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An Expanded Phase I/II Trial of Cyclophosphamide, Etoposide, and Carboplatin Plus Total Body Irradiation with Autologous Marrow or Stem Cell Support for Patients with Hematologic Malignancies

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ABSTRACT

The major cause for failure of autologous stem cell transplantation for hematologic malignancies is the risk of recurrent disease. As a result, new treatment regimens that include novel agents or combinations of agents and approaches are needed. The current report describes a large Phase I/II, single-center trial that includes 60 patients with a variety of hematologic malignancies. These patients received a fixed dose of carboplatin (1 g/m^2/d × 72 hours by CI) etoposide (600 mg/m^2/d × 3 days) and cyclophosphamide (2 g/m^2/d × 3 days), plus escalating doses of total body irradiation (TBI) (at 1000, 1200, and 1295 cGy) over 3 days. Eleven patients received infusion of autologous marrow, 32 received peripheral blood stem cells, and 17 patients received both. The maximum tolerated dose of this regimen was a radiation dose of 1200 cGy given in 200-cGy fractions BID × 3 days. The dose-limiting toxicity was mucositis, with 97% of patients requiring narcotic analgesia for mouth pain. Overall treatment-related mortality was 6.7%, with 2 of the 4 deaths occurring in a group of 9 patients aged 60 and older. Responses were seen in all patient groups, but the most encouraging outcomes were seen in 12 patients with high-risk or advanced acute myelocytic lymphoma (AML), 7 of whom remain alive and free of disease beyond 5 years. This regimen is intensive and causes considerable mucositis but is otherwise well tolerated and has demonstrated activity in a number of hematologic malignancies, especially AML.

KEY WORDS

Autologous transplantation • Carboplatin • Hematologic malignancy

INTRODUCTION

Autologous transplantations for patients with hematologic malignancies have been in widespread use since the mid-1980s. Randomized trials by Philip and Gianni for non-Hodgkin's lymphoma (NHL) and Attal et al. for multiple myeloma have established the value of such treatment in a variety of diseases [1-5]. In each instance, patients with a smaller quantity of chemotherapy-responsive disease before transplantation have had the best chance for durable remission and cure. With the advent of peripheral blood stem cells (PBSC) and cytokines to hasten platelet and neutrophil recovery, overall mortality and major morbidity from such procedures has been reduced to as low as 2% to 3% for patients with multiple myeloma and 5% to 10% for patients with more advanced lymphoma or acute leukemia. For all diseases, the highest likelihood of treatment failure results from tumor recurrence posttransplantation. Whereas second transplantations are an option for some patients, the results with full allogeneic transplantations following failure after autologous transplantations have been poor, especially for adults with recurrent lymphoma or those who

relapse within 2 years of their initial transplantation. Outcomes following second transplantations with nonablative regimens are encouraging but still of uncertain value.

New transplantation approaches have included the use of in vivo purging of CD-20–expressing lymphomas by administration of rituximab antibody therapy during salvage and stem cell mobilization, as well as the use of vaccines and antibody therapy posttransplantation [6-8]. Although these therapies hold promise and offer novel and non–cross-resistant approaches, they also have been accompanied by a reduction in efforts to develop improved transplantation-conditioning regimens. Whereas current programs to reduce toxicity with agents such as protegrin and keratinocyte growth factor are important and valuable attempts at reducing morbidity and mortality, significant improvements in survival for these patients more likely will be derived from the addition of new agents into standard conditioning regimens or new drug combinations [9,10]. It is especially notable that new regimens that combine total body irradiation (TBI) with additional chemotherapy agents have not been explored in recent years, in part because of the increased incidence of secondary leukemia and myelodysplasia that has been seen primarily in patients with low-grade NHL. Whereas there is little doubt that TBI has contributed to the development of secondary tumors in some of these patients, it is more likely that therapy received before stem cell collection and subsequent transplantation have been of greater significance [11-18]. It also is worth noting that secondary malignancies remain uncommon complications of autologous transplantations for patients with intermediate and high-grade lymphomas, Hodgkin's disease, and acute leukemia, in contrast to the much more common problem of death caused by disease recurrence.

In an effort to develop a more effective conditioning regimen, the study described here was developed and implemented in the early 1990s and previously reported in abstract form. The current report describes our experience with a phase I/II trial in patients with a minimum follow-up of 5 years using a novel combination of cyclophosphamide, etoposide, carboplatin, and TBI in patients with a spectrum of hematologic malignancies. This report provides information regarding the toxicity and efficacy of this regimen and compares these results with other commonly used autologous transplantation regimens.

PATIENTS AND METHODS

Patients

From October 1992 to September 1996, 60 patients with advanced hematologic malignancies were enrolled on this expanded phase I/II trial. Eligible patients first included those with acute leukemia at high risk (required second induction therapy to achieve complete response (CR) or with extramedullary disease at presentation) or subsequent complete remission; NHL that was progressive or recurrent after at least 1 prior course of multiagent chemotherapy; multiple myeloma following initial or salvage chemotherapy; and Hodgkin's disease in relapse or beyond a second complete remission. Additional eligibility criteria included age >16 years and physiologic age <65 years, Eastern Cooperative Oncology Group performance status of 0-2, white blood cell count >1500/μL, neutrophil count >500/μL, platelet count >50,000/μL, aspartate transaminase and bilirubin <2 times normal, serum creatinine <2.0 mg/dL or creatinine clearance >60 cc/min, pulmonary diffusion capacity >50% predicted, and negative human immunodeficiency virus and hepatitis B surface antigen. Patients with serious medical or psychiatric illness that would prevent informed consent or general anesthesia; uncontrolled or severe cardiovascular disease including recent (<6 months) myocardial infarction or congestive heart failure; any active, uncontrolled bacterial, viral, or fungal infection; or an active duodenal ulcer were excluded from enrollment. All patients signed informed-consent documents reviewed and approved by the UNC Committee for the Protection of the Rights of Human Subjects.

Treatment Plan

Patients had an indwelling central venous catheter placed before initiation of treatment. In patients with acute leukemia, stem cells were harvested after the patient achieved complete remission. No leukemia patients had stem cells collected in initial remission for use following a subsequent relapse. In other malignancies, stem cell harvest was accomplished following salvage chemotherapy and before initiation of the conditioning regimen. Initial patients underwent bone marrow harvest, but PBSC were routinely used to rescue patients enrolled since 1994. If the collected dose of $CD34^+$ cells was $<2 \times 10^6$/kg, patients received a combination of marrow and PBSC as previously described [19].

High-risk patients with acute leukemia underwent transplantation in complete remission following initial induction and consolidation (for patients with extramedullary disease at presentation or persistent leukemia on the day 14 marrow) or following re-induction of remission for relapsed patients. Other hematologic malignancy patients received pretransplantation salvage therapy to reduce their tumor burden before high-dose chemotherapy whenever possible.

The preparative regimen is detailed in Table 1. It

Table 1. *Preparative Regimen MTD*

Drug	Dose (mg/m²/d)	Route	Day −8	−7	−6	−5	−4	−3	−2	−1
Cyclophosphamide	2000	IV qd × 3				●	●	●		
Etoposide	600	IV over 4 hrs qd × 3				●	●	●		
Carboplatin	333	CIVI qd × 72 hrs				●			●	
*TBI		200 cGy bid × 3 d	●	●	●					

*MTD dose.

was decided to fix the dose of carboplatin, because data suggested that dose escalation beyond the range of 1000 mg/m^2 was of uncertain value, and that this dose was unlikely to exacerbate the mucositis or gastrointestinal and pulmonary toxicity generally observed with TBI-based regimens. Thus, a fixed dose of carboplatin along with already-high doses of etoposide and cyclophosphamide were thought likely to allow escalation of TBI into its optimally effective range, especially for acute myelocytic leukemia (AML) patients, while not generating the toxicities of veno-occlusive disease (VOD) or renal dysfunction reported with higher doses of carboplatin. Patients received intravenous hydration at a minimum of 150 cc/m^2/h during chemotherapy and for a minimum of 24 hours following the completion of chemotherapy (days −5 through −1). Patients did not routinely receive bladder irrigation or mesna therapy.

TBI doses were escalated according to the schema in Table 2. This article will include detailed outcomes of the 60 patients treated at 1000, 1200, and 1295 cGy. Dose-limiting toxicity (DLT) was defined as irreversible grade 3 or 4 nonmyeloid toxicity according to the NCI Cancer Therapy Evaluation Program Common Toxicity Criteria (version 2.0, BMT-Specific Adverse Events, DCTD, NCI, DHHS, April 30, 1999).

Criteria for Response

The following definitions were used when assessing response. Clinical CR was defined as the disappearance of all measurable disease signs, symptoms, and biochemical changes related to the tumor, for >4 weeks, during which no new lesions appeared. A partial response was defined as a reduction >50% in the sum of the products of the perpendicular diameters of all measurable lesions lasting >4 weeks, during which no new lesions appear and no existing lesions enlarge.

Table 2. *TBI Dose Escalation*

Level	Total Dose (cGy)	Fraction S bid (cGy)	Number of Patients
1	1000	5 (200)	4
2*	1200	6 (200)	34
3	1295	7 (185)	22

*MTD dose.

Stable disease was characterized as <50% reduction and <25% increase in the sum of the products of 2 perpendicular diameters of all measured lesions and the appearance of no new lesions for >8 weeks. Disease progression was described as an increase in the product of 2 perpendicular diameters of any measured lesion by >25%, or the appearance of new areas of disease. Increasing symptoms alone did not constitute progression, although their appearance generated a new evaluation of the extent of disease. A complete response for AML and acute lymphoblastic leukemia (ALL) patients constituted elimination of all cytogenetic and morphologic evidence of leukemia with recovery of platelet counts to >50,000/μL without transfusion for a minimum of 30 days' posttransplantation.

RESULTS

Patients

Sixty patients ranging in age from 22 to 65 were enrolled on this phase I protocol. Thirty-six women and 24 men received marrow (n = 11), PBSC (n = 32), or both (n = 17). The initial 11 patients received bone marrow, and subsequent patients received PBSC if adequate cells could be collected, or marrow alone or marrow plus PBSC if the PBSC yield was $<2 \times 10^6$ CD34 cells/kg. Patients had either AML, ALL, NHL, multiple myeloma, or Hodgkin's disease. Seven of 10 patients with low-grade NHL, 9 of 20 with intermediate- (IGL) or high-grade (HGL)-NHL, and 3 of 5 with Hodgkin's disease had marrow involvement at some time before transplantation. Additional patient characteristics are provided in Table 3.

Treatment-Related Mortality

Eight patients died before day 100 posttransplantation. Four deaths were treatment-related, and 4 patients—2 patients with multiple myeloma and 2 patients with IGL-NHL—died from progressive disease. The treatment-related deaths occurred at a median of 17 days' posttransplantation and were primarily related to sepsis and resultant multisystem organ failure. One 62-year-old man with AML died on day +26 after requiring ventilatory support and he-

Table 3. *Patient Characteristics and Pretreatment Diagnosis and Disease Phase*

Patient Characteristics	
Stem Cell Source	**n**
Bone Marrow	11
Peripheral Blood	32
Both	17
Total	60
Gender	
Female 24 (40%)	
Male 36 (60%)	
Age (median, range)	
48 (22–65)	

Pretreatment Diagnosis and Disease Phase					
	Total	CR1	>CR1		
ALL	3	1	2		
AML	12	4	8		
	Total	CR	PR	RD	Marrow Involvement
LGL-NHL	10	0	9	1	7
LGL/HGL-NHL	20	2	12	6	9
Hodgkin's disease	5	1	4	0	3
Multiple myeloma	10	0	10	0	NA

Pretreatment Age-Adjusted IPI					
	Total	0	1	2	3
LGL-NHL	10	0	6	3	1
IGL/HGL-NHL	20	0	12	7	1

*ALL, acute lymphoblastic leukemia, LGL-NHL, low-grade NHL, IGL/HGL, intermediate and high-grade NHL.

modialysis. The only positive culture in this patient was a tracheal aspirate for methicillin-resistant *Staphylococcus aureus*. A 48-year-old woman with Hodgkin's disease developed aspiration pneumonia with cardiopulmonary arrest on day 41. This progressed to include renal failure requiring hemodialysis, and she died on day 49 of refractory hypotension and respiratory failure. A 66-year-old man with IGL-NHL developed atrial fibrillation, sepsis, and subsequent renal failure on day 1. He progressed to respiratory failure on day +6, refused ventilatory support, and died following the initiation of comfort-care measures. A 52-year-old-man man with IGL-NHL developed a sepsis syndrome and underwent liver biopsy for a suspicion of fungal disease. The biopsy was nondiagnostic and complicated by a liver laceration and severe hemorrhage. All cultures were negative. The patient failed to respond to aggressive volume resuscitation and antibiotic therapy, and died from multiorgan failure on day +8. Two deaths occurred in patients treated with 1200 cGy (2/34 [5.9%]) and 2 deaths occurred following 1295 cGy (2/22 [9.1%]). Two of these 4 treatment-related deaths occurred in a group of 9 patients who were older than age 60 (22%) vs 2 of 51 in patients younger than age 60 (3.9%). It is also notable that 2 of the 4 treatment-related deaths occurred in a group of 6 patients treated for refractory large-cell NHL.

Grade III-IV Nonhematologic Toxicities/DLT

Initially, a dose-escalation scheme was employed with 3 patients in the first cohort followed by dose escalation if no DLT was observed. A fourth patient was added at a later time to dose level 1 (1000 cGy) when prior radiation therapy limited his ability to receive a total dose of 1000 cGy of TBI. At dose level 2 (1200 cGy), DLT was identified in 1 of the first 3 patients, so a second cohort of 3 patients was added before expansion into level 3 (1295 cGy). Once the maximum tolerated dose (MTD) was identified, it was planned to expand the cohort enrolled at the MTD and pursue a larger Phase II study. Whereas there was no frank excess in irreversible grade 4 nonhematologic toxicity or deaths at dose level 3 (2/22 TRM deaths), the degree of mucositis was severe and further accrual at that dose level of sufficiently unclear benefit that a decision was made to return to dose level 2 as the MTD (Table 4). One patient experienced grade 2 mucosal toxicity, and 59 patients experienced grade 3 or 4 toxicity with inability to eat solid foods and obvious mucosal hemorrhage. One patient suffered from grade 4 toxicity and required intubation for airway protection. Ninety-eight percent of patients (59 of 60) required parenteral narcotics for a median of 14 days, and 97% received total parenteral nutrition (TPN) for a median of 17 days. TPN was initiated following a 10% loss in baseline body weight or inability to eat solid food for more than 7 days. Further details are provided in Table 4. While not statistically significant, the duration and severity of grade 3 and 4 mucositis appeared worse following 1295 cGy than at 1200 cGy. For this reason and because of the overall intensity of the regimen, it was felt that 1200 cGy was the appropriate MTD in conjunction with the other 3 drugs.

Additional toxicities are detailed in Table 5 and Table 6. The extent of organ toxicity observed was not unexpected given the intensity of this regimen. The median decrease in cardiac ejection fraction was 4%. Seven of 52 evaluable patients (13%) experienced a $\geq$20% drop in their cardiac ejection fraction to subnormal values of $\leq$50% posttransplantation. All pa-

Table 4. *Mucositis*

TBI Dose	Narcotic Use (%)	TPN Use (%)	Narcotic Duration (days)	TPN Duration (days)
1000	4 (100)	4 (100)	12	25
1200	33 (97)	33 (97)	16	16
1295/1300	22 (100)	22 (100)	14	17
Total	59 (98)	59 (98)	15	17

Table 5. *Grade 3–4 Nonhematologic Toxicities*

		Hepatic (n = 59)		Pulmonary (n = 56)		Renal (n = 59)		Cardiac (n = 52)	
TBI Dose	n	3 (%)	4 (%)	3 (%)	4 (%)	3 (%)	4 (%)	†ΔEF > 20%	TRM*
1000	4	1 (25)	0	0	0	0	0	0	0
1200	34	9 (26)	1 (3)	0	2 (6)	1 (3)	4 (11)	4 (12)	2 (6)
1295	22	9 (41)	0	0	2 (9)	1 (5)	1 (5)	3 (14)	2 (9)
Total	60	19 (32)	1 (2)	0	4 (7)	2 (3)	5 (8)	7 (13)	4 (7)
									Age ≥ 60, 2/9
									Age < 60, 2/51

*TRM, treatment-related mortality.

†This includes 7 patients with a posttransplant EF of 50% or less.

tients with cardiac dysfunction except 1 improved with appropriate treatment and returned to baseline or near-baseline function over 3 to 6 months. Six patients required intubation in the setting of sepsis and multiorgan failure or alveolar hemorrhage (1 patient). The median percentage drop in predicted pulmonary diffusion capacity (DLCO) was 10.5% ($P < .0001$).

Other life-threatening, but nonfatal, side effects included a pericardial effusion with tamponade requiring emergent drainage and 1 episode of diffuse alveolar hemorrhage. One patient developed grade 4 VOD, 5 patients required dialysis in the setting of sepsis and multiorgan failure, and 1 additional patient required dialysis in the absence of multiorgan failure or concurrent infection; no patient required long-term dialysis. Late toxicity included 3 patients who developed myelodysplastic syndromes (MDS). All 3 patients carried a diagnosis of LGL-NHL and had extensive, prior chemotherapy before undergoing transplantation. Two patients had 3 prior therapies, and 1 had 4; 2 of the 3 patients had prior involved field irradiation and 2 had inadequate stem cell yields requiring them to receive both PBSC and marrow. Two of these patients were mobilized with 2.5 g/m^2 of cyclophosphamide plus prednisone and granulocyte-colony stimulating factor (G-CSF), and the third patient received 2 g/m^2 cyclophosphamide and 2 g/m^2 etoposide plus G-CSF. MDS was diagnosed at 29, 39, and 49 months' posttransplantation. Two of these patients have since died from progressive NHL, and 1 died from disseminated herpes virus infection. One additional patient has since developed resectable prostate cancer at age 54, 5 years following his transplantation.

Hematologic Toxicity and Engraftment

Fifty-eight patients were evaluable for engraftment as described in Table 7. Median time to recovery to an absolute neutrophil count (ANC) >500 and platelets >20,000 without transfusion were 16.5 and 35 days for patients receiving bone marrow infusions and 10 and 12 days for patients receiving PBSC. These values were significantly shorter for patients receiving PBSC than marrow ($P < .05$), as was the duration of neutrophil, but not platelet recovery, when comparing infusion of both marrow and PBSC to marrow alone. Patients infused with both PBSC and marrow recovered neutrophils and platelets at a median of 11.5 and 18.5 days, respectively. The number of platelet, but not RBC, transfusions was fewer for patients receiving marrow than those receiving PBSC.

Response

Whereas the purpose of this trial was to evaluate the toxicity and define the MTD of this regimen in a group of patients with a variety of hematologic malignancies, the long follow-up of these patients makes it worthwhile to include 5-year disease-free (27%) and overall survival (35%) for both the entire group and different patient subsets (Figure 1, Table 8). The subsets of patients are too small for firm conclusions regarding outcome, but 58% of patients with AML, all

Table 6. *Organ Toxicity (Median Values)*

	EF		DLCO		DLCO % predicted	
TBI Dose	Pre (n)	Post (n)	Pre (n)	Post (n)	Pre (n)	Post (n)
1000	63.5 (4)	55 (3)	21.1 (4)	19.5 (2)	68.5 (4)	55.5 (2)
1200	59 (33)	57.5 (31)	14.8 (32)	13.7 (30)	63 (32)	52 (24)
1295	60.5 (22)	57 (19)	16 (22)	13.4 (18)	62.5 (22)	54 (19)
Total	61 (59)	57 (53)	16 (58)	13.7 (50)	63.5 (58)	53 (45)
			*P < .0001		*P < .0001	

*Paired differences are significant—Wilcoxon sign-rank test.

Table 7. *Engraftment (Median Values)*

	n	Days to ANC > 500	Days to Last Platelets	Number of RBCs Transfused	Number of Platelets Transfused
PBSC	31	10*	11*	8	6*
BMT	11	18	43	12	14
Both	16	12†	23.5	10	13
All	58	11	17	9	8

Wilcoxon two-group test.
*Adjusted $P < .05$, comparing PBSC to BMT.
†Adjusted $P < .05$, comparing BMT to both.

but 4 of whom had disease beyond CR1, remain alive and disease-free at 5 years. There were no long-term disease-free survivors in the group of patients with multiple myeloma or ALL. Twenty percent of patients with low-grade NHL and 25% of patients with intermediate- and high-grade disease, including 1 of 6 patients with refractory large-cell NHL at the time of transplantation, remain alive and disease-free at 5 years. These results also include 3 late deaths seen in patients with low-grade NHL who developed myelodysplasia and secondary leukemia between 29 and 49 months following transplantation.

DISCUSSION

The most common cause for failure for patients undergoing an autologous stem cell transplantation is recurrence of disease. Whereas there is debate as to the role of the infusion of tumor cells administered with stem cells for patients with leukemia, multiple myeloma and low-grade lymphomas, the majority of patients relapse at sites of prior disease, suggesting an inadequate antitumor effect of the conditioning regimen. For this reason, we were interested in evaluating the use of a novel conditioning regimen that added a platinum compound to the cyclophosphamide/etoposide/TBI regimen in use by several centers [8,20-22]. The goal was to provide an enhanced antitumor effect based on the use of platinum compounds for salvage treatment in patients with NHL and Hodgkin's disease. Here, we show that this regimen is well tolerated in patients younger than age 60. The treatment-related mortality in this group was 3.9% and compares favorably with that found using Cy/TBI- or Cy/VP-16/TBI–conditioning regimens. Engraftment of white cells and platelets was comparable with other reports using either bone marrow or blood stem cells. Likewise, the generally transient drop in both DLCO (10.5%) and cardiac ejection fraction (4%) suggests that this regimen has acceptable toxicity in otherwise-healthy transplantation candidates with adequate organ function. At the same time, the increased toxicity observed with this regimen in older patients has caused us to limit its use to patients younger than age of 60 without pre-existing pulmonary or cardiac function. It also should be pointed out that the use of high-dose BCNU in non–TBI-containing transplant regimens is associated with a significantly higher incidence of interstitial pneumonitis than is observed with this or other TBI-based treatments [23-25].

Because this was primarily a phase I trial, we identified an MTD associated with this therapy. The dose-limiting toxicity of this regimen has been the occurrence of severe stomatitis, necessitating near universal use of parenteral narcotics. Whereas the use of TPN in such patients is dependant on less-easily quantifiable factors such as their pre-existing nutritional status, we have found that the more rapid neutrophil recovery afforded by the use of PBSC has led us to use TPN less commonly in the more recently treated patients than those enrolled earlier in the course of this trial. The availability of new agents to decrease mucositis such as keratinocyte growth factor or protegrin therapies is likely to further reduce the incidence of this serious and dose-limiting complication [9,10]. The muscositis seen in these patients was felt to be primarily the result of etoposide and TBI rather than carboplatin, which has not been associated with significant mucosal damage when used in high doses as a single agent [26-28]. It is appreciated that there were no quantifiable differences in organ or mucosal toxicities between the 2 highest dose levels as identified in Tables 4, 5, and 6, and that 1295 cGy could be used in this regimen. Nevertheless,1200 cGy of TBI along with the other 3 agents was felt sufficiently intense as to be identified as the MTD, while providing a slightly greater margin of safety than would have 1295 cGy. The other toxicities found in this trial were sporadic and not unusual for conditioning regimens used in autologous stem cell transplantation. Despite the use of carboplatin with the conditioning regimen, we did not find an increased incidence of VOD or renal dysfunction in patients treated in this trial compared with those treated with other TBI-containing regimens.

Despite wide variation in intensity, toxicity, and chemotherapeutic agents, there have been no prospective trials comparing the outcomes of patients treated with different conditioning regimens in comparable patient populations. This has resulted in phase II comparisons based on registry or other historical data sets, which has led to the conclusion that whereas differences in morbidity and treatment-related mortality have been observed, overall differences in outcome have not been apparent [29-33]. Thus, studies such as this remain hypothesis-generating and provide leads for potential future trials but are not, in and of themselves, definitive. Despite our hypothesis that the addition of a platinum compound would improve the survival for patients with lymphoid malignancies, we found that the outcome for patients with NHL did not

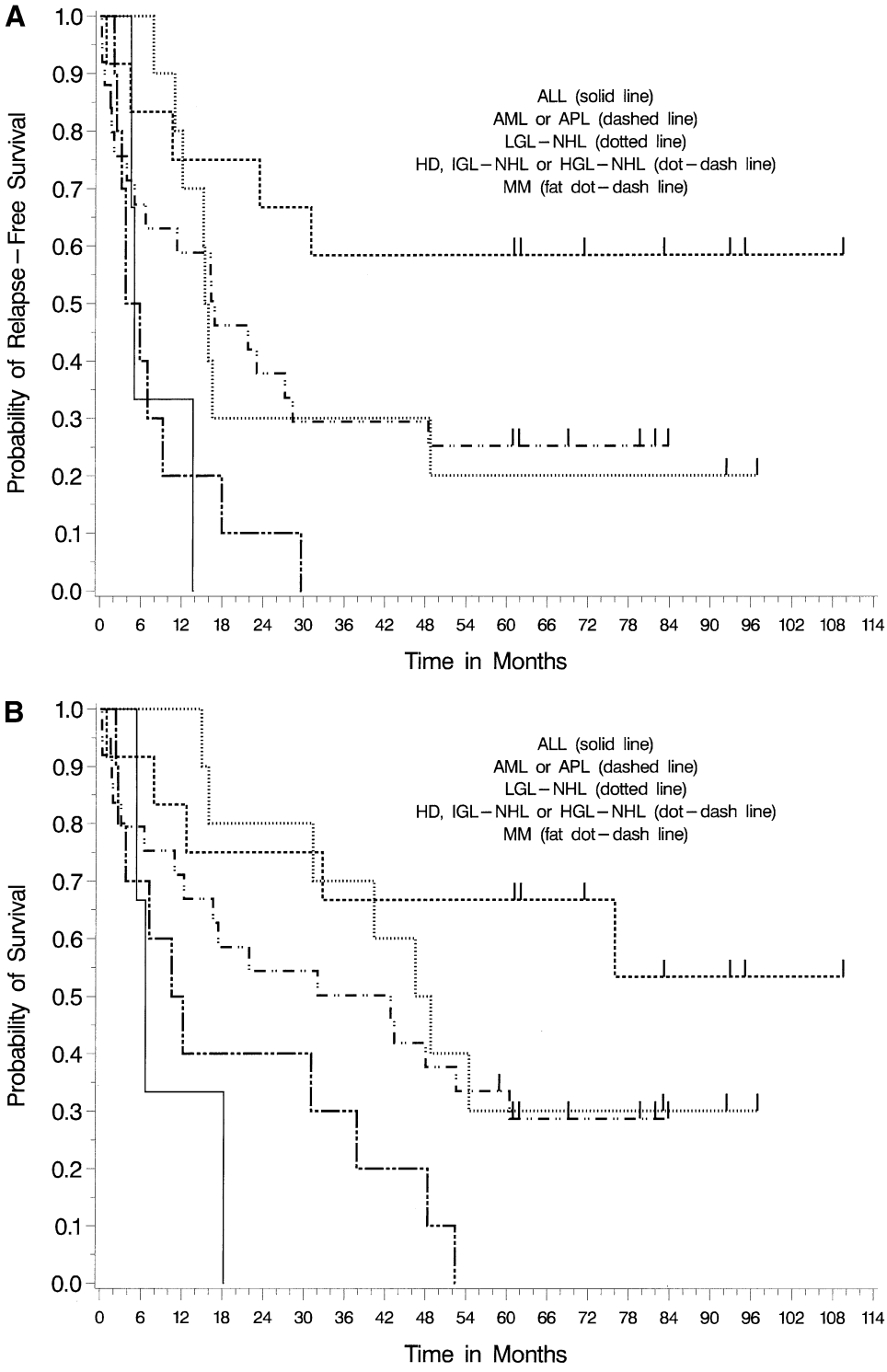

Figure 1. Probability of (A) relapse-free or (B) overall survival for all 60 patients by disease group. ALL, solid line; acute myeloid or acute promyelocytic leukemia (AML or APL), dashed line; LGL-NHL, dotted line; Hodgkin's disease, intermediate- or high-grade NHL (HD, ILG-NHL or HGL-NHL) dotted-dashed line; multiple myeloma (MM) thick dotted-dashed line.

appear to be significantly different compared with other TBI-based regimens. However, patients with AML may have a better outcome using this conditioning regimen compared with those treated with Cy/TBI or Bu/Cy [34,35]. This result is consistent with the single-agent activity demonstrated by Myers [27] and Martinez [28] with carboplatin in relapsed AML. Clearly, this study was not powered to detect a difference in subgroup analysis and while intriguing, this finding will need to be validated in a larger trial. It is

Table 8. *Response*

	n	CR (%)	SD (%)	DP (%)	TRD (%)	5 yr DFS (%)	5 yr OS (%)
ALL	3	2 (66)	0	1 (33)	0	0	0
AML	12	10 (58)	NA	1 (8)	1	58	67
LGL-NHL/Hodgkin's	10	6 (60)	4 (40)	0 (0)	0	20	30
Hodgkin's IG/HG-NHL	25	7 (28)	*11 (44)	4 (16)	3 (12)	25	33
Multiple myeloma	10	1 (10)	6 (60)	3 (20)	0	0	0
Total	60	26 (43)	21 (35)	8 (13)	4 (6.7)	27	35

*Many of these patients would be classified as CR-U because of small residual radiologic abnormalities.

important to note, however, that these results are more mature than many phase I or II trials in that the minimum follow-up was 5 years. Thus, both toxicity and efficacy data should be accurate and stable for all but the low-grade NHL patients who remain in remission at this time.

One of the criticisms of this conditioning regimen could be the concern with second malignancies or MDS that have been found in patients with low-grade lymphomas receiving TBI. This has not been seen in all studies, and whereas it is likely that the DNA damage induced by TBI is contributory to subsequent evolution of dysplastic or leukemic clones, the occurrence of secondary leukemia and MDS appears to be primarily caused by other factors such as the type and extent of prior therapy and pre-existing chromosomal damage [10-14]. Nevertheless, the incidence of MDS/AML observed in these low-grade NHL patients does remain a concern, because each of the fatal cases in this study developed in the group of 10 patients (6 of whom remain alive and 5 of whom are disease-free beyond 5 years) treated for this disease. This has led to an actual incidence of 30% for that group and 0 of 14 for those patients with other diseases surviving beyond 5 years. These data suggest that like any autologous transplantation in heavily pretreated patients, this regimen may be associated with the subsequent development of MDS and should be used with caution in patients with low-grade NHL. On the other hand, the potential benefit of TBI should not be discarded from use, particularly in aggressive lymphomas and leukemias in the absence of controlled trials.

Lastly, whereas comparisons of outcomes between this regimen and others that are commonly in use for autotransplantation of patients with hematologic diseases is difficult, the components of these different regimens can be compared. For example, the dose of cyclophosphamide used in the regimen pioneered by the City of Hope and Stanford and widely used in the Southwest Oncology Group is 100 mg/kg, or about 60% of the dose used in this article [21]. That same regimen uses a dose of 60 mg/kg, or about 20% more VP-16 than the current study, and an identical 1200-cGy dose of TBI. The inclusion of 1000 mg/m^2 of carboplatin and 30% more cyclophosphamide in the UNC regimen suggests that this is appreciably more intense, and potentially more effective without additional grade 4 or fatal toxicity compared with the regimen described by Nademanee [19-21]. Whereas it is important to emphasize the merits of new approaches in treating these patients and to incorporate new modalities such as cell selection and radiolabeled and unlabelled antibodies into their treatment regimens, it is just as important to underscore the central role of the conditioning regimen in these therapies [6-8,36-38]. The lack of benefit from some of the new approaches recently was underscored by the report from Stewart in multiple myeloma patients in which the use of CD34 selection as a means for purging plasma cells from the infusion product was ineffective in prolonging disease-free or overall survival in a randomized trial [36]. Likewise, the use of PBSC as opposed to bone marrow for support of patients undergoing a BEAC-based transplantation-conditioning regimen did not alter the relapse rate and either overall or disease-free survival for these patients [37]. Whereas it appears that these more recent approaches have reduced toxicity, duration of hospitalization, and time to neutrophil and platelet engraftment, death from disease recurrence remains the central problem following autologous transplantation. Assuming that dose intensity remains the cornerstone of both autologous and allogeneic transplantation for such patients, it is clear that the regimen described in this report offers a more intensive approach than the majority of currently available treatment programs. Whether such an approach is more effective than less-toxic and intensive alternatives remains to be seen with carefully designed phase II or III trials that incorporate well-defined patient populations, different regimens, and new adjunctive therapies.

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