

# BRIEF REPORT

## Persistent Multiyear Control of Relapsed T-Cell Acute Lymphoblastic Leukemia With Successive Donor Lymphocyte Infusions: A Case Report

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There are few therapeutic options for patients with T-cell acute lymphoblastic leukemia (T-ALL) who have recurrent disease after initial matched sibling hematopoietic stem cell transplantation. While a second hematopoietic stem cell transplant (HSCT) from a haploidentical donor offers the conceptual possibility of greater graft versus leukemia effect, there is minimal literature to describe the efficacy of this approach in recurrent pediatric T-ALL. We present the case

of a now 9-year-old female in whom second haploidentical HSCT, followed by successive donor lymphocyte infusions in response to minimal residual disease reemergence, has led to 3+ years of ongoing disease control without graft versus host disease and excellent quality of life. *Pediatr Blood Cancer* 2016;63:1279–1282. © 2016 Wiley Periodicals, Inc.

**Key words:** donor lymphocyte infusion; haploidentical bone marrow transplant; relapse; T-cell acute lymphoblastic leukemia

### INTRODUCTION

Relapse of T-cell acute lymphoblastic leukemia (T-ALL), especially after matched sibling bone marrow transplant (BMT), has a dismal prognosis [1,2] and specific T-ALL-directed immunotherapies are only just emerging.[3] One promising strategy for relapsed hematologic malignancies is enhancement of graft versus leukemic effect (GVL) through HLA-haploidentical T-cell replete hematopoietic stem cell transplantation (haplo-HSCT), with posttransplantation high-dose cyclophosphamide to limit graft versus host disease (GVHD).[4] The enhanced GVL conferred by establishment of a haploidentical graft further makes possible subsequent use of haploidentical donor lymphocyte infusions (haplo-DLIs) as a disease control strategy with acceptable toxicities.[5] DLI as a leukemia control strategy may be particularly effective when employed preemptively upon detection of disease recurrence by minimal residual disease (MRD) but before frank relapse.[6]

We report the case of a now 9-year-old female with multiple recurrent T-ALL for whom second haplo-BMT and successive haplo-DLIs are providing persistent (currently 3 years 5 months posttransplant) disease control with minimal side effects and excellent quality of life.

### CASE HISTORY

Our patient initially presented at the age of 4 years 2 months (Table I) with a WBC 703 K/ $\mu$ l, ultimately diagnosed as CD1a–, cCD3+(bright), sCD3–, CD5+(mod), and CD8+(mod) T-ALL with too numerous to count WBC in CSF (CNS3 disease). She was started on induction as per Children's Oncology Group T-ALL protocol (AALL0434) [7] and was CNS negative and bone marrow (BM) MRD 0.016% at the start of consolidation (CR1). T-ALL MRD assessment followed the principle that abnormal T cells in MRD are found in “empty space” not occupied by normal cells;[8] in the case of this patient, previous methods [9,10] were modified to track the patient's original CD5+ cCD3+ sCD3– clone. The combination CD56/CD16 was used to exclude rare NK cells with that phenotype. This method has proven efficacy as its use to detect post-HSCT MRD has been associated with an increased risk of relapse and death.[9]

She had CNS3 relapse (with BM MRD 0.2%) at the start of interim maintenance. She was reinduced with 5 days of nelarabine, etoposide, and cyclophosphamide based on TACL-2008-002 [11] with weekly triple intrathecal (IT) (cytarabine, methotrexate, and hydrocortisone) chemotherapy beginning on Day (D)+8 (Table I) and achieved CNS and BM MRD negative status (CR2).

She underwent 10/10 matched sibling T-cell replete BMT at 4 years 9 months of age (Table I). She engrafted (absolute neutrophil count [ANC] > 500/ $\mu$ l) on D+21 posttransplant. She had no evidence of GVHD and was weaned off tacrolimus by D+98. She was 100% sibling donor chimerism and CSF and BM MRD negative on all successive posttransplant studies until D+176, when she was found to have BM MRD 0.06%. She received 50 mg/kg cyclophosphamide followed by matched sibling unmanipulated peripheral blood DLI dosed on CD3+ count (Table I). By D+67 after matched sibling DLI, the patient was MRD negative, but then had disease reemergence 1 month later (0.085%). Because she had no GVHD in response to matched

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; BMT, bone marrow transplant; CNS, central nervous system; CSF, cerebrospinal fluid; DLI, donor lymphocyte infusion; GVHD, graft versus host disease; GVL, graft versus leukemia effect; HSCT, hematopoietic stem cell transplantation; MMF, mycophenolate mofetil; MRD, minimal residual disease; NK, natural killer; T-ALL, T-cell acute lymphoblastic leukemia

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Conflict of interest: Nothing to declare.

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Received 6 October 2016; Accepted 18 February 2016

TABLE I. Timeline of Disease Course, Interventions, and Disease Assessments

Age	Event	Bone marrow	Treatment
4 years 2 months	Diagnosis T-ALL/CNS3	90% blasts	Induction as per COG AALL0434
4 years 3 months	End induction CNS neg	MRD+ 0.016%	Consolidation as per COG AALL0434 Arm C
4 years 6 months	End consolidation CNS3 relapse	MRD+ 0.02%	reinduction as per TACL-2008-002, dose level 2
			Nelarabine 650 mg/m <sup>2</sup> IV qday D 1–5
			Etoposide 100 g/m <sup>2</sup> IV qday D1–5
			Cyclophosphamide 330 mg/m <sup>2</sup> IV qday D 1–5
			IT MTX 12 mg, hydrocortisone 12 mg, Ara-C 24 mg
			D+8,+15,+22,+29
	End reinduction	MRD–/CNS–	Methotrexate 5,000 mg/m <sup>2</sup> IV qday D 1
			Nelarabine 650 mg/m <sup>2</sup> IV qday D 8–12
4 years 8 months	Matched sibling BMT		D –14, –13, –12 Cranial XRT 600 cGy qday
			D –8 to –6 TBI 200 cGy bid
			D –5, –4 thiotepa 5 mg/kg IV qday
			D –3, –2 cyclophosphamide 60 mg/kg IV qday
			D –2 start tacrolimus PO
			D zero BM infusion
			D +1,+3,+6 methotrexate 5 mg/m <sup>2</sup> IV qday
			Off tacrolimus D+98
	D+31,+59,+87	MRD–	
	D+176 – Dx recurrence	MRD+ 0.06%	
	D+195	MRD+ 0.08%	
5 years 3 months	Matched sibling DLI		Day –1 cyclophosphamide 50 mg/kg IV qday
			Day zero 1 × 10 <sup>6</sup> PB CD3+ cells/kg
	D+31	MRD+ 0.085%	
	D+70	MRD–	
	D+101	MRD+ 0.048%	
	Reinduction		Reinduction as per AALL07P1 Block 1
			IT cytarabine 70 mg D+1
			Vincristine 1.5 mg/m <sup>2</sup> IV qday D+1,+8,+15,+22
			Doxorubicin 60 mg/m <sup>2</sup> IV qday D+1
			Prednisone 20 mg/m <sup>2</sup> PO BID D 1–28
			Bortezomib 1.3 mg/m <sup>2</sup> IV qday D+1,+4,+8,+11
			Peg-asparaginase 2,500 IU/m <sup>2</sup> IV qday D+2,+8
			(peg-asp D+15,+22 doses held for LFTs)
			IT MTX 12 mg qday D+20*,D+29
			*-D+15 IT delayed because of uncertain tap
5 years 8 months	Pre-2nd transplant	MRD+ 0.02%	
	Parental haploidentical BMT		D –6 to –3 busulfan 32 mg/m <sup>2</sup> IV q6hr
	(KIR B haplotype)		(adjust to AUC 900–1,400 micro mol/l*min)
			D –2, –1 cyclophosphamide 50 mg/kg IV qday
			D zero haplo BM infusion
			D +3,+4 cyclophosphamide 50 mg/kg IV qday
			D +5 start tacrolimus, MMF
			IT MTX 10 mg qday weekly ×5, starting D+45
			Off MMF D+35
			Off tacrolimus D+155
	D+28	MRD–	
	D+59,+90,+139,+178,+286	MRD–	
	D+425 – Dx recurrence	MRD+ 0.06%	
	D+433	MRD+ 0.09%	
6 years 11 months	Parental haplo DLI #1		Day –1 cyclophosphamide 50 mg/kg IV qday
			Day zero 1 × 10 <sup>6</sup> BM CD3+ cells/kg
	D+33	MRD+ 0.035%	
	D+77,+120,+200	MRD–	
	D+373 – Dx recurrence	MRD+ 0.07%	
8 years 0 months	Parental haplo DLI #2		Day –1 cyclophosphamide 50 mg/kg IV qday
			Day zero 1 × 10 <sup>6</sup> BM CD3+ cells/kg
	D+37	MRD+ 0.015%	
	D+65,+96,+156, +267, +312, +429	MRD–	

MTX, methotrexate; Ara-C, cytarabine; XRT, radiation; cGy, centigray; BM, bone marrow; LFT, liver enzymes; AUC, area under the curve.

sibling transplant or DLI and no signs of any organ toxicity, the patient underwent myeloablative haploidentical BMT from the patient's mother.

She initially received a single course of standard four drug induction plus bortezomib based on AALL07P1 block 1,[12] with end induction MRD of 0.02%. She then underwent haploidentical BMT from her mother with a favorable KIR B haplotype [13] at 5 years 9 months of age. Preparative regimen was busulfan and cyclophosphamide, followed by posttransplant cyclophosphamide, mycophenolate mofetil (MMF), and tacrolimus as per an institutional protocol.[14] She received weekly IT MTX  $\times 5$  for CNS prophylaxis. Patient's ANC was  $> 500/\mu\text{l}$  by D+24 posthaplo-BMT. As per an institutional regimen, MMF was stopped on D+35 and tacrolimus was weaned to stop on D+125, as the patient was without clinical evidence of GVHD. She had 100% BM haplo donor chimerism at first measurement on D+29 posthaplo-BMT and all subsequent measurements. She returned to school on D+253. She was CSF negative and BM MRD negative on all posthaplo-BMT studies between discharge after haplo-BMT until D+425, when she had BM MRD 0.06%.

She received 50 mg/kg cyclophosphamide and haplo-DLI on D+449. DLIs consisted of unmanipulated peripheral mononuclear cells dosed according to CD3 content. BM MRD was undetectable by D+77 posthaplo-DLI #1 (D+524 s/p haplo-BMT), and remained negative until D+373 posthaplo-DLI#1 (D+878 s/p haplo-BMT), when she had a second posthaplo BM MRD positivity of 0.07%. She then received a second course of 50 mg/kg cyclophosphamide with haplo-DLI on D+841 posthaplo transplant, once again achieving MRD negative status by D+65 posthaplo-DLI#2 (D+906 posthaplo-BMT), and remains without any evidence of disease on serial subsequent BM evaluations (currently 41 months posthaplo-BMT). She tolerated both DLIs without GVHD or any other complications. Except for planned overnight admissions for both infusions of haplo donor lymphocytes, she has had no other hospitalizations and has attended school continuously without limitations and a performance score of 100%.

## DISCUSSION

This unique case illustrates several intriguing points for consideration. It suggests that it is possible to get clinically effective GVL from haplo-DLI even in the absence of post-haplo-BMT clinical GVHD. It further suggests that successive DLI can be effective even when disease recurs after first DLI, even without escalation of the DLI dose. The ready availability of a familial haplo donor (vs. alternative nonmatched unrelated donors) affords the logistical advantage of rapid preemptive DLI immediately upon detection of disease recurrence, as well as the option of serial escalation of DLI dosing.[5]

The indolent course of disease in this particular patient is in marked contrast to the usual rapid progression among hematologic malignancy HSCT patients who relapse.[15] It may be that the indolent course of recurrence in this case (with first MRD recurrence  $> 1$  year after transplant, and only very slowly rising MRD after detection) is itself an indicator of significantly but not completely effective GVL in the original graft that would be most likely to be amenable to a boost with DLI. Alternatively, it is possible that GVL was sufficient such that the de-

tectable MRD might have spontaneously resolved even had DLI been deferred, or that the single cyclophosphamide dose alone was sufficient to reinduce remission. The effectiveness of the DLI may have had contributions from the NK as well as the T-cell fractions, as the maternal haplo donor was selected for a favorable KIR B haplotype.[13] On balance, given emerging suggestion of the value of preemptive DLI prior to frank relapse,[6] and the ready availability of DLI from a familial haplo donor, in cases where disease recurrence is caught while still at MRD levels, serial DLI may be a reasonable, potentially effective and well-tolerated first response in lieu of experimental agents or third transplant. Our institution monitors MRD every 30 days posttransplant  $\times 4$ , then D+180, D+270, D+365, and annually, but more systematic study is needed to establish evidence based standards.

The unique convergence of factors that conferred disease control even in the absence of GVHD is yet unknown. As the experience with the treatment of hematologic malignancies with haploidentical HSCT [16] and DLI [5] grows, more cases like this one may be identified that will enable identification of those factors predictive of the tolerability and effectiveness of serial DLI as a disease control strategy.

## ACKNOWLEDGMENT

This work was supported by National Institutes of Health, National Cancer Institute grant P30 CA006973. J.S.H. is a recipient of a Young Investigator Award from the Alex's Lemonade Stand Foundation and was supported by NIH T32 CA60441.

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