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Clinical Research

HLA-Haploidentical Donor Lymphocyte Infusions for Patients with Relapsed Hematologic Malignancies after Related HLA-Haploidentical Bone Marrow Transplantation

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Treatment of relapse after related HLA-haploidentical T cell–replete bone marrow transplantation (haploBMT) with post-transplantation cyclophosphamide (PTCy) using haploidentical donor lymphocyte infusion (haploDLI) is not documented. All patients who received haploDLI after haploBMT with PTCy between June 2003 and October 2012 were identified and assessed for graft-versus-host disease (GVHD) and outcomes. Forty patients received 52 haploDLI doses. Sixteen patients had acute myeloid leukemia, 11 had lymphomas, and 34 had nonmyeloablative conditioning before haploBMT. The median time from haploBMT to relapse was 183 (range, 0 to 1399) days. The median age at haploDLI was 48 (range, 3 to 70) years. The first haploDLI doses were 1×10^5 $CD3^+$ cells/kg with subsequent escalation. The most commonly used first haploDLI dose was 1×10^6 $CD3^+$ cells/kg. The median follow-up after haploDLI was 7 (mean, 15.4; range, .5 to 96) months for the entire cohort, and 17.5 (mean, 28; range, 2.4 to 96) months for the responders. Acute GVHD developed in 10 patients (25%), 6 patients had grade 3 to 4, and 3 developed chronic GVHD. Twelve (30%) patients achieved a complete response (CR) with a median duration of 11.8 (mean, 22.5; range, .4 to 94) months. At last follow-up, 8 responders were alive in CR; 6 for over a year. HaploDLI for relapse after haploBMT is associated with acceptable toxicities and can result in durable responses.

INTRODUCTION

Donor lymphocyte infusion (DLI) is an established therapeutic option for relapsed disease after HLA-matched sibling or unrelated donor allogeneic blood or marrow transplantation, but it is associated with significant risk of graft-versus-host-disease (GVHD) and only a modest antitumor activity [1-8]. Several factors affect the likelihood of responding to DLI, the most important of which are the underlying disease and extent of relapse at time of DLI [1].

Promising results have been reported with related HLA-haploidentical T cell–replete bone marrow transplantation (haploBMT) with post-transplantation high-dose cyclophosphamide (PTCy) [9-11]. As with other types of bone marrow transplantation (BMT), relapse after haploBMT continues to be a major problem [12-15]. There are limited published data on DLI use after haploBMT [16-18] and none after haploBMT with PTCy. We undertook a dose-escalation approach to evaluate the optimal dosing of DLI for relapsed disease after haploBMT with PTCy. Here, we report a retrospective analysis of our cohort of all patients who received DLI collected from HLA-haploidentical donors (haploDLI) for relapsed disease after haploBMT.

METHODS AND MATERIALS

Study Population

After approval by the institutional review board, we retrospectively identified all patients who received haploDLI for relapsed hematologic malignancies after haploBMT with PTCy at Johns Hopkins University between June 1, 2003 and October 1, 2012. Minimal residual disease (MRD) relapses were defined by the new detection of flow cytometric or cytogenetic evidence of disease after haploBMT or by progressive loss of donor chimerism (LOC) thought to represent recurrence, in the absence of overt evidence of hematologic relapse. All patients were included and there were no exclusion criteria based on age, gender, disease type, conditioning regimen, or any other feature.

Administration of HaploDLI

After obtaining donor's consent, haploDLI were collected by apheresis according to standard protocol at Johns Hopkins University. The $CD3^+$ cell count was determined by flow cytometry and was used for calculating the haploDLI dose. All patients who received haploDLI were off immunosuppressive agents and without evidence of active GVHD at time of administration. We had estimated that the haploDLI dose that can be administered initially without an unacceptable incidence of severe GVHD should be at least 100-fold lower, or approximately 1×10^5 to 1×10^6 $CD3^+$ T cells/kg, than the dose typically used in HLA-identical DLI (1×10^7 to 1×10^8 $CD3^+$ T cells/kg) [19,20]. Therefore, the haploDLI administration was performed in a dose-escalation manner starting with 1×10^5 $CD3^+$ T cells/kg of recipient's ideal body weight.

Response Criteria and GVHD Evaluation

Hematologic relapses and responses were defined using standard disease-specific criteria [1]. A complete remission (CR) after haploDLI administration required disappearance of all MRD (ie, respective flow cytometric or cytogenetic abnormality in bone marrow [BM]). All patients underwent BM examination on day 60 after haploDLI to assess for response, or sooner if clinically indicated. Patients with lymphoma underwent radiologic imaging as well. The Keystone staging system was used to score acute GVHD (aGVHD) [21] and the Seattle criteria were used for chronic GVHD 9 (cGVHD) [22].

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Data Collection and Analysis

Relapses, responses, and GVHD scores were assessed by 2 authors independently (A.M.Z. and P.F.) and then verified by a third investigator (J.B.M.). The electronic medical record was used to collect demographic, clinical, and laboratory data. Characteristics of the haploDLI, including number of infusions and cell doses, were collected from the Cell Therapy Laboratory and electronic medical record. Patients were followed until death or December 1, 2012, whichever was first. Duration of response was calculated from the date of first documentation of response. Overall survival was calculated from date of administration of last haploDLI. Based on the heterogeneity of the patient population in terms of underlying disease, burden at relapse, difference in patients' clinical conditions, the relatively small sample size, the use of various doses of haploDLI, descriptive rather than inferential statistics were used to analyze data.

RESULTS

Demographics and Baseline Characteristics

The demographics and baseline characteristics of 40 patients who have received haploDLI are shown Table 1. All patients had received PTCy, tacrolimus, and mycophenolate mofetil for GVHD prophylaxis after haploBMT. In total, 14 patients developed GVHD after the haploBMT (2 had grade 2 GVHD and 2 had grade 3 GVHD), with resolution in all 4 before haploDLI. The median time from haploBMT to diagnosis of relapse was 183 days (7 relapses within 3 months of BMT, 27 relapses within first year, with only 5 relapses after 2 years). Thirty-five patients received haploDLI for overt hematologic or radiologic relapse, 4 for MRD relapse detected by flow cytometry or cytogenetics, and 1 for progressive LOC concerning for relapse. The median follow-up for the entire cohort from time of first haploDLI administration was 7 months (mean, 15.4; range, .5 to 96 months). For the 12 responders, the median follow-up was 17.5 months (mean, 28; range, 2.4 to 96 months).

Table 1
Demographics and Baseline Characteristics of 40 patients with Hematologic Malignancies Who Received HLA-Haploidentical Donor Lymphocyte Infusions (haploDLI) for Relapsed Disease after HLA-Haploidentical Bone Marrow Transplantation (haploBMT)

Characteristic	Number (N = 40)
Gender	
M	27
F	13
Age at haploDLI (yr)	
≤20	9
21-50	13
≥51	18
Disease	
Acute myeloid leukemia	16
Non-Hodgkin lymphoma	6
Hodgkin lymphoma	5
Multiple myeloma	4
Acute lymphoblastic lymphoma	3
Chronic myeloid leukemia	1
Other*	5
Conditioning regimen	
Myeloablative (BU/Cy)	6
Nonmyeloablative (FLU/Cy/TBI)	34
Type of relapse	
Hematologic	35
MRD or LOC	5
Time from haploBMT to relapse (mo)	
≤3	7
>3-6	8
>6-12	12
>12-24	8
>24	5

Bu indicates busulfan; Cy, cyclophosphamide; FLU, fludarabine; TBI, total body irradiation; MRD, minimal residual disease; LOC, loss of donor chimerism.

* Other diseases included atypical chronic myeloid leukemia (n = 1), myelodysplastic syndrome (n = 1), plasmacytoid dendritic cell neoplasm (n = 1), chronic lymphocytic leukemia (n = 1), and T cell prolymphocytic leukemia (n = 1).

HaploDLI Characteristics

Between August 8, 2003 and September 27, 2012, 52 doses of haploDLI were administered to the 40 patients who relapsed after haploBMT (Tables 1 and 2). Thirty-two patients received only 1 haploDLI dose. Chemotherapy (27 patients) or radiotherapy (1 patient) was administered before administration of 33 haploDLI doses. The patients' median age at time of first haploDLI administration was 48 years (mean, 42; range, 3 to 70 years). The median time from relapse to first haploDLI administration was 56 days (mean, 119 days; range, 7 to 730 days). The first haploDLI doses used in the first 5 patients were 1×10^5 $CD3^+$/kg. Because no clinical responses or GVHD were observed, subsequent patients received higher initial doses, with escalation allowed in absence of GVHD. The majority of patients (29 patients, 72.5%) received 1×10^6 $CD3^+$/kg as their first haploDLI dose, and 8 patients (20%) received escalating doses

Table 2
Characteristics of Haploidentical Donor Lymphocyte Infusions (haploDLI)

HaploDLI Characteristic	Number (HaploDLI, n = 52 Doses; Patients, n = 40)
Cytoreductive chemotherapy or radiotherapy before haploDLI	
Yes	33 doses (28 patients)
No	19 doses (12 patients)
Total number of haploDLI doses received	
1	32
2	5
3	2
4	1
Time from diagnosis of relapse to first haploDLI administration (d)	
≤30	11
31-60	10
61-90	7
91-180	3
181-360	6
≥361	3
First haploDLI dose ($CD3^+$ cells/kg IBW)	
1×10^5	5
1×10^6	29
5×10^6	2
1×10^7	3
5×10^7	1
All haploDLI doses ($CD3^+$ cells/kg IBW)	
1×10^5	5
5×10^5	1
1×10^6	30
3×10^6	1
5×10^6	4
1×10^7	9
1×10^8	2
Year in which first haploDLI was administered	
2003	1
2004	4
2005	2
2006	1
2007	0
2008	5
2009	3
2010	7
2011	9
2012	8

IBW indicates ideal weight.

of haploDLI (Table 2). No GVHD prophylaxis was administered after haploDLI.

GVHD Post HaploDLI

Out of the 40 patients who received haploDLI, 10 developed aGVHD (25%). Eight patients had grade 2 to 4 (20%), and 6 had grade 3 to 4 aGVHD (15%). Grade 2 to 4 aGVHD occurred after 5 of 30 (16.7%) haploDLI doses of 1×10^6 $CD3^+$/kg, after 1 of 4 (25%) haploDLI doses of 5×10^6 $CD3^+$/kg, and after 2 of 9 (22.2%) haploDLI doses of 1×10^7 $CD3^+$/kg. Grade 3 to 4 aGVHD occurred after a haploDLI dose of 1×10^6 $CD3^+$/kg in 3 patients, after 5×10^6 CD3+/kg in 1 patient, and after 1×10^7 $CD3^+$/kg in 2 patients. Only 1 of the 8 patients who developed grade 2 to 4 aGVHD received more than 1 dose of haploDLI; this patient initially received 1×10^6 $CD3^+$/kg without response of GVHD, then developed grade 3 aGVHD after a second dose of 1×10^7 $CD3^+$/kg. Interestingly, no aGVHD was observed after haploDLI in a 13-year-old patient who received 2 separate haploDLI doses of 1×10^8 $CD3^+$/kg, both of them given as final 2 doses of a 4-dose escalation. Six of the 8 patients who developed grade 2 to 4 aGVHD had received chemotherapy or radiation treatment before haploDLI administration. Two patients with severe aGVHD (both grade 3) died within 6 weeks of haploDLI administration: both from sepsis. In total, 3 patients developed cGVHD, of whom 2 had extensive stage, including 1 case of bronchiolitis obliterans. Both patients who developed extensive cGVHD remain alive and disease free.

Responses and Survival

Of the 40 patients treated, 12 received haploDLI without any other therapy, and only 1 of those patients achieved a remission. Of the 28 patients who received cytoreductive therapy before haploDLI, 11 achieved a CR. Overall, 12 (30%) patients responded to haploDLI, all achieving a CR, with a median response duration of 11.8 months (mean, 22.5 months; range, .4 to 94 months) (Table 3). Three of the 4 (75%) patients treated for MRD responded, whereas 9 of the 35 (26%) treated for overt relapse responded. The patient who received haploDLI for progressive LOC did not respond and progressed to hematologic relapse. The median age of responders was 52.5 years (range, 13 to 70 years). Ten responders received haploDLI within 4 months of relapse. Ten patients responded after first haploDLI dose, 1 patient responded after the second haploDLI dose, and another patient responded after the third haploDLI.

Eight (26.7%) patients responded to a haploDLI dose of 1×10^6 $CD3^+$/kg, 1 patient to a 5×10^6 $CD3^+$/kg dose, while 3 patients responded to a 1×10^7 $CD3^+$/kg dose. Five responders had acute myeloid leukemia with a response rate of 31.3% in this disease. The other 7 responders included 1 patient with each of the following diseases: mantle cell lymphoma, enteropathy-associated T cell lymphoma, plasmacytoid dendritic–cell neoplasm, acute lymphoblastic leukemia, myelodysplastic syndrome, Hodgkin lymphoma, and T cell prolymphocytic leukemia.

Five responders developed clinically significant GVHD post haploDLI (3 patients developed grade 2 to 4 aGVHD, 2 with extensive cGVHD). At end of follow-up, 8 of the 12 responders were still alive and in CR, including 5 patients who had hematologic relapse after haploBMT. A ninth patient was still alive at end of follow-up but in relapse. Six patients were still alive 12 months or longer after haploDLI and in CR (96, 78, 44, 24, 18, and 18 months, respectively). Of those 6 patients, 2 had extensive cGVHD post haploDLI, 1 had grade 2 aGVHD, whereas the other 3 never developed GVHD.

DISCUSSION AND CONCLUSIONS

There are limited data on the toxicity and efficacy associated with the use of DLI for relapse after haploBMT [16-18]. This is the first report describing the toxicity and efficacy of DLI administration for relapse after haploBMT with PTCy. Twelve (30%) patients achieved CRs after haploDLI, with a median duration of response of 11.8 months (range, .4 to 94 months). After a median follow-up for the 12 responders of 17.5 months (range, 2.4 to 96 months), 8 were still alive in CR; 6 for a year or longer. Consistent with the feasibility of rapid administration of haploDLI, the median time from relapse to first haploDLI was less than 60 days, and 28 patients received their first haploDLI dose within 90 days of relapse. Cytoreduction before haploDLI appears to be needed to improve outcomes.

Similar to patients who receive DLI after HLA-matched BMT, patients who received haploDLI for MRD had higher response rates (75%) than those who received haploDLI for overt hematologic relapse (26%). The small patient numbers within any specific hematologic malignancy preclude making conclusive statements about disease-specific efficacy of haploDLI. However, the response rate of 31% (5 of 16 patients) in the largest disease group, acute myeloid leukemia, was similar to that reported for DLI given for relapse after HLA-matched BMT [1].

Only 10 (25%) patients developed aGVHD after haploDLI (25%), 6 of whom had grade 3 to 4 aGVHD, but only 2 patients with severe aGVHD (both grade 3) died. Three patients developed cGVHD. A dose of 1×10^6 $CD3^+$/kg appears to be a reasonable starting DLI dose in the related haploidentical setting. This dose was associated with grade 2 to 4 GVHD in 16.7% of patients and a CR rate of 26.7% of patients within a wide spectrum of relapsed hematologic malignancies.

The low rates of severe aGVHD that we observed after haploDLI contrast with the high rates observed by other groups [16,23,24]. Huang et al. reported 20 patients in whom granulocyte colony-stimulating factor–primed therapeutic haploDLI was administered for relapsed leukemia at a median of 177 days after T cell–replete haploSCT [16]. The median haploDLI dose was significantly higher (61×10^6 $CD3^+$/kg; range, 23 to 456×10^6 $CD3^+$/kg). The authors noted a high incidence of aGVHD after haploDLI in the first 9 patients studied, prompting the use of GVHD prophylaxis after haploDLI for subsequent patients. The incidence of severe aGVHD (grade 3 to 4) after haploDLI significantly decreased with GVHD prophylaxis. The reported response to haploDLI was 65%, and at end of follow-up, 8 of their patients were alive in CR at a median of 1118 days with a 2-year leukemia-free survival of 40% [16,17]. A subsequent update from the same group that included 168 haploDLI doses administered to 124 patients following T cell–replete haploSCT (of which 47 DLI doses were therapeutic) confirmed a higher incidence of DLI-associated aGVHD (grade 2 to 4, 53.2%; grade 3 to 4, 28.4%), which was reduced with post-DLI GVHD prophylaxis [18]. We believe that larger haploDLI doses used by the Chinese group accounted for their observed higher rates of aGVHD.

In our experience, haploDLI appears to be associated with similar efficacy and toxicity to matched sibling donor alloSCT. A haploDLI dose of 1×10^6 $CD3^+$/kg of recipient's ideal body weight appears to be well tolerated in most patients and might be considered a reasonable starting haploDLI dose in this setting. Our data indicate that haploDLI administration for relapsed disease after haploBMT with PTCy is feasible,

Table 3
Characteristics of Patients with Hematologic Malignancies Who Responded to Haploidentical-Donor Lymphocyte Infusions (haploDLI) Given after Relapse following HLA-Haploidentical–related Bone Marrow Transplantation (BMT)

Patient No	Sex	Disease	BMT-to-Relapse (d)	Type of Relapse	Age at First DLI (yr)	Relapse-to-First DLI (d)	Date of DLI	Dose of DLI ($CD3^+$/kg IBW)	aGVHD Post DLI (Overall Grade)	cGVHD Post DLI	Duration of Response from Date of Response Documentation, mo	Survival from Date of Last DLI (mo) and Vital Status at End of Follow-up
1	F	MDS	183	M	13	28	Dec 1, 2004	1×10^7	0	Extensive	94	96 (A)
2	M	AML	456	H	66	49	Jul 27, 2005	5×10^6	0	None	3.5	4.5 (D)
3	M	HL	700	H	16	84	Aug 4, 2005	1×10^5	0	None	Proceeded to second DLI	Proceeded to second DLI
							Oct 27, 2005	1×10^6	1	None	Proceeded to third DLI	Proceeded to third DLI
							May 31, 2006	1×10^7	0	Extensive	64	78 (A)
4	M	AML	183	M	44	14	Mar 18, 2009	1×10^6	2	None	35	44 (A)
5	M	T-PLL	441	H	51	56	Aug 4, 2010	1×10^6	0	None	Proceeded to second DLI	Proceeded to second DLI
							Dec 16, 2010	1×10^7	3	None	4	12.5 (D)
6	M	AML	243	H	61	204	Oct 26, 2010	1×10^6	0	None	22	24 (A)
7	F	MCL	243	H	61	304	Apr 1, 2011	1×10^6	0	None	16	18 (A)
8	M	EATCL	1399	H	62	28	May 12, 2011	1×10^6	0	None	2	17 (D)
9	M	AML	167	H	70	35	May 19, 2011	1×10^6	0	None	16	18 (A)
10	M	PDCN	973	H	39	30	Dec 9, 2011	1×10^6	0	None	6	12 (A*)
11	F	AML	183	M	54	61	Feb 17, 2012	1×10^6	1	None	7.5	9.5 (A)
12	M	ALL	152	H	37	106	Sep 20, 2012	1×10^6	4	None	0.4	2.4 (A)

MDS indicates myelodysplastic syndrome; AML, acute myeloid leukemia; HL, Hodgkin lymphoma; T-PLL, T cell prolymphocytic leukemia; MCL, mantle cell lymphoma; EATCL, enteropathy-associated T cell lymphoma; PDCN, plasmacytoid dendritic-cell neoplasm; ALL, acute lymphoblastic leukemia; M, minimal residual disease relapse (detected by flow cytometry or cytogenetics); H, hematologic relapse; IBW, ideal body weight of recipient; GVHD, graft-versus-host-disease; aGVHD, acute graft-versus-host-disease; cGVHD, chronic graft-versus-host-disease; A, alive; D, dead; N/A, not available; C, chemotherapy; R, radiation therapy.
Data censored at December 1, 2012. All patients underwent nonmyeloablative ablative conditioning before BMT except patient no. 11, who underwent myeloablative conditioning before BMT.
* Alive in relapse.

associated with acceptable toxicities, and can result in durable responses. Prospective evaluation is required to confirm these findings.

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