Fludarabine-melphalan as a preparative regimen for reduced-intensity conditioning allogeneic stem cell transplantation in relapsed and refractory Hodgkin's lymphoma: the updated M.D. Anderson Cancer Center experience

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ABSTRACT

Background
The role of reduced-intensity conditioning allogeneic stem cell transplantation in relapsed/refractory Hodgkin's lymphoma remains poorly defined. We here present an update of our single-center experience with fludarabine-melphalan as a preparative regimen.

Design and Methods
Fifty-eight patients with relapsed/refractory Hodgkin's lymphoma underwent RIC and allogeneic stem cell transplantation from a matched related donor (MRD; n=25) or a matched unrelated donor (MUD; n=33). Forty-eight (83%) had undergone prior autologous stem cell transplantation. Disease status at transplant was refractory relapse (n=28) or sensitive relapse (n=30).

Results
Cumulative day 100 and 2-year transplant-related mortality rates were 7% and 15%, respectively (day 100 transplant-related mortality MRD *vs.* MUD 8% *vs.* 6%, p=ns; 2-year MRD *vs.* MUD 13% *vs.* 16%, p=ns). The cumulative incidence of acute (grade II-IV) graft-versus-host disease in the first 100 days was 28% (MRD *vs.* MUD 12% *vs.* 39%, p=0.04). The cumulative incidence of chronic graft-versus-host disease at any time was 73% (MRD *vs.* MUD 57% *vs.* 85%, p=0.006). Projected 2-year overall and progression-free survival rates are 64% (49-76%) and 32% (20-45%), with 2-year disease progression/relapse at 55% (43-70%). There was no statistically significant differences in overall survival progression-free survival, and disease progression/relapse between MRD and MUD transplants. There was a trend for the response status pretransplant to have a favorable impact on progression-free survival (p=0.07) and disease progression/relapse (p=0.049), but not on overall survival (p=0.4)

Conclusions
Fludarabine-melphalan as a preparative regimen for reduced-intensity conditioning allogeneic stem cell transplantation in progression-free survival Hodgkin's lymphoma is associated with a significant reduction in transplant-related mortality, with comparable results in MRD and MUD allografts. Optimizing pretransplant response status may improve patients' outcome.

Key words: Hodgkin's lymphoma, stem cell transplantation.

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Introduction

Hodgkin's lymphoma (HL) remains a chemotherapy-sensitive disease with favorable outcomes following combination chemotherapy and radiation therapy. However, the prognosis for many patients with relapsed and refractory disease remains poor.[1-4] Many of them can be successfully salvaged with high-dose chemotherapy and autologous stem cell transplantation (SCT). However, patients who relapse after autologous SCT have a particularly poor prognosis, especially those who are chemorefractory.[4-6]

For these chemoresistant, multiply relapsed patients, allogeneic SCT employing conventional myeloablative conditioning has generally had poor results,[7-11] with prohibitive transplant-related mortality (TRM) and high relapse rates. Still, a minority (15-20%) of these extensively pretreated patients with advanced, chemoresistant disease have achieved long-term remissions and presumably cure. Data from some studies also suggested the presence of a graft-versus-HL effect.[10-11] This concept has been supported by case reports of disease response following donor leukocyte infusions (DLI).[12-14]

Reduced-intensity conditioning (RIC) prior to allogeneic SCT has been proposed as a means to achieve engraftment and induce graft-versus-malignancy effects without the morbidity and mortality associated with myeloablative conditioning regimens.[15] This approach has recently been employed in patients with relapsed and refractory HL.[14,16-19] Such patients seem well suited for this approach. Despite their young age, they are heavily pretreated and tolerate conventional myeloablative conditioning poorly. In addition, by reducing TRM, RIC could allow a demonstrable and clinically relevant graft-versus-HL effect to emerge, thereby improving outcome.

While published experience in this developing area remains limited, reduced-intensity regimens have been successful in improving TRM.[14, 16-19] Data for long-term progression-free survival are still lacking. Outcome data for transplants from matched unrelated donor (MUDs) transplants are even more scarce. This has to be viewed as a high-priority area, since, without recourse to MUDs most (75-80%) HL patients would otherwise lack an HLA-compatible donor.

We have previously reported preliminary results of a study comparing two fludarabine-based RIC regimens. Fludarabine-melphalan proved more effective than fludarabine-cyclophosphamide.[16] We, therefore, focused on the RIC approach with the fludarabine/melphalan regimen, with expanded patient accrual and a special emphasis on MUD transplants. We here provide an update of our experience with this strategy, including more complete and mature results, as well as an analysis of prognostic factors.

Design and Methods

Eligibility of patients

All patients with relapsed or refractory HL who underwent allogeneic SCT with fludarabine-melphalan conditioning at the University of Texas M. D. Anderson Cancer Center (UT-MDACC) during a five-year period (2001-2005) were analyzed. Study entry criteria were as follows: histologically confirmed HL, chemosensitive or stable disease after salvage treatment, no active or uncontrolled infection, and adequate cardiac, pulmonary, renal and hepatic function. Patients were required to have either an HLA-identical related donor or an HLA-matched unrelated donor willing to and capable of donating filgrastim-mobilized peripheral blood progenitor cells or bone marrow. Unrelated donors were matched for HLA-A, -B and –C (serologically matched or, more recently, molecularly identical), and were HLA-DR/DQ compatible (i.e. one single micromismatch allowed) by high resolution molecular typing. The study was approved by the UT-MDACC Institutional Review Board. Patients with disease progression and/or lack of insurance coverage for clinical trial participation who were otherwise eligible and transplanted during the same time period following the same treatment plan were also included. They were analyzed as part of a separate Institutional Review Board-approved protocol. All patients and donors were required to sign written informed consent. All individual patients' data presented in this report have been rendered anonymous.

Conditioning regimen

The conditioning regimen consisted of fludarabine, 25 mg/m^2 daily for 5 days (day -6 to day -2, until 4/2004) or 33 mg/m^2 daily for 4 days (day -5 to day -2; from 4/2004 to 8/2005) intravenously, and melphalan 70 mg/m^2 intravenously daily for 2 days (day -3 and -2). In six patients the melphalan dose was increased to 90 mg/m^2 daily x2 as part of a dose escalation trial, stopped because of excessive toxicity (i.e. mucositis). Antithymocyte globulin (ATG, thymoglobulin), 2 mg/kg intravenously daily for 3 days (day -4 to -2), was introduced to ameliorate graft-versus-host disease (GVHD)[20] in the most recent matched unrelated transplant patients (n=14). Day 0 was the day of infusion of the marrow or peripheral blood progenitor cells.

GVHD prophylaxis and supportive care

All patients received tacrolimus intravenously beginning 2 days before transplantation, dosed to maintain therapeutic serum levels (4-12 ng/mL) and switched to oral administration as soon as oral intake was feasible. In the absence of persistent or progressive disease, tacrolimus was continued for a minimum of 6 months and subsequently tapered off. Methotrexate (5 mg/m^2 intravenously) was administered on days 1, 3 and 6. An additional dose of methotrexate was administered on day 11 for MUD transplants. Supportive care was administered as outlined previously.[21]

Criteria for study evaluation

Engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count ≥0.5×10^9/L. Platelet recovery was considered to have occurred on the first of 7 consecutive days of an unsupported platelet count ≥20×10^9/L. Patients were evaluable for engraftment if they survived at least 30 days following transplant and had a chimerism assay performed. Chimerism was determined at day 30-100 post-transplant on bone marrow or peripheral blood samples by restriction fragment length polymorphism and, more recently, by polymerase chain reaction (PCR)-based microsatellite polymorphism analysis.[22-23]

Acute and chronic GVHD were graded according to established criteria.[24-25] Patients were considered evaluable for acute GVHD if they had achieved engraftment. Transplant-related mortality (TRM) included all causes of death other than disease progression or relapse occurring at any time after transplant. Relapse-related mortality included all deaths in patients with active disease after transplantation. However, in patients reinduced into remission (e.g. who received salvage chemotherapy and/or DLI) after disease progression or relapse, deaths were considered as transplant-related.

Response definitions

A complete remission (CR) was defined as disappearance of all clinical and radiological evidence of active disease in all known sites for a minimum of 4 consecutive weeks. Complete remission, unconfirmed/uncertain (CRu) was defined as the presence of residual radiographic abnormalities of unclear clinical significance, unchanged or decreased in size during an observation period of at least 4 weeks and not-gallium-avid or negative on positron-emission tomography (PET) scan (if initially gallium-avid or positive on a PET scan). CRu patients were reclassified as having CR after 1 full year without disease progression. Partial remission (PR) was defined as an at least 50% decrease in the sum of the products of diameters of any measurable lesion persisting for at least 4 weeks. Stable disease (SD) was defined as any response not meeting the criteria for PR or lack of evidence of progressive disease. Progressive disease (PD) was defined as at least a 50% increase in measurable disease or the appearance of disease at new sites. A sensitive relapse was defined as the achievement of at least a PR to salvage treatment, whereas failure to achieve at least a PR was qualified as refractory relapse. Both disease progression and relapse were considered as PD. Patients with evidence of PD and no active GVHD had their immunosuppression tapered or stopped and were eligible, at the discretion of the investigator, to receive DLI, with or without preceding salvage chemotherapy and/or radiation therapy.

Study design

This prospective study was originally conceived as a pilot study evaluating the feasibility of two preparative regimens (fludarabine-cyclophosphamide and fludarabine-melphalan). Following an initial data analysis,[16] accrual continued only on the fludarabine-melphalan regimen. Primary study end-points included engraftment (i.e., neutrophil and platelet recovery), chimerism, acute GVHD and day 100 TRM. Additional end-points included 2-year TRM, chronic GVHD, disease progression or relapse, overall survival (OS) and progression-free survival (PFS).

Actuarial rates of OS, PFS and time-to-progression (TTP) were estimated by the method of Kaplan-Meier.[26] The cumulative incidence method was used to estimate the rates of acute and chronic GVHD, TRM and PD. Acute GVHD (grades II-IV) was estimated prior to DLI (i.e. first 100 days), as well as before and after DLI. The 2-year time point was selected as it coincided with the median follow-up of the patients. Death attributed to disease was considered a competing risk for TRM, and death in remission or without GVHD was considered a competing risk for disease progression and GVHD, respectively.

A Cox proportional hazards model[27] (HR: hazard ratio; CI: confidence interval) was used to evaluate outcomes (OS, PFS, PD) according to pre-transplant response status and donor type, as well as to assess the impact of the CD3$^+$ cell dose infused on acute GVHD among patients who received DLI. The effect of acute and chronic GVHD on PD was evaluated considering GVHD as a time-dependent variable. Only univariate analysis was possible given the small sample size. OS and PFS were measured in months from the day of transplantation until death or disease progression.

Results

Patients' characteristics

The patients' characteristics are summarized in Table 1. The median age at transplantation was 32 years (range 19-59). The median number of chemotherapy regimens received prior to allogeneic SCT was five (range, 2-9). Forty-eight patients (83%) had undergone prior autologous SCT and the median TTP after autologous SCT was 6 months (range, 2-38).

Response status at transplantation was almost evenly distributed between sensitive relapse (n=30; MRD n=13, MUD n=17) and refractory relapse (n=28; MRD n=12, MUD n=16), with no significant difference in chemosensitivity between patients undergoing MRD or MUD allografts. Ten patients (17%) underwent upfront allogeneic SCT without a prior autologous SCT because of refractory disease.

Stem cell source

Peripheral blood progenitor cells were employed in 28 patients (MRD transplants n=24; MUD transplants n=4) and bone marrow in 30 patients (all but one with MUD transplants). The median CD34$^+$ cell dose infused was 4.7×10^6/kg (range, 0.9-29.1).

Engraftment and chimerism

The median time to neutrophil recovery was 12 days (range, 10-24). The median time to platelet recovery was 17 days (range, 7-132). Chimerism data at day 30-100 indicated 100% donor-derived engraftment in 57/57 (100%) evaluable patients (one patient died prior to his chimerism assessment).

Graft-versus-host disease

The actuarial incidence of grade II-IV acute GVHD at day 100 without DLI was 28% (range, 18-42). The incidence in MRD and MUD transplants was 12% (range, 4-36) and 39% (range, 26-60), respectively (HR 0.3, 95% CI 0.1-0.9; p=0.04). The cumulative incidence of chronic GVHD was 73% (range, 62-87). The incidence for MRD and MUD allogeneic SCT were 57% (range, 40-82) and 85% (range, 73-99), respectively (HR 0.4, 95% CI 0.2-0.7; p=0.006). Administration of thymoglobulin did not significantly affect the incidence of grade II-IV acute GVHD or chronic GVHD (*data not shown*).

Patients' outcome: TRM and causes of death

Early (day 100) and 2-year TRM rates for the whole group were 7% (range, 2-12%) and 15% (range, 8-28%), respectively. There was no statistically significant difference between MRD and MUD transplants with regard to day 100 (8% *vs.* 6%; HR 1.3; 95% CI 0.2-9.4; p=0.8) or 2-year (13% *vs.* 16%; HR 0.7; 95% CI 0.2-3.1; p=0.7) TRM.

Twenty-two patients died (38%). The causes of death were PD (n=14), GVHD (n=3), thrombotic thrombocytopenic purpura (n=1), heart failure (n=1), and pneumonia and/or sepsis (n=3). Of the non-relapse related deaths, four occurred before day 100.

Patients' outcome: OS, PFS, and disease progression

At the latest follow-up, 36 patients are alive (62%), with a median survivor follow-up of 24 months (range, 4-78). Twenty-three of these patients are in CR or CRu. OS, PFS (actuarial estimates) and PD (cumulative incidence rates) at 24 months and at the last follow-up are 64% (95% CI 49-76), 32% (95% CI 20-45) and 55% (95% CI 43-70), and 48% (95% CI 30-64), 26% (95% CI 12-42) and 61% (95% CI 47-80), respectively (Figure 1). The median time to disease progression after allogeneic-SCT was 141 days (range, 29-1047).

Among the 48 patients in whom a prior autologous

Table 1. Patients' characteristics.

Number of patients	58
Age (years)	32 (19-59)
Men/women	41/17
Performance status (ECOG)	
0	31
1	25
2	1
Unknown	1
Donor	
Matched related	25 (43%)
Matched unrelated	33 (57%)
Conditioning regimen*	
Fludarabine-melphalan	44 (MRD n=25; MUD n=19)
Fludarabine-melphalan-thymoglobulin	14 (all MUD)
Patients who had had a previous autograft	48 (83%)
No prior autograft	10 (17%)
Time to progression after autograft (months)	6 (2-38)
Response status at transplant	Chemosensitive: n=30 (52%) CR/CRu: n=14 PR: n=16 Chemorefractory: n= 28 (48%)

*ECOG: Eastern Cooperative Oncology Group. For performance status, see reference #. 28 MRD: matched related donor. MUD: matched unrelated donor. CR: complete remission; CRu: complete remission, unconfirmed/uncertain. PR: partial response. See text for response definitions. *The first cohort of MUD transplant patients (n=19) did not receive antithymoglobulin (see text for details). In six patients the melphalan dose was 90 mg/m² daily x2 as part of a dose escalation trial, stopped because of excessive toxicity (i.e. mucositis).*

Table 2. Prognostic factors for outcome at 2 years.

	N	*OS (HR, 95% CI, p value)*	*PFS*	*PD*
Response status at transplant				
CR/CRu	14	Reference	Reference	Reference
PR	16	2 (0.5-7.8), p=0.3	2.4 (0.9-6.5), p 0.07	2.7 (0.85-9.0), p=0.09
Refractory	28	1.5 (0.4-5.7), p=0.5	2.2 (0.9-5.5), p 0.09	2.9 (0.9-8.8), p=0.05
CR/CRu *vs.* all others	14 *vs.* 44	0.6 (0.2-2.0), p=0.4	0.4 (0.2-1.1), p 0.07	0.34 (0.1-0.99), p=0.049
Donor type				
MRD	33	0.45 (0.2-1.3), p=0.1	0.97 (0.5-1.8), p 0.9	1.1 (0.5-2.3), p=0.8
MUD	25	Reference	Reference	Reference
Acute GVHD (grade II-IV)				0.7 (0.3-1.6), p=0.3
Chronic GVHD				2.0 (0.7-5.9), p=0.2

OS: overall survival; PFS: progression-free survival; PD: progressive disease; CR: complete remission; CRu: complete remission, unconfirmed/uncertain; PR: partial response. See text for response definitions. MRD: matched related donor; MUD: matched unrelated donor.

SCT had failed, 31 had achieved a CR/CRu following their autologous SCT. Among these 31 patients, 16 (51%) achieved a CR/CRu following allogeneic SCT. In these 16 patients, the median TTP after autologous SCT was 6 months (range, 2-37). With a median follow-up after achieving CR/CRu following allogeneic SCT of 16 months (range, 5-52), the median TTP after allogeneic SCT in the same 16 patients has not yet been reached, with five patients progressing after a median of 4 months (range, 2-13). The difference in remission duration was statistically significant (p=0.003, log-rank). Of the ten patients who received an upfront allogeneic SCT (i.e. without prior autologous SCT), six are alive (five in CR) and four have died (PD n=3; GVHD after DLI n=1). Among the six patients who received melphalan 90 mg/m^2 daily x2, five patients are alive (three in CR), while one is dead (PD).

Patients' outcome according to donor type and pre-transplant response status

Donor type and response status prior to allogeneic SCT were evaluated as prognostic factors (Table 2). When OS and PFS were stratified according to the donor type (MRD *vs.* MUD), there was no statistically significant difference between MRD and MUD transplants with regard to OS (HR 0.45; 95% CI 0.2-1.3; p=0.1), PFS (HR 0.97; 95% CI 0.5-1.8; p=0.9) (Figure 2) and PD (HR 1.1; 95% CI 0.5-2.3; p=0.8).

OS and PFS were also stratified according to the response status prior to allogeneic SCT (i.e. CR/CRu *vs.* all other outcomes, including PR, SD and PD). There was a borderline significant trend favoring complete responders with regard to PFS (HR 0.4; 95% CI 0.2-1.1; p=0.07) (Figure 3) and PD (HR 0.34; 95% CI 0.1-0.99; p=0.049), although not OS (HR 0.6; 95% CI 0.2-2.0; p=0.4). When PR patients were analyzed separately, their outcome (i.e. OS, PFS, PD) was not different from that of chemorefractory patients (*data not shown*).

Impact of acute and chronic GVHD on disease progression

The impact of GVHD on PD was evaluated considering GVHD as a time-dependent variable (Table 2). There was no statistically significant impact of acute GVHD (grades II-IV, 100 days) or chronic GVHD (at any time) on PD (HR 0.7; 95% CI 0.3-1.6; p=0.3 and HR 2.0; 95% CI 0.7-5.9; p=0.2, respectively).

Donor leukocyte infusions

Fourteen patients with disease progression received a total of 25 DLI (median 1; range, 1-5), with (n=11) or without (n=3) preceding salvage chemotherapy and/or radiation therapy (Table 3). The overall response rate (PR plus CR/CRu) was 6/14 (43%). The response rate among patients receiving DLI alone was 1/3 (33%), with two patients achieving SD. The overall cumulative incidence of grades II-IV acute GVHD before and after DLI was 32% (range, 22-47%). There was a significant correlation between CD3$^+$ cell dose infused and development of GVHD. Grades II-IV acute GVHD developed in 1/19 cases *vs.* 4/6 cases when the infused CD3$^+$ cell dose was less or more than 0.8×10^7/kg, respectively (HR 16.7; 95% CI 1.8-150.5; p=0.012). The frequent concomitant administration of salvage chemotherapy (or radiation therapy)

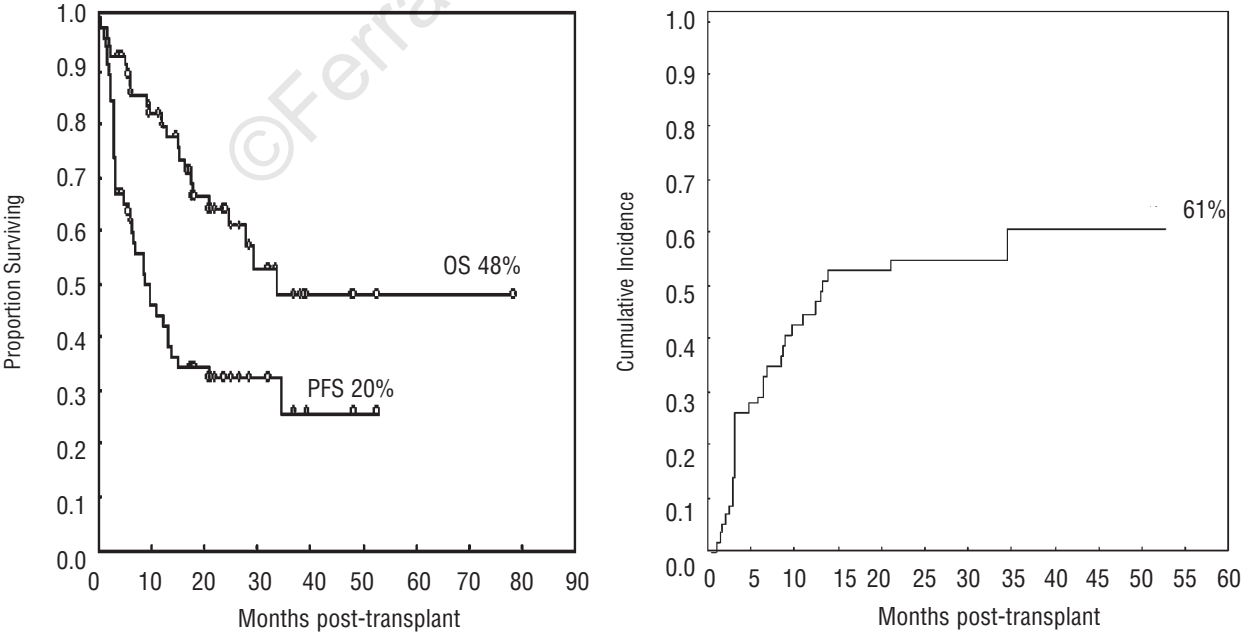

Figure 1. Kaplan-Meier estimates for overall survival and progression-free survival (left) and cumulative incidence of disease progression (right) for the whole group.

and the small sample size precluded any meaningful analysis of prognostic factors, such as CD3+ cell dose infused or development of GVHD, for response.

Discussion

RIC allogeneic SCT is now widely employed for the treatment of many hematologic malignancies.[15] Conventional myeloablative allogeneic SCT has been largely disappointing for HL because of high rates of toxicity and TRM.[7-10] In principle, HL is an attractive malignancy for a RIC approach, as it is a chemotherapy-sensitive malignancy in which heavily pretreated patients have a limited ability to tolerate myeloablative therapy. Indeed, preliminary data from this and other studies of RIC indicate a substantial reduction in TRM.[14,16-19] A retrospective registry analysis of this approach also showed an improvement in survival.[29] Still, as with other hematologic malignancies, the comparative roles of myeloablative and RIC approaches in HL remain, at present, poorly defined.

The sample size of 58 patients is adequate to draw preliminary conclusions. Early TRM was indeed substantially lower in our patients than in other recent studies. The patients' outcomes reported here are largely consistent with the ones reported recently by Peggs *et al.*,[14] although our approach is substantially different, as it does not include alemtuzumab in the preparative regimen.

Limited data on the use of MUD transplants for HL are available in the literature. In this study, patients transplanted from MUD experienced more acute and chronic GVHD, but their TRM, OS and PFS were largely comparable to those of patients who received MRD transplants. These findings, along with comparable results reported by others,[14] indicate that transplants from MUD are an appropriate option for patients who do not have a matched sibling donor.

While the difference did not quite reach statistical significance, this study supports the prognostic role of the pretransplant response status, particularly a CR, with regard to patients' outcome.[14,17] It seems reasonable to attempt cytoreduction by salvage chemotherapy prior to allogeneic SCT. More effective pre-transplant salvage strategies and regimens would be desirable, including new effective agents such as gemcitabine.[30-34] In addition, early withdrawal of immunosuppression or prophylactic DLI in high-risk patients should be considered to augment the graft-versus-malignancy effect.

Whether a graft-versus-HL effect exists has been the subject of considerable interest and debate.[35] This report does not allow any final conclusions to be drawn on this issue because of its small sample size and its limited statistical power to detect such an effect. Acute and chronic GVHD had no measurable impact on PD. However, rapid disease progression post-transplant in many patients (the median time to progression was only about 5 months) could conceivably prevent the mounting of an effective graft-versus-HL reaction, emphasizing once again the key issue of preventing PD. One finding supporting the presence of a graft-versus-HL effect was a significantly longer median time to progression following allogeneic SCT in the cohort of complete responders in whom an autologous SCT had previously failed.

DLI responses are often viewed as the gold standard to establish a graft-graft-versus-HL effect. The published data on this topic are fairly convincing, albeit scarce.[12-14, 35,36] In this report, most patients received DLI after salvage chemotherapy, making it difficult to interpret the response data. Whether more frequent or prophylactic DLI or possibly a higher CD3+ cell dose would be more effective, remains to be determined. The correlation between CD3+ cell dose infused and the development of acute GVHD is noteworthy, although not unexpected.[37] Acute GVHD was uncommon in patients who received CD3+ cell doses lower than 1×10^7/kg.

In conclusion, RIC allogeneic SCT using fludarabine and melphalan as the preparative regimen allows a significant reduction in TRM, with comparable results in

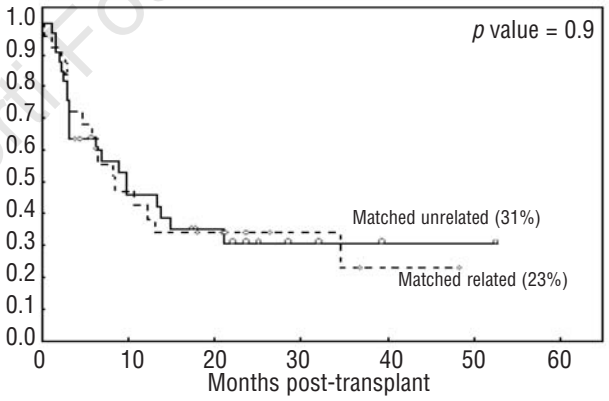

Figure 2. Kaplan-Meier estimates for progression-free survival according to donor type.

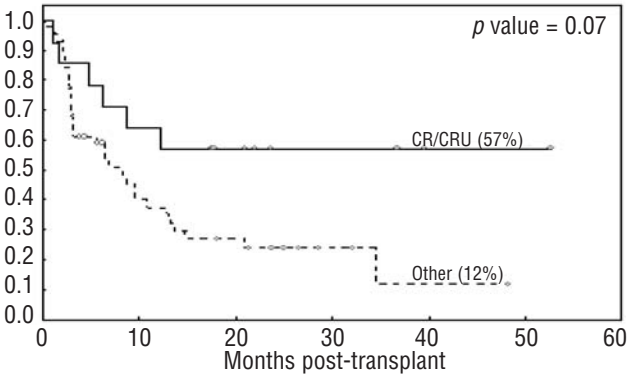

Figure 3. Kaplan-Meier estimates for progression-free survival according to pre-transplant response status. CR: complete remission; CRu: complete remission, unconfirmed/uncertain (*see text for response definitions*).

Table 3. Donor leukocyte infusions: CD3+ cell dose and patients' outcomes.

UPN	Donor type	Days after allogeneic SCT and DLI CD3+ cell dose (×10⁷ CD3+ cells/kg)					Chemotherapy or Radiation therapy	Acute GvHD grades II–IV	Best response	Current status	Days post BMT (Death/ Follow-Up)
		0.1	0.5	1	5	10					
030069	MRD				360	408	Chemotherapy	No	PD	Dead	527
030030	MRD			486			Radiation therapy	No	CRU	PD	1168
030009	MRD					111	Chemotherapy	No	CR	PD	1147
020161	MRD			600		765, 829	Chemotherapy	Yes	PR	PR	1093
030224	MRD			139	192, 247	304, 354	None	No	PR	SD	716
040362	MRD			124		158	Chemotherapy	Yes	PD	Dead	385
000765	MRD				196	224	Both	Yes	CRU	Dead	355
000741	MUD		215		307		None	Yes	SD	Dead	1005
020181	MUD	739					Chemotherapy	No	PD	Dead	871
040047	MUD			146			None	Yes	SD	Dead	525
030140	MUD	687					Chemotherapy	No	PD	PD	1102
030389	MUD			116	208		Chemotherapy	No	PR	Dead	478
040094	MUD		261				Chemotherapy	No	PD	Dead	732
000674	MUD					157	Chemotherapy	Yes	SD	Dead	267

UPN: unique patient number; MRD: matched related donor; MUD: matched unrelated donor; PD: progressive disease; CR: complete remission; CRu: complete remission, unconfirmed/uncertain; PR: partial response; SD: stable disease. See text for response definitions. UPN 020161 received his third DLI (day +829) as previously collected mobilized peripheral blood progenitor cells following melphalan 140 mg/m².

inducing long-term PFS with matched related and unrelated donor transplants. While these results are encouraging, much work remains to be done. Longer follow-up data are needed to put these results in perspective. Future studies should focus on inducing greater cytoreduction with salvage therapy prior to transplantation, as this is likely to improve patients' outcome. Prevention of early disease progression and more effective management strategies for GVHD are other high-priority areas.

Authorship and Disclosures

PA: conception and design, provision of study material or patients, collection and assembly of data analysis and interpretation, manuscript writing, final approval of manuscript; RS: data analysis and interpretation; SA: collection and assembly of data: SAG: provision of study material or patients; BA: provision of Study Material or Patients; NTU: manuscript writing, provision of study material or patients; CH: provision of study material or patients; IFK: provision of study material or patients; DC: provision of study material or patients; MdL: provision of study material or patients; MHQ: provision of study material or patients; BP, JR, LF, FH: provision of study material or patients; AY: manuscript writing, provision of study material or patients; MFM: conception and design; REC: provision of study material or patients, manuscript writing, final approval of manuscript. The authors reported no potential conflicts of interest.

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