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A phase I dose escalation study of high-dose thiotepa, melphalan and carboplatin (TMCb) followed by autologous peripheral blood stem cell transplantation (PBSCT) in patients with solid tumors and hematologic malignancies

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Summary:

The purpose of this study was to determine the maximum tolerated dose of carboplatin administered with 500 mg/m² thiotepa and 100 mg/m² melphalan followed by autologous peripheral blood stem cell (PBSC) infusion in patients with refractory malignancies. Twenty-eight patients with refractory malignancies received high-dose thiotepa (500 mg/m², melphalan (100 mg/m²) and escalating doses of carboplatin 900–1500 mg/m²) followed by infusion of cryopreserved autologous PBSCs. The maximum tolerated doses were determined to be 500 mg/m² thiotepa, 100 mg/m² melphalan and 1350 mg/m² carboplatin. Two consecutive patients receiving 1500 mg/m² carboplatin experienced grade 3 mucositis and colitis. Ten patients were enrolled at the maximum tolerated dose and none had grade 3–4 regimen-related toxicity and mortality. All patients at this level experienced grade 1–2 mucositis, 90% grade 1–2 gastrointestinal toxicity, 30% grade 1–2 cardiac and renal toxicity, and 10% experienced grade 1 hepatic toxicity. The median time to achieve a granulocyte count of 0.5×10^9/l was 9 days (range 7–12 days) and platelet count of 20×10^9/l was 10 days (range 7–15 days). Of eight patients with stage IV refractory breast cancer, even were evaluable for response, one patient on day 75 will be evaluated soon. Five of seven (71.5%) evaluable patients achieved a complete remission (CR) and two had no response. Of seven patients with non-Hodgkin's lymphoma ($n = 4$) or Hodgkin's disease ($n = 3$), five achieved a CR (71.5%). Thiotepa, melphalan and carboplatin can be administered in high doses with tolerable mucositis as the major side-effect. This combination has significant activity in patients with breast cancer, and phase II studies in patients with breast cancer and other chemotherapy-sensitive malignancies are warranted. *Bone Marrow Transplantation* (2000) **25**, 697–703.

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The principles of dose–response and combination chemotherapy have been a basic approach for the design of the initial curative standard-dose treatment regimens for leukemias, lymphomas and testicular cancer. Agents were selected with different dose-limiting toxicities, resulting in subadditive toxicity in combination. One of the most important principles in the design of curative regimens was to combine agents with different mechanisms of action to avoid cross-resistance. Based on these principles, combinations of the highest tolerated doses of active noncross-resistant agents are required to decrease the emergence of drug resistance and achieve optimum cytotoxicity. Hematopoietic stem cell support provides a mechanism for significantly increasing the doses of active agents, a strategy that has resulted in the cure of 20–50% of selected patients with lymphoma who could not be cured with standard-dose therapy.[1,2] Because of the success which is seen in the treatment of hematologic malignancies, high-dose chemotherapy (HDC) and autologous peripheral blood stem cell transplantation (PBSCT) is being used increasingly in patients with solid tumors where a dose–response relationship is thought to exist.[3–8] High-dose chemotherapy with autologous PBSCT has been demonstrated to produce prolonged disease-free survival in some patients with advanced breast and ovarian cancer as well as refractory testicular cancer.[9–14] Reasons for poor outcome in some studies following HDC and autologous PBSCT using currently available treatment regimens include relapse and transplant-related mortality. The lack of sufficiently effective cytoreductive conditioning regimens remains the major impediment to improving the HDC of patients with solid tumors. In this study our objective was to develop a high-dose chemotherapy regimen with a low mortality rate, and significant activity against solid tumors. Thiotepa, melphalan and carboplatin (TMCb) are all myelosuppressive at conventional doses and can be individually dose-escalated several-fold with peripheral blood stem cell (PBSC) support.[15–18] Melphalan and thiotepa are active drugs in the treatment of hematologic

malignancies.[19–21] Melphalan and thiotepa are among the most active single agents in the treatment of breast and ovarian cancer.[15,22–26] Similarly, carboplatin as a single agent has significant activity against ovarian, testicular and lung cancer.[3] Carboplatin as a part of ICE (ifosfamide, carboplatin and etoposide) and CTCb (cyclophosphamide, thiotepa, carboplatin) HDC regimens has been used for the treatment of various solid tumors with autologous PBSCT.[3,27–31] Based on these observations, we hypothesized that a HDC regimen of thiotepa, melphalan and carboplatin would have substantial antitumor activity. We report the results of a dose escalation study of carboplatin administered with a fixed dose of 500 mg/m^2 thiotepa and 100 mg/m^2 melphalan to determine the maximum tolerated dose (MTD) in patients with refractory malignancies.

Patients and methods

Patients and treatment regimen

From January 1998 to May 1999, 28 patients with refractory malignancies were entered into the study. All patients were <60 years of age, had a Karnofsky score of >70% and had normal cardiac, renal, hepatic and pulmonary function. Oral and written informed consent was obtained from all patients or their guardians. Patients characteristics are given in Table 1.

A cumulative dose of 500 mg/m^2 thiotepa was administered on days −9 and −8. This was given in two equally divided doses of 250 mg/m^2/day i.v. All patients received a cumulative dose of 100 mg/m^2 melphalan administered in two doses of 50 mg/m^2/day i.v. infused over 30 min on days −7 and −6. A cumulative dose of 900–1500 mg/m^2 carboplatin was administered on days −5, −4 and −3. This was given in three equally divided doses of 300–500 mg/m^2/day i.v.

Treatment schedule

Treatment schedule was as follows: days −9 to −8: thiotepa 250 mg/m^2/day i.v.; days −7 to −6: melphalan 50 mg/m^2/day i.v.; days −5, −4, to −3: carboplatin 300–500 mg/m^2/day i.v.; days −2 to −1: rest; day 0: autologous stem cell infusion.

Table 1 Patient characteristics

No. of patients	
Total	28
Female	18
Male	10
Age (years)	
Median	38
Range	26–59
Karnofsky score	
<90%	2
>90%	26
Histology	
Breast	13
NHL/HD	7
Multiple myeloma	2
Ovarian cancer	2
Small cell lung cancer	2
Other	2

NHL = non-Hodgkin's lymphoma; HD = Hodgkin's disease.

Autologous stem cell harvest and cryopreservation

Twenty-eight patients received peripheral blood stem cells (PBSC) collected following the administration of chemotherapy followed by recombinant human granulocyte colony-stimulating factor (rhG-CSF-Neupogen; Amgen-Roche, Thousand Oaks, CA, USA). Eighteen of 28 patients received chemotherapy consisting of cyclophosphamide (CY) 4 g/m^2/day × 1 on day 1 and paclitaxel 250 mg/m^2/day × 1 on day 2 followed by rhG-CSF 10 μg/kg/day (subcutaneously twice daily) starting the day after completion of paclitaxel until the last day of apheresis.[32–35] The remaining 10 patients received CY + etoposide 200 mg/m^2/day × 3 on days 1, 2 and 3 (CE) followed by rhG-CSF.[36] The techniques of PBSC harvest, cryopreservation, thawing and transfusion have been described elsewhere.[37–39] Day 0 designates the day of PBSC infusion. All patients in this study received post-transplant growth factor (rhG-CSF) at the dose of 5 μg/kg/day until successful engraftment occurred.

Regimen-related toxicity grading

Regimen-related toxicity (RRT) was graded using a previously described system to assess morbidity.[40] Toxicities affecting renal, hepatic, cardiac, pulmonary, gastrointestinal, bladder, the central nervous system and mucous membranes were evaluated. RRTs were graded prospectively from day 0 to day 28. Grade 3 toxicity was considered life-threatening and grade 4 toxicity was a fatal consequence of the treatment regimen.

Drug dose levels and patient allocation

The method of patient allocation was designed to limit treatment at dose levels associated with >20% grade 3 or 4 RRT. A modification of Hsi's method was used to allocate patients to each dose level as described previously.[41] Patients were treated in groups of four with a maximum of eight patients to be treated at each dose level (Table 2). The first group of patients was treated on dose level 2. The treatment of subsequent groups of four patients was at the appropriate dose level if the previous group had none, one, two or more cases of severe RRT.

Table 2 Dose escalation scheme

Dose level	*Thiotepa (mg/m^2)*	*Melphalan (mg/m^2)*	*Carboplatin (mg/m^2)*	*No. of patients entered*
1	500	100	750	0
2	500	100	900	8
3	500	100	1050	4
4	500	100	1200	4
5	500	100	1350	10
6	500	100	1500	2

Patients were not treated at a higher dose level if the estimates indicated a >80% probability that the incidence of RRT would exceed 20% at that dose level. If two patients were being evaluated at a given dose level, additional patients were enrolled at the next lower dose level.

Definitions

Engraftment was defined as the first of 2 consecutive days on which the patient's neutrophil count was greater than 0.5×10^9/l following the nadir and first of 7 consecutive days on which the patient's unsupported platelet count was greater than 20×10^9/l.

For pre-transplant classification, patients with stage 4 breast cancer that progressed during chemotherapy or relapsed after one chemotherapeutic regimen were considered refractory.

Complete remission (CR) is defined as the disappearance of all measurable tumor for >30 days. Partial remission (PR) is defined as a >50% reduction in the size of a measurable lesion or lesions based on the sum of the products of the greatest tumor diameter and its perpendicular for at least 30 days without the appearance of new lesions. Duration of response was calculated from day of stem cell infusion. Responses less than PR, or progressive disease were considered no response (NR).

Results

Protocol compliance

All 28 patients received all of the prescribed doses of drugs. High-dose chemotherapy and autologous PBSC infusion was performed at the Bone Marrow Transplantation Unit of Ankara University Medical School. Median hospital stay was 18 days (range 13–45).

PBSC mobilization

Twenty-eight patients received chemotherapy followed by rhG-CSF for PBSC mobilization and a median of 7.55×10^6 $CD34^+$ cells/kg (range 1.52–33.2) was collected with a median of 2 (range 1–4) aphereses. In 18 patients receiving CY + paclitaxel followed by rhG-CSF for PBSC mobilization, a median of 7.9×10^6 $CD34^+$ cells/kg (range 1.59–33.2) were collected with a median of 2 (range 1–3) aphereses. In 10 patients receiving CE followed by rhG-CSF, a median of 6.61×10^6 $CD34^+$ cells/kg (range 1.52–28.07) were collected with a median of 2 (range 1–4) aphereses. Patients began the preparative regimen a median of 33 days (range 28–46) following administration of chemotherapy for PBSC mobilization.

Engraftment

All patients were evaluable for engraftment. All patients received PBSCs and achieved granulocytes 0.5×10^9/l and platelet transfusion independence ($>20 \times 10^9$/l) at a median 9 days (range 7–12) and 10 (7–15) after stem cell infusion, respectively. Median numbers of RBC and platelet transfusion requirements in this study were 2 units (range 1–4) and 8 units (4–16), respectively.

Regimen-related toxicities and determination of maximum tolerated dose

Twenty-eight patients were enrolled at five dose levels and all were evaluable for toxicity (Table 2). Four patients were initially enrolled at dose level 2. One patient with stage IV breast cancer (UPN 9808) had grade 3 cardiac toxicity associated with a severe heart failure and a decrease in voltage by more than 50%. Therefore, four more patients were enrolled at dose level 2 and none of these had grade 2–3 toxicities. Of eight patients who were enrolled at dose level 2, seven had grade 1 mucositis. Four patients were enrolled at dose level 3 and all had grade 1 mucositis. One patient with stage IV breast cancer (UPN 9813) at this dose level had grade 2 mucositis and colitis. No grade 3 or 4 RRT was observed. Four patients were enrolled at dose level 4. Two patients at this dose level had grade 1 mucositis. Two of four patients, one with relapsed non-Hodgkin's lymphoma (UPN 9814) and one with relapsed Hodgkin's disease (UPN 9905) had grade 2 mucositis and colitis. No grade 3 or 4 RRT was observed at this dose level. Four patients were initially enrolled at dose level 5. All patients had grade 1–2 mucositis and two patients also developed grade 2 colitis. One patient at this dose level had grade 1 cardiac toxicity. No grade 3 or 4 RRT was observed.

Two consecutive patients enrolled at dose level 6 experienced grade 3 toxicities; therefore this was considered to be a toxic dose, and dose level 5 was deemed the MTD. At dose level 6, one patient with refractory stage 4 breast cancer with bone only disease (UPN 9910) had grade 3 mucositis and colitis associated with severe oral ulceration and abdominal pain with hemorrhagic enterocolitis, evidenced by CT scan showing diffuse bowel wall thickening, affecting cardiovascular status and requiring bolus normal saline (%0.9) infusions and RBC transfusions twice. One patient with relapsed ovarian cancer (UPN 9909) had grade 3 mucositis and colitis associated with severe oral ulcerations and dysphagia resulting in documented aspiration pneumonia. Abdominal pain due to colitis was associated with hemorrhagic diarrhea requiring platelet and packed

Table 3 Regimen-related toxicities in 10 patients given dose level 5

Category	*Toxicity grade*									
	0		*1*		*2*		*3*		*4*	
	No.	*(%)*	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*
Pulmonary	10	(100)	0	(0)	0	(0)	0	(0)	0	(0)
Cardiovascular	7	(70)	2	(20)	1	(10)	0	(0)	0	(0)
Skin	10	(100)	0	(0)	0	(0)	0	(0)	0	(0)
Liver	9	(90)	1	(10)	0	(0)	0	(0)	0	(0)
Mucositis	0	(0)	4	(20)	6	(60)	0	(0)	0	(0)
Renal	7	(70)	2	(30)	1	(10)	0	(0)	0	(0)
Gastrointestinal	1	(10)	3	(30)	6	(60)	0	(0)	0	(0)
Neurologic	10	(100)	0	(0)	0	(0)	0	(0)	0	(0)
Bladder	10	(100)	0	(0)	0	(0)	0	(0)	0	(0)

RBC infusions. Bowel thickening of the transverse and descending colon was demonstrated on CT scan.

An additional six patients were enrolled at dose level 5 for a total of 10 patients. The RRT for all 10 patients at the MTD are shown in Table 3. Of 10 patients who were enrolled at dose level 5, one developed grade 2 cardiac, six grade 2 mucositis and colitis, and one grade 2 renal toxicity.

The patients enrolled on dose level 5 experienced a median peak bilirubin of 1.1 (range 0.2–3.5), and a median peak creatinine of 1 (range 0.9–3.8) during the first 28 days following stem cell infusion.

All 28 patients developed febrile neutropenia and antibiotics were administered empirically. Documented infections with positive cultures occurred in 11 of 28 (39%) patients. Of 11 patients with documented infections, five had *E. coli*, four *Coag (–) staph. aureus*, one *P. pseudomallei* and one had *Coag(–) staph. aureus* plus *E. coli*. The site of infection was documented in only two patients. Of these two patients, one had *E. coli* in bloody diarrhea and the other had *Coag(–) staph. aureus* in sinus secretions.

Response to thiotepa, melphalan and carboplatin

Thirteen patients with stage IIIB ($n = 2$) and stage IV ($n = 11$) breast cancer received treatment and seven were evaluable for response (Table 4). Five patients with no evidence of disease at the time of transplant remain disease-free at 229–471 days. Eight patients had relapsed after at least one chemotherapy regimen (range 1–8) and were considered refractory at the time of transplant. One patient with stage IV breast cancer who is now 75 days post transplant will be evaluated for response soon. Five of seven patients achieved a CR (71.5%) and two had no response following the TMCb regimen. Patient UPN 9805 with a CR following transplant had a relapse on day 170 and died of extensive liver metastasis on day 210. Patient UPN 9804 with no response following transplant had disease progression despite post-transplant chemo- and hormonotherapies but is still alive on day 558. Patient UPN 9812 with no resonse following transplant also had disease progression despite post-transplant chemo and hormonotherapies. This patient was *Her-2 neu* receptor positive and therefore trastuzumab (Herceptin; Genentech, South San Francisco, CA, USA) was started on day 278 post transplant. She is still alive on day 348. Five patients are still in CR 171–591 days after transplant (Table 4). Complete remissions were also observed in patients with Hodgkin's disease ($n = 2$), non-Hodgkin's lymphoma ($n = 3$), multiple myeloma ($n = 1$), and non-seminomatous testicular cancer ($n = 1$) (Table 5).

Discussion

Alkylating agents are a class of chemotherapeutic drugs that have marked differences in their biological mechanism of action and in selectivity toward cancer cells. It has been demonstrated that alkylating agents are not cross-resistant with each other, and may even exhibit selective toxicity toward tumor cells.[42,43] Furthermore, these agents do not always have additive toxicity to normal cells. The major dose limiting toxicity is myelosuppression while non-marrow toxicities vary from drug to drug. The dose–response curve is steep for both therapeutic and toxic effects of chemotherapy for many experimental and clinical tumors. Data derived from laboratory investigations have provided persuasive evidence for a log–linear relationship between dose of alkylating agents and tumor cell kill in several animal tumors.[43,44] This relationship did not appear to plateau in the range studied. This finding suggested that if alkylating agents could be used at much higher doses, greater cytoreduction might result. This steep dose–response curve renders alkylating agents appealing for use in dose escalation studies in the transplant setting.[42,43] However, a dose–toxicity relationship may also exist for these agents.[42–44] Many examples now exist of increased responses to high doses of alkylating agents in patients with diseases refractory to conventional doses. Alkylating agents used in combination have been shown to be curative in Hodgkin's disease and produce increased median survivals in patients with metastatic ovarian and breast cancer as well as other solid tumors. Hyrniuk and Broder have demonstrated a consistent correlation between the dose of chemotherapy administered and the frequency of response in metastatic

Table 4 Breast carcinoma: summary of response to thiotepa, melphalan and carboplatin

UPN	*Age*	*Dose level*	*Site of disease*	*Status*	*Stage*	*Response*	*Outcome*
9802	38	2	Supraclavicular LAP	Refractory	IV	CR	Alive on day 551
9803	41	2	Supraclavicular LAP + marrow	Refractory	IV	CR	Alive on day 591
9804	40	2	Bone only	Refractory	IV	NR	Alive with progression day 558
9805	30	2	Axillary/supraclavicular LAP	Refractory	IV	CR	Died of liver disease on day 210
9807	53	2		NED	IIIB	—	Alive on day 388
9808	33	2	Supraclavicular LAP + lung	Refractory	IV	CR	Alive on day 466
9809	43	2		NED	IV	—	Alive on day 471
9810	32	3		NED	IV	—	Alive on day 381
9812	31	4	Bone only	Refractory	IV	NR	Alive with progression day 348
9813	20	3		NED	IV	—	Alive on day 391
9816	59	5		NED	IIIB	—	Alive on day 229
9902	41	5	Bone only	Refractory	IV	CR	Alive on day 171
9910	37	6	Bone only	Refractory	IV	*	Alive on day 75

UPN = unique patient number; NED = no evidence of disease; CR = complete response; PR = partial remission; LAP = lymphadenopathy; * = will be evaluated later.

Table 5 Summary of response to thiotepa, melphalan and carboplatin

UPN	*Age*	*Diagnosis*	*Dose level*	*Pretransplant status*	*Response*	*Outcome*
9801	48	Multiple myeloma, St III	5	Refractory disease	PR	Alive on day 489
9806	46	SCLC limited to thorax	3	NED	—	Died of MI on day 180
9811	22	Thymic carcinoma	3	Refractory	PR	Alive on day 330
9814	37	NHL, Intermediate grade	4	Relapse-1	CR	Alive on day 227
9815	32	HD, Nodular sclerosing	4	Relapse-1 (refractory)	CR	Relapsed on day 135 and alive on day 219
9817	48	NHL, Mantle cell	2	Relapse-1	CR	Alive on day 464
9901	33	HD, Nodular sclerosing	5	Relapse-1 (Sensitive)	CR	Alive on day 146
9903	41	Ovarian cancer	5	Relapse-2 (NED)	—	Alive on day 136
9904	28	Testicular (non-seminomatose)	5	Relapse (refractory)	CR	Alive on day 137
9905	24	HD	4	Relapse-1	NR	Alive on day 166
9906	32	NHL, Intermediate	5	Relapse-1	CR	Alive on day 120
9907	42	Multiple myeloma, St-III	5	Chemo-sensitive (plateau)	CR	Alive on day 103
9909	47	Ovarian cancer	6	Relapse-1 (NED)	—	Alive on day 78
9911	56	SCLC (extensive)	5	Primary refractory	*	Alive on day 72
9908	40	NHL, Intermediate	5	Primary refractory	NR	Alive on day 70

UPN = unique patient number; CR = complete remission; PR = partial remission; NR = no response; NED = no evidence of disease; HD = Hodgkin's disease; NHL = non-Hodgkin's lymphoma; SCLC = small cell lung cancer; St = stage.

breast cancer.[45,46] Alkylating agents appear more effective than other classes of drugs and have been shown to have single agent response rates from 20 to 54% in metastatic breast cancer.[46] Response rates of 75% have been achieved in high-dose single alkylating agent therapy in failed or refractory breast cancer.[22–24]

The major obstacle to curing patients with advanced breast cancer and other malignancies with HDC and autologous PBSCT is relapse.[1,9–12,32] Strategies to reduce relapse rates include increasing the intensity of the preparative regimen and administering the HDC earlier in the course of the disease when disease burden is small and tumor resistance is less likely to have developed. Increasing the dose intensity of HDC regimens can increase response rates but this is often at the expense of additional toxicity. In order to successfully utilize HDC early in the course of a disease, HDC regimens should have a minimal risk of transplant-related mortality. Therefore, in the current study we sought to develop a HDC regimen that would have increased activity in solid tumors, and have minimal transplant-related mortality associated with an improved outcome.

Chemotherapeutic agents such as thiotepa and melphalan with myelosuppression as the initial conventional dose-limiting toxicity and non-overlapping non-hematologic toxicities can be combined and maximally dose-escalated to take full advantage of a dose–response relationship. Melphalan and thiotepa are two of the most effective alkylating agents for the treatment of breast cancer[15,22–24] and have widespread activity against other malignancies including Hodgkin's disease, NHL and ovarian cancer.[20,21,25,26] They both exhibit a steep dose–response curve[42] and are not cross-resistant in some settings.[43] Other investigators have attempted to take advantage of these agents in HDC regimens combined with CY and concluded that gastrointestinal toxicity precluded the use of melphalan and thiotepa together.[5] A majority of patients undergoing HDC has already been exposed to CY and may have developed resistance. In addition, in the current and other studies CY combined with taxol or other agents is frequently being used for cytoreduction and PBSC mobilization prior to transplantation.[32–35]

Carboplatin is a platinum coordination compound which is a cell cycle non-specific agent. Carboplatin produces interstrand DNA cross-links, similar to those with bifunctional alkylating agents. Carboplatin has been used for treatment of several solid tumors including ovarian, testicular, lung and head–neck cancers. High doses of carboplatin without hematopoietic stem cell support produce responses in patients with advanced ovarian carcinoma who have failed conventional doses of cisplatin.[27] Carboplatin can be dose-escalated as a single agent to 2000 mg/m^2 when followed by autologous marrow or stem cell infusion resulting in a high response rate in patients with refractory ovarian carcinoma.[28] Carboplatin has also been used as a part of CTCb and ICE regimens for treatment of various solid tumors with HDC and autologous PBSCT.[3,28–31] Calvert *et al*[47] have documented the importance of dosing by a calculated target formula which compensates for renal function, age and gender when conventional doses of carboplatin are administered. It has been demonstrated that estimated AUC values of carboplatin in several studies overlapped with dosing on a mg/m^2 basis.[28,48] Shea *et al*[28] administered carboplatin in doses of 375–2400 mg/m^2 and found a direct correlation between mg/m^2 and measured AUC suggesting that dosing could be based on body surface area. Therefore, the current high-dose trial was designed to administer carboplatin on a mg/m^2 basis over 3 consecutive days, as in the other previously reported HDC trials with carboplatin-containing conditioning regimens.[29–31]

As expected, the dose-limiting toxicity of TMCb regimen was gastrointestinal, manifesting as colitis and mucositis in two consecutive patients treated with a carboplatin dose of 1500 mg/m^2. The current study with no fatal RRT and only grade 1–2 toxicities in the 10 patients treated at the MTD compares favorably with other regimens developed in refractory patients (Table 6).[3–7,49] No significant cardiac, pulmonary, renal, hepatic or central nervous system toxicities were observed in this study.

Commonly used HDC preparative regimens for the treatment of breast cancer have resulted in CR rates of 0–50% in the initial phase I trials.[3–5,7,49] Five of seven evaluable patients with refractory breast cancer achieved a CR in this

Table 6 Phase I trials in refractory breast cancer

Author/Ref.	*Regimen*	*Response rate*	*CR (%)*
Eder *et al*[7]	CPB	14/16	6/16 (38)
Williams *et al*[6]	CT	3/3	1/3 (33)
Eder *et al*[5]	CT	6/8	0/8 (0)
Eder *et al*[3]	CTCb	13/16	1/16 (6)
Moormeier *et al*[4]	CTB	7/13	1/13 (8)
Weaver *et al*[49]	BuMT	7/10	5/10 (50)
Demirer *et al* (this study)	TMCb	5/7	5/7 (71.5)

C = cyclophosphamide; B = carmustine; P = cisplatin; T = thiotepa; Cb = carboplatin; M = melphalan; Bu = busulfan.

study with the TMCb regimen comparing very favorably with these phase I trials (Table 6). These regimens are now in widespread use and CR rates of 37–59% have been reported in patients with previously untreated or chemosensitive metastatic disease. Despite an increase in CR rates following HDC, only 10–20% of patients remain free of disease 15–27 months after therapy.[9–12] From these observations, it is clear that some patients may experience prolonged remissions with HDC, but the majority still succumb to their disease. More active preparative regimens used alone or in sequence with additional HDC and/or post-transplant therapy will probably be necessary to improve cure rates in patients with metastatic breast cancer. The number of patients treated in this study is small but a CR was produced in five of seven patients with metastatic breast cancer that had failed a median of four regimens and all had failed at least one doxorubicin-containing regimen.

Srivastava *et al*[50] have recently reported a 58% relapse-free survival at 3 years in patients with intermediate grade NHL treated with a preparative regimen of busulfan and melphalan. Schiffman *et al*[51] reported a 2-year event-free survival rate of 46% in patients with NHL and HD treated with a preparative regimen containing busulfan, melphalan and thiotepa (BuMelTT). In that study, the authors concluded that a regimen of BuMelTT was well tolerated in patients with aggressive NHL or relapsed HD, and results were at least equivalent to other published regimens, including TBI-based regimens.[51] In the current study, we observed complete remissions in patients with HD and NHL receiving TMCb. Of seven patients with NHL ($n = 4$) or HD ($n = 3$), five achieved a CR (71.5%). These encouraging response rates suggest that TMCb may also be an effective preparative regimen for the treatment of patients with HD or NHL. Since this regimen appears to be well tolerated when given with autologous PBSCT support, phase II studies in other malignancies will help to define its spectrum of activity.

References

1 Petersen FB, Appelbaum FR, Hill R *et al*. Autologous marrow transplantation for malignant lymphoma. A report of 101 cases from Seattle. *J Clin Oncol* 1990; **8**: 638–647.
2 Gorin NC, Aegerter P, Auvert B *et al*. Autologous bone marrow transplantation (ABMT) for acute leukemia in remission: an analysis of 1322 cases. *Bone Marrow Transplant* 1989; **4** (Suppl. 2): 3–5.
3 Eder JP, Elias A, Shea TC *et al*. A phase I–II study of cyclophosphamide, thiotepa, and carboplatin with autologous bone marrow transplantation in solid tumor patients. *J Clin Oncol* 1990; **8**: 1239–1245.
4 Moormeier JA, Williams SF, Kaminer LS *et al*. High-dose trialkylator chemotherapy with autologous stem cell rescue in patients with refractory malignancies. *J Natl Cancer Inst* 1990; **82**: 29–34.
5 Eder JP, Antman K, Elias A *et al*. Cyclophosphamide and thiotepa with autologous bone marrow transplantation in patients with solid tumors. *J Natl Cancer Inst* 1988; **80**: 1221–1226.
6 Williams SF, Bitran JD, Kaminer L *et al*. A phase I–II study of bialkylator chemotherapy, high-dose thiotepa and cyclophosphamide with autologous bone marrow reinfusion in patients with advanced cancer. *J Clin Oncol* 1987; **5**: 260–265.
7 Eder JP, Antman K, Peters W *et al*. High-dose combination alkylating agent chemotherapy with autologous bone marrow support for metastatic breast cancer. *J Clin Oncol* 1986; **4**: 1592–1597.
8 Stiff PJ, McKenzie RS, Albert DS *et al*. Phase I clinical and pharmacokinetic study of high-dose mitoxantrone combined with carboplatin, cyclophosphamide and autologous bone marrow rescue: high response rate for refractory ovarian carcinoma. *J Clin Oncol* 1994; **12**: 176–183.
9 Antman K, Rowlings PA, Vaughan WP *et al*. High-dose chemotherapy with autologous hematopoietic stem-cell support for breast cancer in North America. *J Clin Oncol* 1997; **15**: 1870–1879.
10 Demirer T, Buckner CD, Appelbaum FR *et al*. High-dose busulfan, and cyclophosphamide followed by autologous transplantation in patients with advanced breast cancer. *Bone Marrow Transplant* 1996; **17**: 769–774.
11 Peters WP, Shpall EJ, Jones RB *et al*. High-dose combination alkylating agents with bone marrow support as initial treatment for metastatic breast cancer. *J Clin Oncol* 1988; **6**: 1368–1376.
12 Williams SF, Mick R, Desser R *et al*. High-dose consolidation therapy with autologous stem cell rescue in stage IV breast cancer. *J Clin Oncol* 1989; **7**: 1824–1830.
13 Holmberg LA, Demirer T, Rowley S *et al*. High-dose busulfan, melphalan and thiotepa followed by autologous peripheral blood stem cell (PBSC) rescue in patients with advanced stage III–IV ovarian cancer. *Bone Marrow Transplant* 1998; **22**: 651–659.
14 Ozols RF, Ihde DC, Linehan M *et al*. A randomized trial of standard chemotherapy v a high-dose chemotherapy regimen in the treatment of poor prognosis nonseminomatous germ cell tumors. *J Clin Oncol* 1988; **6**: 1031–1040.
15 Lazarus HM, Reed MD, Spitzer TR *et al*. High-dose i.v. thiotepa and cryopreserved autologous bone marrow transplantation for therapy of refractory cancer. *Cancer Treat Rep* 1987; **71**: 689–695.
16 Wolff SN, Herzig RH, Fay JW *et al*. High-dose N, N′, N″-triethylenethiophosphoramide (thiotepa) with autologous bone marrow transplantation: phase I studies. *Semin Oncol* 1990; **17**: 2–6.
17 Lazarus HM, Herzig RH, Graham-Pole J *et al*. Intensive melphalan chemotherapy and cryopreserved autologous bone marrow transplantation for the treatment of refractory cancer. *J Clin Oncol* 1983; **1**: 359–367.
18 Demirer T, Petersen FB, Bensinger WI *et al*. Autologous transplantation with peripheral blood stem cells collected after granulocyte-colony stimulating factor in patients with acute

myelogenous leukemia. *Bone Marrow Transplant* 1996; **18**: 29–34.
19 Sarosy G, Leyland-Jones B, Soochan P *et al*. The systemic administration of intravenous melphalan. *J Clin Oncol* 1988; **6**: 1768–1782.
20 Wright JC, Golomb FM, Gumport SL *et al*. Summary of results with triethylenethiophosphoramide. *Ann NY Acad Sci* 1958; **68**: 937–966.
21 Farber S, Appleton R, Downing V *et al*. Clinical studies on the carcinolytic action of triethylenephosphoramide. *Cancer* 1953; **6**: 135–141.
22 Lemaistre CF, Herzig GP, Herzig RH *et al*. High-dose thiotepa and autologous bone marrow rescue for the treatment of breast cancer. *Breast Cancer Res Treat* 1987; **10**: 89–94.
23 Maranichi D, Piana L, Blaise D *et al*. Phase I–II studies of high-dose alkylating agents in poor risk patients with breast cancer with autologous bone marrow transplant. In: Dicke K, Spitzer TR, Jagannath S (eds). ABMT: Proceedings of the 3rd international symposium. University of Texas MD Anderson Hospital: Houston, TX, 1987, 475–480.
24 Corringham R, Gilmore M, Prentice H *et al*. High-dose melphalan with autologous bone marrow transplant: treatment of poor prognosis tumors. *Cancer* 1983; **52**: 1783–1787.
25 Bateman JC. Chemotherapy of solid tumors with triethylene thiophosphamide. *New Engl J Med* 1955; **252**: 879–887.
26 Ultmann JE, Hyman GA, Crandall C *et al*. Triethylenephosphoramide (thiotepa) in the treatment of neoplastic disease. *Cancer* 1957; **10**: 902–911.
27 Ozols RF, Behrens BC, Ostchega Y *et al*. High-dose cisplatin and high-dose carboplatin in refractory ovarian cancer. *Cancer Treatment Rev* 1985; **12**: 59–62.
28 Shea TC, Flaherty M, Elias A *et al*. A phase I clinical and pharmacokinetic study of carboplatin and autologous bone marrow support. *J Clin Oncol* 1989; **7**: 651–655.
29 Antman K, Ayash L, Elias A *et al*. A phase II study of high-dose cyclophosphamide, thiotepa, and carboplatin with autologous marrow support in women with measurable advanced breast cancer responding to standard-dose therapy. *J Clin Oncol* 1992; **10**: 102–110.
30 Holland K, Dix SP, Geller RB *et al*. Minimal toxicity and mortality in high-risk breast cancer patients receiving high-dose cyclophosphamide, thiotepa, and carboplatin plus autologous marrow/stem-cell transplantation and comprehensive supportive care. *J Clin Oncol* 1996; **14**: 1156–1164.
31 Ayash L, Elias A, Ibrahim J *et al*. High-dose multimodality therapy with autologous stem-cell support for stage IIIB breast carcinoma. *J Clin Oncol* 1998; **16**: 1000–1007.
32 Demirer T, Buckner CD, Bensinger WI *et al*. Peripheral blood stem cell (PBSC) collections after taxol, cyclophosphamide and recombinant human granulocyte-colony-stimulating factor (rhG-CSF). *J Clin Oncol* 1995; **13**: 1714–1719.
33 Demirer T, Buckner CD, Bensinger WI *et al*. Optimization of peripheral blood stem cell mobilization. *Stem Cells* 1996; **14**: 106–116.
34 Demirer T, Buckner CD, Storer B *et al*. Effect of different chemotherapy regimens on peripheral-blood stem-cell collections in patients with breast cancer receiving granulocyte-colony stimulating factor. *J Clin Oncol* 1997; **15**: 684–690.
35 Demirer T, Bensinger WI, Buckner CD. Peripheral blood stem cell mobilization for high-dose chemotherapy. *J Hematother* 1999; **8**: 103–113.
36 Weaver CH, Schwartzberg LS, Birch R *et al*. Collection of peripheral blood progenitor cells following the administration of cyclophosphamide, etoposide and granulocyte-colony stimulating factor: an analysis of 497 patients. *Transfusion* 1997; **37**: 896–903.
37 Bensinger W, Singer J, Appelbaum FR *et al*. Autologous transplantation with peripheral blood mononuclear cells collected after administration of recombinant granulocyte-stimulating factor. *Blood* 1993; **81**: 3158–3163.
38 Thomas ED, Storb R. Technique for human marrow grafting. *Blood* 1970; **36**: 507–515.
39 Buckner CD, Appelbaum FR, Thomas ED. Bone marrow and fetal liver. In: Karow AM Jr, Pegg DE (eds). *Organ Preservation for Transplantation*. Marcel Dekker: New York, 1981, pp 355–375.
40 Bearman SI, Appelbaum FR, Buckner CD *et al*. Regimen related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol* 1988; **6**: 1562–1568.
41 Hsi BP. The multiple sample up-and-down method in bioassay. *J Am Stat Assoc* 1969; **64**: 147–162.
42 Frei E III, Canellos GP. Dose: a critical factor in cancer chemotherapy. *Am J Med* 1986; **69**: 585–599.
43 Frei E III, Cucchi GA, Rosowsky A *et al*. Alkylating agents resistance: *in vitro* studies with human cell lines. *Proc Natl Acad Sci USA* 1985; **82**: 2158–2162.
44 Frei E III, Teicher B, Cucchi GA *et al*. Resistance to alkylating agents: basic studies and therapeutic implications. In: Wooley P III, Tew K (eds). *Mechanism of Drug Resistance in Neoplastic Cells*. Academic Press: New York, 1988, pp 69–87.
45 Hyrniuk WM. Relative dose intensity and the impact on design of clinical trials. *Semin Oncol* 1987; **14**: 65–74.
46 Broder LE, Tormey DC. Combination chemotherapy of carcinoma of the breast cancer. *Cancer Treat Rev* 1974; **1**: 183–203.
47 Calvert AH, Newell DR, Gumbrell LA *et al*. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989; **7**: 1748.
48 Weaver CH, Greco FA, Hainsworth J *et al*. A phase I–II study of high-dose melphalan, mitoxantrone and carboplatin with PBSC support in patients with advanced ovarian or breast carcinoma. *Bone Marrow Transplant* 1997; **20**: 847–853.
49 Weaver CH, Bensinger WI, Appelbaum FR *et al*. Phase I study of high-dose busulfan, melphalan, and thiotepa with autologous stem cell support in patients with refractory malignancies. *Bone Marrow Transplant* 1994; **14**: 813–819.
50 Srivastava A, Bradstock KF, Szer J *et al*. Busulfan and melphalan prior to autologous bone marrow transplantation. *Bone Marrow Transplant* 1993; **12**: 323–329.
51 Schiffman K, Buckner CD, Maziarz R *et al*. High-dose busulfan, melphalan, and thiotepa followed by autologous peripheral blood stem cell transplantation in patients with aggressive lymphoma or relapsed Hodgkin's disease. *Biol Blood Marrow Transplant* 1997; **3**: 261–266.