Bone Marrow Transplantation (2004) 34, 781–786
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www.nature.com/bmt

Conditioning regimens

High-dose thiotepa, melphalan and carboplatin (TMCb) followed by autologous peripheral blood stem cell transplantation in patients with lymphoma – a retrospective evaluation

T Demirer[1], M Ayli[2], T Fen[3], M Ozcan[1], M Arat[1], S Buyukberber[4], O Arslan[1], G Gurman[1], H Akan[1] and O Ilhan[1]

[1]*Department of Hematology/Oncology, Ankara University Medical School, Ankara, Turkey;* [2]*Department of Bone Marrow Transplantation Unit, Ankara Numune Education and Research Hospital, Ankara, Turkey;* [3]*Department of Medical Oncolgy, Ankara Oncology Hospital, Ankara, Turkey; and* [4]*Department of Medical Oncolgy, Gaziantep University Medical School, Ankara, Turkey*

Summary:

The purpose of this evaluation was to investigate the efficacy of high-dose chemotherapy with thiotepa, melphalan, and carboplatin (TMCb), and of autologous peripheral blood stem cell (PBSC) infusion in patients with aggressive non-Hodgkin's lymphoma (NHL) or Hodgkin's disease (HD). A total of 42 patients, 23 with intermediate-grade NHL and 19 with HD, received thiotepa (500 mg/m^2), melphalan (100 mg/m^2), and carboplatin (1050–1350 mg/m^2) followed by autologous PBSC infusion. Of 21 patients with more advanced disease, four had primary refractory disease, one was in complete remission (CR)-2, 11 were in first refractory relapse, and five were beyond first relapse. Of 21 patients with less advanced disease, two were in CR-1, four were in CR-2, and 15 were in first responding relapse. In all, 14 patients (33%) had received prior radiotherapy prohibiting a total-body irradiation (TBI)-based conditioning regimen. The projected 2-year probabilities of survival, event-free survival (EFS), and relapse for all patients were 0.65, 0.60, and 0.21 (0.85, 0.80, and 0.10 for patients with less advanced disease and 0.47, 0.42, and 0.33 for patients with more advanced disease). The probability of nonrelapse mortality in the first 100 days was 0.12. Grade 3–4 regimen-related toxicities (RRT) occured in five of 42 (12%) patients and death due to grade-4 RRT occured in only one (2.5%) patient. These preliminary data suggest that 0.42% EFS in this study for advanced disease patients is highly encouraging and high-dose TMCb followed by autologous PBSC transplantation is well tolerated as well as an effective regimen in patients with intermediate-grade NHL or HD, and may be comparable to some previously used regimens including TBI-based regimens.

Bone Marrow Transplantation (2004) **34,** 781–786. doi:10.1038/sj.bmt.1704672
Published online 6 September 2004
Keywords: TMCb; lymphoma; autologous PBSC transplant

Thiotepa and melphalan are active drugs in the treatment of hematologic malignancies.[1,2] The busulfan, melphalan, and thiotepa (Bu/Mel/TT) regimen has shown high activity in the treatment of patients with agressive lymphoma or relapsed Hodgkin's disease.[3] Carboplatin as a part of ICE (ifosfamide, carboplatin, and etoposide) HDC regimen has been used for the treatment of malignant lymphomas with autologous PBSC transplantation.[4] While considering the present literature data for carboplatin in the setting of autologous transplantation for solid tumors, we decided to combine carboplatin with thiotepa and melphalan in a previous phase-I study and developed a regimen of thiotepa, melphalan, and carboplatin (TMCb).[5] These drugs have marrow ablation as their dose-limiting toxicity, allowing significant dose escalation with the infusion of autologous hematopoietic stem cells.[5] The maximum-tolerated dose (MTD) of carboplatin that could be added to fixed doses of thiotepa 500 mg/m^2 and melphalan 100 mg/m^2 was 1350 mg/m^2, associated with a demonstrable activity in patients with breast cancer.[6] Upon observing intractable diarrhea at this dose level, we decided to use a cumulative carboplatin dose of 1200 mg/m^2 (one step down) in this regimen. In our previous phase-I study, five of seven patients with non-Hodgkin's lymphoma (NHL) ($n=4$) or Hodgkin's disease (HD) ($n=3$) achieved a complete remission (CR; 71.5%). Based on these encouraging results, we evaluated the efficacy of this regimen in patients with malignant lymphomas. Here, we retrospectively evaluate the efficacy of TMCb regimen in 42 patients with aggressive NHL and HD to verify these initial observations and extend them to a larger group of patients with lymphoma.

Correspondence: Dr T Demirer, Department of Hematology/Oncology and Bone Marrow Transplant Unit, Ankara University Medical School, Ibn-i Sina Hospital EBMT Office, Floor 05, Sıhhıye, 06100, Ankara, Turkey; E-mail: demirer@medicine.ankara.edu.tr
Received 27 October 2003; accepted 22 June 2004
Published online 6 September 2004

Patients and methods

Patient characteristics

Between January 1998 and October 2002, 42 patients with aggressive malignant lymphoma (NHL = 23 and HD = 19) were treated with high-dose TMCb followed by autologous PBSCs. Of 42 patients, 25 were treated at the Numune Hospital Bone Marrow Transplant Unit from September 1999 to September 2001, and 17 were treated at the Ibn-i Sina Hospital from January 1998 to October 2002. Seven patients (NHL = 4, HD = 3) were reported as part of a phase-I trial and are included in the present analysis with longer follow-up.[5]

NHL was classified according to the Working Formulation[7] and HD by the Rye classification.[8] Patients were eligible for this treatment if they had a Karnofsky score of $>70\%$, a left ventricular ejection fraction $\geqslant 50\%$, a creatinine clearance $\geqslant 50$ ml/min, a bilirubin <2 mg/dl, and a Dlco $\geqslant 60\%$. Oral and written informed consent was obtained from all patients or their guardians. Patient characteristics are given in Table 1.

Definitions

Patients treated in first or second CR and patients treated in untreated first relapse or chemosensitive first relapse were classified as having less advanced disease, while all others were classified as having more advanced disease.[3,9] These classifications were based on clinical history and laboratory evaluation before the administration of chemotherapy for PBSC mobilization. Patients who were in CR before transplantation were categorized as having no evidence of disease and were not evaluated for response (NE), but were evaluated for survival and relapse.

Complete baseline staging, including computerized tomographic (CT) scans of head, chest, abdomen, pelvis, and marrow aspiration and biopsies, was carried out before HDC and restaging at sites of known disease after transplantation. Duration of response was calculated from the day of PBSC infusion (day 0). Responses for patients with measurable disease were defined as CR if there was disappearance of all tumors for more than 30 days, and as partial remission (PR) if there was a reduction of 50% or more in the size of all measurable diseases for at least 30 days. Responses of less than PR or progressive disease were considered no response (NR). All patients were restaged at sites of prior disease 60–80 days, 6 months, and annually after transplantation.

Table 1 Patient characteristics

N	NHL (23)	HD (19)	Total (42)
Gender			
Male	18	11	29
Female	5	8	13
Age – median (range)	42 (16–57)	26 (18–55)	35 (16–57)
Disease phase at transplant			
More advanced	13	8	21
Primary refractory	4	—	4
>CR-2	1	—	1
First refractory relapse	6	5	11
>Relapse-1	2	3	5
Less advanced	10	11	21
CR-1	—	2	2
CR-2	2	2	4
First responding relapse	8	7	15
Prior radiotherapy	16	13	29
Mediastinal	9	9	18
Abdominal	4	2	6
Spinal	3	2	5
Median number of prior chemo regimens – median (range)	2 (1–6)	2 (1–5)	2 (1–6)
Time from diagnosis to transplant, days – median (range)	508 (137–1827)	447 (179–1455)	492 (137–1827)
Time from PBSC mobilization to transplant, days – median (range)	35 (27–41)	36 (29–43)	35 (27–43)

Regimen-related toxicity grading

Regimen-related toxicity (RRT) was graded using a previously described system to assess morbidity.[10] Toxicities affecting renal, hepatic, cardiac, pulmonary, gastrointestinal (GI), bladder, the central nervous system, and mucous membranes were evaluated. RRTs were graded prospectively from days 0 to 28. Grade 3 toxicity was considered life threatening and grade 4 toxicity was a fatal consequence of the treatment regimen. Infection was excluded from this grading system. Veno-occlusive disease (VOD) of the liver was defined clinically by hepatomegaly or liver tenderness, weight gain $>2\%$ of baseline, and an elevated serum bilirubin >2 mg/dl or histopathologically by damaged endothelial cells of the terminal hepatic venules, dilatation of the sinusoids, and necrosis of hepatocytes.[11] Idiopathic pneumonia syndrome (IPS) was defined as pulmonary infiltrates not associated with pulmonary edema or an identifiable infectious cause.[12]

PBSC mobilization, cryopreservation, and infusion

Out of 42 patients, 40 received PBSC collected following the administration of chemotherapy, followed by recombinant human granulocyte colony-stimulating factor (rhG-CSF-Neupogen, Amgen-Roche, Thousand Oaks, CA, USA). In all, 37 of 40 patients received chemotherapy consisting of cyclophosphamide (CY) $4\,g/m^2/day \times 1$ on day 1 and etoposide $200\,mg/m^2/day \times 3$ on days 1, 2, and 3 (CE), followed by rhG-CSF.[6,13,14] All patients received MESNA for the prevention of hemorrhagic cystitis. MESNA at $4\,g/m^2$ was administered in equally divided doses prior to, and 4 and 8 h after, infusion of CY. Two of 40 patients received DHAP (dexamethasone, high-dose cytarabine, and cisplatin), followed by rhG-CSF $10\,\mu g/kg/day$ (subcutaneously BID), starting the day after completion of the chemotherapy schedule until the last day of apheresis. One of 40 patients received mini-BEAM followed by rhG-CSF $10\,\mu g/kg/day$ (subcutaneously BID), starting the day after completion of chemotherapy. Two of 42 patients received rhG-CSF alone for PBSC mobilization at the dose of $10\,\mu g/kg/day$ (subcutaneously

BID) for 4 days, and apheresis was performed on day 5. The techniques of PBSC harvest, cryopreservation, thawing, and transfusion have been described elsewhere.[15–17] Based on our previous studies, a minimum cell dose of 2.5×10^6/kg was established and a target dose of 4×10^6/kg CD34+ cells/kg was used.[18,19] Day 0 designates the day of PBSC infusion.

Tumor debulking prior to HDC

Out of 42 patients, 35 received DHAP regimen for either tumor debulking or determination of relapse status (responding or refractory) before PBSC mobilization.[20] Of these 35 patients, four had primary refractory disease, 11 had first refractory relapse, five had beyond relapse-1, and 15 had first responding relapse.

Treatment regimen

A cumulative thiotepa dose of 500 mg/m^2 was administered on days −9 and −8. This was given in two equally divided doses of 250 mg/m^2/day i.v. Thiotepa was given in 1000 cm^3 normal saline as a 2-h infusion. All patients received a cumulative dose of melphalan 100 mg/m^2 administered in two doses of 50 mg/m^2/day i.v. infused in 500 cm^3 normal saline over 60 min on days −7 and −6. A cumulative carboplatin dose of 900–1350 mg/m^2 was administered on days −5, −4, and −3.[5,6] This was given in three equally divided doses of 300–450 mg/m^2/day i.v. Carboplatin was given in 1000 ml D5W with 50 g mannitol (5% solution) as a 2-h infusion. Renal function was monitored during the last 3 days of carboplatin infusion. For significant change in renal function (clearance drops below 60 ml/min), carboplatin was discontinued. On the basis of a dose-finding process, four patients received a cumulative carboplatin dose of 1050 mg/m^2, eight received 1350 mg/m^2, and the remaining 30 patients received 1200 mg/m^2.[5,6]

Treatment schedule

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 350–450 mg/m^2/day i.v.
Days −2 to −1:	rest
Day 0:	autologous stem cell infusion

Statistics

Actuarial probabilities of survival and event-free survival (EFS) were computed according to the method of Kaplan and Meier.[21] Survival was calculated from the time of PBSC infusion until death or date of last contact. The end points for EFS were death or relapse. Patients not achieving CR were considered to have relapsed on day 1 after transplantation. Patients who died after day 100 with evidence of recurrent or persistent disease were categorized as dying from relapse, irrespective of the proximate cause.

Results

Engraftment

One patient died on day 9 due to grade-4 GI toxicity without recovery of neutrophils or platelets. The remaining patients achieved an ANC $>0.5 \times 10^9$/l at a median of 10 days (range 8–13) and an unsupported platelet count of $>20 \times 10^9$/l at a median of 11 days (range 9–19) after infusion of PBSC.

RRT and transplant-related mortality (TRM)

In all, 64% of patients developed grade 1–2 RRT, mainly including mucositis and GI toxicities. Grade 3–4 RRTs occurred in five of 42 (12%) patients and death due to grade-4 RRT occurred in only one (2.5%) patient with more advanced disease (Table 2). Of four patients with grade-3 RRT, three had less advanced disease and one had more advanced disease. Altogether, five patients (12%) died of treatment-related causes before day 100. Of these five patients, two (one with more and one with less advanced disease) died of sepsis on post-transplant days 15 and 80, one with more advanced disease died of suicide on day 2, one with more advanced disease died of

Table 2 Regimen-related toxicities

	Grade-1–2		*Grade-3*		*Grade-4*	
	LAD (n)	*MAD (n)*	*LAD (n)*	*MAD (n)*	*LAD (n)*	*MAD (n)*
Pulmonary	—	1	1	—	—	—
Gastrointestinal	13	13	2	1	—	1
Skin	—	2	—	—	—	—
Mucositis	14	8	2	—	—	—
Renal	1	2	—	—	—	—
Bladder	1	—	—	—	—	—
Liver	—	1	—	—	—	—
Cardiac	1	2	—	—	—	—
Neurologic	—	3	—	—	—	—
Total patients	14 (33%)	13 (31%)	3 (7%)	1 (2.5%)	—	1 (2.5%)

LAD = less advanced disease; MAD = more advanced disease. In addition to the above-given table, one patient died of MI and two others died of sepsis during the transplant.

Table 3 Responses

Disease	*Number*	*Early deaths*	*NE*	*CR*	*PR*	*NR*	*Disease-free survivors*	*Median days from HDC (range)*
NHL	23	2	2	13	2	4	12 (52%), 12 CR	864 (99–1771)
Less advanced	10	1	2	6	1	—	7	
More advanced	13	1	—	7	1	4	5	
HD	19	2	4	12	—	1	14 (73%), 10 CR, 4 NED	868 (490–1531)
Less advanced	11	—	4	7	—	—	10	
More advanced	8	2	—	5	—	1	4	
Total patients	42	4	6	25	2	5	26 (62%), 22 CR, 4 NED	866 (99–1771)

NE = not evaluable; CR = complete remission; PR = partial remission; NR = no response; NED = no evidence of disease.

myocardial infarction on day 6, and one with more advanced disease died of grade-4 GI toxicity on day 9. Therefore, the probability of nonrelapse mortality in the first 100 days was 0.12.

Response and survival

In all, 10 patients were not evaluable (NE) for response because of early death ($n = 4$) or disease status ($n = 6$) (Table 3). Out of 32 patients, 25 (78%) evaluable for response achieved CR and 22 of 25 (88%) survived a median of 855 days (range 99–1771). The projected 2-year probabilities of survival and EFS for all patients were 0.65 and 0.60, respectively. The 2-year probability of relapse was 0.21. The median time to relapse was 195 days (range 81–973) after PBSC infusion.

The probabilities of survival and EFS in patients with less and more advanced disease were 0.85, 0.80 and 0.47, and 0.42, respectively (Figures 1 and 2). The probabilities of survival and EFS at 2 years for patients with HD and NHL were 0.82, 0.78 and 0.50, 0.46, respectively. The probabilities of relapse among patients with HD and NHL were 0.11 and 0.31, respectively.

Effect of disease phase on outcome

Among 21 patients with more advanced disease, three died within 100 days (one due to sepsis, one suicide, and one myocardial infarction). Thus, 18 patients were evaluated for response, of whom 12 (67%) achieved CR and nine survived disease-free at a median of 878 days (range 555–1585) after PBSC infusion. The probabilities of survival and EFS in patients with more advanced disease were 0.47 and 0.42, respectively (Figures 1 and 2). The 2-year probability of relapse for patients with more advanced disease was 0.33.

Among the 21 patients with less advanced disease, one died due to sepsis within 100 days and six were not evaluable for disease. Thus, 14 patients were evaluated for response, of whom 13 (93%) achieved CR and one achieved PR. Out of 20 patients, 17 are disease-free survivors at a median of 854 days (range 63–1764) after transplant. The probabilities of survival and EFS in patients with less advanced disease were 0.85 and 0.80, respectively (Figures 1 and 2). The 2-year probability of relapse for patients with less advanced disease was 0.10.

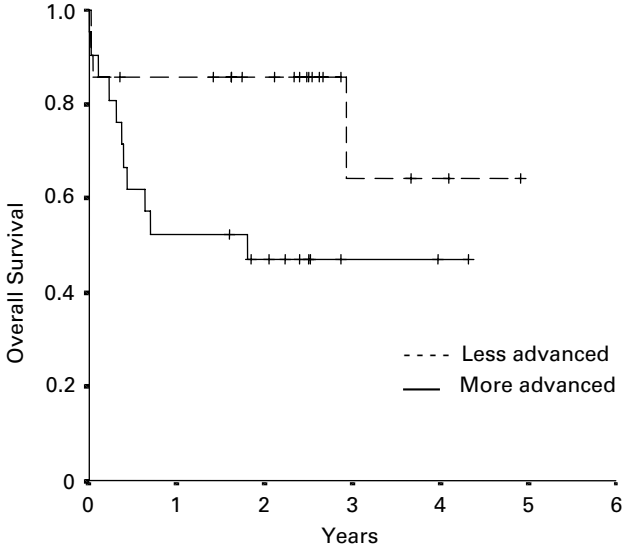


Figure 1 Comparison of overall survival in patients with less advanced and more advanced disease.

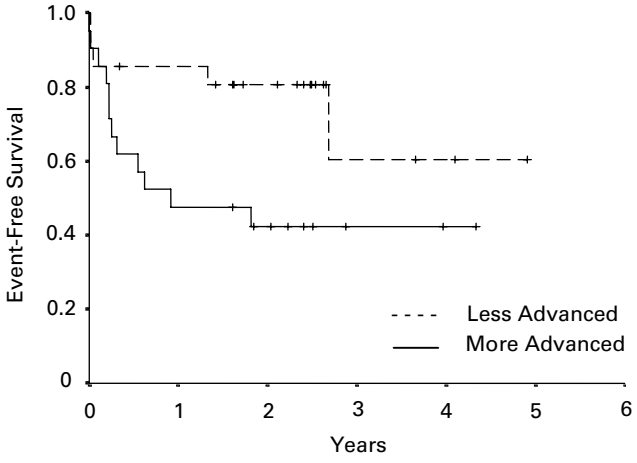


Figure 2 Comparison of EFS in patients with less advanced and more advanced disease.

Discussion

Since the demonstration that some patients with refractory NHL or HD could be cured with high-dose CY and TBI followed by marrow transplantation, many treatment regimens have been evaluated in patients with advanced lymphoid malignancies. The single most important cause of treatment failure has been relapse.[22–25] Previous attempts at intensification of the pretransplant conditioning regimen have not resulted in an increase in long-term EFS, and have usually been associated with TRM.[23,25,26] Srivastava *et al*[27] reported a 58% relapse-free survival at 3 years in patients with intermediate grade NHL treated with busulfan and melphalan. Schiffman *et al*[3] reported a 2-year EFS 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 the BuMelTT regimen 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.[3] In our previous phase-I study, we observed CRs in patients with HD and NHL receiving TMCb.[5] In that study, of seven patients with NHL ($n=4$) or HD ($n=3$), five achieved a CR (71.5%). These encouraging response rates suggested 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 PBSC support, we have decided to expand our experience in patients with lymphoid malignancies.

It has previously been demonstrated that patients who undergo transplantation in remission or with chemosensitive disease have improved EFS rates and decreased TRM rates when compared with patients who undergo transplantation with resistant or refractory disease.[22,28,29] Previous experience in Seattle with a TBI-etoposide-CY regimen was associated with TRMs of 8 and 25% in patients with less and more advanced disease, respectively.[9] The probabilities of survival, EFS, and relapse for the entire group at 2 years following TBI-etoposide-CY were 0.54, 0.45, and 0.43, respectively. When analyzed according to disease status at transplant, the 2-year probabilities of EFS for patients with less and more advanced disease were 0.61 and 0.31, respectively ($P=0.006$). The K-M estimates of relapse were 0.34 for patients with less advanced disease and 0.53 for patients with more advanced disease ($P=0.05$).[9] Another study from Seattle which was reported by Schiffman *et al*[3] in patients with aggressive lymphoma or relapsed HD receiving BuMelTT showed a projected 2-year probabilities of survival, EFS, and relapse rates of 0.85, 0.85, and 0.15, respectively, for patients with less advanced disease, and 0.48, 0.30, and 0.37 for patients with more advanced disease. In one study with CBV, predominantly in patients with less advanced disease, Wheeler *et al*[30] reported a TRM of 8% and an EFS of 0.46 (0.82 for patients with less advanced and 0.28 for patients with more advanced disease). Similarly, investigators at Stanford reported an EFS of 46% following CBV and stem cell transplantation in patients with less advanced disease who had received prior dose-limiting radiotherapy.[31] In the current study, EFS of 0.42 for more advanced disease patients are highly encouraging and this result seems to be superior to the BuMelTT regimen of Seattle[3] and TBI-etoposide and CY experience of Weaver *et al*.[9]

In the current study, a regimen of high-dose TMCb followed by autologous PBSC was administered to 42 patients with NHL or HD. In all, 25 (78%) of 32 patients evaluable for response achieved CR and 22 of 25 (88%) survived a median of 855 days (range 99–1771). The projected 2-year probabilities of survival and EFS for all patients were 0.65 and 0.60, respectively. The 2-year probability of relapse was 0.21. Thus, the EFS results of the present study using TMCb appear superior to those of a BUMelTT- and TBI-based regimens, and resemble the findings from Stanford in which there were no significant differences in TRM, EFS, or relapse between CBV and TBI-etoposide-CY preparatory regimens.[32]

In summary, in the current study, outcomes for patients treated with TMCb compare well with the BuMelTT- and TBI-containing regimens and may be superior to previous CBV or Bu/Cy regimens administered at many centers in the past. In addition, 0.42% EFS in this study for advanced disease patients is highly encouraging and deserves further investigation.

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