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High-dose chemotherapy regimens for solid tumors

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Abstract

High-dose chemotherapy with blood progenitor cell transplantation is increasingly recognized as a potentially valuable treatment for breast cancer, germ cell cancer, ovarian cancer and other solid tumors. A variety of cytotoxic drugs, particularly alkylating agents, have been investigated either alone or in combinations. Current, predominantly small, phase I and phase II clinical trials to not adequately compare the efficacy of these regiments and patterns of dose-limiting extramedullary toxicity are emerging. Busulfan, carmustine (BCNU) and mitomycin C cause veno-occlusive disease (VOD) of the liver in some patients and the latter two agents also cause interstitial pneumonitis. Cisplatin and ifosfamide only allow minor dose escalation before renal failure becomes prohibitive. Cyclophosphamide, thiotepa, melphalan and etoposide allow substantial dose escalation above standard and are mainly associated with mucositis. Moderate dose escalations of mitoxantrone and carboplatin are possible, limited by cardiotoxicity and neurotoxicity, respectively. Advances in supportive care have abolished bone marrow suppression as the dose-limiting toxicity in chemotherapy. Severe and potentially fatal extramedullary toxicity following high-dose chemotherapy can only be avoided by administering agents with predictable toxicity patterns and by carefully considering their clinical pharmacology.

Introduction

High-dose chemotherapy with autologous blood stem cell support is increasingly recognized as a potentially valuable treatment in the management of solid tumors. The situation in some chemosensitive solid tumors, such as relapsing germ cell

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cancer or childhood neuroblastoma, resembles the state of affairs of a few years ago in non-Hodgkin's lymphoma. Anecdotal evidence and studies employing historical control groups have suggested the superiority of high-dose chemotherapy over standard-dosed treatment, but randomized studies are lacking. Non-randomized studies (1, 2, 3) indicate efficacy in the adjuvant treatment of high-risk breast cancer and data from the American and European Bone Marrow Transplantation Registries (4, 5) suggest that a specific group of patients with advanced breast cancer may achieve long-term disease-free survival after high-dose chemotherapy. Results in ovarian cancer and in small-cell lung cancer may be viewed as 'encouraging' but are essentially inconclusive (6).

Recent advances in supportive care have significantly contributed to the feasibility of high-dose chemotherapy. Hematopoietic growth factors and peripheral blood progenitor cell transplantation have led to a marked reduction in the duration of the aplastic period following high-dose chemotherapy. With the *in vitro* expansion of hematopoietic progenitor cells on the horizon, cancer chemotherapy is entering a new era when myelosuppression is no longer the dose-limiting toxicity. Inevitably, damage to other tissues and organs is becoming more pronounced. It is this frequently irreversible or even lethal organ toxicity that must be dealt with if further dose intensification is to be achieved.

There are currently two approaches to prevent severe extramedullary toxicity in patients exposed to high-dose chemotherapy. The first is to prevent overdosing, which can be achieved by carefully considering the pharmacology of the agents to be employed and to correct for renal function of hepatic abnormalities or even to apply a test-dose to predetermine pharmacokinetic parameters. Another approach is to avoid drugs or combinations of drugs that are known to be associated with excess toxicity. Careful consideration of the mechanisms of action, pharmacokinetics and toxicity profiles of the different agents to be used is therefore imperative.

In the absence of meaningful efficacy evaluations, the frequency and prevention of severe organ toxicity is a critical consideration in the selection of high-dose regimens for clinical studies.

Single agents in high-dose therapy

The cytotoxic agents most frequently used in the autotransplant setting for solid tumors will be discussed separately. An overview of the pharmacokinetics and toxicity of each drug as used in high-dose chemotherapy regimens will be given (Table 1).

Cyclophosphamide

Cyclophosphamide belongs to the group of oxazaphosphorines, which are derivatives of nitrogen mustard. Cyclophosphamide is a pro-drug and requires hydroxylation by hepatic cytochromes P450 to exert its cytotoxic activity. 4-Hydroxycyclophosphamide and its tautomer, aldophosphamide, yield the strong alkylating agent phosphoramide mustard after elimination of acrolein (7, 8). Cytotoxicity is believed to occur by the formation of crosslinks between DNA strands.

Table 1. Cytotoxic agents most frequently used in high-dose chemotherapy regimens for solid tumors

Drug	Standard dose single agent, (mg/m^2)	Dose-limiting toxicity single agent	MTD high-dose single agent in ABMT (mg/m^2)	Commonly used dose in combination with ABMT, (mg/m^2)	Organ toxicity in high-dose regimens
Cyclophosphamide	400–1200	Myelosuppression	7,000	4,000–8,000	Pancarditis, hemorrhagic cystitis
Ifosfamide	5,000–9,000	Renal failure	16,000	10,000–12,000	Renal failure, hemorrhagic cystitis
Cisplatin	75–100	Renal failure	200	165	Renal failure, neuro-ototoxicity
Carboplatin	250–400	Myelosuppression	2,400	800–1,800	Neuro-ototoxicity, renal failure
Thiotepa	30–65	Myelosuppression	1,125	480–800	CNS, mucositis
Carmustine	200	Hepatoxicity	1,500	300–1,200	Pneumonitis, VOD
Mitoxantrone	12–14	Myelosuppression	NA	60	Muscositis, heart failure
Melphalan	30	Myelosuppression	245	140–220	Muscositis
Busulfan	2–10 mg/day	Myelosuppression	NA	16 mg/kg	VOD, hyperbilirubinemia
Etoposide	300–500	Myelosuppression	2,000	1,200–1,800	Muscositis
Mitomycin C	10–15	Myelosuppression	50	50	VOD, pneumonitis, heart failure

MTD = maximum tolerated dose, ABMT = autologous bone marrow transplantation, CNS = central nervous system, NA = not available, VOD = veno-occlusive disease.

Acrolein itself is devoid of cytotoxic properties. It is excreted in the urine and is the major cause of hemorrhagic cystitis associated with cyclophosphamide therapy (9).

Pharmacokinetics and toxicity

Cyclophosphamide metabolism exhibits autoinduction as shown by a decrease in plasma half-life following repetitive intravenous (IV) administration (7, 11, 12), with mean plasma half-lives of 8.7 ± 4.6 h (range 4.4–25.0) and 3.6 ± 0.9 h (range 1.7–6.0) after two consecutive doses of 60 mg/kg of cyclophosphamide, respectively (11). The area under the concentration-time curve (AUC) of the active metabolites remains, however, unchanged under these conditions explaining why the therapeutic and toxic effects of cyclophosphamide are not influenced by the autoinduction phenomenon (7). Elimination occurs mainly by hepatic metabolism and approximately 10% is excreted unchanged into the urine (13, 14). Dose adjustment of cyclophosphamide is not required in the presence of liver or renal dysfunction (15).

The maximum tolerated dose (MTD) of cyclophosphamide, without bone marrow support, has been reported to be 7 g/m^2, the dose-limiting toxicity being myelosuppression (10). In high-dose chemotherapy regimens with autologous bone marrow support, the dose-limiting toxicity of cyclophosphamide is cardiotoxicity. In doses over 1.55 g/m^2 per day, cyclophosphamide-associated cardiotoxicity has been reported in 25% of patients (16). Endothelial damage may occur inducing myocardial necrosis which can cause severe and often refractory congestive heart failure. This usually occurs 1-10 days after the first dose of cyclophosphamide (16).

Hemorrhagic cystitis, due to the hepatic metabolite acrolein, has been observed in 12 to 35% patients following high-dose cyclophosphamide therapy (17). Simultaneous administration of sodium-2-mercapto-ethane sulphonate (mesna) is widely used and prevents the occurrence of hemorrhagic cystitis. Forced hydration, urinary alkalinization and bladder irrigation have also been used, alone or in combination, but the optimal combination for the prevention of cyclophosphamide-induced hemorrhagic cystitis is, however, still a matter of debate (17, 18).

In addition, a transient but direct toxic effect of cyclophosphamide on the renal tubules has been described which may mimic the syndrome of inappropriate antidiuretic hormone secretion (19).

Ifosfamide

Ifosfamide is an oxazaphosphorine, which, like its analog cyclophosphamide, requires biotransformation in order to become cytotoxic (20). Ifosfamide is activated through hydroxylation by the hepatic cytochrome P-450 mixed function oxidases yielding 4-hydroxy-ifosfamide, a potent alkylating agent *in vitro*, with a steep linear log dose-response curve (21).

4-Hydroxyifosfamide is in equilibrium with its tautomer aldoifosfamide. Both can be inactivated either by oxidation with aldehyde dehydrogenase or produce the cytotoxic alkylating species ifosforamide mustard by elimination of acrolein (20). When compared with cyclophosphamide metabolism, the rate of ring hydroxylation is reduced by the presence of the ring N-chloroethyl group in the ifosfamide molecule. Consequently, oxidation to inactive metabolites is a more important

metabolic pathway for ifosfamide (20). As a result, serum concentrations of the activated ifosfamide species are lower than those of activated cyclophosphamide, measured after the same dose of the parent drug. This explains the difference in dose between cyclophosphamide and ifosfamide that is required to obtain equitoxic alkylating effects; for this purpose, the dose of ifosfamide must be 3 to 4 times higher than that for cyclophosphamide (20, 22).

Ifosforamide mustard induces cytotoxicity by DNA crosslinking. Based on studies in animals, ifosfamide has been reported to be more active and less toxic than cyclophosphamide with an improved therapeutic/toxic ratio achieved with a fractionated dose schedule (22).

Pharmacokinetics and toxicity. The pharmacokinetic parameters of ifosfamide exhibit large inter- and intrapatient variability, suggested to arise mainly from genetic factors (20).

Ifosfamide is commonly administered intravenously. Fractionated dose schedules are used which allow for an increase of the total dose by nearly 50% (23). The mean elimination half-life is 6 h and may be prolonged in obese individuals. Similar to cyclophosphamide, ifosfamide induces its own metabolism as shown in a decreased elimination half-life and an increased total body clearance following repeated daily administrations (20). Less than 20% of ifosfamide is bound to plasma proteins. The concentration of the active compound 4-hydroxyifosfamide detected in cerebrospinal fluid (CSF) is about 15% of that measured in the plasma. Between 2.5 and 50% of the administered dose is excreted unchanged in the urine (20).

Animal studies and phase I and II studies in various solid tumors have suggested a lack of cross-resistance between ifosfamide and cyclophosphamide (24–26).

The dose-limiting toxicity of high-dose ifosfamide is renal failure, manifested by renal tubular acidosis. This has been observed at a dose of 18 g/m^2, given in divided doses over 4 days (22). At that dose level, hematological toxicity has not required autologous bone marrow support. However, due to renal toxicity, the maximum tolerated dose has been reported to be 16 g/m^2, provided that adequate uroprotection with mesna is performed. In the absence of mesna, hemorrhagic cystitis has been the dose-limiting toxicity, with an overall incidence of 18 to 40%.

Neurotoxicity is dose-related and may be due to the presence of the metabolite chloroacetaldehyde. As with busulfan, decreased levels of glutathione, responsible for the detoxification of chloroacetaldehyde, could be the underlying mechanism (27). The symptoms are somnolence, hallucinations, confusion and disorientation and usually begin on day 4 of the administration. The symptoms continue for a median of 5 days. The reversible neurotoxicity of ifosfamide seems to occur more often in patients who also develop renal failure (22).

Pretreatment with doxorubicin may compound ifosfamide-related congestive heart failure. In contrast to cyclophosphamide, there is no reported cardiotoxicity of ifosfamide in other settings. Other dose-related toxicities reported include nausea, vomiting and mucositis.

Cisplatin

Cisplatin (cis-diammine-dichloroplatinum) is activated by hydrolysis to produce the highly reactive alkylating *cis*-diammine diaquated species. The hydrolysis rate is

partially determined by the chloride concentration of the solubilizing media (28). The active compound exerts its cytotoxic effect through formation of inter- and intrastrand crosslinking of DNA (29). Cisplatin is active in all phases of the cell cycle, but it is most active in the G1-phase.

Pharmacokinetics and toxicity. Cisplatin is extensively and irreversibly bound to plasma proteins; the free-drug fraction is responsible for its pharmacological activity (30). The initial plasma half-life of free cisplatin (5% of total platinum) is about 30 min; the terminal half-life is considerably longer, greater than 24 h (31). Cisplatin is eliminated by renal filtration, tubular secretion and tissue alkylation (28).

Nephrotoxicity is prominent, prohibiting dose escalation of cisplatin above 200 mg/m^2. Acute renal failure is related to the peak plasma concentration and its duration, and is more frequent in the presence of a decreased glomerular filtration rate (29). Adequate and prolonged hydration with a urine flow above 200 ml/h is the mainstay of prophylactic treatment (28). Platinum is known to be present in renal tissue for up to 4 months following administration. This may eventually potentiate nephrotoxic effects of other agents, such as aminoglycoside antibiotics (32). Damage to the renal tubuli induces hypomagnesemia and hypokalemia (33).

Disabling peripheral neuropathy, manifested as numbness, pain and small motor dysfunction, which is only partially reversible, has been reported in 26% of patients receiving 200 mg/m^2 cisplatin (34). Ototoxicity is irreversible and is more pronounced at high frequencies (35).

Myelosuppression is dose-related and characterized by a profound and prolonged granulocytopenia. A marked increase in platelets and red blood cell transfusion occurs when the dose of cisplatin is increased from 100 to 200 mg/m^2 (34).

Carboplatin

Carboplatin is a second generation, platinum-containing compound. Carboplatin is metabolized to monoaquo and diaquo species, similar to the activation process of cisplatin although it is associated with a lower conversion rate (36). The generated electrophillic species are capable of a covalent binding to nucleophils such as proteins and DNA. It is assumed that the formation of intra- and interstrand DNA cross-links is responsible for the cytotoxicity of this compound (37).

Pharmacokinetics and toxicity. Carboplatin unlike cisplatin, is only 25% protein bound following IV administration. As a result, the AUC, expressed in μmol.min/l, of the free drug is 15 to 17.5 times higher for carboplatin than for cisplatin (36). The pharmacokinetic profile of the free drug can be described with a biexponential equation with $t_{1/2}\alpha$ of 6-20 min and a $t_{1/2}\beta$ of 1.5 to 7.5 h.

Glomerular filtration accounts mainly for the renal excretion of carboplatin and is the major route to elimination (38, 39). Active tubular secretion is irrelevant which, together with the minimal protein binding, explains why the creatinine clearance is highly predictive for carboplatin elimination (38). Formulas incorporating the glomerular filtration rate (GFR) and AUC have been designed to allow the calculation of the carboplatin dose yielding a pre-defined AUC (40).

At higher dosages of carboplatin (up to 2,400 mg/m^2), no alterations in drug

clearance or differences in the rate or route of elimination have been observed. The interpatient variability in pharmacokinetics after high-dose carboplatin has been found to be relatively minor, resulting in a reasonably predictable AUC for patients treated with a given dose of the drug, when the GFR is taken into account (41). Following high-dose carboplatin, presence of the drug can be found in ascites, pleural effusions and in the CSF (41, 42).

Myelosuppression is the dose-limiting toxicity of carboplatin (43). In patients treated with a dose of 1,600 mg/m^2 carboplatin, profound neutro-and thrombocytopenia have been observed for more than 14 days (41, 44). The addition of autologous bone marrow support in patients treated with such high doses of carboplatin has therefore been recommended (41).

Administration of doses up to 400 mg/m^2 carboplatin rarely induces renal toxicity in patients with adequate renal function (36). A decrease of renal function of greater than 30% has been observed in patients receiving high-dose carboplatin, with a temporary loss of more than 80% of pretreatment renal function in patients receiving 2,400 mg/m^2 (41, 44).

The principal dose-limiting non-hematological toxicity with high-dose ($\geqslant$2,000 mg/m^2) carboplatin as a single agent has been reported to be hepatic toxicity, which is characterized by biliary stasis (41). Ototoxicity becomes significant at doses exceeding 1,000 mg/m^2 (41, 44) and has been found to be more closely related to the cumulative dose of carboplatin than to prior cisplatin therapy (41). Neurotoxicity is also dose-related, but is compounded by prior administration of cisplatin (41, 44).

Thiotepa

N,N′,N″-triethylenethiophosphoramide (thiotepa) is mainly metabolized to triethylene phosphoramide (tepa) by the hepatic cytochrome P-450 enzyme system (45). Cytotoxicity by thiotepa is thought to be mediated by the formation of DNA interstrand crosslinks (46). However, *in vitro* studies have also suggested that thiotepa mainly serves as a prodrug for aziridine, which exerts its cytotoxicity by the production of single-strand DNA breaks or alkali-labile DNA-lesions (47). In a similar way, the cytotoxic effect of tepa has been found to differ from its parent compound by the production of alkali-labile DNA-lesions (46). The clinical relevance of these *in vitro*, however, has not yet been established (46).

Pharmacokinetics and toxicity. Following IV administration, a very rapid and wide tissue distribution of thiotepa has been reported equivalent to that of total body water (48). The terminal half-life of thiotepa has been observed to be independent of dose, with a range from 52 to 212 min (49). The half-life of its metabolite tepa is considerably longer, ranging from 3 to 21 h (49).

The AUC of thiotepa has been found to be proportional to the dose, although the relationship is not linear, particularly when doses over 55 mg/m^2 are administered. With increasing doses of thiotepa, a concomitant increase of the AUC of tepa is absent. It has therefore been suggested that the metabolism of thiotepa to tepa is an enzymatic process which becomes saturated at lower doses (49). Less than 15% of thiotepa is bound to plasma proteins as opposed to tepa which is extensively protein-bound and unstable; free tepa cannot usually be measured (50). Thiotepa

penetrates the CSF. Of the administered dose, 5% is recovered in the urine as either thiotepa or tepa whereas 24% is present as non-specific alkylating metabolites, some of which are probably related to aziridine (47, 51).

The highest dose of thiotepa that can be given safely intravenously without hematopoietic stem cell support is 65 mg/m^2 (49). Phase I studies of high-dose thiotepa in the transplantation setting have demonstrated a maximal tolerated dose of 900 to 1,125 mg/m^2 given in divided doses in a 2 h infusion for 3 days (52).

The dose-limiting toxicity of conventional doses of thiotepa is myelosuppression. The time to the nadir following high-dose thiotepa with autologous bone marrow support is 7 to 10 days. At doses of 405 mg/m^2 or more, irreversible bone marrow suppression has been observed (52).

The occurrence of nausea and vomiting is dose-dependent and generally responds well to the administration of standard antiemetics. Mucositis, esophagitis or enterocolitis are most commonly reported in high-dose chemotherapy regimens, and may be difficult to manage after administration of doses exceeding 900 mg/m^2 (52). At doses over 1,125 mg/m^2, transient elevations of liver enzymes or bilirubin have been encountered (52).

Central nervous system toxicity is the dose-limiting toxicity of high-dose thiotepa. Patients present with symptoms that resembles an organic brain syndrome. At doses of over 1,125 mg/m^2, more than 15% of the patients develop CNS toxicity (52). Skin toxicity consists of an acute erythroderma affecting the palms and soles and a general darkening of the skin which can persist for months but is reversible.

Carmustine (BCNU)

Carmustine is a chloroethylnitrosourea derivative which is metabolized by hepatic enzymes, but can also be decomposed chemically to produce alkylating products and isocyanates (53). The alkylating products produce DNA-interstrand crosslinks in a two-step reaction sequence. Cytotoxicity is caused by alkylation of the O^6 position of a guanine followed by interstrand crosslinking with a cytosine on the complementary strand of DNA (54). Cellular resistance to the cytotoxic activity of carmustine mainly occurs through an increase in the enzyme O^6-alkylguanine-alkyltransferase (0^6AT) which repairs the alkylated 0^6 guanine (55–57).

Pharmacokinetics and toxicity. Carmustine can only be administered intravenously. After infusion of high-dose (600 mg/m^2) carmustine, plasma levels could be detected up to 30 min following administration (58). The peak concentration was observed at the end of a 2-h infusion and the average half-life was reported to be 22 min (range 10–33) after discontinuation of the infusion (58). At doses of 600 mg/m^2, a large patient-to-patient variation in the clearance has been found, with an AUC ranging from 82 to 887 μmol.min/l. Consequently, there was a considerable variation in drug exposure between patients (58).

Carmustine is highly (77%) bound to plasma proteins. Similar to other nitrosoureas, carmustine is highly lipophilic and easily crosses the blood-brain barrier. Active pharmacological concentrations can be detected in the central nervous system (59). Within 24 h following administration, approximately 80% of the administered carmustine is found in the urine in the form of degradation products (53).

In conventional doses of carmustine up to 200–300 mg/m^2 every 6 to 8 weeks, myelosuppression is the dose-limiting toxicity.

Hepatotoxicity (non-infectious hepatitis or VOD) has been found to be the dose-limiting toxicity in high-dose carmustine regimens, with a high incidence of fatal outcomes following doses above 1,200 to 1,500 mg/m^2 (58, 60). The dose of carmustine and the presence of CNS tumors have been observed to be prognostic factors for the development of severe hepatotoxicity (60).

Immediate drug-related toxicity includes acute cardiovascular effects resulting in hypotension, tachycardia and flushing (58). These effects are dose-related and persist beyond the half-life of carmustine. The underlying mechanism for this phenomenon is unknown. Cardio-toxicity, expressed as cardiac necrosis by pathologic examination, has rarely been described at cumulative doses over 3,000 mg/m^2 (60).

Carmustine-related interstitial pneumonitis has frequently been observed at doses of 1,000 mg/m^2 or more, but is probably not strictly dose-related (60). (Fatal) pulmonary toxicity has been encountered up to 17 years after administration of carmustine (61, 62). The role of corticosteroid treatment in these patients still remains unclear (60, 62).

Delayed renal toxicity has been documented following cumulative doses of 1,500 mg/m^2 (59), although in a large phase I-II study when carmustine was administered in doses up to 2,850 mg/m^2, nephrotoxicity did not develop (60). Encephalomyelopathy has been encountered in patients receiving more than 2,000 mg/m^2 carmustine (60).

Mitoxantrone

Mitoxantrone is a hydroxyquinone, which is structurally related to doxorubicin but lacks the amino sugar moiety (63). It has been suggested that mitoxantrone, unlike the classical intercalating agents, binds to DNA by non-intercalative electrostatic interactions (64). Induction of DNA-protein crosslinks by mitoxantrone has also been reported (65, 66). DNA breakage by stabilization of a complex between DNA and topoisomerase II, caused by mitoxantrone, suggests additive cytotoxicity through topoisomerase II inhibition (67). The precise mechanism of antitumor activity of mitoxantrone, however, remains to be elucidated (68). The cellular toxicity of mitoxantrone is cell-cycle non-specific; *in vitro* the drug is cytotoxic for both proliferating and non-proliferating cells (65).

Pharmacokinetics and toxicity. Following intravenous administration, the plasma clearance rate has been described according to biphasic and triphasic models, with terminal half-lives of 37.4 and 42.6 h, respectively (69, 70). Mitoxantrone is extensively bound to plasma proteins (>95%), blood cells and body tissues (70). The main route of excretion is in the bile with less than 7% of the drug being eliminated in the urine. In patients with hepatic dysfunction, a decreased total body clearance rate of mitoxantrone has been observed, suggesting that the dose of mitoxantrone should be adjusted in these patients (69).

The dose-limiting toxicity of mitoxantrone is myelosuppression, predominantly granulocytopenia, with a cumulative effect on bone marrow function following repetitive administration (66, 71, 72). The maximum tolerated dose is 12–14 mg/m^2,

when administered as a single bolus injection intravenously every 3 weeks (72). The degree of myelosuppression appears to be related to prior therapy, the presence of bone marrow involvement and the performance status of the patient (63).

Mitoxantrone has not been investigated as a single-agent in dose escalation studies. Stomatitis and mucositis are dose-dependent and appear to be the dose-limiting toxicities in high-dose mitoxantrone-based regimens (73). In combination with high-dose alkylating agents and autologous bone marrow support, the MTD is 60 mg/m^2 (71, 73). The degree of nausea, vomiting and diarrhea at this dose-level has been reported to be mild to moderate and minor signs of liver toxicity are common (71).

The development of cardiac toxicity is related to pre-existing risk-factors such as underlying cardiovascular disease, prior anthracycline exposure and prior mediastinal radiation (63, 71). Following standard doses of mitoxantrone, clinically significant cardiotoxicity has been observed in about 3% of patients with a poor performance status, who had previously been treated with anthracyclines (74). Overall, the incidence of congestive heart failure increases with cumulative doses of over 100 mg/m^2 in patients who have had previously received anthracyclines and with a cumulative dose of 160 mg/m^2 or more in patients without prior treatment (71).

Melphalan

DNA lesions caused by melphalan (*L*-phenylalanine mustard) are produced by a mustard-like reactive intermediate (75). Cytotoxicity is induced by the formation of DNA-crosslinks and melphalan acts as a cell-cycle non-specific alkylator.

Melphalan is transported into the cell through a high-affinity carrier, the l-amino acid transport system, which is also responsible for the transport of the amino acids leucine and glutamine. Alterations in the amino acid content of plasma or malignant effusions may therefore influence the uptake and cytotoxicity of this drug (76).

Pharmacokinetics and toxicity. Following the intravenous administration of high-dose (140–240 mg/m^2) melphalan, pharmacokinetic parameters have been shown to be independent of dose and highly variable between patients. It has therefore been suggested to individualize the dose of melphalan by prior pharmacokinetic characterization of each patient; a test-dose should be given to determine the clearance and should then be followed by the administration of a calculated dose aimed to achieve an optimal target AUC (77). To our knowledge, such a procedure has not been implemented in clinical trials.

Immediately following i.v. administration, up to 50% of melphalan will bind to plasma proteins, which increases in time to over 90% (78). The plasma elimination half-life is short, with a $t_{1/2}\alpha$ of 6 to 10 min and a $t_{1/2}\beta$ of 40 min to 2 h (77). Hydrolysis to dihydroxymelphalan is the main route of elimination (75). Less than 15% of the intact drug is excreted in the urine which explains why alterations in renal function have not been shown to influence melphalan pharmacokinetics significantly (77). The CSF to plasma ratio is less than 10%.

The dose-limiting toxicity of conventional doses of melphalan consists of myelosuppression. When high-dose i.v. melphalan is administered with autologous bone marrow support, gastrointestinal toxicity is usually dose-limiting. Its major

manifestations are stomatitis and diarrhea (79). Pretreatment with cyclophosphamide appears to reduce the degree of melphalan-associated gastrointestinal toxicity. The maximum tolerated single dose is up to 245 mg/m^2 as compared with 170 mg/m^2 in patients not primed with cyclophosphamide (79). In addition, bone marrow recovery following high-dose melphalan has been documented to be accelerated by cyclophosphamide pretreatment (80).

Busulfan

Busulfan is a bifunctional alkylating agent which produces protein-DNA and intrastrand DNA crosslinks. The agent is mainly active on cells in the G0 or G1 phase of the cell cycle (81).

Pharmacokinetics and toxicity. Busulfan is only available as an oral preparation; a dose of 1 mg/kg every 6 h for 4 days is commonly used in high-dose regimens. The peak plasma concentration is reached 50 min to 3 h after a single administration. Steady-state concentrations are reached after 2–3 doses (82). Following repeated administration, the clearance of busulfan increases, whereby the half-life decreases, indicating that the drug accelerates its own metabolism (82). The mean elimination half-life is about 2 h (83).

Busulfan is highly lipophilic and is for less than 55% bound to plasma-proteins. The combination of these properties may partially explain the high CSF/plasma ratio observed with high-dose busulfan (82, 84). Busulfan is partially metabolized through reactions with glutathione. This process is catalysed by glutathione-S-transferase and results in three recently discovered urinary metabolites (82).

The dose-limiting toxicity of high-dose busulfan is VOD of the liver (83). Although VOD is the second leading cause of death in patients receiving autologous bone marrow transplantation, the pathogenesis of this clinical syndrome remains obscure. Multivariate logistic regression analysis has shown the AUC to be the only significant pharmacokinetic predictor of the development of VOD following high-dose busulfan (83).

Neurotoxicity occurs during administration of high-dose busulfan in 10% of patients. This neurotoxicity, characterized by the occurrence of seizures, is transient and without sequelae (84). Other reported side-effects include interstitial pulmonary fibrosis following prolonged administration, and an Addison's disease-like syndrome characterized by cutaneous hyperpigmentation and general weakness but without adrenal insufficiency. Radiation therapy following high-dose busulfan induces enhanced skin radiation side-effects (85).

Etoposide

Etoposide is a semisynthetic epipodophyllotoxin derivative. This drug is most toxic in the late S or early G2 phase of the cell cycle, thereby inducing a pre-mitotic block (86). Etoposide causes dose-dependent single-and double-stranded breaks in DNA, DNA-protein crosslinks and chromosomal aberrations. Interference with the function of the enzyme DNA-topoisomerase II is thought to underly the mechanism of DNA strand breakage induced by the epipodophylotoxines.

Pharmacokinetics and toxicity. Pharmacokinetic parameters of etoposide show a considerable interpatient variability. The AUC and the peak plasma concentration are both linearly related to the dose of etoposide. The half-life is independent of the dose with a terminal elimination half-life ranging from 4 to 8 h (86).

More than 95% of etoposide is bound to plasma proteins. Following high-dose intravenous administration, presence of etoposide in the CSF has been observed (87). Etoposide is predominantly excreted in the urine, 20–45% as unchanged drug and 20–33% as metabolites; excretion of etoposide by the hepatobiliary route is negligible (86).

In contrast with alkylating agents, the efficacy of etoposide strongly depends on the schedule of administration. Divided doses administered over 3 to 5 days have been shown to be superior to a single dose. A plasma concentration of above 1 μg/ml appears to be essential for its antitumor activity.

Following administration of high-dose etoposide (800–3500 mg/m^2) with bone marrow support, reversible mucositis is the dose-limiting toxicity (88). Nausea and vomiting are not dose-related (88, 89). Acute hypersensitivity reactions have been reported infrequently (90).

Mitomycin C

Mitomycin C (MMC) is an antibiotic originating from *Streptomyces caespitosus.* MMC is a bioreductive alkylating agent producing DNA-protein crosslinks and DNA-inter- and intrastrand crosslinks; the drug is most effective in the late G1 and early S1 phases of the cell cycle (91, 92).

Pharmacokinetics and toxicity. The pharmacokinetic behavior of MMC is linear and fits a 2-compartment model (93). After intravenous bolus administration, MMC is rapidly cleared from the plasma. Major routes of elimination are liver metabolism and renal excretion. The $t_{1/2}\alpha$ varies from 6 to 17 min; the $t_{1/2}\beta$ is between 28 and 112 min (94). Up to 20% is excreted unchanged in the urine, mainly by glomerular filtration (93). Renal excretion of MMC is independent of renal function.

The dose-limiting toxicity of MMC is delayed and cumulative myelosuppression. The non-hematological toxicities observed in high-dose MMC regimens with autologous bone marrow support have been considerable and were the reason to discontinue the use of MMC in high-dose chemotherapy regimens (95). These toxicities included severe, and sometimes lethal side-effects, such as VOD of the liver, interstitial pneumonitis, frequently associated with pulmonary fibrosis, and intractable congestive heart failure. The latter has predominantly been observed in patients previously treated with anthracyclines (94–97). Gastrointestinal toxicity has been reported to be cumulative following sequential high-dose MMC administration (95). The hemolytic uremic syndrome associated with a high mortality may occur several months after MMC therapy in 0.5–8% of patients (94).

High-dose combination regimens

A variety of high-dose chemotherapy regimens with autologous bone marrow or peripheral stem cell support are currently under clinical evaluation in solid tumors.

The majority are multiple-alkylating agent based combinations, for reasons well described by Frei and Teicher (98–102). In the following section, the high-dose chemotherapy regimens most frequently investigated in the treatment of solid tumors will be described. Since randomized studies are not yet available and the current studies vary widely with respect to patient selection, induction chemotherapy regimens and definition of response duration, this section will mainly focus on feasibility and toxicity. An overview of the studies discussed is presented in Table 2.

Cyclophosphamide–thiotepa based combinations

Cyclophosphamide and thiotepa were among the first alkylating agents to be used in high-dose chemotherapy regimens. This was based on the results of studies performed by Frei and Teicher, who demonstrated synergistic activity *in vitro* between these two agents (99, 100). In 1987, Williams *et al.*, reported the administration of high-dose cyclophosphamide and thiotepa in patients with advanced cancer (103). As confirmed in subsequent studies (104–106), the main extramedullary toxicity of this bi-alkylator regimen is mucositis. A wide range in the number of toxic deaths has been reported in different studies. Toxic deaths have been primarily caused by infectious complications following severe bone marrow suppression. These differences in fatal toxicity may be explained in part by differences in patient selection.

Phase II studies with high-dose cyclophosphamide and thiotepa in metastatic breast cancer have shown considerable differences in response rates, and the response durations were usually brief (105, 106). In animal studies, the cytotoxicity of the combination of cyclophosphamide and thiotepa depends on the schedule of administration (107). Simultaneous administration of cyclophosphamide and thiotepa appears to be inferior to sequential dosing. The optimal interval between the administration of both drugs was 8 h, irrespective of the sequence (107). When cyclophosphamide and thiotepa were injected within a 4-h interval, additional tumor-cell kill was only achieved when thiotepa was administered first (107). In clinical studies, information about the sequencing of the alkylating agents is rarely reported; whether differences in scheduling contribute to the differences in response rates observed, remains to be elucidated.

Since alkylating agents can have different mechanisms of DNA damage and generally lack cross-resistance, the addition of a third alkylator to this combination was hoped to reduce the likelihood of resistance further and to increase dose intensity (108).

Cyclophosphamide, thiotepa and carboplatin. In the Solid Tumor Autologous Marrow Program (STAMP) of Antman and co-workers, melphalan was initially added to the combination of cyclophosphamide and thiotepa (STAMP III). Due to life-threatening mucositis in the first two patients, the combination was considered too toxic and was subsequently abandoned (104). The substitution of melphalan by carboplatin as the third alkylating agent resulted in the well-known STAMP V (CTCb) regimen (109). A phase II trial which included 29 patients with metastatic breast cancer, confirmed the results of the preceding phase I study, and showed that CTCb is a regimen with acceptable morbidity and a low mortality rate (110). This was

Table 2. High-dose chemotherapy regimens with autologous stem cell support in solid tumors. Overview of the most frequently used combinations

Regimen	Tumor	No. of patients	Dose (mg/m^2)	Pretreatment	Median DFS (months)	Major organ toxicity	Cause of death	Ref.
C T	Various, advanced	20	7,500–700[a]	Chemotherapy, various (65%)	3,5	Gastrointestinal, Hematological	Infection (20%)	103
	Various, advanced	23	6,000–720[a]	Chemotherapy, various (74%)	2	Mucositis	Pneumonitis (4%), VOD with heart failure (4%)	104
	Breast, advanced	27[b]	7,500, 675	Adjuvant chemotherapy (63%), induction with LOMAC	6,2	Hematological	Infection (18%)	105
	Breast, advanced	30[c]	6,000, 800	Adjuvant chemotherapy no anthracyclines, induction with CAMFV	13	Hematological, mucositis		106
CTL (STAMP III)	Various, advanced	2	6,000, 680, 40	NA	NA	Mucositis		104
CTC_b (STAMP V)	Various, advanced	27	6,000, 500–720, 600–1,000	Chemotherapy various (85%)	2	Mucositis	Infection (7%)	109
	Breast, advanced	29	6,000, 500, 800	Adjuvant chemotherapy (48%), induction with AFM (55%)	6	Hematological, mucositis	Hemorrhage (3%)	110
$L \rightarrow CTC_b$	Breast, advanced	20	$140–180 \rightarrow CTC_b$	Adjuvant, chemotherapy (55%), induction with CA-AF	NA	Hematological, mucositis		111
CTC_a	Various, advanced	16	6,000, 480, 1,600	Chemotherapy, various	NA	Gastrointestinal		112
	Breast stage I, II	28	6,000, 480, 1,600	None	NA	Hematological		113
$CTC_a \times 2$	Germ cell relapsed, refractory	8	$CTC_a \times 2$	Chemotherapy, cisplatin-based	NA	Gastrointestinal		114
CTP	Breast, advanced	39	120 mg/kg, 750, 150[d]	Chemotherapy (82%), with anthracycl. (36%)	8	Renal, gastrointestinal	Infection (10%) hemorrage (5%)	115
CBP (STAMP I)	Breast, advanced	17	5,625, 600, 165	Chemotherapy with anthracyl. (59%)	5	Hepatic	VOD (12%), infection (6%)	116
	Breast, advanced	22	5,625, 600, 165	Adjuvant chemotherapy (64%)	9	Hepatic	Pulmonary toxicity (9%), hemorrhage, myocarditis (5%), hepatitis, VOD (5%), renal failure (5%)	117
	Breast stage II, III	85	5,625, 600, 165	Induction with CAF	72% DFS at 3.3 years	Pulmonary toxicity	HUS (4%), pulmonary toxicity (2%), infection (4%) hepatitis (1%) hemorrhage (1%)	1

Table 2. (*Continued*)

CE	Various, advanced	13	7,000, 1,500[c]	Chemotherapy, various	NA	Mucositis		122
CEB[f]	SCLC	23	6,000, 500, 300	Induction with CAVM–CE*	7	Hematological	Infection (13%) hemorrhage (4%)	123
CEC_a	Various, advanced	20	6,000, 1,800, 1,600[g]	Chemotherapy, various	NA	Hematological	Infection (15%)	124
	Germ cell, refractory	30	150 mg/kg[h], 1,200, 1,500 × 2	Chemotherapy cisplatin-based	8	Hepatic	Hemorrhage (3%), infection (3%)	125
C_sE (× 2)	Germ cell, refractory	33 (20)	1,500–1,200[g]	Chemotherapy, cisplatin-based	NA	Hematological	Infection (18%), VOD (3%)	126
	Germ cell, refractory	38 (22)	1,500, 1,200	Chemotherapy, cisplatin-based	NA	Hematological	Hemorrhage (6%), infection (3%), VOD (3%), hepatic failure (3%)	127
C_sE (I)	Germ cell, relapsed	28 (11)	1,350, 1,200–1,800, (12,000)	Chemotherapy, cisplatin-based	NA	Mucositis	VOD (4%)	130
CBu	Breast, advanced	15	6,000, 16 mg/kg	Chemotherapy, various; with anthracyline (87%)	5	Hepatic	Infection (7%), hemorrhage (7%)	132
MiC	Various, advanced	11	75, 7,000[i]	Chemotherapy, various; with anthracyline (55%)	NA	Hematological		73
MiL	Breast, advanced	30	60, 180	Chemotherapy various	27	Mucositis	Infection (3%)	133
MiT	Breast, advanced	44	60,900[i]	Chemotherapy, various	5	Hematological, mucositis	Infection (7%), cardiotoxicity (2%), unknown (2%)	135

Dose escalation studies of [a]thiotepa, [d]cisplatin, [e]etoposide, [g]carboplatin, [h]cyclophosphamide, [i]mitoxantrone, [b]high-dose C T in 22 patients, [c]high-dose C T in 24 patients, [f]randomized study versus conventional doses CEB

C = cyclophosphamide, T = thiotepa, L = L-PAM (melphalan), C_b = carboplatin, P = cisplatin, B = BCNU, E = etoposide, I = ifosfamide, Bu = busulfan, Mi = mitoxantrone

DFS = disease free survival, VOD = veno-occlusive disease of the liver, HUS = hemolytic uremic syndrome, SCLC = small cell lung cancer, STAMP = solid tumor autologous marrow program, NA = not available

LOMAC = leucovorin 25 mg, 6 doses, oncovin 1,4 mg/m^2, methotrexate 200 mg/m^2, adriamycin 50 mg/m^2, cyclophosphamide 1000 mg/m^2 × 3

CAMFV = cyclophosphamide 700 mg/m^2 orally, doxorubicin 40 mg/m^2, methotrexate 100 mg/m^2, fluorouracil 1,200 mg/m^2, vincristine, 1 mg × 8.

CA-AF = cyclophosphamide 1,200 mg/m^2, doxorubicin 75 mg/^{2}, × 4—doxorubicin 75 mg/m^2, fluorouracil 1,500 mg/m^2, × 2

CAF = cyclophosphamide 600 mg/m^2, doxorubicin 60 mg/m^2, fluorouracil 600 mg/m^2, × 4

CAVM = cyclophosphamide 600 mg/m^2, doxorubicin 60 mg/m^2, vincristine, 1,5 mg/m^2, methotrexate 40 mg/m^2, × 3

CE* = cisplatin 80 mg/m^2, etoposide 360 mg/m^2, × 2

confirmed in later studies, in which CTCb was preceded by high-dose melphalan (111). In the CTCb phase I study, the occurrence of severe stomatitis prevented further dose-escalation (109) and the MTDs were established at cyclophosphamide 6,000 mg/m^2, thiotepa 500 mg/m^2, and carboplatin 800 mg per m^2 (110, 111).

In the Netherlands Cancer Institute, a similar high-dose regimen has been developed. The dose of carboplatin is, however, twice that of the STAMP V regimen (i.e. 1600 mg/m^2), but the dose of thiotepa is similar (i.e. 480 mg/m^2) (112). The total dose of cyclophosphamide is identical, 6000 mg/m^2. In spite of the high carboplatin dose, this CTC regimen has been shown to be well-tolerated without severe non-hematological toxicity, even when administered sequentially in a tandem transplantation setting (113, 114). Mucositis was manageable, requiring total parenteral nutrition in only few patients (113). In eight heavily pretreated patients receiving two cycles of high-dose CTC-chemotherapy, some oto-and neurotoxicity were observed. All patients had been pretreated with cisplatin (114). Toxic deaths were not observed in either study, which included 60 CTC courses in a total of 52 patients (112–114).

Cyclophosphamide, thiotepa and cisplatin. Recently, Ghalie and co-workers published data on a high-dose regimen incorporating cyclophosphamide, thiotepa and cisplatin in a split-course schedule for metastatic breast cancer (115). It was hypothesized that by applying this schedule of administration, the occurrence of toxic side-effects would be reduced, allowing further dose-escalation. The toxicity of this regimen, however, was considerable, contributing to a 15% toxic death rate. All 39 patients developed neutropenic fevers requiring the administration of aminoglycosides, which, in combination with high-dose cisplatin, may have contributed to the high incidence of renal toxicity observed (32, 115).

Cyclophosphamide, BCNU (carmustine), and cisplatin based combinations

Among the most comprehensively investigated intensification regimens is the STAMP 1 regimen, which consists of cyclophosphamide, BCNU and cisplatin (CBP). In a phase I study, the MTD of this triple-alkylating regimen was reported to be 5,625, 600 and 165 mg/m^2 respectively (116). The major dose-limiting toxicity consisted of hepatotoxicity, and the development of (fatal) VOD. Thrombocytopenia-associated hemorrhage occurred only at higher dose levels in contrast to pulmonary toxicity which was not dose-related (116, 117). The addition of melphalan resulted in unacceptable renal and gastrointestinal toxicity (116). Therefore this agent was subsequently omitted from the regimen.

The MTD of combination therapy with CBP for metastatic breast cancer has been associated with considerable treatment-related toxicity, including VOD, gastrointestinal hemorrhage and a mortality rate of 14% (118). This was thought to be, at least partly, due to the cumulative effects of extensive pretreatment. Attempts were made to reduce toxicity by including only those patients who had not received prior chemotherapy for metastatic disease (119). Treatment-related toxicity, however, remained substantial and was also confirmed in a subsequent study that evaluated the role of CBP dose-intensification in stage II-III breast cancer (1). The pattern of toxicity was not affected by omitting cisplatin. Following high-dose cyclophosphamide and BCNU, major organ toxicities remained similar to those

observed with CBP, i.e. pulmonary and hepatic toxicity (119, 120). The substitution of cisplatin with carboplatin resulted in the development of severe VOD in three out of four patients (121). The death in two out of three of these patients led to the conclusion that the use of carboplatin in this combination was not feasible (121).

Cyclophosphamide–etoposide based combinations

The majority of the cyclophosphamide-etoposide based intensification regimens have been investigated for their efficacy in small cell lung cancer (SCLC) and in germ cell cancer. In a phase I study with cyclophosphamide and escalating doses of etoposide, mucositis of the upper gastrointestinal tract was the dose-limiting toxicity. Cyclophosphamide 7,000 mg/m^2 and etoposide 1,500 mg/m^2 were recommended for further investigation. In addition, the dose of etoposide was considered sufficient to produce effective concentrations in the central nervous system (88, 122).

Cyclophosphamide, etoposide, and BCNU (CEB). In 1987, the results of the first randomized study were published which evaluated the role of high-dose chemotherapy in 45 patients with SCLC (123). Following induction chemotherapy, which included cyclophosphamide and etoposide, responding patients were randomized to either CEB at the conventional dosages of 750 mg/m^2, 600 mg/m^2 orally and 60 mg/m^2 respectively, or a high-dose CEB, consisting of cyclophosphamide 6,000 mg/m^2, etoposide 500 mg/m^2 and BCNU 300 mg/m^2. The median disease-free survival, from the time of randomization, was 7 months in the high-dose CEB-arm, compared to 2.5 months in the control arm ($p = 0.002$) (123). However, a significant difference in overall survival could not be established, which was partly due to the high percentage of deaths during the period of bone marrow aplasia following high-dose CEB. It was suggested that improvement in supportive care and the use of alternative agents, such as carboplatin, might eventually contribute to an increase in the efficacy of high-dose chemotherapy in this patient group (123).

Cyclophosphamide, etoposide and carboplatin (CEC). Two phase I studies have evaluated the feasibility of a high-dose CEC chemotherapy regimen with ABMT or peripheral blood stem cell transplantation (PSCT) (124, 125). Both studies applied a dose-escalation schedule for one of the two alkylating agents. Dose-escalation of carboplatin resulted in acute renal failure as the dose-limiting toxicity (124). This occurred in two of 14 patients who had received a dose of 1,600 mg/m^2 carboplatin. Both patients had previously been treated with cisplatin and/or carboplatin and were 'markedly obese'. The dose of carboplatin had been prescribed on the basis of their total body weight, and both had creatinine clearances of slightly above 60 ml/min prior to the administration of CEC. If the creatinine clearance had been expressed as clearance according to the standard body surface area of 1.74 m^2, it would have been below 60 ml/min in both patients. The investigators therefore suggested that the dose of carboplatin should have been adjusted to ideal body weight in order to prevent overdosing and serious renal damage (124).

In a subsequent study in 30 patients with cisplatin-refractory germ cell cancer, dose-escalation of cyclophosphamide with fixed doses of carboplatin (1500 mg/m^2) and etoposide (1200 mg/m^2) was evaluated (125). Fourteen patients who responded

to the first course were retreated. The second cycle was administered 4 to 6 weeks after hematologic recovery. Two toxic deaths occurred related to myelosuppression, while other major toxicity involved the liver, manifested as cholestasis which occurred in 17 patients (57%); VOD was not observed (125). Interestingly, the seven patients (23%) who achieved a durable complete remission, at a median follow-up of 11.4 months (range 5.6–35.5), were those who received two courses of high-dose CEC. The two patients who achieved a complete response after a single course of CEC were not retreated and subsequently relapsed (125).

Carboplatin–etoposide based combinations

The combination of high-dose carboplatin and etoposide followed by autologous bone marrow rescue has particularly been applied in relapsing or refractory germ cell cancer. In a phase I study performed in the Indiana University programme, the MTD of carboplatin was 1500 mg/m^2 in combination with etoposide 1200 mg/m^2 (126). The dose-limiting toxicity was enterocolitis; toxic deaths (21%) were observed and doses above 1500 mg/m^2 carboplatin. At these dose levels, hepatic toxicity developed in eight patients (24%) with a fatal outcome in one (126).

The feasibility and efficacy of combination therapy with carboplatin 1500 mg/m^2 and etoposide 1200 mg/m^2 was subsequently investigated in a phase II trial in refractory germ cell cancer (127). Patients who responded to the first high-dose chemotherapy cycle, received a second one. Five of 38 patients (13%) remained disease-free for more than 1 year. However, the toxicity of this regimen was substantial including treatment-related deaths in five patients (13%). All deaths occurred after the first transplantation (127). Toxic deaths were due to sepsis, hemorrhage or hepatic failure, including one VOD. Patients with refractory mediastinal germ cell tumors did not appear to benefit from this high-dose chemotherapy regimen and were therefore excluded from further studies (127, 128).

In an attempt to improve the efficacy, ifosfamide has been added to the high-dose carboplatin-etoposide regimen (129). Severe renal toxicity was, however, observed at the first dose level (10 g/m^2), which precluded the planned further dose escalation. This is in contrast to data available from an Italian multicenter study, in which 11 patients received 12 g/m^2 ifosfamide, 1350 mg/m^2 carboplatin and 1200 mg/m^2 etoposide (130). No renal toxicity was observed despite the simultaneous administration of the aminoglycoside antibiotic amikacine in some of these patients. Severe mucositis was the major toxicity recorded. Neurotoxicity has not been observed in either of the high-dose single-agent ifosfamide studies (129, 130).

Cyclophosphamide–busulfan based combinations

Limited data are available on the use of high-dose cyclophosphamide and busulfan in solid tumors. In hematological malignancies it is a well-known preparative regimen for autologous or allogeneic bone marrow transplantation (131).

A phase II study has been published recently which investigated the administration of high-dose cyclophosphamide and busulphan in 15 patients with advanced breast cancer (132). Despite a high complete response rate, the response duration was brief. Hyperbilirubinemia developed in three patients (20%) without

clear-cut evidence of VOD; two patients (13%) died of treatment-related toxicity, the first due to sepsis and the second following diffuse alveolar hemorrhage (132).

Mitoxantrone based combinations

Mitoxantrone and melphalan. A high-dose chemotherapy regimen which included mitoxantrone has been used in advanced breast cancer (133). Thirty patients who were in complete remission after standard-dose chemotherapy, received a combination of mitoxantrone, 60 mg/m^2, and melphalan, 180 mg/m^2—supported by ABMT or PSCT. This resulted in a median disease-free survival (DFS) of 27 months and a 43% DFS at 3 years (133). In an earlier study, cyclophosphamide had been substituted by melphalan when the combination of high-dose cyclophosphamide and mitoxantrone frequently resulted in hemorrhagic cystitis (73) and cardiotoxicity (134). Significant cardiotoxicity has not been reported for the combination of mitoxantrone and melphalan, despite the inclusion of patients previously treated with anthracyclines or those having received external thoracic radiation (132, 133). The major toxicity of this regimen is mucositis (133).

Mitoxantrone and thiotepa. A dose-escalation study of mitoxantrone administered with thiotepa for metastatic breast cancer has recently been published (135). The dose-limiting toxicity of mitoxantrone in combination with thiotepa, 900 mg/m^2, appeared to be cardiotoxicity. The MTD of mitoxantrone was 50 mg/m^2 (135). Infectious complications and severe mucositis were other frequently encountered toxicities of this regimen.

Mitoxantrone and carboplatin. Mitoxantrone, 40–50 mg/m^2, in combination with carboplatin, 1500 mg/m^2, has little or no activity in the treatment of breast cancer and is associated with considerable toxicity (136).

Discussion

Until recently, high-dose chemotherapy with autologous stem cell support in solid tumors had almost exclusively been evaluated in small feasibility-or phase II studies. Compelling reasons not to proceed to prospective randomized studies included the high cost of treatment, the need for prolonged hospitalization, the extensive toxicity and the significant treatment-related mortality rates. Dramatic advances in the technology of supportive care and essential information on the toxicity of high-dose regimens specifically designed for solid tumors are currently changing the scene. Several randomized phase III studies are now in progress to study the role of high-dose adjuvant chemotherapy in high-risk breast cancer and many more studies are being designed for advanced breast cancer, germ cell cancer and ovarian cancer.

Several non-randomized studies utilizing historical controls have suggested substantial advantages of high-dose therapy over conventional treatment. High-dose therapy has been shown to achieve long-term disease-free survival in some patients with incurable germ cell cancers and many oncologists (and patients) believe that high-dose therapy may become the standard for adjuvant chemotherapy in breast

cancer patients with unfavorable characteristics. Randomized studies are urgently needed to substantiate these claims. At the same time, high-dose therapy is rapidly evolving and regimens and techniques that appear to be adequate today may be viewed as outdated next year. It is quite possible that some high-dose regimes will eventually prove to be associated with significant cure rates in certain tumors, while others may not. Meaningful comparisons of efficacy are impossible at this stage (Table 2), and the treatment results in individual studies may illustrate patient selection rather than the choice of agents and doses in the chemotherapy regimen.

The selection of agents to be included in a high-dose regimen is essentially based on a number of theoretical considerations that currently lack sufficient clinical confirmation. For example, it is commonly believed that each agent in a high-dose regimen should have activity in the relevant tumor type at conventional doses. Agents that have steep dose-response curves *in vitro* or in animal systems are preferred and combinations of drugs that show little cross-resistance *in vitro* are particularly attractive. Most alkylating agents share these properties and since the dosages of many of these can be escalated several times in humans before dose-limiting organ toxicity appears, multiple alkylator regimens are currently in favor (98–102).

In the absence of convincing evidence that one regimen is more active than the other, it is reasonable to focus on toxicity if a regimen must be selected for a randomized study. This is even more important if the study aims to evaluate high-dose therapy in the adjuvant setting, especially when some patients may already be cured. The level of toxicity is often difficult to determine from the published literature. The treatment-related death rate, for instance, may be influenced significantly by the performance status and extent of pre-treatment. It may depend on the experience and expertise of the investigators, and it may be influenced by the type of supportive care employed. Nevertheless, it is clear that certain drugs are associated with severe organ toxicities (Table 1). Busulfan, mitomycin C and BCNU are associated with VOD and the latter two may also cause interstitial pneumonitis. Both toxicities are not strictly dose-dependent, but are frequently fatal. Cisplatin and ifosfamide have been associated with acute renal failure when administered in high doses. In addition, high-dose cisplatin is associated with severe and irreversible hearing loss and neuropathy, both of which may significantly impair the quality of life in survivors.

The alkylating agents cyclophosphamide, thiotepa, carboplatin and melphalan are not associated with irreversible or unpredictable fatal organ toxicities and have been studied widely in high-dose regimens. The dose of each of these agents can be escalated at least four-fold if adequate supportive care is employed, and all have a broad-spectrum activity in solid tumors. Combinations of cyclophosphamide, thiotepa and carboplatin have been studied by several groups and found to be safe and tolerable (Table 2). The addition of melphalan to cyclophosphamide and thiotepa appeared to be associated with severe mucositis and was therefore abandoned by the Boston group (104). Thus, combinations of cyclophosphamide, thiotepa and carboplatin may presently be considered the most suitable triple-alkylator regimens for adjuvant chemotherapy studies in solid tumors. It must be stressed, however, that this statement is tentative and that randomized studies will be required to confirm or deny it.

If one assumes that a combination of cyclophosphamide, thiotepa and car-

boplatin constitutes a suitable basis for a high-dose regimen, the relevant question is whether or not a single course of this regimen is sufficient. Tandem high-dose regimens have been shown to be feasible and clearly lead to a further increase in dose intensity. Recent experience from the Boston group has shown that CTCb can be administered shortly after a course of high-dose single-agent melphalan (111), and experience in our institute has shown that two courses of CTC can be delivered safely within 6 weeks (114). Employing autologous peripheral stem cell transplantation and—eventually—*ex vivo* expansion of progenitor cells may enable investigators to administer three or even four courses of high-dose therapy at only 3- or 4-week intervals. There is little doubt that the feasibility of these approaches will be limited by organ toxicities other than myelosuppression.

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