment ^{99m}Tc-HDP-scintigraphy performed within 8 weeks of study entry. Regions of interest (ROI analysis) were used to calculate lesion-to-normal-bone ratio's (geometric mean corrected for soft tissue uptake and background). The mean counts per pixel calculated over 3 metastases were used as lesion value, the mean counts per pixel for a ROI over the femur was used as normal bone value. The same ROI's were used for post- and pre-treatment scans in the same patient.
Urinary excretion of activity was measured during the first 8 hours after treatment and compared to literature values of ^{188}Re-HEDP as mono-therapy. Pooled urine samples were collected from 0-4 hours and 4-8 hours following ^{188}Re-HEDP administration. The amount of activity in these samples was determined by measurement of 15-mL, non-diluted samples with a dose calibrator. For comparison with the administered activity, the exact injected dose was determined by measurement of the syringe before and after administration. This procedure enabled determination of the amount of activity excreted and, as a corollary, the relative amount of activity retained within the body.
The extent of osteoblastic bone disease was determined using the bone scan index as described by Blake et al [21]. The skeleton was divided into four anatomical regions: (1) spine and skull; (2) pelvis; (3) shoulder girdle and ribs; and (4) extremities. Each region was scored visually on a scale of 0 to 10 for the apparent proportion of skeleton involved. Scores for each region are summed, and the sum was normalized to a scale of 0 to 100 as an index for the extent of skeletal involvement.

Statistical methods

Descriptive statistics (n, mean, standard deviation [SD], minimum, and maximum) were calculated for quantitative variables; frequency counts by category were determined for qualitative variables.
The bone scan index was correlated with the excreted activity in urine using Pearson's bivariate correlation-coefficient for continuous variables (R). The hypothesis 'no correlation' versus the alternative hypothesis 'significant correlation' was tested using the students' t-test (1-tailed).

Results

A total of 17 patients were enrolled in this study. Five patients were excluded after screening because 1 patient withdrew consent before the start of treatment (because of to much visits to the hospital), 3 patients had trombocyte levels < 150 x 10^9/L and 1 patient had rapidly progressive disease with a Karnofsky performance score < 60% before the start of treatment. All 12 treated patients were included in the safety and toxicity analysis (the primary end-

point). All 12 treated patients were Caucasian with a mean age of 70 years (range 60 – 83) (***Table 1***).

Among the 12 patients who entered the treatment period, 11 patients completed both the treatment period and the study course (9 weeks). One patient (patient 15) did not complete the last visit because of progressive disease. Adverse events (> grade 1 or > 1 patient) are listed in ***Table 2***. The first 2 cohorts were treated without unacceptable adverse events. Five out of 6 patients in the last cohort were treated without unacceptable adverse events. One patient (treated with 37 MBq/kg ^{188}Re-HEDP and 2500 mg/m^2/day capecitabine) suffered from progressive complaints of fatigue (grade 3) which made it impossible to comply to the last follow up visit. Laboratory values showed a progressive increase of PSA and alkaline phosphatase together with a prolonged and unrecovered bone marrow suppression with anemia (grade 3), thrombopenia (grade 4) and leucopenia / neutropenia (grade 2). He died of cancer related events (progressive bone marrow disease) 2 months after the end of the study. Out of 6 patients in the highest cohort he was the only patient who suffered from a dose limiting toxicity. It was probably caused by treatment related toxicity aggravated by severe progression of disease. The maximum tolerable dose of capecitabine in combination with 37 MBq/kg ^{188}Re-HEDP was therefore 2500 mg/m^2/day.

Table 1 Baseline findings and study treatment (^{188}Re-HEDP and Capecitabine)

Patient	Age	TNM[a]	PSA[b]	KPS[c]	CTx[d]	RTx[e]	NTx[f]	^{188}Re-HEDP	Capecitabine
2	70	T4NxMx	670	70%	6x	Yes	-	3359 MBq	800 mg 2dd
3	73	T4N0M+	550	70%	10x	Yes	2x	3163 MBq	1000 mg 2dd
5	74	TxNxM+	620	90%	6x	-	-	2889 MBq	800 mg 2dd
6	65	T3N2M0	220	70%	-	Yes	-	3744 MBq	1800 mg 2dd
7	83	T3NxM0	800	60%	-	-	-	2566 MBq	1500 mg 2dd
8	69	T3NxM0	11	60%	-	Yes	-	3472 MBq	1800 mg 2dd
10	69	T4N+M+	250	80%	10x	-	4x	4040 MBq	2800 mg 2dd
11	66	TxNxM+	1500	60%	10x	Yes	-	3116 MBq	2500 mg 2dd
14	74	T4NxM+	510	80%	-	-	-	3132 MBq	2500 mg 2dd
15	61	T4NxM+	440	90%	-	-	-	3251 MBq	2500 mg 2dd
16	60	T4N+M0	2200	70%	-	-	-	2476 MBq	2300 mg 2dd
17	76	T4N0Mx	360	60%	-	Yes	-	3146 MBq	2500 mg 2dd

a TNM-stage at diagnosis
b PSA at screening / baseline in ng/mL
c KPS = Karnofsky Performance Score at screening /baseline
d CTx = docetaxel chemotherapy: 75 mg/m^2 every three weeks plus prednisone
e RTx = local radiotherapy received for pain palliation < 25% of the skeleton
f NTX = nuclear therapy: patient 3 received 2x ^{186}Re-HEDP, patient 10 4x ^{153}Sm-EDTMP

After onset of the study treatment, hematological parameters were measured on a weekly basis (***Figure 1***) and serum chemistry on a monthly basis (***Table 2***). All patients experienced an expected temporary decline in platelet count in week 4 (mean ± 1 SD: -61.8% ± 16.5%), 3 weeks after ^{188}Re-HEDP administration, with subsequent recovery (***Figure 1***). Also as expected, there was a temporary decline in white blood cell count in week 4 (mean ± 1 SD: -34.4% ±

17.8%), 3 weeks after ^{188}Re-HEDP administration, with recovery thereafter. The temporary increase in mean white blood cell count in week 5 may be due to inter- and intra-patient variations, typically seen in white blood cell count. It was probably not related to the study treatment. Hemoglobin levels were steady throughout the study course with a mean change compared to baseline of -0.8% ± 12.7% 4 weeks after ^{188}Re-HEDP administration and -5.8% ± 11% at the end of the study (***Figure 1***).

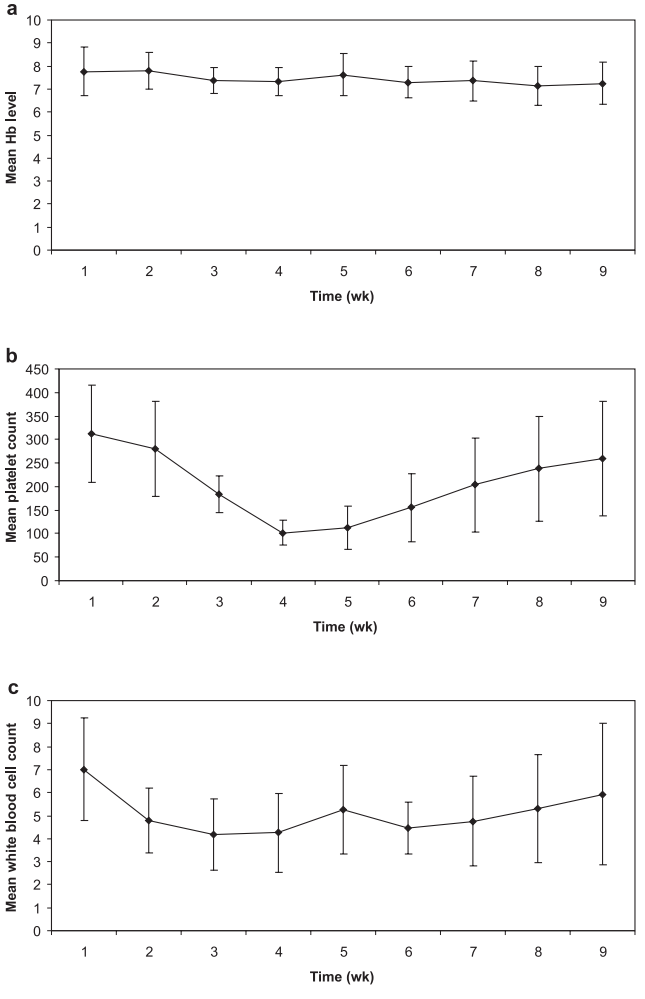

Figure 1 Mean hematological parameters (±1 standard deviation) during the study period of 9 weeks: hemoglobin in mmol/L(a), platelet count x 10^9/L (b) and white blood cell count x 10^9/L (c)

Grades 1, 2, 3, and 4 hematological toxicity occurred in 6, 3, 0, and 1 out of 12 patients, respectively. Creatinine levels were stable throughout the study period for all patients. Clinical adverse events included pain, fatigue , nausea, vomiting, stomatitis and diarrhea. Most adverse events were probably related to capecitabine and were more frequently encountered in cohort 2 and 3 (***Table 2***).

Table 2 Adverse events, listed per patient with grade of toxicity given [a]

	Cohort 1				Cohort 2				Cohort 3			
Patient	**2**	**3**	**5**	**6**	**7**	**8**	**10**	**11**	**14**	**15**	**16**	**17**
Alkaline phosphatase increase										4	2	3
Anemia						1		2		3		1
AST/SGOT increase									1		1	
Confusion						2		2				
Cor pulmonale					3							
Diarrhea					2			1				
Fatigue		2				2				3		
Hand-foot syndrome					2							
Hypo-albumine	1	1							2			
Hypo-phosphatemia					2							
INR increase					2							
Leukopenia			1	2		1	1	2		2		
Nausea						2		1			1	1
Neutropenia								2		2		
Pain increase	3						2	3	2			
Pneumonia					3							
Stomatitis					2							
Trombopenia	1	1	1	1		1	1	1	1	4		2
Vomiting					1			1				
Weight loss											2	1

a This table includes adverse events which are related or unrelated to study drugs, with either an intensity > grade 1 (according to NCI Common Terminology Criteria for Averse Events version 3.0) or frequency > 1 patient

An increase in pain happened in 4 patients, all more than 4 weeks after treatment with initially a good response. These complaints were considered disease progression, not related to study medication. One patient experienced the hand-foot syndrome (grade 2) typically related to capecitabine. The hand-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) is characterized by numbness, dysesthesia, tingling, swelling, pain, erythema, desquamation, blistering and sometimes ulceration (not in this case). This patient proved not to have a dihydropyrimidine dehydrogenase deficiency. He fully recovered. As mentioned above 1 serious adverse reaction was observed (grade 4 thrombopenia), probably related to study treatment (patient 15). Other grade 3 toxicities were probably related to disease progression (pain increase, alkaline phosphatase increase) or other non-related causes (exacerbation of cor pulmonale with pneumonia). The latter patient was hospitalized. He was successfully treated with antibiotics and diuretics. One of the 4 patients who experienced an increase of bone pain was hospitalized for better medical palliation. These 2 hospitalizations (serious adverse events) were most probably not related to the study treatment. No suspected unexpected serious adverse reactions (SUSAR) occurred.

Secondary endpoints included evaluation of urinary excretion and uptake of ^{188}Re-HEDP in pathological bone lesions. Major protocol deviations leading to exclusion from analysis of secondary endpoints were found in 2 patients. Urine collection after treatment was not

complete in these patients. The mean urinary excretion of activity during the first 8 h after injection was 45.7% ± 11.9% (range 24% – 60%). As expected no focal activity was visualized outside the skeleton, kidneys and bladder (***Figure 2***).

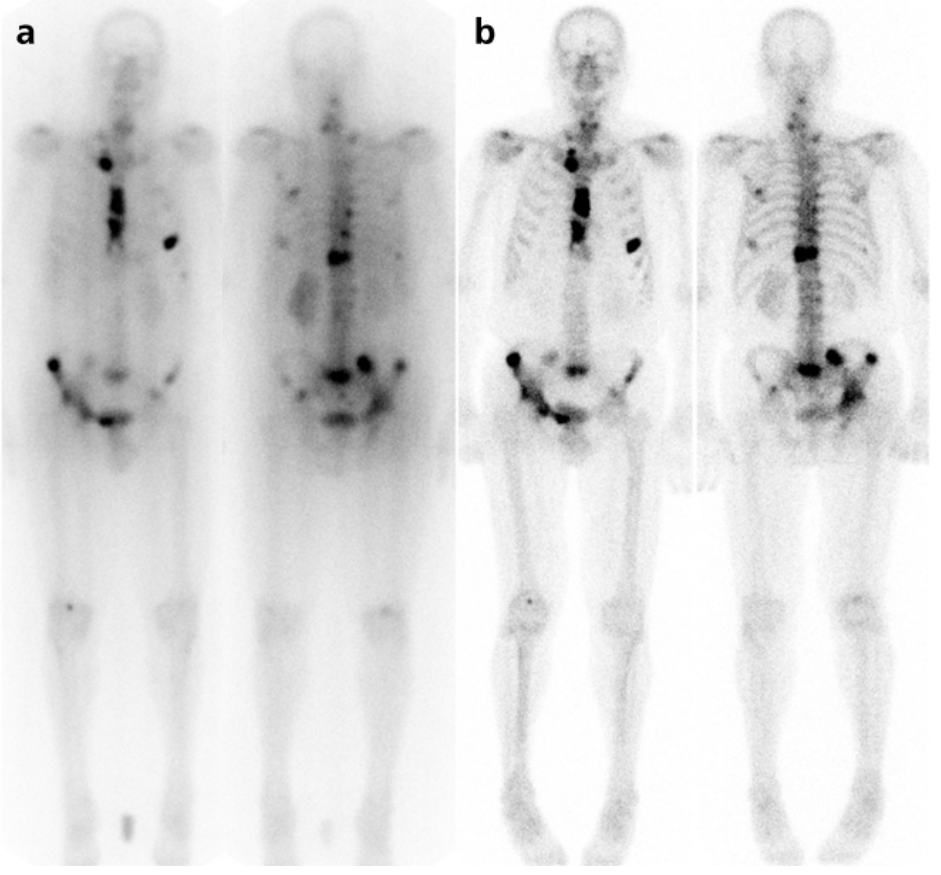

Figure 2 Post-treatment scintigraphy 6 hours after injection of 37 MBq/kg ^{188}Re-HEDP (anterior and posterior; 10% energy window around the peak of 155 keV, medium energy collimator, scan speed 6 cm per min.) (a) compared to pre-treatment skeletal scintigraphy 3 hours after injection of 600 MBq ^{99m}Tc-HDP (b)

So the retained activity was mostly retained in the skeleton. An expected negative correlation was therefore found between urinary excretion of activity and the extent of osteoblastic bone disease (R = -0.83; p = 0.001). The mean bone scan index was 42.7% ± 15.9% (range 23% – 75%). Considering skeletal uptake of activity: the lesion-to-normal-bone ratio was 13.4 ± 4.9 for ^{188}Re-HEDP and 14.4 ± 6.8 for ^{99m}Tc-HDP.
Efficacy will be further studied in a phase II study using 37 MBq/kg ^{188}Re-HEDP in combination with 2500 mg/m^2/day. In the present phase I dose-escalation study no conclusions were drawn on efficacy.

Discussion

The hematological toxicity profile of ^{188}Re-HEDP in combination with capecitabine (up to 2500 mg/m^2/day) is comparable to that of mono-therapy with ^{188}Re-HEDP. An expected decline in platelet and white blood cell count occured 3 – 4 weeks after treatment with subsequent recovery. Additive toxicity was attributed to capecitabine use. One patient out of six patients in the highest cohort experienced unacceptable dose limiting toxicity. This patient had widespread metastatic disease but was in good clinical condition before treatment (Karnofsky performance score 90%) and was not treated with chemotherapy, nuclear therapy nor radiotherapy before study treatment. His PSA was 260 ng/mL with a doubling time of 2 weeks before treatment. After treatment his PSA and alkaline phosphatase further increased, reflecting progressive disease. He experienced grade 4 hematological toxicity (trombopenia) and was not able to recover due to progressive bone marrow disease.

^{188}Re-HEDP is currently used to relieve pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on ^{99m}Tc-HDP-scintigraphy. Experience with ^{188}Re-HEDP in pain reduction is somewhat limited but results have been quite promising. A number of publications show its efficacy [9-12]. Repeated treatment with ^{188}Re-HEDP with an interval of 8 weeks enhanced pain palliation and improved progression-free and overall survival [11]. Administered doses of around 37 MBq/kg proved to be safe in several studies [10, 11, 22]. Expected bone marrow depression occurred in most cases, but with subsequent recovery. The severity of this depression is related to the bone marrow reserve, which might be compromised as a result of previous treatments or disease progression [22]. Treatment regimens that combine ^{188}Re-HEDP with other modalities have never been tested. The present study shows the safety of ^{188}Re-HEDP combined with capecitabine (up to 2500 mg/m^2/day).

Carrier-added ^{188}Re-HEDP shows identical chemical characteristics to ^{186}Re-HEDP. The degree of skeletal uptake of ^{188}Re-HEDP correlated with the extent of osteoblastic bone disease. The uptake of ^{188}Re-HEDP in skeletal lesions in the present study (mean ratio 13.4 ± 4.9) is comparable to pre-treatment skeletal scintigraphy using ^{99m}Tc-HDP (mean ratio 14.4 ± 6.8). These findings correlate with pre-clinical data of ^{188}Re-HEDP in rabbits [7]. However, because of differences in scanning parameters (6 hours versus 3 hours p.i.; energy peak; energy window, scanning speed) a direct comparison has several limitations. The present study was not designed for equivalence testing. Nevertheless, it may be concluded that uptake of ^{188}Re-HEDP in skeletal lesions is sufficient when combined with capecitabine. It is comparable to what may be expected from pre-treatment scintigraphy using ^{99m}Tc-HDP.

Like ^{186}Re-HEDP clearance of ^{188}Re-HEDP is exclusively renal, with the remainder of the dose retained in the skeleton. The mean urinary excretion of activity during the first 8 hours after injection in the present study was 45.7% ± 11.9% (range 24% – 60%). In another study ^{188}Re-HEDP showed a rapid urinary excretion within the first 8 hours after therapy, with approximately 41% of the ^{188}Re-HEDP administered being excreted [23]. This is comparable to our data. The large range is attributed to large differences in the extent of metastatic disease. It is unlikely that capecitabine has any effect on urinary excretion nor skeletal uptake of ^{188}Re-HEDP. The combination seems feasible.

Capecitabine is indicated as mono-therapy in patients with colorectal cancer and breast cancer. It is administered as oral tablets in a dose of 1250 mg/m^2 twice daily for 14 days and one week rest in cycles of three weeks [14]. Early in vitro studies in human prostate cancer cell lines demonstrated high levels of thymidine phosphorylase inside these cells, necessary for the conversion to active 5-FU [19]. After administration of capecitabine a high anti-tumor effect was found, with a 77% inhibition of growth [24]. The beneficial effect of capecitabine in patients with hormone-refractory prostate cancer was first reported in a patient with advanced disease (multiple bone and liver metastases). Capecitabine was given in a dose of 2000 mg/m^2/day for 14 days of a 21-day cycle for 6 months. His PSA normalized, the liver size decreased by 7 cm, to a normal size and the liver enzymes and alkaline phosphatase also normalized [25]. This finding could not be confirmed in phase II studies using capecitabine as a single agent in hormone-refractory prostate cancer patients [26, 27]. It was however concluded that combined treatment regimens containing capecitabine should be considered, because capecitabine appeared to modulate tumor biology [27].
The results of these early trials indicate that the role of the 5-FU prodrug capecitabine alone or in combination is yet unclear. Evidence is still low. However, prostate cancer cells are sensitive to radiotherapy (both external beam radiotherapy and systemic radionuclide therapy) and potentially to capecitabine [24]. The proven effects of capecitabine as a radiation sensitizer in other cancer types, the lack of data on capecitabine as a radiation sensitizer in advanced prostate cancer and the convenience and toxicity profile of capecitabine make it a good candidate for phase I / II testing in hormone-refractory prostate cancer patients in combination with ^{188}Re-HEDP.
Another agent that may be used in combination with ^{188}Re-HEDP is docetaxel. In contrast to capecitabine it is not commonly used as a radiation sensitizer and it has some disadvantages in comparison with capecitabine (i.e. intravenous infusion, costly, more side effects). In the present study capecitabine was therefore tested instead of docetaxel. As an anti-tumor agent docetaxel is however more effective in hormone-refractory prostate cancer and it may be used as a radiation sensitizer nevertheless [28]. Moreover, docetaxel and capecitabine may be combined with ^{188}Re-HEDP together. Taxanes were found to upregulate the tumoral activity of thymidine phosphorylase (a critical enzyme for capecitabine activation) and have shown synergistic cytotoxic activity when combined with capecitabine [29, 30]. Docetaxel in combination with capecitabine has already been tested in clinical phase I / II studies with promising results [31, 32]. The docetaxel / capecitabine combination proved to be tolerable and effective. Randomized trials have so far not been conducted.
Capecitabine in combination with ^{188}Re-HEDP proved to be feasible and safe. The next step in the enhancement of efficacy may be docetaxel, capecitabine and ^{188}Re-HEDP as triple therapy in hormone-refractory prostate cancer patients with multiple osseous metastases.

Conclusion

The maximum tolerable dose of capecitabine in combination with 37 MBq/kg ^{188}Re-HEDP is 2500 mg/m^2/day. The combination is feasible and safe. Efficacy, using the maximum dose will be tested in a phase II trial.

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Chapter 10

General discussion and future prospects

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Introduction

Prostate cancer is the most common malignancy in men in the Netherlands. Skeletal metastases in advanced prostate cancer pose a significant medical problem. Metastatic bone pain is a frequent symptom. Amongst other treatments bone seeking radiopharmaceuticals are used to palliate metastatic bone disease. Efficacy has been sufficiently proven as well as safety and feasibility. Practical issues as well as new developments and future prospects will be discussed. First, radiation safety and treatment recommendations will be considered. Radiation safety for caregivers and other bystanders is the first and foremost restriction in the use of radiopharmaceuticals. In contrast to non-radioactive substances (e.g. chemotherapy), radiation is relatively easy to measure in and around a patient. This safety condition will be met before treatment efficacy and toxicity will be discussed. Secondly, multimodality treatment, including bone seeking radiopharmaceuticals, will be discussed with an emphasis on prostate cancer patients. And finally, future prospects will be discussed and conclusions drawn.

Radiation safety considerations

Patients treated with $^{89}SrCl_2$, ^{186}Re-HEDP or ^{153}Sm-EDTMP are a source of radiation, including beta-radiation that has proven to be measurable outside the patient. Beta-particles in superficial tissue (such as in bones, blood vessels) cross the skin and contribute to the ambient equivalent dose. This aspect must be considered when using beta-emitting radiopharmaceuticals in general as has been described in chapter 3. The calculated effective doses for bystanders are well below the recommended values and do not lead to unacceptable additional radiation burden to health care workers and patients' families. The mean total effective doses absorbed by bystanders at 30 cm distance from a patient were 0.02 mSv for $^{89}SrCl_2$, 0.3 mSv for ^{186}Re-HEDP, and 1.6 mSv for ^{153}Sm-EDTMP. These observations however should be placed in some perspective. First the individual variation in effective dose to bystanders and second the potential risk of internal contamination of bystanders.
The total effective dose, as given above, is estimated for bystanders who reside at exactly 30 cm from the patient for an indefinite time. Because this is never the case, these estimations must be corrected for variations in time and distance between bystanders and patients. In a Dutch Ministry of Housing, Spatial Planning and Environment publication accurate calculations were made to cover the various persons who may have contact with patients [1, 2]. These calculations are based on residence times T (in fractions of days) with the patient and distances R (in meters) from the patient. The actual effective doses for bystanders will depend on residence times and distances in relation to the patient. Estimations were made for residence times and distances during a 24-hour period. This was done in the case of an elderly patient in relation to his or her partner and in the case of a patient in relation to his or her child (***Tables 1 and 2***). Assuming that the estimated distances and times are a reflection of reality, corrections were made for these circumstances. Estimations of the effective doses for these persons (partner and child) are given for the three most used radiopharmaceuticals. In the case of a patient and his or her partner, without instructions a correction factor of 0.15 (15%) was applied. This is explained by the fact that bystanders do not stay within 30 cm of

patients 24 hours a day. Because of work and other activities a correction factor should be applied. As an example a correction factor of 0.15 may be applied. The effective dose may be further reduced by instructing the patients and their families to keep distance as much as reasonably possible (e.g. watching TV and sleeping apart). With proper instructions to family, residence times may be reduced and distances increased, lowering the correction factor to as low as 0.02 (2%), an almost eight-fold decrease in radiation burden to bystanders (***Table 1***). In the case of a patient and his or her child an estimated correction factor of about 0.43 (43%) should be applied without instructions and 0.11 (11%) with instructions. In all instances effective doses will be < 1 mSv and with proper instructions they will be < 0.1 mSv or even < 0.01 mSv (Tables 1 and 2). According to the data of the study described in chapter 3 and the considerations of the corrections mentioned it may be concluded that patients treated with bone seeking radiopharmaceuticals do not pose any threat to others.

Table 1 Effective dose (external radiation) of *an elderly partner* with and without instructions

	Without instruction			With instruction		
	Residence time (hrs/24hrs)	Distance (m)	Correction factor [a]	Residence time (hrs/24hrs)	Distance (m)	Correction factor [a]
outdoors activities	3/24	-	0	3/24	-	0
watching TV	5/24	0.5	0.075	5/24	2	0.0047
dinner	2/24	1	0.0075	2/24	1	0.0075
sleeping	8/24	0.7	0.061	8/24	2	0.0075
other	6/24	3	0.0025	6/24	3	0.0025
total			0.15			0.02
	Mean effective dose (mSv)			Mean effective dose (mSv)		
^{153}Sm-EDTMP	0.24			0.03		
^{186}Re-HEDP	0.05			< 0.01		
^{89}Sr-Chloride	< 0.01			< 0.01		

a Correction factor applicable for measurements at 30 cm from the patient using the inverse-square law

Table 2 Effective dose (external radiation) of *a young child* with and without instructions

	Without instruction			With instruction		
	Residence time (hrs/24hrs)	Distance (m)	Correction factor [a]	Residence time (hrs/24hrs)	Distance (m)	Correction factor [a]
playing	8/24	4	0.0019	8/24	4	0.0019
close contact	1/24	0.1	0.375	0.25/24	0.1	0.094
dinner	2/24	0.5	0.03	2/24	2	0.0019
sleeping	10/24	-	-	10/24	-	-
other	3/24	2	0.0094	3/24	2	0.0094
total			0.43			0.11
	Effective dose (mSv)			Effective dose (mSv)		
^{153}Sm-EDTMP	0.69			0.18		
^{186}Re-HEDP	0.13			0.03		
^{89}Sr-Chloride	< 0.01			< 0.01		

a Correction factor applicable for measurements at 30 cm from the patient using the inverse-square law

However, an exception has to be made considering urinary excretion of activity and the possible internal contamination of bystanders. Besides radiation exposure to non-patients from direct emission by the patient, another potential radiation hazard is formed by excreted radioactivity. In this thesis, the calculated mean total urinary excretion percentage of ^{89}Sr during the first 3 days after administration was 16%. Using a hypothetical contamination scenario, that is used in radiation protection evaluation [1], that 0.01% of the excreted amount of radioactivity will cause internal contamination to non-patients closely related to the patient, an internal dosage of 0.0024 MBq for $^{89}SrCl_2$ therapy (administered dose of 150 MBq) was calculated. For ^{186}Re-HEDP therapy (administered dose of 1295 MBq), the corresponding amount of radioactivity will be 0.064 MBq (49% of the injected dose is excreted [3]). After treatment with 37 MBq/kg ^{153}Sm-EDTMP 53.1% ± 15.1% of the administered dose was excreted in urine during the first 48 hours. Potential contamination with 0.01% of the excreted radioactivity will lead to an internal dosage of 0.15 MBq ^{153}Sm-EDTMP. The dose conversion coefficient for ingestion of ^{89}Sr is (e_{ing}) = 2.6 x 10^{-9} Sv/Bq, of ^{186}Re (e_{ing}) = 1.5 10^{-9} Sv/Bq, and of ^{153}Sm (e_{ing}) = 7.4 10^{-10} Sv/Bq. The present data show that the effective radiation absorbed dose, caused by a potential internal contamination (0.01% of the administered dose), is 6.2 microSv for ^{89}Sr, 96 microSv for ^{186}Re and 111 microSv for ^{153}Sm. These numbers are in the same order of magnitude as the numbers given for external exposure (***Table 1 and 2***).

The total effective dose for non-patients may be caused by both external radiation exposure and internal contamination. In contrast to the mean effective dose caused by external radiation, the effective dose after ingestion of 0.01% of the administered dose is hypothetical and may be much higher or much lower. In the case of ^{131}I it proved to be less. The uptake of ^{131}I in the thyroid of family members was measured [4]. A maximum uptake of 3.8 Bq per MBq administered was found. So on one hand it must be considered that 0.01% is a hypothetical figure, while the external radiation exposure is a fact. On the other hand, internal contamination poses a real threat to non-patients. Patients that were treated with bone seeking radiopharmaceuticals are often severely disabled (in contrast to ^{131}I patients). Especially in the case of prostate cancer patients, they often have dysurea. Personal hygiene is not as obvious as it is to others. It is therefore advisable to give the patients simple, easy-to-follow instructions, in order to reduce the risk for non-patients. Using a separate toilet, sitting while urinating and washing hands afterwards, are highly recommended. In the case of incontinence, patients must be catheterized for a certain time depending on urinary excretion of the administered activity. Due to fast renal excretion this may be 12 hours after injection of ^{186}Re-HEDP and ^{153}Sm-EDTMP. $^{89}SrCl_2$ is being administered in relatively low doses and therefore has a relatively low risk for high effective dose due to ingestion of this radiopharmaceutical (6.2 microSv for ^{89}Sr). These patients do not have to be catheterized. The risk for significant internal contamination of non-patients is much lower and acceptable for this radiopharmaceutical.

In general it is advised to hospitalize patients treated with ^{186}Re-HEDP and ^{153}Sm-EDTMP for at least 8 hours. This is mostly based on urinary excretion and the risk for internal contamination, because the radiation exposure to non-patients is < 20 microSv/hour (1 meter from the patients) directly or within a few hours after administration in all cases. In the case of incontinence it is advised to treat patients with either ^{186}Re-HEDP or ^{153}Sm-EDTMP with a urinary catheter for 12 hours after administration. Patients treated with $^{89}SrCl_2$ may return home directly.

After discharge it is advisable to keep distance where possible (***Table 1 and 2***), following the ALARA ('as low as reasonably achievable') principles. This means, for example, that older patients (> 60 years) may still sleep close to their older partner, while being more stringent towards younger relatives to avoid any unnecessary radiation dose. The ICRP has proposed an effective dose limit of 1 mSv per year for individuals. In special circumstances a higher value may be allowed in a single year provided that the average over 5 years does not exceed 1 mSv per year. In clinical practice, the use of bone seeking radiopharmaceuticals will give rise to a degree of radiation exposure to all those in contact with patients, albeit in very low doses. The present results further confirm the safety of treatment with bone seeking radiopharmaceuticals.

Treatment recommendations

$^{89}SrCl_2$ (Metastron®) and ^{153}Sm-EDTMP (Quadramet®) are both FDA approved and registered in the Netherlands. Together with ^{186}Re-HEDP (registered in some countries, not in the Netherlands) these bone seeking radiopharmaceuticals are mostly used. Most of the randomized double-blind placebo controlled trials have been performed using $^{89}SrCl_2$ or ^{153}Sm-EDTMP. An evidence based approach would be a choice between these radiopharmaceuticals. One of the differences between these two is the magnitude and rate of renal excretion. Both may be used without confining a patient to the hospital but from a radiation safety perspective it is advised to keep the patient in a controlled setting for at least 8 hours after injection in the case of ^{153}Sm-EDTMP. This could influence the choice on practical grounds in favour of $^{89}SrCl_2$. Not all nuclear medicine departments have such facilities.
Other differences include the longer half-life and higher energy (with higher range in tissue) of $^{89}SrCl_2$ compared to ^{153}Sm-EDTMP. ^{153}Sm-EDTMP and ^{186}Re-HEDP are highly comparable with regard to energy and half-life. Most comparative randomized studies have been performed using $^{89}SrCl_2$ and ^{186}Re-HEDP. It was found that no difference exist with regard to pain response between treatment with ^{89}Sr-Chloride and ^{186}Re-HEDP in patients with painful osseous metastases [5, 6]. And that the onset of the pain response of ^{186}Re-HEDP is faster than the onset of the pain response of ^{89}Sr-Chloride in patients with painful osseous metastases from a breast carcinoma [5]. So one might argue that when a faster pain response is indicated one should use ^{186}Re-HEDP or ^{153}Sm-EDTMP. Other differences are the longer duration of response of ^{89}Sr-Chloride on one hand, and the prolonged bone marrow toxicity of ^{89}Sr-Chloride on the other hand. These differences were not investigated in direct comparative studies but should be considered nevertheless. In summary:

in favour of ^{89}Sr-Chloride are:

- No confinement necessary
- Longer duration of response (suitable in relatively good clinical condition in which a prompt response is not warranted)

in favour of ^{186}Re-HEDP or ^{153}Sm-EDTMP are:

- Fast response (suitable in bad clinical condition in which immediate response is wanted)
- Favourable toxicity profile (suitable in heavily pre-treated patients, in wide spread metastatic disease and possibly in combination with other myelotoxic treatments)

In most cases today a fast response is needed. Besides that most patients, including prostate cancer patients, are heavily pre-treated. They have end stage disease with minimal bone marrow reserve. And last but not least short-living bone seeking radiopharmaceuticals like ^{186}Re-HEDP, ^{153}Sm-EDTMP and others may prove to be more suitable in combination with other treatment modalities, not just because of their toxicity profile but also because of their high dose rate, offering an effective treatment with fast recovery.

Multimodality treatment

The propensity of prostate cancer to metastasize to bone and the prognostic significance of bone metastases suggest that effective treatment of bone metastases may provide clinical benefits [7, 8]. With regard to the 'seed' and 'soil' theory on bone metastases the seed may comprise the so-called cancer stem cells. Whereas the soil may comprise a unique microenvironment, that facilitate the growth and survival of cancer stem cells. Targeting the microenvironment may offer another way to improve treatment of prostate cancer bone metastases. The microenvironment consists of osteoclasts, osteoblasts, endothelium and stroma. In the presence of cancer stem cells they interact leading to a disruption in normal coupling between osteoclasts and osteoblasts. An improved understanding of this process will influence how we select agents to target bone metastases and how we design strategies to treat prostate cancer bone metastases. Treatments may be directed to the cancer stem cells, the osteoblasts, the osteoclasts, the endothelium or the stroma [9].
Osteoblasts may be targeted by several pharmaceuticals including bone seeking radiopharmaceuticals, which are thoroughly discussed in this thesis. Other osteoblast directed treatments include endothelin-1-antagonists (atrasentan) [10], vitamin D analogs (1,25-hydroxyvitamin D_3) [11], monoclonal IGF-1R (insulin-like growth factor-1-receptor) antibodies [12] and CXRC4 (G-protein-coupled receptor) inhibitors (MSX-122), which inhibit the homing behaviour of cancer stem cells. Osteoclast activity may be inhibited by bisphosphonates (zolendronate) [13], RANK ligand inhibitors (denosumab) [14], tyrosine kinase inhibitors (dasatinib) or IL-6 antagonists (CNTO328) [15]. And the endothelium and/or stroma may be targeted by anti-angiogenesis therapies. These include the vascular endothelial growth factor (VEGF) receptor antagonists bevacizumab, thalidomide and lenalidomide [16]. They reduce VEGF levels and basic fibroblast growth factor, inhibit growth and survival of tumor cells by modulation of adhesion molecules and mediate various cytokines. Also targeted to the endothelium are platelet-derived growth factor receptor (PDGFR) tyrosine kinase inhibitors (imatinib, sunitinib and tandutinib) [17]. They may also have anti-angiogenetic potential. Most of these agents are under investigation. Many clinical studies in prostate cancer patients are ongoing [9].

Combining different treatment modalities may be interesting because of additive effects or synergy effects. In the case of bisphosphonates and bone seeking radiopharmaceuticals the combined use has always been contra-indicated because of presumed interaction at the bone matrix level. In this thesis it was shown that the combined use of ^{153}Sm-EDTMP and bisphosphonates in patients with hormone-refractory prostate carcinoma is feasible. The combined treatment regimen is safe and may prove to be an effective long-term treatment regimen (Chapter 6-8). The data on the efficacy show some interesting results with a stable and long lasting duration of response in a small but significant group of patients. These patients may be identified using specific bone markers like bone specific alkaline phosphatase [BAP], procollagen type I N propeptide [PINP], N-terminal type I collagen peptide [NTX]. They will be discussed further on.

Another combined treatment regimen would be a combination of bone seeking radiopharmaceuticals and chemotherapy. It is likely that combined treatment with ^{89}Sr-Chloride and chemotherapy (platinum based) yields a better pain response than treatment without chemotherapy in patients with painful osseous metastases from a prostate carcinoma [18, 19]. And it has been suggested that adding ^{89}Sr-Chloride to chemotherapy may lead to improved survival and a longer duration of the pain response compared to treatment with chemotherapy alone [20]. Studies are yet limited but they are encouraging. Most of them have been performed using ^{89}Sr-Chloride and some using ^{153}Sm-EDTMP [21]. Patients may possibly have an improved pain response and longer survival. In prostate cancer patients a most interesting choice would be combining docetaxel and a bone seeking radiopharmaceutical. These studies, using ^{153}Sm-EDTMP or ^{186}Re-HEDP, are underway. In this thesis the combination of ^{188}Re-HEDP and capecitabine (Xeloda®) is described. This treatment regimen proved to be feasible and safe. Phase II efficacy testing using the maximum tolerable dose of 2500 mg/m^2/day capecitabine is underway. Capecitabine is primarily used as a radiation sensitizer. It offers a convenient therapy with acceptable toxicity, ease of use as oral tablets and low costs. The same is true for ^{188}Re-HEDP. It is homemade on demand and has favourable physical characteristics with a short half-life (16.9 hours) and high beta-energy ($E_{ß\ max}$ 2.12 MeV; $E_{ß\ mean}$ 0.76 MeV). In theory, this high dose rate could lead to improved efficacy with rapid recovery. This is ideal for combined treatment regimens and for repeated treatment, which has already shown to be favourable with regard to pain response and survival [22].

Several other combinations using bone seeking radiopharmaceuticals are under investigation. Currently, a randomized phase III study (MDA-3410/CTSU in M.D. Anderson Cancer Center, Houston, Texas) combining weekly doxorubicin (20 mg/m^2) with ^{89}Sr-Chloride after response to induction chemotherapy is underway, as well as another phase I trial combining docetaxel/prednisone and ^{153}Sm-EDTMP, also at M.D. Anderson [9]. It remains to be established whether targeting both the tumor (chemotherapy) and bone compartments will improve therapeutic efficacy. This concept is also being tested in multiple other trials, mostly combining docetaxel/prednisone with bone environment directed treatments, like the agents described above [9]. The described studies in this thesis add to this search for optimized treatment regimens in hormone-refractory prostate cancer patients.

Prediction of efficacy and toxicity

Most patients with advanced prostate cancer have disease limited to the bone, which is notoriously difficult to assess for response, with a small subset having soft tissue lesions. To limit response evaluation to only patients with bidimensionally measurable disease would eliminate 70% to 80% of patients who would otherwise be evaluable [23]. With regard to prostate cancer patients efficacy of treatment has been monitored by PSA in a majority of studies. However it is doubtful whether PSA changes correlate with clinical benefit [24]. A 50% decrease in PSA level seems a reasonable predictor of a favourable outcome, but this was certainly not the case in all studies [25, 26]. It was advised not to use PSA level drops as a surrogate marker for survival [24].

In patients with advanced disease, survival and quality of life, including pain palliation, are the most important criteria of clinical response. Besides survival these parameters are difficult to measure and subject to errors. With an attempt to standardize treatment response monitoring in cancer patients the European Organization for Research and Treatment of Cancer (EORTC) has developed quality of life questionnaires (EORTC QLQ-C30 version 3.0). They were validated in many clinical trials [27]. They include questions on global health status / quality of life, functional scales and symptom scales. The functional scales are subdivided in physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning. The symptom scales are subdivided in fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties. Each domain was scored on a scale of 0 – 100, according to the EORTC scoring manual [28]. The changes in scores may be used to monitor clinical effect.

Other often used clinical monitoring tools include the visual analogue scales (VAS) to monitor pain, changes in analgesic intake and, more basic, the physician's assessment based on anamnesis and physical examination. A matter of debate is the frequency of evaluation. It seems that daily assessment is necessary to appreciate the wide variation in clinical status that patients may experience from day to day [29]. In all cases it is difficult to find a good balance between accuracy and compliance. PSA is therefore still popular to measure an objective level of response [24, 30].

However, other predictors of response may prove to be much more reliable than PSA. In hormone-refractory prostate cancer patients in advanced stages of their disease the extent of metastatic disease in the skeleton is of high prognostic significance [7]. Furthermore it was shown that patients with advanced disease who had experienced a so-called skeletal related event (defined as: pathologic fracture, spinal cord compression with vertebral compression fracture, the need for surgery to treat or prevent pathologic fractures or spinal cord compression, or the need for radiation to bone) had a significant worse survival and poorer quality of life, in comparison with patients who had not experienced a skeletal related event [8]. These results further confirm the importance to treat skeletal metastases adequately. Markers of skeletal metabolism were found to be related to outcome and survival. In several clinical studies in prostate cancer patients it was observed that markers of bone metabolism were able to predict outcome, both as absolute levels pre-treatment and as changes after treatment [31, 32]. In large series of cancer patients, including a majority of prostate cancer

patients, treated with zoledronic acid, it was found that baseline levels of the bone marker urinary N-terminal type I collagen peptide [NTX], as well as changes of NTX after treatment were able to predict improved survival [33, 34]. Other studies emphasized the importance of the bone marker serum bone specific alkaline phosphatase [BAP] as a predictor of outcome [35, 36]. Most of these studies used the same bone markers as we did in the study on the combined treatment of prostate cancer patients with ^{153}Sm-EDTMP and zoledronic acid (i.e. NTX, BAP and serum procollagen type I N propeptide [PINP],). Although this study comprises a small study the results are of interest because they confirm the utility of these markers as predictors of clinical outcome, even in small numbers. Besides, they were first tested in the treatment monitoring of bone seeking radiopharmaceuticals. The bone formation markers BAP and PINP were in agreement with the clinical effect of the combined treatment regimen evaluated by EORTC questionnaires. The bone resorption marker NTX and PSA were not in agreement with the clinical effect. This supports the hypothesis that the extent of osteoblastic metastasis in hormone-refractory prostate cancer patients is an important parameter for clinical outcome [6, 7]. Both treatment itself and treatment monitoring should be directed to these osteoblastic metastases. Bone markers may well prove to be very useful predictors of clinical effect in the treatment with bone seeking radiopharmaceuticals. They should be used in future trials.

Last but not least the importance of imaging modalities should be mentioned with regard to individualized treatment monitoring. Functional rather than anatomical imaging techniques may be used to predict response. Several PET (Positron Emission Tomography) techniques are being developed for this purpose [37, 38]. In fact, functional imaging will prove to be one of the major contributions of nuclear medicine to clinical oncology in the future. Does the treatment work? That question needs to be answered for each oncologic treatment on an individual basis. Nuclear imaging and PET in particular may be helpful.

Besides predictors of efficacy, predictors of toxicity are equally important for individualized patient management. Radiopharmaceuticals are important resources in the management of bone pain, but they need to be utilized in a manner that does not prevent other systemic therapy [39]. Thrombocytopenia is the dose limiting factor in treatment of painful bone metastases with bone seeking radiopharmaceuticals. De Klerk *et al* evaluated thrombocytopenia in patients with hormone refractory prostate carcinoma, treated with ^{186}Re-HEDP [40]. As an index of the extent of bone involvement, the bone scan index (BSI) was determined from the pre-treatment ^{99m}Tc-HDP scintigram. The BSI is a tool to describe the extent of skeletal metastases on a scale from 0 to 100% [41]. They described a functional relation ($r = 0.78$; $p < 0.001$) of the percentage of platelet decrease after treatment with the extent and distribution of skeletal metastases (BSI) and administered activity, normalized to standard body surface area. Using this relation, it is possible to predict thrombocytopenia by pre-treatment skeletal scintigraphy and to adjust the dosage for each patient to avoid unacceptable toxicity [40]. However, more sophisticated indices of bone marrow function might also be of paramount importance. Recently, some very interesting reports have been published on 'reticulated platelets' [42, 43]. In systemic radionuclide therapy, the megakaryocyte seems to be most vulnerable to radiation. It is of great interest to gain more knowledge of bone marrow function pre-treatment using 'biological' parameters like 'reticulated platelets'. These newly released platelets are larger and contain RNA. They were suggested to be the platelet analogue of

the red cell reticulocyt. Assessment of platelet production using 'reticulated platelets' would distinguish between thrombocytopenia due to bone marrow failure and impending bone marrow recovery after cytotoxic therapy or thrombocytopenia due to increased peripheral platelet destruction and turnover. In both cases platelet levels are low, but in the latter 'reticulated platelet' levels will be high due to increased production [43]. This non-invasive measurement could further increase our knowledge of platelet production and the influence of radiation on this process.
By adding hematological, chemical and biological parameters, combined with the bone scan index, body surface area, administered activity and retained activity, an extended version of 'De Klerk's formula' may be developed. This is probably best done as a so called nomogram. Smaletz *et al* developed a nomogram to predict survival for patients with hormone refractory prostate carcinoma [44]. A nomogram is a model in which individual parameters lead to a chance (from 0 to 100%) to experience a pre-defined outcome. The outcome may be defined as survival or for example toxicity. Such a model can be made to predict hematological toxicity (thrombocytopenia, leucopenia) after treatment with bone seeking radiopharmaceuticals to improve individualized patient management.

Future prospects

Several future implications have already been discussed above. One of the most important developments for bone seeking radiopharmaceuticals will be individualized medicine. The search for an optimized balance between efficacy and toxicity will be found rather in an individualized treatment plan than in new agents. Good predictors of efficacy and toxicity are needed for treatment monitoring. Several potential candidates were described above. They may be found in clinical evaluation, imaging and several laboratory parameters. A combination of these parameters may lead to a prediction model which may be used in daily practice. Multimodality treatment has also been described above. Many combinations have potential. It has to be investigated which regimen will be most effective. Besides a direct anti-tumor effect which may be reached with chemotherapy (i.e. docetaxel), it is recognized that treatment directed to the bony environment may add to the overall efficacy of the treatment regimen. Bone seeking radiopharmaceuticals are bone-directed and may be of value in combination with other treatment modalities. Besides combinations with chemotherapy or bisphosphonates other interesting combinations may include for example atrasentan, or denosumab. An important other issue is the timing of treatment with bone seeking radiopharmaceuticals. The frequency and interval of sequential treatment should be considered. Bone seeking radiopharmaceuticals are mostly used as a single shot treatment. When patients respond to the treatment repeated treatment is considered. In most instances this does not happen with a planned interval in mind but rather when symptoms reappear after an initial response. In fact this might be too late. It seems better to treat patients sequentially before symptoms reoccur. This was confirmed in a randomized controlled trial in prostate cancer patients treated with two dosages of 1.1 mCi ^{188}Re-HEDP with an interval of eight weeks compared to single shot treatment. They did not only find an improved pain response with longer duration but surprisingly an improved survival as well [22]. Safety of repeated treatment with bone

seeking radiopharmaceuticals was also confirmed [45]. This enhancement of efficacy may be attributed to chronic inhibition of osseous metabolism preventing cancer cells to thrive in the bony environment. Most other oncologic compounds are used in a repeated fashion using several cycles to reach sufficient effect. It should be investigated which multiple treatment regimen is most suitable for bone seeking radiopharmaceuticals, and whether it is safe and more effective. It may be suggested that the best result in hormone-refractory will be reached using a multimodality treatment regimen with fractionation of all treatments to be effective over a prolonged period of time.

Conclusion

Treatment with bone seeking radiopharmaceuticals in patients with multiple painful skeletal metastases is safe and effective when proper protocols are being used. Important improvements may be found in multimodality treatment in long-term treatment regimens and in individualized patient management. Identification of powerful indicators of toxicity and efficacy may guide patient selection and therapy monitoring to optimize the patient's outcome. This may possibly lead us beyond pain palliation towards improvement of survival.

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Chapter 11

Summary and conclusions

Summary

So called bone seeking radiopharmaceuticals are pharmaceuticals that consist of a radionuclide and a carrier. The radionuclide emits beta-radiation and delivers a therapeutic dose to the target site. The carrier is used to target the radiopharmaceutical to the site of interest: the bone. These pharmaceuticals are indicated in cancer patients with multiple painful skeletal metastases. The majority of these patients are hormone-refractory prostate cancer patients in advanced stages of their disease. Bone seeking radiopharmaceuticals relieve pain and improve the patient's quality of life. The mostly used radiopharmaceuticals $^{89}SrCl_2$ (Metastron®), ^{153}Sm-EDTMP (Quadramet®) and ^{186}Re-HEDP are discussed in detail in **chapter 2**.

Some precautions must be taken into account before treatment with bone seeking radiopharmaceuticals. As with every radionuclide therapy it is of utmost importance to understand the physical and chemical properties of the compounds used. The radiation hazard to patients' relatives depends on biodistribution, pharmacokinetics and physical decay. This may be different depending on the administered radiopharmaceutical. **Chapter 3** of this thesis describes the differences between $^{89}SrCl_2$, ^{153}Sm-EDTMP and ^{186}Re-HEDP. It was found that urinary excretion of activity is rapid in patients treated with ^{153}Sm-EDTMP and ^{186}Re-HEDP, in contrast to $^{89}SrCl_2$. Together with differences in biodistribution and physical decay this leads to differences in radiation burden to bystanders. The effective dose for a person standing at 30 cm from the patient for indefinite time was calculated. The effective doses are < 0.1 mSv for $^{89}SrCl_2$, 0.3 mSv for ^{186}Re-HEDP and 1.6 mSv for ^{153}Sm-EDTMP. Interestingly it was also found that beta-radiation contributes significantly to these doses (> 99% for $^{89}SrCl_2$, 87% for ^{186}Re-HEDP and 27% for ^{153}Sm-EDTMP). This was never described before. In all cases however it was concluded that treatment with bone seeking radiopharmaceuticals is feasible and safe. To draw proper guidelines the effective doses to bystanders were considered, as well as the risk for internal contamination, which may be profound, especially in prostate cancer patients. Besides radiation safety other important issues include the patient's clinical condition (performance, bone marrow reserve, renal function), logistics, radiation burden to the patient and toxicity. The guideline on treatment of refractory metastatic bone pain with bone seeking radiopharmaceuticals, put forward by the European Association of Nuclear Medicine (EANM), is presented in **chapter 4**. Physicians may use this guideline for patient selection and management. The guideline and this thesis may also be used for a choice between the available radiopharmaceuticals.

In order to improve the patients' clinical condition it may be beneficial to combine different treatment modalities. This may possibly lead to additive or even synergistic effects. **Chapter 5** is an introduction to multimodality treatment in hormone-refractory prostate cancer patients. A multimodality long-term treatment regimen combining several modalities is proposed. In prostate cancer patients bisphosphonates are used to treat and prevent so called skeletal related events (fractures, hypercalcemia, spinal cord compression). This may add to the palliative effect of bone seeking radiopharmaceuticals. Nevertheless, the European label of ^{153}Sm-EDTMP includes the contra-indication that "it should not be used concurrently with other bisphosponates if an interference is shown on the ^{99m}Tc-labeled bisphosphonate bone scan." This contra-indication is based on the hypothesis that as both drugs interact at the hydroxyapatite crystal surface of the skeleton, competition may exist for uptake by bone. However, in **chapter 6** it is shown that the combined use

of zoledronic acid has no effect on the uptake of ^{153}Sm-EDTMP in skeletal metastases of hormone-refractory prostate carcinoma. The present results show that combining ^{153}Sm-EDTMP and zoledronic acid is both feasible and safe. Individual patients responded very well to the combined treatment regimen as described above. In **chapter 7** an example is given of a patient who had a complete remission of pain, a PSA decline of > 50% and partial remission of metastases on skeletal scintigraphy. The efficacy data on the patients treated in this phase I setting may be regarded as pilot data. Although the study comprises small numbers the results are of interest because they confirm the utility of bone markers (bone specific alkaline phosphatase [BAP], procollagen type I N propeptide [PINP], N-terminal type I collagen peptide [NTX]) as predictors of clinical outcome, even in small numbers (**chapter 8**). Besides, they were first tested in the treatment monitoring of bone seeking radiopharmaceuticals. Bone markers may well prove to be very useful predictors of response in the treatment with bone seeking radiopharmaceuticals. They should be used in future trials. In **chapter 9** another combination of ^{188}Re-HEDP and capecitabine (Xeloda®) is described. This treatment regimen was tested in a phase I capecitabine dose-escalation study. The combined regimen proved to be feasible and safe. Capecitabine is primarily used as a radiation sensitizer. It offers a convenient therapy with acceptable toxicity, ease of use as oral tablets and low costs. The same is true for ^{188}Re-HEDP. It is homemade on demand and has favourable physical characteristics with a short half-life (16.9 hours) and high beta-energy ($E_{ß\ max}$ 2.12 MeV; $E_{ß\ mean}$ 0.76 MeV). In theory, this high dose rate could lead to improved efficacy with rapid recovery. Phase II efficacy testing using the maximum tolerable dose of 2500 mg/m^2/day capecitabine in combination with 37 MBq/kg ^{188}Re-HEDP is underway.

Conclusions

The most important conclusions that may be drawn from the clinical studies in this thesis are:

1) Patients treated with $^{89}SrCl_2$, ^{186}Re-HEDP or ^{153}Sm-EDTMP emit a spectrum of radiation, including beta-radiation, measurable outside the patient. The calculated effective doses for bystanders are well below the recommended values and do not lead to unacceptable additional radiation burden to health care workers and patients' families.
2) Combined treatment with the bisphosphonate zoledronic acid has no effect on the skeletal uptake of ^{153}Sm-EDTMP in patients with hormone-refractory prostate carcinoma and normal calcemia. Combined treatment is feasible and safe.
3) Markers of bone metabolism are feasible for response monitoring in the treatment of hormone-refractory prostate cancer patients with zoledronic acid in combination with ^{153}Sm-EDTMP. They may prove to be good predictors of response, especially the bone formation markers BAP and PINP. They perform better than PSA and may be used to evaluate the additive effect of radionuclide therapy in multimodality treatments. They should be further tested in clinical trials on bone seeking radiopharmaceuticals.
4) The maximum tolerable dose of capecitabine in combination with 37 MBq/kg ^{188}Re-HEDP is 2500 mg/m^2/day. The combination is feasible and safe.

Chapter 12

Samenvatting in het Nederlands

Marnix G.E.H. Lam

Samenvatting

In dit proefschrift wordt de behandeling van pijnlijke uitzaaiingen van kanker in de botten bestudeerd. Welke behandelmogelijkheden zijn er voor de patiënt? Wat is er nodig om deze behandeling adequaat uit te voeren? Hoe kan de behandeling verder verbeterd worden? Deze vragen worden besproken in deze samenvatting van het proefschrift.
Veel patiënten met kanker krijgen uiteindelijk uitzaaiingen naar de botten. Als dat gebeurt, is de ziekte niet meer te genezen. Er ontstaan vaak klachten van pijn en een verminderde kwaliteit van leven (pijn, verminderde mobiliteit, vermoeidheid, fracturen). Dit proefschrift richt zich voornamelijk op patiënten met prostaatkanker. Dit is de meest voorkomende vorm van kanker bij mannen. Uitzaaiingen naar de botten komen veelvuldig voor en leiden tot een hoge mate van morbiditeit (ziekte) en mortaliteit (sterfte). Om klachten zoveel mogelijk tegen te gaan bestaan er verschillende behandelmogelijkheden. Daartoe behoren onder andere bepaalde vormen van chemotherapie, uitwendige bestraling, hormonale behandeling, pijnmedicatie en zogenoemde botzoekende radiofarmaca.
Botzoekende radiofarmaca zijn radioactieve medicijnen. Ze bestaan uit een radioactief deel (het radionuclide) en een drager. De drager zorgt ervoor dat het medicijn na injectie in de bloedbaan in het bot terecht komt. Het medicijn concentreert zich in de uitzaaiingen. Vervolgens zendt het radionuclide straling uit voor lokale bestraling van de uitzaaiingen in de botten. Door lokale bestraling treedt er reeds na enkele dagen een vermindering van de pijn op. Dit effect houdt enkele maanden aan. Daarna is herhaling van de therapie mogelijk.
Omdat de botten, behalve voor stabiliteit, ook zorgdragen voor de productie van bloed, moet goed gecontroleerd worden of die bloedproductie niet in gevaar komt. Omdat de radioactiviteit zich ophoopt in de botten zal behalve de kanker in de botten ook de 'bloedfabriek' bestraald worden. Dit is een belangrijke bijwerking van botzoekende radiofarmaca.
De meest gebruikte radiofarmaca zijn $^{89}SrCl_2$ (Metastron®), ^{153}Sm-EDTMP (Quadramet®) en ^{186}Re-HEDP, ook wel populair aangeduid als respectievelijk strontium, samarium en rhenium. Zij worden in dit proefschrift uitvoerig besproken.
Omdat botzoekende radiofarmaca radioactieve geneesmiddelen zijn is er een potentieel stralingsrisico voor de omgeving van de patiënten. In de omgang met radioactieve geneesmiddelen is het zeer belangrijk de eigenschappen van de verschillende middelen goed te bestuderen. Waar hoopt het op na injectie (biodistributie)? Hoe, hoeveel en hoe snel verlaat het botzoekende radiofarmacon het lichaam (farmacokinetiek)? Hoe is het verval van de radioactieve stof? Al deze factoren beïnvloeden de stralingrisico's voor de omgeving. In dit proefschrift zijn zij uitvoerig bestudeerd. Het blijkt dat met een aantal simpele maatregelen de behandeling volkomen veilig is voor de omgeving van de patiënt. De kennis die hieruit voort komt is vervolgens gebruikt om de richtlijn voor behandeling van pijnlijke uitzaaiingen in de botten van de European Association of Nuclear Medicine (EANM) inhoud te geven.
Als er uitzaaiingen zijn van prostaatkanker in de botten is de ziekte in een ver gevorderd stadium. Zoals gezegd bestaan er dan verschillende behandelmogelijkheden met elk hun eigen indicaties en voordelen voor de patiënt. Gecombineerd gebruik van verschillende geneesmiddelen tegelijk zou mogelijk complementair kunnen zijn. Wellicht is er zelfs sprake van synergie. Voordat dit onderzocht kan worden is het echter van het grootste belang dat

eerst geëvalueerd wordt of het veilig is om bepaalde middelen samen te gebruiken en of er geen interactie of competitie is waardoor de middelen elkaar zouden kunnen tegenwerken. In dit proefschrift werden twee combinaties klinisch getest. Dat wil zeggen bij patiënten met uitzaaiingen in de botten van prostaatkanker.
Het botzoekende radiofarmacon ^{153}Sm-EDTMP (Quadramet®) of samarium werd gecombineerd met zoledroninezuur (Zometa®). Zoledroninezuur is een bisfosfonaat. Het bindt, net als samarium, aan het bot en accumuleert op die plaatsen in het bot waar zich uitzaaiingen bevinden. Gelijktijdig gebruik wordt volgens de registratie in Europa officieel afgeraden vanwege vermeende competitie. Echter, uit de studie beschreven in dit proefschrift blijkt dat er geen competitie optreedt. Gecombineerde toediening is mogelijk en tegelijk ook veilig voor de patiënten. Er traden geen onverwachte bijwerkingen op.
Een aantal patiënten uit de boven beschreven studie reageerde erg goed op de behandeling. Beter dan verwacht van elke therapie afzonderlijk. Zij hadden gedurende een half jaar geen pijn meer, het Prostaat Specifiek Antigeen (PSA) was flink gedaald en de uitzaaiingen leken in uitzonderlijke gevallen zelfs minder geworden te zijn. Uit de data blijkt niet alleen dat de behandeling voor geselecteerde patiënten zeer effectief zou kunnen zijn, maar vooral ook dat zogenaamde botmarkers goede voorspellers zijn van dit effect. Het is bekend dat het PSA niet zo goed correleert met de kliniek. Dat wil zeggen: een daling van het PSA als gevolg van de behandeling betekent niet altijd dat het beter gaat met de patiënt. In plaats van het PSA zouden zogenaamde botmarkers wat dat betreft betere voorspellers kunnen zijn van een gunstig effect voor patiënten. De eerste resultaten bij patiënten die behandeld zijn met botzoekende radiofarmaca lijken in ieder geval gunstig te zijn.
De tweede combinatie betrof het gelijktijdig gebruik van het botzoekende radiofarmacon ^{188}Re-HEDP (rhenium) en capecitabine (Xeloda®). Capecitabine is chemotherapie. Het zijn tabletten voor oraal gebruik, die gedurende twee weken rond de injectie van rhenium worden gegeven. Capecitabine heeft relatief weinig bijwerkingen en zou goed kunnen dienen als zogenaamde radiosensitizer (het gevoeliger maken voor straling). Het totale effect zou daarmee verhoogd kunnen worden. In deze studie werd langzaam de dosis capecitabine verhoogd. Dit bleek geen onverwachte bijwerkingen op te leveren. Daarom zal de effectiviteit van deze gecombineerde therapie bestudeerd worden met de maximale dosis capecitabine (2500 mg/m^2/dag). Deze studie is gaande.

Conclusie

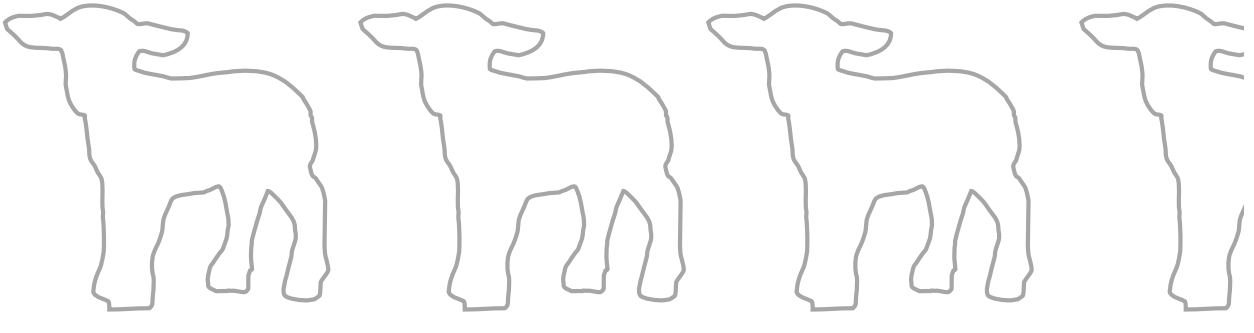
Uit dit proefschrift kunnen de volgende conclusies getrokken worden:

1) Behandeling van pijnlijke botuitzaaiingen met botzoekende radiofarmaca is niet alleen veilig voor de patiënt maar ook veilig voor zijn omgeving.

2) Het is mogelijk om het botzoekend radiofarmacon ^{153}Sm-EDTMP (Quadramet®) gelijktijdig te gebruiken met het bisfosfonaat zoledroninezuur (Zometa®). Er treedt geen competitie op en het is veilig voor de patiënt.

3) Het is mogelijk om het botzoekend radiofarmacon ^{188}Re-HEDP gelijktijdig te gebruiken met het chemotherapeuticum capecitabine (Xeloda®). Dit is veilig voor de patiënt.

4) Bij gecombineerde behandeling met het botzoekende radiofarmacon ^{153}Sm-EDTMP (Quadramet®) en het bisfosfonaat zoledroninezuur (Zometa®) zijn botmarkers goed te gebruiken om het effect van de behandeling te evalueren.



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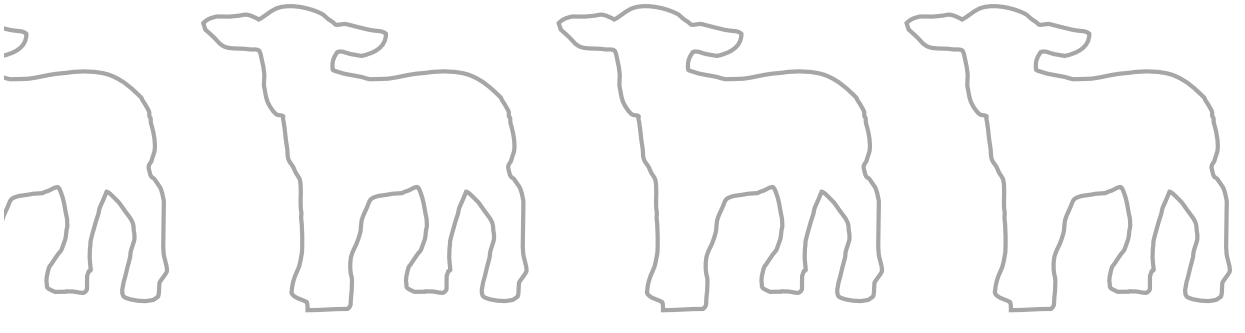


Verschillende personen zijn direct en indirect betrokken geweest bij mijn promotie. Op de eerste plaats wil ik daarbij de patiënten bedanken die mee hebben gedaan aan het klinisch onderzoek. Hun positieve houding is een les voor ons allen.

Voorts is een goed begin het halve werk. Dat goede begin bestaat in de klinische wetenschap uit interesse in je vakgebied.

Dr. B. de Keizer, beste Bart, dank voor je vriendschap en de introductie in ons mooie vak. Door jou werd mijn interesse voor Nucleaire geneeskunde gewekt. Inmiddels werken we al jaren samen als nucleair geneeskundigen en als radiologen in opleiding. En natuurlijk de racefiets. Aan het infuus na Alpe d'Huez, kopje thee bij het kaarten of toch maar gewoon een glaasje wijn? Blijft lastig, dat fietsen.

Dr. J.M.H. de Klerk, geachte co-promotor, beste John, mijn tijd in de Nucleaire geneeskunde begon goed. Jouw enthousiasme was nogal aanstekelijk. Via het 'trapoverleg', kabouter prikkeprak en New Orleans kwamen we tot goede ideeën. Ik hoop nog lang met je te kunnen samenwerken.

Dr. B.A. Zonnenberg, geachte co-promotor, beste Bernard, de patiënt staat altijd voorop. Dat is wat je uitstraalt en dat is wat je uitdraagt. Ik heb veel van je geleerd, niet alleen op medisch gebied. Dank.

Prof. Dr. P.P. van Rijk, geachte promotor, beste Peter, dank voor je vertrouwen. Toen de integratie met Radiologie concreet in beeld kwam kon ik mede dankzij jou de eerste stappen in die richting zetten.

Dr. Ir. A. Hoekstra, beste Oane, de discussies en berekeningen bij jou thuis aan de keukentafel waren onvergetelijk. Boeken van decennia terug werden er bijgehaald om stellingen te bewijzen. Ondanks de nodige tegenwerking is het ons toch gelukt om ons punt te maken.

Mevr. A. van Dongen, beste Alice, je was voor mij en voor de afdeling een wetenschappelijk mentor. Zonder jouw inspanningen zouden veel klinische studies nooit tot stand zijn gekomen. Daarbij bewaakte je altijd zeer resoluut de kwaliteit en de voortgang van het onderzoek. Dank voor al je hulp.

Mevr. T. B. Bosma, beste Tjitske, na het afscheid van Alice kwam voor jou enige tijd later de uitdaging om haar werkzaamheden over te nemen. Vol enthousiasme ging je er tegenaan. Ik heb respect voor hoe snel je in die rol bent gegroeid. Je bent bereid te leren en aan te pakken. Inmiddels heb je daarbij ook al de nodige resultaten behaald.

Drs. M.G.G. Hobbelink, beste Monique, het zijn geen gemakkelijke tijden geweest. Het is dan prettig om te weten dat je er niet alleen voor staat. Ik waardeer je loyaliteit en je inzet. Zonder jouw aanwezigheid was er geen Nucleaire geneeskunde in Utrecht.

Dr. J.W. van Isselt, beste Hans, veel aspecten van het vak heb ik van jou geleerd. Daarnaast heb ik veel aspecten van jou leren kennen. Weet dat ik je zeer waardeer vanwege je kennis van het vak, je liefde voor de patiënt en je vriendschap.

Dr. A. Dahmane, dear Amel, thank you for your input in difficult matters regarding our clinical studies. It was nice working with you.

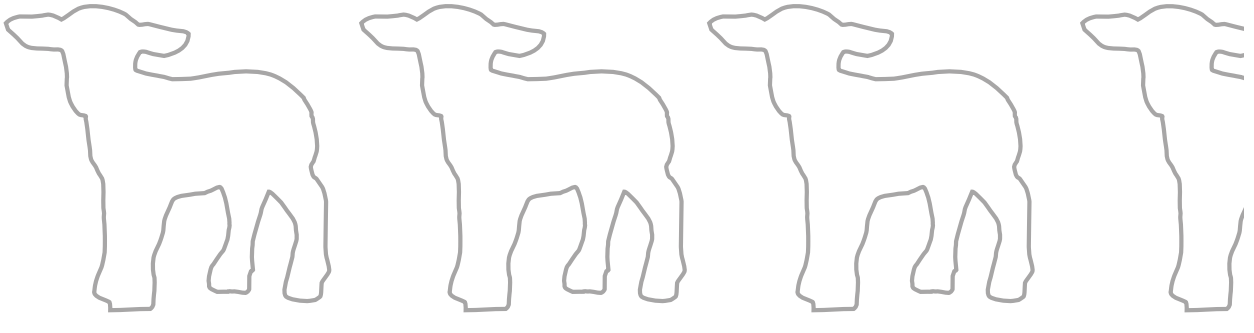
De verpleging van de stralingsunit van de afdeling Nucleaire geneeskunde wil ik bedanken voor de liefdevolle verzorging van de patiënten. De patiënten zijn daar altijd zeer over te spreken. Dat telt.

De medisch nucleair werkers wil ik bedanken voor de goede samenwerking en het werk dat jullie hebben verricht om de klinische studies mogelijk te maken.

Overige collega's van Nucleaire geneeskunde, de kracht van onze groep is de teamgeest en het multidisciplinaire karakter van ons vakgebied. Dat moeten we koesteren. Vanuit die basis kunnen we profiteren van de mogelijkheden die de integratie met Radiologie ons biedt. Dank voor de samenwerking.

Bij het doen van wetenschappelijk onderzoek is het belangrijk dat je onafhankelijk en vrij kunt denken. Pa en ma, dank voor alles wat jullie mij hebben meegegeven.

En tot slot natuurlijk Mariette en Janne. Mariette, dank voor je liefde, steun en geduld. Wij kunnen het wel aan zo met z'n twee. Genieten van Janne en al het moois dat nog komen gaat!



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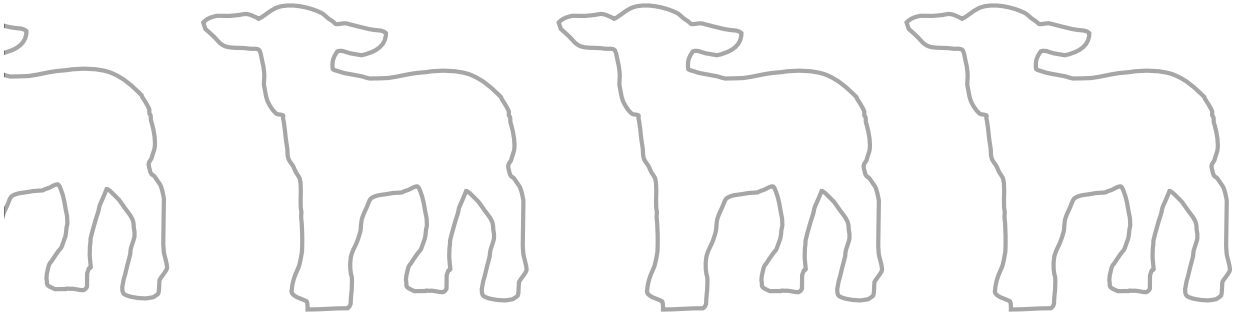
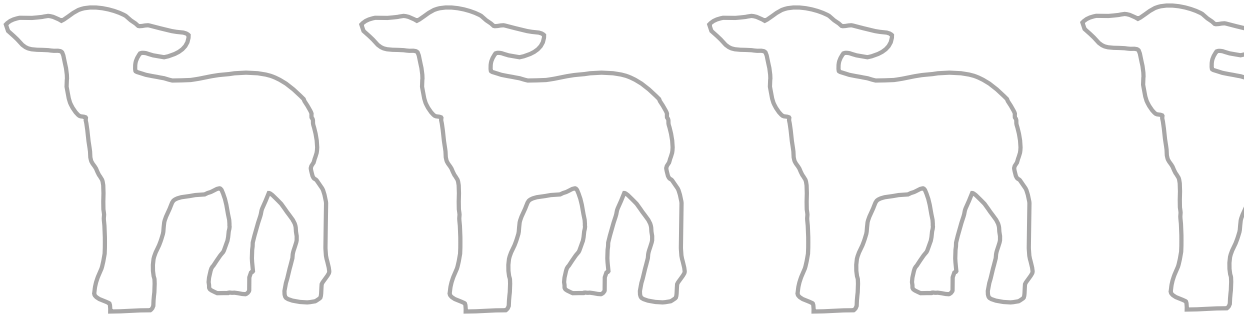
Publications



The author of this thesis, Marnix Gerard Ernest Hendrik Lam, was born on October 24, 1975 in Berkel en Rodenrijs, The Netherlands. After graduating at the Stedelijk Gymnasium Leiden in 1994, he enrolled in the study Pharmaceutical Sciences at Utrecht University in the same year. The next year he enrolled in medical school at Utrecht University. After studying medical sciences, and the world behind the steering wheel of an ugly red duck, he received his medical board certificate in 2003 and started a residency in Nuclear Medicine. Dr. John de Klerk and Dr. Bernard Zonnenberg triggered his interest in clinical research with a particular interest in bone seeking radiopharmaceuticals. The first clinical study started in 2004. During his residency he continued working on clinical research in the field of nuclear therapy with a focus on oncology and bone seeking radiopharmaceuticals. This eventually culminated in the present thesis. Besides clinical research he gained interest in Radiology, augmented by the growing collaboration between the two medical specialties at the University Medical Center Utrecht, but also by the growing dialogue nationally and internationally. After completion of his residency in Nuclear Medicine in 2007, he started a second residency in Radiology. Currently he is member of the medical staff of the department of Radiology and Nuclear Medicine, Nuclear Medicine Physician and Radiologist in training. Besides clinical work he continues his clinical research. His special interest areas include oncology, nuclear therapy and image guided therapy.



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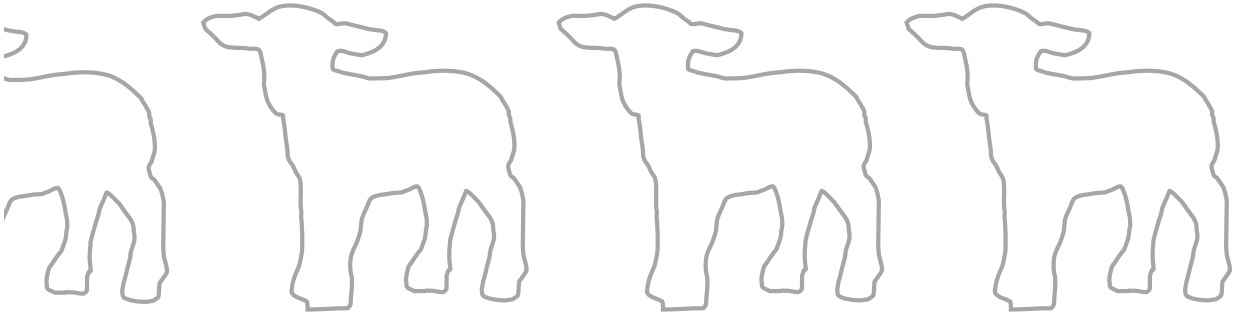
Publications



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