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High dose chemotherapy in breast cancer reviewed

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Breast cancer develops in approximately 10% of women in Western Europe and the United States of America (1-4). Of those who contract the disease, one out of three to four will die (1-4).
Despite modern treatment techniques (3,4), the mortality rate has remained essentially unchanged in the last 50 years.

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It is well known that the probability of survival at 10 years after diagnosis correlates with the number of involved axillary nodes at the time of mastectomy (1,2,5). Following local regional treatment with surgery, women with 1-3 axillary lymph node metastases have a 10 year relapse rate of 65%-70%. The outlook for women with 4 or more lymph node metastases is even worse, with a 10 year relapse rate of 84%-86% (6). A meta-analysis conducted by The Early Breast Cancer Trialists Collaborative Group (EBCTC) confirmed the data of randomised trials that the disease-free and overall survival of premenopausal stage II (axillary lymph node metastases) breast cancer patients can be improved by adjuvant chemotherapy (7). Although the benefit of adjuvant chemotherapy could be observed in all nodal categories, the final

outcome is mainly determined by the number of involved axillary nodes (8). The differences were most marked in premenopausal women with 1-3 positive nodes. Despite modern chemotherapy, the prognosis for women with 4 or more positive nodes is still poor and the therapy for these women clearly needs improvement.

Metastatic breast cancer is an essentially incurable disease (1,2,9). The median survival for women with metastatic breast cancer is approximately 2 years. The response rates for first line chemotherapeutic regimens are reported to be between 40% and 60%, with median durations of 6-12 months (1,2,9).

Clinical, theoretical and experimental data suggest that breast cancer recurs despite initial response to chemotherapy because of endogenous or acquired resistance to cytostatic drugs (10,11). One strategy of circumventing the emergence of resistance is to use a combination of cytostatic drugs instead of a single agent (12,13). Despite higher remission rates (13), this approach has not clearly improved the final outcome for patients with multiple axillary lymph node metastases or distant metastatic disease (1,2,9). Another strategy to overcome resistance is to increase the doses of the chemotherapeutic agents, a concept excellently reviewed by Henderson et al and Frei et al (10,11).

Rationale for high dose chemotherapy in breast cancer

The importance of dose intensity with respect to the treatment of patients with breast cancer is a subject of considerable debate and controversies. There is neither consensus about the dosages and the combinations of drugs to be used, nor about the timing and schedule of the chemotherapy. It is not clear whether one should aim at a very intensive schedule in a short period or at giving a cumulative drug dose within a defined period of time (10). As outlined by Henderson and colleagues (10), the success of high dose intensity treatment depends upon the characteristics of the tumour, the drugs used and the dose-schedule interactions (10).

Experimental data indicate that human breast cancer growth follows the Gompertzian model, in which the growth is a function of the starting size of the tumour N(0), the time of growth t, a constant b and limiting size $N_\bullet$ ($N(t)=N(0) \times \exp\{k \times [1-\exp(-bt)]\}$, $k=\log_e[N(\bullet)/N(0)]$). The implications of this model with respect to the treatment of breast cancer have been excellently summarised by Norton and Henderson et al (10,14) and will not be repeated in this article. According to this model, breast cancer should be treated at an early stage (i.e. with minimal disease burden) and intensively for best results (14).

The clinical situation is, however, far more complex. The use of very high dose therapy is based on the hypothesis that the dose response will be steep and linear throughout. Provided that the tolerance of normal tissues for the given drug(s) is acceptable, one high dose regimen may be all that is required to obtain cure in a tumour with such behaviour (10). Breast cancer, however, with its inherently rather slow proliferation rate, may follow another dose-response curve, showing a shallow slope or showing a plateau phase beyond a certain threshold dose. In these circumstances, an increase of the dose beyond a certain level will only provide a marginal improvement in results at the cost of considerable toxicity (10).

Studies, discussed below, will show that dose intensity can improve the results obtained with chemotherapy in breast cancer, although the benefit is modest and, in other studies, is too preliminary to draw definite conclusions.

With respect to the drugs used, laboratory and experimental data show that resistance to chemotherapeutic drugs, especially the alkylating agents, can be overcome by increasing the dose 5-10 fold (10,11). Alkylating agents have a steep-dose response curve which, in contrast to agents like vincristine and the antimetabolites, is maintained through multiple logs of cell kill (10,11). These drugs are not cell cycle-specific, less schedule-dependent, minimally prone to cross resistance with other alkylating agents and not known to produce resistance by mechanisms of gene amplification or pleiotropic multidrug resistance (10,11). Alkylating agents are thus suited to be incorporated into high dose regimens for patients with breast cancer because of their intrinsic properties and the fact that breast cancer is sensitive to many alkylating drugs.

The dose limiting toxicity of many chemotherapeutic drugs, including the alkylating agents, is myelotoxicity, which can be overcome by the use of haematopoietic growth factors and autologous bone marrow or peripheral stem cell support. It has been shown that with the use of haematopoietic growth factors the dose of chemotherapy could be increased by 1.5-2 fold in young patients with breast cancer (15,16). Further dose escalation requires autologous bone marrow or peripheral stem cell support. Peripheral stem cell support is increasingly used instead of autologous bone marrow because it results in a much more rapid engraftment, associated with a reduction in duration of the pancytopenic period and complications due to the high dose treatment (17). The development of haematopoietic growth factors and peripheral blood stem cell support have paved the way to studying the dose-response concept in more detail than was feasible in the past because of the reduction of morbidity and mortality associated with high dose chemotherapeutic regimens.

Results of high dose chemotherapy in metastatic breast cancer

The response to chemotherapy in metastatic breast cancer has been shown to be linked to dose intensity. In a retrospective study of standard dosed chemotherapy regimens, Hryniuk et al found a relationship between response rate, duration of the response and the administered chemotherapy dose (18). Data from randomised trials of dosages feasible without growth factor or peripheral stem cell transport are, however, not conclusive. Despite the fact that higher remission rates could be achieved with higher dosages, there was no clear survival advantage (19-22).

The introduction of haematopoietic growth factors has facilitated the clinical evaluation of dose intensity. Higher remission rates could be achieved with dose escalation, but, as was the case with the studies without growth factors, higher remission rates did not correspond to significantly better duration of responses or survival times (15,23,24).
The fact that no major improvement in survival is detectable with enhanced dose intensity might be due to minor differences in the actual dosages administered or to lack of any effect of standard-dosed chemotherapy on survival in metastatic breast cancer.
Results of high dose therapy with support of autologous bone marrow in metastatic breast cancer have been reported by Antman et al (25). Of the 267 transplanted women with metastatic breast cancer, who were treated with high dose chemotherapy followed by autologous bone marrow transplantation, 26% were in continuous complete remission, with durations reported to be between 10 and 42+ months after the transplantation. These encouraging results were, however, achieved at the cost of considerable morbidity and mortality. Twenty-six percent of the women died due to complications of the high dose chemotherapy (25). Partial remissions achieved after high dose chemotherapy were of short duration. This can be explained by the fact that the effect of 2 log cell kill (i.e. partial remission, 50% reduction of all measurable metastatic disease) is small if tumour-growth kinetics are assumed to be in accordance with the Gompertzian model (14,25). The results summarized by Antman et al. (25) could be confirmed by other studies (26-30). In a selected patient population consisting of young women in good condition, durable complete remission rates between 15 and 30% can be achieved in patients with chemotherapy sensitive disease.
The morbidity and mortality rate of this procedure could be diminished by the use of peripheral blood stem cell transplants (faster bone marrow recovery) and adjustment of the used regimens for high dose intensity treatment, with mortality rates reported to be between 5 and 10%.

Adjuvant high dose therapy in breast cancer patients with axillary lymph node metastases at the time of initial diagnosis

As outlined above, the prognosis for (premenopausal) patients with axillary lymph node metastases can be improved by adjuvant chemotherapy (1,2,6-9). Also for this subgroup of patients, a dose response relationship has been reported (31,32). Patients receiving at least 85% of the planned dose of chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) had a better overall (52%) and disease free survival rate (49%) at 20 years after the initial diagnosis than patients who received less (31). This conclusion was, however, derived from a retrospective analysis and it is known that numerous problems can be associated with this kind of analysis. The distribution of patients within each dose level is possibly the result of patient selection that may also affect treatment outcome, independent of the administered dose of chemotherapy. Although several retrospective analyses of higher versus lower doses of adjuvant chemotherapy report similar results to Bonadonna et al (31), an equal number of adjuvant studies analysed in this way fail to show any survival advantage (32).
Wood et al (33) conducted a randomised trial of different levels and dose intensity of cyclophosphamide, adriamycin and 5-fluorouracil (CAF) chemotherapy in patients with 1-3 axillary lymph node metastases. They randomised 1572 node-positive breast cancer patients to receive three different schedules with CAF. After a median follow-up of 3 years, the results show a statistically significant disease-free survival (74% versus 64%, $p<0.00001$) and overall survival advantage (92% versus 84%, $p=0.004$) for the patients randomised to high dose CAF (who received exactly twice the dose of low dose CAF) in comparison to those who received low dose CAF. There was no statistically significant difference between the disease free and overall survival time between the patients receiving the moderate or high dose CAF schedule (33). Thus, the results of this trial are compatible with either a dose-response effect or a threshold effect (32, 33).
Referring to the article by Bonadonna et al (31), Henderson addressed some important questions in an editorial published in the same journal (34). The first question was whether adjuvant chemotherapy is able to cure patients whereas others derive no benefit at all or induces only transient survival advantage with no or very few patients cured. The latter possibility seems more probable, since there was no difference between the percentage of women dying of breast cancer in the control group or the group receiving adjuvant chemotherapy: only the time at which they died was different (31, 34).
The second question Henderson addressed was whether the survival advantage induced by adjuvant chemotherapy was either due to ovarian ablation or to the direct cytotoxic effect of the adjuvant chemotherapy. If the results are primarily due to ovarian ablation, then therapy involving manipulation of growth factors might be promising (35, 36). If the results are due to direct cytotoxicity, high dose intensity chemotherapy might improve the outcome of patients with node positive disease (34).
Most data published on the treatment of breast cancer with high dose chemotherapy are derived from studies of patients with metastatic disease, having a high tumour load.
In similar situations of high tumour load, other malignancies such as acute leukaemia, germ cell tumours and small cell lung cancer have shown to be incurable. Several malignancies, including acute leukaemia and non-Hodgkin lymphoma of intermediate and high grade malignancy can be cured with high dose chemotherapy when only minimal residual disease is present (37, 38).
Breast cancer growth in accordance with the Gompertzian model (14), the experience in other malignancies that cure with high dose chemotherapy can only be achieved in situations of minimal residual disease and the fact that patients with metastatic

breast cancer in complete remission are those that profit most of high dose therapy, are arguments in favour of using this kind of therapy in patients who have not had prior chemotherapy, have micrometastatic and still have chemo-sensitive disease. High dose chemotherapy in the adjuvant setting has become more feasible, because of the reduction of mortality and morbidity due to the use of peripheral stem cell support and the use of haematopoietic growth factors.
Many institutions are currently investigating adjuvant high-dose therapy in patients with more than 3 lymph node metastases (39-41). A non-randomised study by Peters et al (39) in 85 patients with 10 or more axillary lymph node metastases has shown that high dose chemotherapy can lead to an actuarial event free survival at a median follow-up of 2.5 years of 72%. A comparison with three historical or concurrent Cancer and Leukemia Group B (CALGB) adjuvant chemotherapy trials selected for similar patients showed an event free survival at 2.5 years between 38% and 52% (40). Therapy related mortality was, however, 12% (39).
In a Dutch study reported by de Graaf et al (40), 24 breast cancer patients with 5 or more axillary lymph node metastases were treated with induction chemotherapy followed by high-dose chemotherapy and autologous bone marrow support. Median observation time was 3 years, the disease free survival at 5 years is predicted to be 84%, which is clearly better than for historical controls (40). Two out of 24 women died due to toxic complications of the high dose regimen.
A recent report about 29 patients with high risk breast cancer showed that high dose chemotherapy followed by peripheral stem cell support is feasible without toxic deaths (41).
In the near future, ongoing studies will show whether or not high dose treatment followed by autologous bone marrow or peripheral stem cell support will improve the dismal prognosis of breast cancer patients with (multiple) axillary lymph node metastases.

Which patients benefit from high dose treatment with autologous bone marrow or peripheral stem cell support?

It has become increasingly evident that high dose chemotherapy in the autologous transplant setting should be restricted to patients responding to standard doses of chemotherapy with minimal residual disease (14,37,38). Patients with high tumour load, who have been heavily pretreated with resistant disease, will not benefit from this approach (25-30).
Advancing knowledge of molecular genetics might be of help to find useful markers for improved selection of patients in the near future (42,43).
Because of the morbidity associated with high dose chemotherapy in combination with autologous bone marrow or peripheral stem cell transplantation, it is only feasible to apply this type of treatment to patients below the age of 55-60 years with no serious comorbid diseases.
Approximately 80% of breast cancer patients are 50 years of age or older at the time of the initial diagnosis and 40% is over 69 years of age (3,7,44).
It is clear from these facts that only a very selected patient population will benefit from high dose chemotherapy in autologous transplant setting and that we have to focus also on other treatment modalities in order to improve the prognosis for patients with high risk or metastatic breast cancer.

Conclusions

Laboratory and experimental data show a dose response curve for cytostatic drugs, especially for the alkylating agents. Clinical evidence for a steep dose response relationship is limited. For breast cancer this evidence is often derived from retrospective or non-randomised trials. Data available from randomised trials without support of autologous bone marrow or peripheral stem cell support fail to show a significant survival advantage for patients with advanced breast cancer.
Despite promising results from small trials with high dose intensity treatment in a selected population of young patients with high risk or metastatic breast cancer, they do not justify the use of this approach outside the setting of clinical studies. The most optimal timing and best preparative regimen have to be defined. We have to gain more knowledge of selecting the patients who benefit most from such an approach, as well as to continue focusing on improvement of efficacy, reduction of non-haematologic toxicities and the high costs of this treatment.

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Summary

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Laboratory and experimental data show a dose response curve for cytostatic drugs, especially for alkylating agents. For many malignancies, clinical evidence of a dose response relationship is limited .

The dose limiting toxicity of most cytostatic drugs is myelosuppression, which can be circumvented by the use of haematopoietic growth factors and/or autologous bone marrow or peripheral stem cell support.

Clinical data derived from studies in patients with metastatic breast cancer, show that dose escalations of 1.5-2 x standard dosages, possible without autologous bone marrow or peripheral stem cell transport can induce higher remission rates, which did not, however, correspond to a significant survival advantage. Despite promising results from small trials with high dose intensity treatment in combination with peripheral stem cell or bone marrow support (depending on the schedule used, dose escalations possible of 5-10 x the standard dosages) in a selected patient population with high risk or metastatic breast cancer, they do not justify the use of this approach outside the setting of clinical studies. We have to gain more knowledge of selecting the patients who are likely to profit from high dose chemotherapy as well as to continue focusing on improvement of efficacy, reduction of the considerable morbidity and costs of this treatment.

Key-words: breast cancer, high dose chemotherapy, peripheral stem cell transplantation, autologous bone marrow transplantation, haematopoietic growth factors.