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ORIGINAL ARTICLE

400 cGy TBI with fludarabine for reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation

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Fludarabine and 200 cGy TBI are commonly used for reduced-intensity conditioning preceding allogeneic hematopoietic SCT (HSCT). However, graft rejection and disease relapse are significant causes of treatment failure with this regimen. We modified this regimen by escalating the TBI dose to 400 cGy in 40 patients with hematologic malignancies. Thirty-four patients achieved complete donor T-cell chimerism at a median of 40 days following HSCT. The incidences of grades II–IV and III–IV acute GVHD were 40 and 15%, respectively, whereas that of limited and extensive chronic GVHD were 12 and 20%, respectively. Two patients rejected their grafts and 12 relapsed. The 100-day mortality was 18%, 2-year transplant-related mortality 20% and overall survival was 58% at a median follow-up of 16 months. There were no significant survival differences between patients with lymphoid compared to myeloid malignancies. A dose of 400 cGy TBI administered with fludarabine is well tolerated and further study is needed to determine whether outcomes are superior to those with 200 cGy TBI.
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Introduction

Allogeneic hematopoietic SCT (HSCT) using reduced-intensity conditioning (RIC) is effective for many patients who are at high risk of transplant-related mortality (TRM) with myeloablative allogeneic HSCT.[1–5] This approach lowers non-relapse mortality rates post transplant. However, disease relapse remains an important cause of treatment failure, particularly for aggressive malignancies such as acute leukemia. Also, while RIC allogeneic HSCT may avoid many of the organ toxicities associated with myeloablative preparative regimens, the risk for developing GVHD and infection still remain significant.

Fludarabine and 200 cGy TBI is a commonly used preparative regimen for RIC allogeneic HSCT.[6–7] We observed a 14% graft rejection rate and a 43% incidence of disease relapse with this regimen at our institution. We hypothesized that these may be improved with escalation of the TBI dose, which was empirically increased to 400 cGy. This report presents our experience with this regimen and compares outcomes observed to our patients who had received fludarabine and 200 cGy TBI.

Patients and methods

Patient characteristics

From December 2003 through April 2007, 40 patients with hematologic malignancies underwent T-cell replete, RIC allogeneic HSCT with 400 cGy TBI and fludarabine at the Cleveland Clinic (Cleveland, OH, USA). Our analysis compared outcomes with 42 patients who received fludarabine and 200 cGy TBI from January 2000 through November 2003. All patients and donors were treated on RIC allogeneic HSCT protocols that were reviewed and approved by the Cleveland Clinic's Institutional Review Board with signed informed consent obtained from all patients before the transplant procedure.

Patient eligibility criteria included a documented diagnosis of a hematologic malignancy. In addition, they were required to have an HLA-matched related donor or an eight of eight HLA-matched unrelated donor by DNA-based typing (HLA-A, -B, -Cw, -DR) as previously described.[8–10] There was no specific upper age limit. Other eligibility requirements included an ECOG performance status of 0 or 1 and a life expectancy of at least 100 days based on the attending physician's assessment. Patients were required to have a normal serum creatinine, a serum total bilirubin <2 mg/dl and AST <2 times the upper limit of normal. Patients were also required to have a left ventricular ejection fraction of at least 45% and an FEV1 and DLCO of $\geqslant 45\%$ predicted. Patients were excluded

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from enrollment on an RIC allogeneic HSCT trial if they had central nervous system involvement with their disease, an HIV positive status, pregnancy or a concurrent medical or psychiatric illness that could not be controlled with appropriate therapy.

Treatment

Patients received fludarabine 30 mg/m^2/day on days −5, −4 and −3 and then TBI 200 cGy on days −1 and 0 (total dose 400 cGy). The TBI dose was delivered using 6 MV photons prescribed to the midplane umbilicus at a dose rate of 5–10 cGy/min at depth. Although no selective lung blocking was used, thermoluminescent dosimetry was performed on each patient to verify final delivered radiation doses. Of note, the first three patients received the total 400 cGy dose on day −1. Due to delayed nausea in these patients, the protocol was amended and all subsequent patients received fractionated TBI as noted above. The donors received G-CSF 10 mcg/kg s.c. daily for PBSC mobilization. Leukapheresis began on the fifth day of G-CSF administration and continued for 2 or 3 days. The minimum number of PBSCs collected was 2.0×10^6 CD34$^+$ cells per kg.

The GVHD prophylaxis for patients with matched sibling donor transplants consisted of CYA 100 mg twice daily starting day −1 and mycophenolate mofetil 500 mg three times per day starting day +1. Patients who had matched unrelated donor transplants were treated on a different protocol in which they received tacrolimus 0.03 mg/kg/day administered in a divided dose twice daily starting day −1 and mycophenolate mofetil 500 mg three times per day starting day +1. In the absence of GVHD, mycophenolate mofetil was discontinued on day +56, whereas CYA and tacrolimus were tapered beginning at day +100 until discontinuing by day +180. On day +5 itraconazole, amoxicillin and acyclovir were started. CMV monitoring was performed with the Digene hybrid capture DNA quantitative assay (Digene Corp., Gaithersburg, MD, USA). Prophylactic gancyclovir (5 mg/kg/day) was routinely administered until day +100 for those patients who were CMV seropositive or whose donors were CMV seropositive.

T-cell chimerism

Short tandem repeat analysis for T-cell chimerism was performed on peripheral blood samples as previously described.[8] Specimens were collected initially on day +28, then every 2 weeks for 3 months, then monthly for 3 months, then every 3 months for 4 times, then every 4 months until 2 years post transplant (or more frequent if clinically indicated), then yearly.

Definitions

T-cell complete donor chimerism (CDC) was defined as achievement of ⩾95% DNA of donor origin in the T-cell-enriched fraction. Mixed chimerism was defined as ⩾1% and <95% DNA of donor origin in the T-cell-enriched fraction. Primary graft rejection was defined as severe pancytopenia with failure to ever achieve any donor-derived hematopoiesis. Secondary graft rejection was defined as the complete loss of donor-derived hematopoiesis after complete or mixed chimerism was achieved.

The GVHD grading was performed according to the standard criteria for acute[11] and chronic GVHD.[12] Relapse-free survival was defined as the time from the date of transplantation until that of first relapse, death or last follow-up. Overall survival was defined as the interval from the date of transplantation until that of death or last follow-up. TRM included patients dying from causes other than relapsed disease, which included GVHD, organ toxicity, infection, hemorrhage, secondary malignancy and graft rejection. Patients were censored for TRM at the time of relapse.

Statistical analysis

Categorical variables were summarized as frequencies and percentages and were compared between the 200 cGy and 400 cGy TBI groups with the χ^2 test. Continuous variables were summarized as the median and range and compared between the TBI groups with the Wilcoxon rank sum test. Time-to-event variables without competing risks were estimated with the Kaplan–Meier method[13] and compared using the log-rank test, whereas those variables with competing risks (acute and chronic GVHD, achievement of CDC, CMV, other infections, graft rejection, relapse, TRM, donor lymphocyte infusions and subsequent transplants) were estimated with the cumulative incidence method and compared using the Pepe–Mori test.[14]

Results

Patient pretransplant characteristics are shown in Table 1. Diagnoses were comparable between the 400 and 200 cGy TBI groups, with AML being the most common myeloid disease and non-Hodgkin's lymphoma (NHL) the most common lymphoid disease for each group. There were no significant differences in other baseline characteristics between the groups.

Achievement of T-cell CDC was similar between the two TBI groups (Table 2). The median times to achieve T-cell CDC was 57 days (range, 13–374 days) for the 200 cGy TBI patients and 40 days (range, 19–360 days) for the 400 cGy TBI patients ($P = 0.80$). There were no differences between the patients who had achieved CDC and those who did not with regards to median CD34$^+$ cell dose infused (200 cGy group: 6.66 *vs* 6.82×10^6/kg, respectively, $P = 0.59$; 400 cGy group: 4.92 *vs* 5.20×10^6/kg, respectively, $P = 0.75$) or median CD3$^+$ cell dose infused (200 cGy group: 3.21 *vs* 3.81×10^8/kg, respectively, $P = 0.42$; 400 cGy group: 4.11 *vs* 1.60×10^8/kg, respectively, $P = 0.13$). The median times to achieve T-cell CDC for patients with lymphoid *vs* myeloid diseases were 41 (range, 13–286 days) *vs* 77 days (range, 19–374 days) in the 200 cGy TBI group ($P = 0.26$) and 30 (range, 19–251 days) *vs* 61 days (range, 26–360 days) in the 400 cGy TBI group ($P = 0.29$), respectively.

The 200 cGy TBI group received a higher median CD34$^+$ cell dose than those who received 400 cGy TBI (Table 2). However, there were no differences between the TBI dose groups in severity or incidence of acute or chronic GVHD, time to platelet and neutrophil engraftment, CMV

Table 1 Pretransplant characteristics

Variable	*200 cGy (N = 42)* N *(%)*	*400 cGy (N = 40)* N *(%)*	P-*value*
Gender			
Male	22 (52)	25 (62)	0.35
Female	20 (48)	15 (38)	
Race			
Caucasian	37 (88)	39 (98)	0.10
African-American	5 (12)	1 (2)	
Age at transplant (years)			
Median (range)	52 (15–63)	57 (26–67)	0.08
Prior transplant			
Autologous	11 (26)	6 (15)	0.46
Allogeneic	1 (2)	1 (2)	
None	30 (71)	33 (82)	
No. of prior chemo regimens			
0	7 (17)	1 (3)	—
1	4 (10)	10 (27)	
2	11 (26)	14 (38)	
3	10 (24)	2 (5)	
⩾4	10 (24)	10 (27)	
Median (range)	2 (0–7)	2 (0–8)	0.91
Prior radiation therapy			
Yes	9 (21)	6 (17)	0.59
No	33 (79)	30 (83)	
Diagnosis			
NHL	12 (29)[a]	9 (22)[b]	—
AML	6 (14)	11 (28)	
MDS	5 (12)	6 (15)	
Multiple myeloma	6 (14)	2 (5)	
CLL	3 (7)	4 (10)	
Myelofibrosis	3 (7)	3 (8)	
CML	5 (12)	0 (0)	
Hodgkin's lymphoma	2 (5)	1 (2)	
Myeloproliferative disorder	0 (0)	2 (5)	
ALL	0 (0)	1 (2)	
Bilineal acute leukemia	0 (0)	1 (2)	
Diagnosis category[c]			
Myeloid	19 (45)	22 (56)	0.32
Lymphoid	23 (55)	17 (44)	
Months from diagnosis to transplant			0.74
Median (range)	15 (2–162)	18 (2–246)	

Abbreviations: MDS = myelodysplastic syndrome; NHL = non-Hodgkin's lymphoma.
[a]Two diffuse large cell, three follicular, four mantle cell, two lymphoplasmacytoid, one angioimmunoblastic T cell.
[b]Five follicular, two extranodal marginal zone, two mantle cell.
[c]One patient with bilineal acute leukemia not included.

reactivation/infection, other infections or non-infectious toxicities.

Although fewer 400 cGy TBI patients experienced graft rejection than that observed for the 200 cGy TBI group, this did not reach statistical significance (Table 2). The two 400 cGy TBI patients included one with AML who had primary graft rejection and died 2 months post transplant with relapsed disease and one with mantle cell lymphoma who had primary graft rejection and died at 2 months post transplant. The six 200 cGy TBI patients all had secondary graft rejection. These included two AML patients whose graft rejection occurred on days +55 and +125 post transplant in the setting of relapsed disease; a CLL patient who had initially achieved T-cell CDC but then developed graft rejection on day +135 in the setting of disease relapse and gancyclovir-resistant CMV viremia; and three chronic phase CML patients whose graft rejection occurred at 61, 129 and 140 days post transplant. There were no differences between the patients who had graft rejection and those who did not with regards to median $CD34^+$ cell dose infused (200 cGy group: 6.43 vs 6.77×10^6/kg, respectively, $P = 0.96$; 400 cGy group: 4.60 vs 4.94×10^6/kg, respectively, $P = 0.78$) or median $CD3^+$ cell dose infused (200 cGy group: 3.50 *vs* 3.23×10^8/kg, respectively, $P = 0.99$; 400 cGy group: 1.48 *vs* 3.72×10^8/kg, respectively, $P = 0.11$).

Table 2 Transplant and post transplant characteristics

Variable	*200 cGy (N = 42)* N *(%)*	*400 cGy (N = 40)* N *(%)*	P-*value*
Donor relationship			
Sibling	32 (76)	26 (65)	0.27
Unrelated	10 (24)	14 (35)	
HLA mismatch			
No mismatch	32 (76)	30 (75)	0.90
HLA-DPB1 mismatch	10 (24)	10 (25)	
Donor–recipient gender			
Female to male	6 (14)	13 (32)	0.28
Female to female	10 (24)	8 (20)	
Male to male	16 (38)	12 (30)	
Male to female	10 (24)	7 (18)	
CD34+ cell dose ($\times 10^6$/kg)			
Median (range)	6.77 (2.04–12.51)	4.94 (2.21–7.03)	<0.001
$CD3^+$ cell dose ($\times 10^8$/kg)	(*N* = 39)		
Median (range)	3.30 (0.68–8.10)	3.56 (0.94–8.18)	0.54
Days to ANC >500/μl	(*N* = 19)[a]	(*N* = 33)[b]	
Median (range)	11 (3–51)	11 (6–18)	0.81
Days to platelet count >20 k/μl	(*N* = 14)[c]	(*N* = 26)[d]	
Median (range)	12 (4–29)	12 (9–159)	0.55
Achieved CDC	(*N* = 39)	(*N* = 39)	
Yes	33 (85)	34 (87)	0.61
No	6 (15)	5 (13)	
Worst episode of acute GVHD			
None	10 (24)	18 (45)	0.30[e] (any aGVHD)
Grade I	12 (29)	6 (15)	
Grade II	9 (21)	10 (25)	
Grade III	6 (14)	4 (10)	
Grade IV	5 (12)	2 (5)	
Worst episode of chronic GVHD			
None	18 (43)	27 (68)	0.30[f] (any cGVHD)
Limited	9 (21)	5 (12)	
Extensive	15 (36)	8 (20)	
Graft rejection	6 (14)	2 (5)	0.23
CMV reactivation	22 (52)	12 (30)	0.24
Grade II–V toxicity			
Gastrointestinal	0 (0)	1 (3)	0.30
Vascular	2 (5)	2 (5)	0.96
Pulmonary	3 (7)	1 (3)	0.33
Neurologic	4 (10)	3 (8)	0.74
Cardiac	2 (5)	1 (3)	0.59
Skin	2 (5)	1 (3)	0.59
Renal	0 (0)	2 (5)	0.14
Bacterial infection	25 (60)	19 (48)	0.28
Fungal infection	1 (2)	2 (5)	0.53
Viral infection	17 (41)	9 (23)	0.08
Received DLI	5 (12)	1 (3)	0.08
Received subsequent transplant			
Myeloablative allogeneic	3 (7)	0 (0)	0.033
RIC allogeneic	1 (2)	0 (0)	
Myeloablative and RIC transplants	1 (2)	0 (0)	
100-day mortality	2 (5)[g]	7 (18)[h]	0.06
Survival status			
Alive	12 (29)	23 (58)	0.94

Table 2 Continued

Variable	*200 cGy (N = 42)* N *(%)*	*400 cGy (N = 40)* N *(%)*	P-*value*
Months of follow-up for patients alive			
Median (range)	52 (43–85)	16 (3–37)	<0.001
Transplant-related mortality[i]			
Day 180	10%	13%	0.77
Overall	12 (29)	7 (18)	

Abbreviations: CDC = T-cell complete donor chimerism; DLI = donor lymphocyte infusion; RIC = reduced-intensity conditioning.
[a]Twenty-three patients never decreased their ANC to <500/μl.
[b]Seven patients never decreased their ANC to <500/μl.
[c]Twenty-eight patients never decreased their plt count to < 20k/μl.
[d]Eleven patients never decreased their plt count to < 20k/μl and three expired before recovering their plt count to >20k/μl.
[e]$P = 0.77$ for comparison of grades II to IV acute GVHD and $P = 0.34$ for grade III and IV acute GVHD.
[f]$P = 0.66$ for comparison of extensive chronic GVHD.
[g]Death due to acute GVHD for both patients.
[h]Death due to disease relapse (three), cardiac arrest (one), heart failure (one), acute GVHD (one), graft failure (one).
[i]*P*-value from cumulative incidence estimates; actual numbers and percentages are reported for overall treatment-related mortality unadjusted for length of follow-up.

Response and survival data for specific diagnoses and TBI dose groups are shown in Table 3. Among the patients who received 400 cGy, there were 12 (30%) with disease relapse/progression. Seventeen (42%) deaths occurred, the majority being due to disease relapse (eight patients) followed by acute GVHD (two patients). Thirty patients in the 200 cGy TBI group died, the majority due to disease relapse (10 patients) followed by acute GVHD (6 patients) and chronic GVHD (6 patients). At current follow-up, there are no significant differences in overall and relapse-free survival between the 200 and 400 cGy groups. The TRM at 2 years for the two groups was 26 *vs* 20% ($P = 0.77$), respectively. However, in the 200 cGy group, patients with lymphoid diseases had superior overall survivals compared to those with myeloid diseases ($P = 0.047$; Figure 1). This difference was no longer observed upon escalating to 400 cGy TBI. Lymphoid malignancy patients treated with 200 cGy TBI also tended to have better relapse-free survival than those with myeloid diseases ($P = 0.07$). In the 400 cGy TBI groups, no differences in relapse-free survival were observed between patients with lymphoid or myeloid diseases. Among those patients with myeloid malignancies the 2-year TRM was 42 *vs* 19% for the 200 and 400 cGy TBI groups, respectively ($P = 0.45$). For patients with lymphoid malignancies the 2-year TRM was 13 *vs* 20%, respectively ($P = 0.71$).

There were no significant differences between related and unrelated donors with regards to relapse-free survival, overall survival and TRM for the 200 cGy or the 400 cGy TBI groups. Graft rejection occurred in 4 (17%) of the 24 who had unrelated donors and 4 (7%) of 69 who had related donor transplants ($P = 0.25$).

Six patients in the 400 cGy TBI group (two NHL, one Hodgkin lymphoma, two multiple myeloma, one myelodysplastic syndrome after a prior autologous HSCT for NHL) had received autologous HSCTs at a median of 24 months (range, 10–78 months) before RIC allogeneic HSCT. Five remain alive at a median of 24 months (range, 5–37 months) post transplant. Only one with Hodgkin lymphoma had a disease relapse and one NHL patient had a stable partial response. One multiple myeloma patient died from relapsed disease at 8 months post transplant. Eleven patients in the 200 cGy TBI group (four NHL, five multiple myeloma, two myelodysplastic syndrome after prior autologous HSCT for NHL and Hodgkin lymphoma) had prior autologous HSCTs at a median of 19 months (range, 3–47 months) before RIC allogeneic HSCT. Three remain alive at 45, 49 and 60 months after RIC allogeneic HSCT. For those who died, the causes of death included three disease relapses, two chronic GVHD, one pulmonary embolism, one pneumonia and one central nervous system hemorrhage at a median of 14 months (range, 4–40 months) post transplant.

In comparison to the patients who received 400 cGy TBI, those in the 200 cGy TBI group more often received second transplants after RIC allogeneic HSCT and more often tended to receive donor lymphocyte infusions post transplant (Table 2).

Discussion

Reduced-intensity conditioning has allowed allogeneic HSCT to be used for many patients who would otherwise not be candidates for transplantation due to older age or comorbidities.[1–5,15–17] The ideal regimen would provide sufficient immunosuppression to permit engraftment of donor hematopoietic stem cells, adequate intensity for disease cytoreduction and limited toxicity to normal host tissues. Differences in the intensity of such conditioning may also be appropriate depending on the specific diagnosis being treated and the disease status. More indolent diseases such as CLL and certain lymphomas[7,15] may be managed with less intense regimens, whereas more aggressive malignancies such as AML may require more intense conditioning.[6,17] However, AML patients receiving nonmyeloablative conditioning with only fludarabine and 200 cGy TBI have been reported to do well if the transplant is performed in first CR.[18]

Table 3 Responses and survival for the different diagnoses and TBI dose groups

Diagnosis	N	*Pretransplant disease status*	*Best response post transplant*	*No. of deaths and causes*	*Median overall survival (months) (range)*[a]
AML					
200 cGy	6	1 CR1, 3 CR2→	4 continued CR→	2 relapsed AML, 1 acute and 1 chronic GVHD	9 (2–21)
		1 Rel2→	CR2→	Relapsed AML	
		1 PR →	Continued PR→	Acute GVHD	
400 cGy	11	4 CR1, 4 CR2→	8 continued CR→	5 relapsed AML, 1 MVA, 1 HF	8 (2–12)
		1 PR→	None (relapse)→	—	
		2 Rel 1→	2 CR→	—	
ALL					
200 cGy	0	—	—	—	—
400 cGy	1	PR	PR	Acute GVHD	4
Bilineage acute leukemia					
200 cGy	0	—	—	—	—
400 cGy	1	PR	CR	Relapsed acute leukemia	13
Myelodysplasia					
200 cGy	5	1 CR→	Continued CR→	1 relapsed disease	16 (10–43)
		4 untreated→	2 CR1, 2 PD→	2 chronic GVHD, 1 relapse	
400 cGy	6	2 PR→	2 CR→	1 acute GVHD	15 (1–24)
		3 PD after prior therapy→	2 CR, 1 PR→	—	
		1 untreated→	CR→	—	
CML					
200 cGy	5	All 1st chronic phase (CP)	2 CR→	1 sepsis	22 (7–82)
			2 continued CP→	1 PD, 1 acute GVHD	
			1 none (graft failure)→	1 acute GVHD (post-second transplant)	
400 cGy	0	—	—	—	—
CLL					
200 cGy	3	2 PD→	1 CR, 1 PR→	1 chronic GVHD	19 (9–85)
		1 PR→	PR→	1 hemolytic anemia	
400 cGy	4	2 PD→	1 CR, 1 PR	—	22 (4–36)
		2 PR→	1 CR, 1 PR	—	
Hodgkin's lymphoma					
200 cGy	2	2 PR	2 PR	1 PD	29 (10–48)
400 cGy	1	PR	CR	—	37
Myelofibrosis					
200 cGy	3	All untreated	1 CR	2 acute GVHD	7 (2–78)
			2 unknown response due to death		
400 cGy	3	2 PD→	1 CR, 1 none (PD)→	1 PD	8 (2–34)
		1 untreated→	? PR→	1 multisystem organ failure	
Multiple myeloma					
200 cGy	6	1 CR2→	CR→	1 pulmonary embolus	17 (4–47)
		5 PR→	1 CR, 4 PR→	1 chronic GVHD, 3 PD	
400 cGy	2	2 PR	2 PR	1 PD	19 (8–29)
Myeloproliferative disorder					
200 cGy	0	—	——	—	—
400 cGy	2	1 untreated, 1 no response	Unknown	1 chronic GVHD	9 (4–13)
Non-Hodgkin's Lymphoma					
200 cGy	12	2 CR 2, 1 CR 4→	All continued CR→	1 chronic GVHD	50 (4–78)
		3 PR 4, 1 PR 6, 1 PR 7→	All continued PR→	1 pneumonia, 1 CNS bleed; 1 unknown	
		1 Rel 2, 1 Rel 3, 1 Rel 4→	2 CR, 1 PR→	1 unknown etiology; 1 CNS bleed	
		1 PD [b]→	PR→	—	
400 cGy	9	2 PR 2, 1 PR 3, 1 PR 5, 1 PR6, 2 PR7, 1 PR9→	2 CR, 4 PR, 2 unknown[c]→	1 sepsis, 1 cardiac arrest, 1 graft failure, —	15 (2–32)
		1 Rel 1→	PR	—	

Abbreviations: CR1 = first CR; CR2 = second CR; PR = partial remission; PR 2 = second PR; PR 3 = third PR; PR 5 = fifth PR; PR 6 = sixth PR; PR 7 = seventh PR; PR 9 = ninth PR; Rel 1 = first relapse; Rel 2 = second relapse; Rel 3 = third relapse; Rel 4 = fouth relapse; PD = progressive disease; MVA = motor vehicle accident; HF = heart failure.
[a]The median follow-up for patients alive in the 200 cGy TBI group was 52 months (43–85 months) and for the 400 cGy TBI group this was 16 months (3–37 months) ($P < 0.001$).
[b]Lymphoplasmacytoid non-Hodgkin's lymphoma.
[c]These two patients died before they could be reassessed for responses.

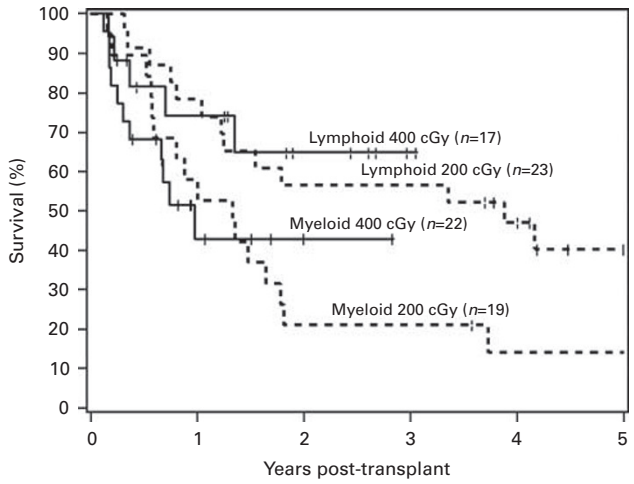

Figure 1 Kaplan–Meier curves for overall survival on the basis of TBI dose and disease category.

Increasing dose intensity has been demonstrated to be important for improving disease control and enhancing establishment of long-term CDC after RIC allogeneic HSCT.[19,20] We escalated the TBI dose from 200 to 400 cGy in combination with fludarabine for RIC allogeneic HSCT. There were less relapses in our 400 cGy TBI group, but longer follow-up is needed to confirm the efficacy of this approach for specific disease subtypes. Although we observed fewer cases of graft rejection in the 400 cGy TBI group, this did not reach statistical significance. Escalated TBI doses have been successfully used for RIC allogeneic HSCT and may further enhance engraftment.[21,22] However, much of this experience has been with myeloid malignancies,[21,23–25] whereas almost half of our patients treated with 400 cGy TBI had lymphoid diseases. At the current follow-up, however, there have been no significant differences in survival outcomes between our myeloid and lymphoid malignancy patients.

Monitoring donor chimerism after RIC allogeneic HSCT has been used to assess for hematopoietic engraftment as well as to determine whether residual disease persists. Achievement of T-cell CDC post transplant has also been considered important to generate a graft *vs* malignancy effect.[3,26] We observed that most patients treated with 400 cGy TBI achieved T-cell CDC, but this did not significantly differ from those who received 200 cGy TBI. Factors such as the type of hematologic malignancy, amount of pretransplant therapy, source of hematopoietic stem cells, composition of the hematopoietic graft and whether patients received a related *vs* unrelated donor have been correlated with the development of CDC after RIC allogeneic HSCT.[27–29] We have also previously reported that killer immunoglobulin-like receptor/ligand matching may influence the achievement of T-cell CDC and the development of graft rejection after RIC allogeneic HSCT.[8] Strategies to enhance achievement of T-cell CDC may include increasing pretransplant conditioning intensity further and the use of prophylactic donor lymphocyte infusions.

Our results demonstrate that RIC allogeneic HSCT may also successfully salvage patients with recurrent disease after prior autologous HSCT. In our series with 400 cGy TBI, 83% of these patients remained alive at 2 years and 50% were without evidence of recurrent/progressive disease. These results compare favorably to outcomes of lymphoid malignancy patients from prior reports.[30,31] Escalón *et al.*[32] had also reported that nonmyeloablative allogeneic HSCT is an effective option in lymphoma patients with chemosensitive or stable disease who experience disease recurrence following autologous transplantation.

We conclude that 400 cGy TBI administered with fludarabine for RIC allogeneic HSCT is well tolerated and further follow-up is needed to determine if outcomes are superior to those with 200 cGy TBI. The survival difference between patients with lymphoid and myeloid diseases who received 200 cGy TBI was no longer appreciated upon escalating to 400 cGy TBI. This may be due to more comparable relapse-free survivals between these disease groups when treated with 400 cGy TBI. Although this may potentially be due to better cytoreduction from increasing the TBI dose, patient selection may also have influenced outcomes. Future investigation of strategies to further intensify RIC may be appropriate, particularly for patients with myeloid diseases. In addition, prospective comparative trials will be needed to validate the results observed from phase II trials with RIC allogeneic HSCT and to help better define which RIC regimens are most appropriate for specific disease subtypes.

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