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ORIGINAL ARTICLE

Single center experience with total body irradiation and melphalan (TBI-MEL) myeloablative conditioning regimen for allogeneic stem cell transplantation (SCT) in patients with refractory hematologic malignancies

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Abstract We retrospectively evaluated the tolerability and efficacy of fractionated total body irradiation (TBI) (1,200 cGy) and melphalan (MEL) (100–110 mg/m^2) myeloablative conditioning in 48 patients with nonremission AML (n=14), ALL (n=10), NHL (n=18), and other refractory hematologic malignancies (n=6) who received allogeneic stem cell transplantation (SCT) between 2002 and 2011. Median age was 48 years (22 to 68); 14 out of 26 leukemia patients (54 %) had circulating blasts at transplant, 20 (50 %) evaluable patients had poor-risk cytogenetics, 12 (25 %) had prior SCT, and 10 (21 %) received stem cells from a mismatch donor. All patients received tacrolimus with or without methotrexate for GVHD prophylaxis. At the time of analysis, 13 patients (27 %) were alive and disease free. Engraftment was complete in all patients. The median time to ANC recovery (>500) was 12 days (range, 6–28). The most common grade III and IV toxicities were mucositis and infections. Eighteen patients (43 %) developed grade II–IV acute GVHD, and eight (26 %) had extensive chronic GVHD. Of 44 evaluable patients for response, 28 (64 %) achieved a complete remission (CR), and seven (15 %) had a partial remission after the transplant. With a median follow-up of 30 months (4 to 124 months) for surviving patients, the cumulative incidence of relapse was 45 % at 1 year, and the probability of overall survival (OS) at 5 years was 22.5 %. Multivariate analysis showed that platelet count (<80,000/mL) and lactic dehydrogenase (>500 IU/L) at SCT were associated with relapse. Age less than 53 years and CR after SCT were associated with better OS. Our data suggest that TBI-MEL can result in CR in two thirds, durable remission in one third, and 5-year survival in about one quarter of patients with nonremission hematologic malignancies. Further studies with TBI-MEL in standard risk transplant patients are warranted.

Keywords Melphalan · TBI · Allogeneic · Refractory · Nonremission · Leukemia

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Introduction

Allogeneic stem cell transplantation (SCT) offers a potential curative treatment option for patients with a wide variety of hematologic malignancies. However, patients with relapsed or refractory disease at the time of SCT experience poor outcomes due to the increased risk of transplant-related mortality (TRM) and relapse after transplant, due, in part, to inadequate eradication of the disease by the selected conditioning regimen. Therefore, the use of alternative conditioning regimens may improve disease control and increases long-term survival in these high-risk patients.

Total body irradiation and melphalan (TBI-MEL)-containing regimens have been used more commonly in children with hematologic malignancies; this regimen has been less well studied in adults. A small prospective study at M.D. Anderson Cancer Center in which 29 pediatric patients with high-risk leukemia and lymphoma were conditioned with TBI, MEL, and fludarabine resulted in CR in all patients with median remission duration of 1 year [1]. Thirty-seven percent of patients were able to achieve long-term CR following SCT. Aside from stomatitis and gastrointestinal toxicities, this regimen was generally well tolerated.

When TBI-MEL was used prior to autologous stem cell transplant in 53 pediatric AML patients in first complete remission (CR), approximately 70 % were alive and remained in CR by the completion of the study with 5-year disease-free survival (DFS) rate of 68 % [2]. Two recent Japanese studies in which pediatric patients with advanced leukemia or lymphoma received TBI and MEL prior to allogeneic HSCT also demonstrated encouraging results with respect to DFS and overall survival (OS) with minimal treatment-related toxicities [3, 4].

The few studies that have evaluated this preparative regimen in adults with relapsed or refractory hematologic malignancies have produced conflicting results. While one small study using this regimen did not demonstrate high activity [5], another study using TBI, MEL, and busulfan prior to allogeneic SCT in 20 high-risk adult leukemia patients resulted in a 3-year DFS rate of 50 % [6]. In a recent retrospective analysis, patients with multiple myeloma who received TBI and MEL experienced lower rates of TRM and higher rates of CR, OS, and progression-free survival (PFS) compared to those who received the more conventional conditioning regimen of TBI and cyclophosphamide (Cy) [7]. Additionally, patients who received TBI and MEL had more advanced disease compared to the TBI/Cy group.

In view of these findings, we performed a retrospective analysis of 48 patients, treated at our institution, with relapsed and refractory hematologic malignancies who received TBI-MEL conditioning prior to SCT, primarily to assess the efficacy and tolerability of this regimen. Survival and other standard transplant outcomes were also studied as secondary endpoints.

Materials and methods

Refractory disease was defined by the presence of active hematologic malignancy (nonremission) at the time of admission for transplant, documented by pathology and/or radiologic findings. Two patients with high-risk AML in a second complete remission (CR2) were also included in the study population. All study procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Patients were required to sign informed consent which included permission for the use of their data for registration to the Center for International Blood and Marrow Transplant Research. Patients were also required to meet our standard institutional guidelines to be eligible for a myeloablative conditioning allogeneic SCT. These criteria included having adequate cardiac (LVEF of ≥40 %), pulmonary (FEV1 of ≥50 % predicted and adjusted DLCO of ≥50 % predicted), renal (creatinine clearance of >50 mL/min), and hepatic (ALT/AST of <2× ULN, bilirubin of <2.0 mg/dl) functions; negative viral and syphilis serology; and no active infection as assessed by CT scans of the chest and sinuses. Patients with active CNS involvement were not eligible for the transplant.

Patients were admitted to the inpatient Blood and Marrow Transplant Unit at the University of Maryland Marlene and Stewart Greenebaum Cancer Center. The TBI-MEL conditioning regimen consisted of 1,200 cGy fractionated TBI given twice a day at 200 cGy per dose on days −5, −4, and −3 and high dose melphalan (100–110 mg/m^2) on day −2, followed by allogeneic stem cell infusion on day 0. Tacrolimus with (n = 34) or without (n = 14) low-dose methotrexate (5 mg/m^2 on days +1, +3, and +6) was used as GVHD prophylaxis. Patients received ursodiol for sinusoidal obstruction syndrome (SOS) prophylaxis. Antimicrobial prophylaxis included acyclovir, voriconazole, and pentamidine inhalation.

Statistical analysis

After obtaining IRB approval, we retrospectively collected data through electronic medical records and analyzed patient outcomes. For the purpose of statistical analysis, disease types were categorized into three groups: leukemia (group I) included all acute leukemia patients and a single advanced chronic myelogenous leukemia patient, lymphoma (group II) constituted all Hodgkin and non-Hodgkin lymphoma as well as CLL and other lymphoid malignancies, and myeloma (group III) included patients with plasma cell neoplasms. The chi-square test (for categorical variables) and Wilcoxon test (for continuous variables) were used to compare patient characteristics and pretransplant factors. Pearson correlation coefficient was used for correlation analyses. OS was calculated from the day of transplantation (day 0) until death. Relapse-free survival (RFS) was calculated from the day of transplantation until the detection of persistent or relapsed disease after transplant. OS and RFS were estimated using the Kaplan–Meier method. The log-rank test and Cox proportional hazard models were used to analyze the relationships of patient characteristics and transplant variables with OS and RFS. Patient's demographic, clinical, and laboratory characteristics were all considered in the multivariate survival analysis if they were significant relative to patient's survival time (p <0.05) by univariate survival analysis. Backward variable selection in the Cox proportional hazard models was used. Forty-eight and

44 patients were included in the overall and relapse-free survival analyses, respectively. The variable was excluded from the survival analysis if it was not associated with the outcome in the univariate model.

Results

Patient and transplant characteristics

Forty-eight consecutive patients with nonremission ($n=46$) hematologic malignancies and those beyond the first complete remission ($n=2$) received SCT after conditioning with a TBI-MEL myeloablative regimen between 2002 and 2011. Patient, disease, and transplant characteristics are summarized in Table 1. Of 48 patients, 32 patients were male (67 %), and 16 patients were female (33 %), and the median age was 48 years (range, 22 to 68 years). Twenty-six (54 %) patients had acute leukemia ($n=25$) or advanced chronic myelogenous leukemia ($n=1$), 19 patients (40 %) had non-Hodgkin lymphoma or CLL, and 3 patients (6 %) had plasma cell neoplasms. The median time from an initial diagnosis to SCT was 13.3 months (range, 1.8 to 59.2 months). The number of treatments given prior to SCT ranged from 1 to 6 (median 2). At the time of transplant, 20 (50 %) evaluable patients had poor-risk or complex cytogenetics, 14 leukemia patients (54 %) had circulating blasts, the remaining leukemia patients had leukemia in their bone marrow (>5 % blasts), 9 patients had prior autologous SCT, and 3 had prior allogeneic SCT. The stem cell product was T cell replete in all but one patient. Twenty-four (50 %) patients received unrelated donor (URD) transplant, and 10 (21 %) donor-recipient pairs were mismatched at one antigen or allele level. Forty-two (90 %) and six patients (10 %) received a peripheral blood and bone marrow stem cell products, respectively.

Conditioning regimen-related toxicities

Conditioning regimen-related toxicity (CRRT) was moderate in the majority of patients (Table 2), and mucositis was the most common grade III and IV nonhematologic toxicity occurring in 56 % of patients. Other frequently observed toxicities were documented infections (51 %). ARDS/respiratory failure developed in four (8 %) of patients. While renal failure was seen in five (10 %) patients, severe SOS and hepatorenal syndrome was seen in one patient (2 %). The median duration of hospitalization was 29 days (range, 14 to 113 days).

Engraftment

Forty-seven patients were engrafted. The median time to neutrophil recovery (ANC of >500/μL) was 12 days (range, 6–28), and platelet engraftment was 16 days (range, 8–403).

Table 1 Demographic, clinical, and laboratory characteristics of patients and their association (univariate) with the overall (OS) and relapse-free survival (RFS)

Variable	Median or *N* (range or %)	Related to OS *p* value	Related to RFS *p* value
Age (years)	48 (22–68)	0.039	0.315
Race		0.74	0.85
Caucasian	33 (69)		
AA	9 (19)		
Other	6 (12)		
Gender		0.25	0.035
Male	32 (67)		
Female	16 (33)		
Diagnosis		0.37	0.03
Leukemia (AML, ALL, CML)	26 (54)		
Lymphoma (NHL, CLL)	19 (40)		
Plasma cell (Myeloma, others)	3 (6)		
Time from diagnosis to SCT (days)	399 (55–1,777)	0.38	0.32
Duration of hospital stay (days)	29 (14–113)	0.01	0.13
Number of previous treatments	2 (1–6)	0.61	0.23
History of prior SCT		0.95	0.48
Yes	12 (25)		
No	36 (75)		
Donor type		0.63	0.07
MUD	24 (50)		
MRD	24 (50)		
Antigen mismatch		0.42	0.26
Yes	10 (21)		
No	38 (79)		
MEL dose		0.59	0.70
≤100 mg/m^2	22 (46)		
>100 mg/m^2	26 (54)		
Cytogenetics		0.07	0.81
Normal	20 (42)		
Abnormal	20 (42)		
Unknown	8 (16)		
Laboratory at SCT			
Hemoglobin	9.6 (7.2–13.8)	0.42	0.50
Platelet	65 (7–201)	0.33	0.042
LDH	355 (92–3,400)	0.08	0.006
Albumin	3.1 (1.7–4.3)	0.19	0.63
Circulating blasts at SCT ($N=26$)		0.059	0.08
Yes	14 (54)		
No	12 (46)		
Disease response ($N=44$)		<0.0001	0.0007
CR	28 (64)		

Table 1 (continued)

Variable	Median or *N* (range or %)	Related to OS *p* value	Related to RFS *p* value
VGPR	2 (4)		
Good PR	2 (4)		
PR	3 (7)		
NR	9 (20)		
Unknown	4 (9)		

N number of patients, *CI* confidence interval, *AA* African American, *BMT* bone marrow or stem cell transplantation, *MUD* match-related donor, *MRD* match-related donor, *MEL* melphalan, *LDH* lactic dehydrogenase, *CR* complete response, *VGPR* very good partial remission, *PR* partial response, *NR* no response

One patient could not be evaluated because of early death on day +6 after transplant. All evaluable patients achieved 100 % donor lymphoid, myeloid, and NK chimerism at an initial evaluation posttransplant.

Graft-versus-host disease

Grade II–IV and III–IV acute GVHDs were observed in 18 (43 %) and 8 (19 %) evaluable patients, respectively. Thirty-one patients were in remission and evaluable for chronic GVHD. Of these, eight patients (26 %) developed chronic GVHD requiring immunosuppressive therapy.

Disease response

After excluding four patients who died early (≤50 days) after transplant, 44 patients were evaluable for response. The overall response rate was 79 % with 28 (64 %) CRs and 7 (15 %) partial remissions (PRs). Disease response was associated with patient hemoglobin values at SCT. While all 14 patients with Hb of >10.4 g/dL at SCT had a response (CR or PR) after the transplant, only 70 % of patients with hemoglobin ≤10.4 at SCT ($n=30$) had response ($p=0.04$). Wilcoxon rank sum test showed that CR was also correlated with the number of previous treatments ($p=0.03$). All four patients who received one prior treatment had CR, while 70 % of patients with two previous treatments ($n=23$) had CR, and only 47 % of patients who received more than two lines of previous treatments ($n=17$) had CR. Patients who achieved CR had received a median of two prior lines of treatment, while those not in CR had received a median of three prior lines of therapy.

Relapse-free survival

Twenty-one patients (44 %) relapsed at a median of 5.3 months (range, 1–51.5 months) after SCT. Of 21 patients who relapsed after transplant, 13 (62 %) received donor lymphocyte infusion (DLI) after chemotherapy for treatment of relapse. The median RFS time was 10.6 months for all patients (Fig. 1). One AML patient relapsed with a different clone after remaining in CR for 4.9 years. The cumulative incidence of relapse was 25 % at 6 months, 37.5 % at 1 year, and 41.7 % at 2 years.

According to univariate analysis, patient gender ($p=0.035$), diagnosis ($p=0.03$), platelet count at SCT ($p=0.042$), lactic dehydrogenase (LDH) at SCT ($p=0.006$), and complete response ($p=0.0007$) were associated with RFS.

Table 2 Conditioning regimen-related toxicity and causes of mortality

	n (%)
Acute graft-versus-host disease ($n=42$)[a]	
None	24 (57)
Grades II and IV	18 (43)
Grade III and IV	8 (19)
Extensive chronic GVHD ($n=31$)[a]	8 (26)
Grades III and IV toxicities ($n=48$)[a]	
Mucositis	27 (56)
Infections	
Clostridium difficile colitis	12 (25)
Bacterial pneumonia	5 (10)
Gram-negative bacteremia/sepsis	8 (17)
Gram-positive bacteremia	7 (15)
Enterococcal (including VRE) bacteremia	5 (10)
CMV pneumonitis	2 (4)
HSV infection (encephalitis, $n=1$)	2 (4)
Norwalk virus enteritis	1 (2)
Respiratory syncytial virus	1 (2)
BK-related hemorrhagic cystitis	1 (2)
Fungemia (cryptococcal, $n=1$)	2 (4)
ARDS/respiratory failure	4 (8)
Renal failure ± dialysis	5 (10)
Diffuse alveolar hemorrhage	1 (2)
Thrombotic thrombocytopenic purpura	1 (2)
BOOP/lung GVHD	1 (2)
Veno-occlusive disease	1 (2)
Transaminitis	1 (2)
Typhlitis	1 (2)
Confusion	1 (2)
Main causes of death ($n=35$)[a]	
Infection	12 (34)
Underlying malignancy	12 (34)
Respiratory failure	4 (8)
GVHD	3 (6)
Veno-occlusive disease/renal failure	1 (3)

VRE vancomycin-resistant *Enterococcus*, *CMV* cytomegalovirus, *HSV* herpes simplex virus, *ARDS* adult respiratory distress syndrome, *BOOP* bronchiolitis obliterans with organizing pneumonia

[a] Evaluable patients

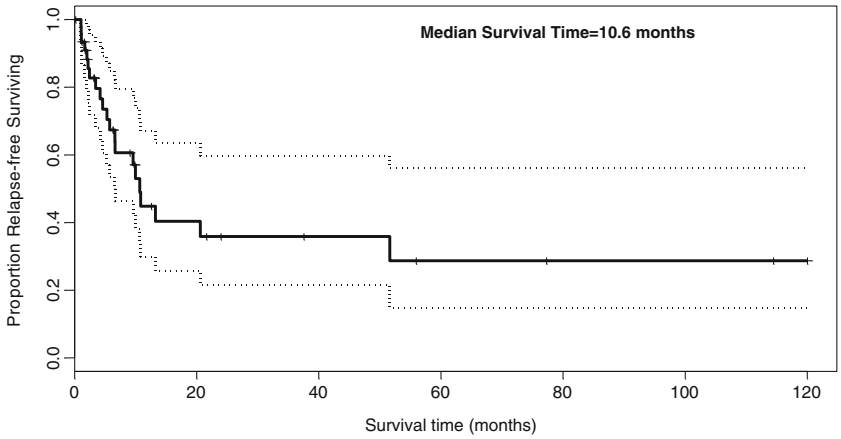

Fig. 1 Kaplan–Meier relapse-free survival

Male patients had longer RFS than female patients (median 20.5 vs. 5.2 months). Lymphoma/CLL patients had longer RFS [the estimated probability of RFS of >13.2 months than leukemia patients (median RFS of 9.9 months) and myeloma patients (median RFS of 6.1 months) ($p=0.638$)]. Higher platelet count (>80,000) and lower LDH (<500) at SCT were both associated with a longer RFS (Table 1). For leukemia patients ($n=26$), the median RFS of patients with and without circulating blasts at SCT was estimated to be 138 and 323 days, respectively ($p=0.08$).

A multivariate Cox proportional hazard model showed platelet count ($p=0.04$) and LDH ($p=0.001$) at the time of SCT which were the two independent predictive factors for RFS (Fig. 2). The median time to relapse was 42, 19.9, and 1.9 months for patients with platelet count of >80,000 and LDH of >500, platelet count of ≤80,000 and LDH of ≤500, and platelet count of ≤80,000 and LDH of >500 at the time of transplant, respectively. The longest time to relapse was 76 months in patients with platelet count of >80,000 and LDH of ≤500. With these cutoffs, the hazard ratios were 0.56 ($p=0.0028$) and 9.56 ($p=0.0001$) for platelet count and LDH, respectively.

Nonrelapse mortality

Twenty-three patients (48 %) died without relapse at the time of analysis. Four patients (8 %) died within the first 50 days following the transplant (days +7, +32, +40, and +50). The 1-year cumulative incidence of nonrelapse mortality (NRM) was 34.6 % for leukemia patients and 37.5 % for all patients. Causes of NRM were summarized in Table 2.

Overall survival

Out of 48 patients, 35 (73 %) were dead at the time of analysis. The median survival after SCT was 9.1 months (Fig. 3). After a median follow-up of 30 months (range, 4–124 months) for surviving patients, the probability of survival at 1, 2, and 5 years were 45 % (95 % confidence interval (CI), 33–62 %), 28 % (95 % CI, 17–45 %), and 22.5 % (95 % CI, 12–43 %), respectively. Of the 35 patients who died, 12 (34.3 %) died from the relapse.

According to univariate analysis, older age ($p=0.039$), longer hospitalization ($p=0.014$), longer time to myeloid engraftment ($p=0.027$), and not achieving CR following

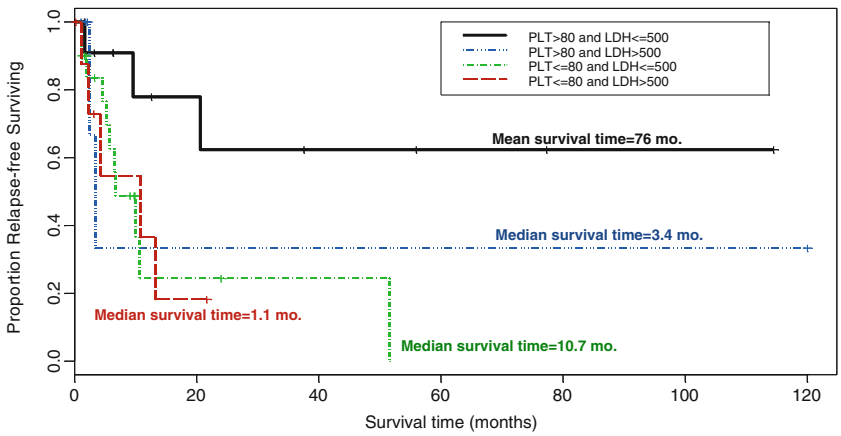

Fig. 2 Relapse-free survival based on platelet count and LDH at BMT

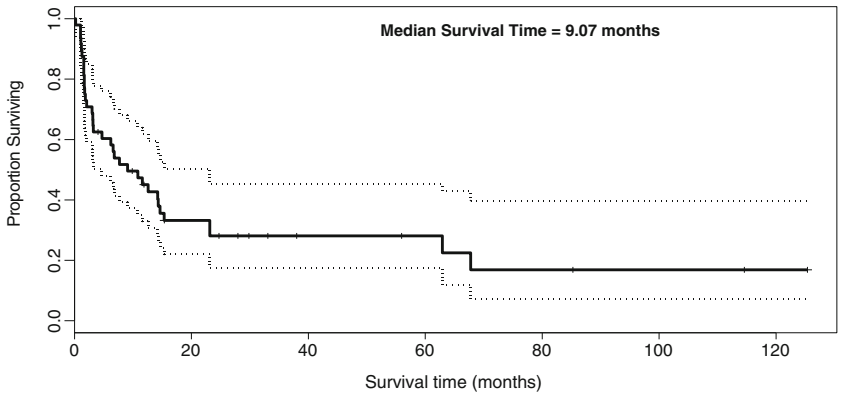

Fig. 3 Kaplan–Meier overall survival

SCT ($p<0.0001$) were associated with shorter survival. The median survival for patients with or without CR was 23.1 and 3 months, respectively. The median overall survival in patients who received DLI treatment ($n=13$) was estimated to be 14.3 months, and those who did not receive DLI ($n=8$) was 3.9 months ($p=0.18$). For leukemia patients (26 patients), the median survival of patients with and without circulating blasts at the time of SCT was 3.1 and 10.8 months, respectively ($p=0.059$).

Multivariate Cox proportional hazard models showed that patient age (≥52 years old) (hazard ratio (HR) 1.04, $p=0.02$) and CR after SCT (HR 0.52, $p<0.0001$) were associated with overall survival (Fig. 4). The median survival times were 62.9, 6.8, 3.2, and 1.3 months for patients with CR and age of <53 years, CR and age of ≥52 years, CR and age of <53 years, and without CR and age of >52 years, respectively. With these cutoffs, the hazard ratios were 3.72 ($p=0.0019$) and 0.13 ($p<0.0001$) for age and CR, respectively.

Discussion

The ideal preparative regimen for patients with relapsed or refractory hematologic malignancies has not yet been defined and remains an important consideration as SCT offers some of these patients the only possibility of long-term remission or cure. Our data on 48 consecutive patients with nonremission, or very high-risk, hematologic malignancies who underwent allogeneic SCT after receiving TBI and melphalan myeloablative conditioning indicate that this regimen is a feasible and effective choice of therapy.

Two thirds of our study population achieved a complete remission, and half of these patients had durable remissions that exceeded 2 years. The median overall survival, however, was approximately 9 months for the entire cohort. Multivariate analysis showed that patients who were of <53 years of age and achieved CR after SCT had the best survival outcome as half of these patients were alive at 5 years (Fig. 4). One third of the patients in this study did not appear to benefit from TBI-MEL, and four died within the first 2 months following the transplant. The limited sample size precludes any definitive conclusions relating to risk factors predictive of disease response; however, in this series, younger age and remission status following SCT appeared to be associated with overall survival and warrant further investigation. Given the high probability of achieving CR in patients with fewer than three lines of prior cytotoxic therapy, TBI-MEL conditioning can be offered to patients with nonremission hematologic malignancies who are less than 53 years of age and not heavily pretreated (<3 lines) with reasonable confidence.

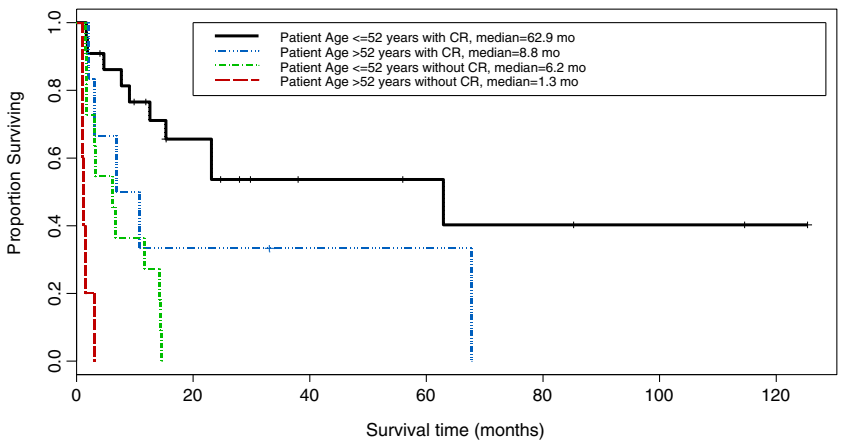

Fig. 4 Overall survival based on patient age and CR after SCT

The risk factors identified for transplant outcomes in this cohort may not be generalizable to all transplant patients with relapsed/refractory disease since our results reflect the effect of a new regimen, TBI-MEL in this particular cohort. While caution must be exercised in interpreting these results due to a small sample size, multivariate analysis showed that durable remission was possible in 60 % of our patients with platelet counts greater than 80,000/μL and LDH less than 500 IU/L at the time of SCT. Of note, high LDH levels (>500 IU/L) at the time of transplant was a stronger predictor of relapse than a low platelet count. Whether these pretransplant predictors of LDH and platelet count having a general utility will require larger multicenter studies evaluating this regimen. Another potential predictor of relapse was the presence of circulating malignant cells at the time of SCT, although we could not demonstrate a significant difference in RFS ($p=0.08$) and OS ($p=0.06$) between patients with and without circulating blasts. We suspect that this was probably due to small sample size. The median survival time of patients with circulating blasts was notably shorter (3 vs. 10.8 months) as compared to those without circulating blast at stem cell transplantation (SCT). Therefore, leukemia patients with circulating blasts are probably not suitable candidates for SCT using TBI-MEL conditioning alone.

Grades III and IV toxicities were not increased in this study in comparison to those observed using other myeloablative conditioning regimens. Also, the incidence of opportunistic infections was not higher in our patient population compared to infection rates seen in myeloablative transplant recipients with optimal disease control. Mucositis severity may be reduced with the use of keratinocyte growth factor (KGF) as demonstrated previously in patients who received TBI-based conditioning [8]. None of our patients received KGF.

One possible advantage of TBI-MEL over cyclophosphamide- or busulfan-based myeloablative conditioning is a lower incidence of SOS since both agents are known risk factors for this complication as well as a lack of bladder toxicity. We did not observe a high incidence of SOS or diffuse alveolar hemorrhage even though a majority of patients had received multiple lines of therapy including prior SCT. In addition, many patients will have been exposed to cyclophosphamide earlier in their treatment courses and possibly developed resistance to it.

In earlier studies, the possible higher leukomogenicity of melphalan therapy had been of major concern [9], but a large prospective analysis demonstrated that, compared to cyclophosphamide-containing regimens, there was no increased risk of secondary malignancies using TBI-MEL [10].

While many centers are attempting to move away from using TBI as a part of pretransplant conditioning, the addition of TBI may be more effective in eradicating disease and achieving better outcomes, although this, too, warrants further investigation. TBI-based regimens are preferred in certain hematologic malignancies such as acute lymphoblastic leukemia, T cell lymphomas, certain subtypes of AML (M5), and extranodal non-Hodgkin lymphoma that carry a significant risk for central nervous system involvement. A recent study in which 23 AML patients with advanced disease were treated with high-dose melphalan followed by allogeneic SCT, but no TBI, demonstrated a marked reduction of leukemia burden or leukemia-free state in nearly all patients following melphalan conditioning, but this did not result in better posttransplant outcomes [11].

There are other novel preparative regimens that have been evaluated in patients with advanced acute leukemia [12–14]. Adding gemtuzumab to melphalan and fludarabine or intensive multiagent chemotherapy and TBI combination did not appear to produce better outcomes than what we observed using the TBI-MEL regimen [12, 14]. A more recent study from the University of Michigan reported the efficacy of clofarabine and busulfan conditioning in patients with nonremission hematologic malignancies [15]. Both patient characteristics and transplant outcomes were similar to what was appreciated using the TBI-MEL regimen. Forty-six adult patients, including 31 patients with nonremission AML, received this myeloablative conditioning. Toxicity was acceptable. Complete remission was achieved in 80 % of all patients by day 30 and in 100 % of AML patients without prior hematopoietic stem cell transplantation. Two-year nonrelapse mortality for all patients was 31 %, and the overall survival was 28 %. For AML patients, specifically, the overall survival was 48 % at 1 year and 35 % at 2 years [15].

Relapse remains a major cause of treatment failure in this report as well as in several others. In an effort to prevent disease relapse, a number of agents are currently being explored as a maintenance treatment in the posttransplant setting. Lenalidomide, bortezomib, and thalidomide as single agents, or in combinations, have demonstrated improvements in PFS and OS in select multiple myeloma patients following autologous SCT [16–22]; however, the literature pertaining to the role of maintenance therapy following allogeneic SCT is scant. A recent phase I study of 45 AML and MDS patients showed that at least four courses of maintenance azacitidine following transplant, at an optimal dose of 32 mg/m^2 for 5 days, produced 1-year event-free survival and OS rates of 58 and 77 %, respectively [23]

Furthermore, our data also demonstrate that patients who relapse after achieving remission from TBI-MEL may still respond to further treatment. Subsequent DLIs following cytoreductive chemotherapy were able to salvage some patients. Indeed, the difference between projected OS for those who received DLI and those who did not was 14.3 versus 3.9 months ($p=0.2$, not significantly possible due to small sample sizes).

However, this difference could also be related to the time of relapse, overall performance status, and treatment bias. The

association between GVHD and relapse was not studied due to the heterogeneity of diseases and limited sample size.

In conclusion, TBI-MEL regimen appears to be an effective myeloablative conditioning option and may offer long-term remission in select patients with active (nonremission) hematologic malignancies at the time of transplant. Our long-term experience with this regimen suggests that the upfront use in a more favorable risk group is worthy of prospective study.

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Conflict of interest The authors declare no conflict of interest.

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