Published in final edited form as:

Pediatr Blood Cancer. 2016 July ; 63(7): 1279–1282. doi:10.1002/pbc.25971.

Persistent multi-year control of relapsed T-cell Acute Lymphoblastic Leukemia with successive donor lymphocyte infusions: a case report

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Abstract

There are few therapeutic options for patients with T-ALL who have recurrent disease after initial matched sibling hematopoietic stem cell transplantation. While a second HSCT from a haploidentical donor offers the conceptual possibility of greater graft-vs-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 girl in whom second haploidentical HSCT, followed by successive donor lymphocyte infusions (DLI) in response to minimal residual disease (MRD) reemergence, has led to three-plus years of ongoing disease control without GVHD and excellent quality of life.

Keywords

T-cell acute lymphoblastic leukemia; haploidentical bone marrow transplant; donor lymphocyte infusion; relapse

Introduction

Relapse of T-cell Acute Lymphoblastic Leukemia (T-ALL), especially after matched sibling bone marrow transplant, 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 vs leukemic effect (GvL) through HLA-haploidentical T cell-replete hematopoietic stem cell transplantation (haplo-HSCT), with post-transplantation high-dose cyclophosphamide to limit graft vs host disease [4]. The

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Conflict of Interest Statement

The authors report no relevant conflicts of interest.

enhanced GvL conferred by establishment of a haploidentical graft further makes possible subsequent use of haploidentical donor lymphocyte infusions (haplo-DLI) 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 girl with multiply-recurrent T-ALL for whom second haplo-BMT and successive haplo-DLIs are providing persistent (currently 3 years 5 months post-transplant) disease control with minimal side effects and excellent quality of life.

Case History

Our patient initially presented at the age of four years two months (Table I) with a WBC 703K/ μ L, ultimately diagnosed as CD1a–, cCD3+(bright), sCD3–, CD5+(mod), CD8+(mod) T-ALL with TNTC WBC in CSF (CNS3 disease). She was started on induction as per Children's Oncology Group (COG) T-ALL protocol (AALL0434) [7] and was CNS negative and 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 this patient's case 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 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 four years nine months of age (Table I). She engrafted (ANC > 500/ μ L) on D+21 post-transplant. 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 post-transplant 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 one month later (0.085%). Because she had no GVHD in response to matched 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 five years nine months of age. Preparative regimen was busulfan and cyclophosphamide, followed by post-transplant cyclophosphamide, MMF, and tacrolimus as per an institutional protocol

[14]. She received weekly IT MTX x5 for CNS prophylaxis. The patient's ANC was > 500/ μ L by D+24 post-haplo-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% bone marrow haplo donor chimerism at first measurement on D+29 post-haplo-BMT and all subsequent measurements. She returned to school on D+253. She was CSF negative and BM MRD negative on all post-haplo-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. Donor lymphocyte infusions consisted of unmanipulated peripheral mononuclear cells dosed according to CD3 content. Bone marrow MRD was undetectable by D+77 post-haplo-DLI #1 (D+524 s/p haplo-BMT), and remained negative until D+373 post-haplo-DLI#1 (D+878 s/p haplo-BMT), when she had a second post-haplo BM MRD positivity of 0.07%. She then received a second course of 50 mg/kg cyclophosphamide with haplo-DLI on D+841 post-haplo transplant, once again achieving MRD negative status by D+65 post-haplo-DLI#2 (D+906 post-haplo-BMT), and remains without any evidence of disease on serial subsequent BM evaluations (currently 41 months post-haplo-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 non-matched 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 detectable 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, potentially well tolerated first response in lieu of experimental agents or third transplant. Our institution monitors MRD every 30 days post-transplant x4, 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 experience with 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.

Acknowledgments

Funding Source:

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. This work was also supported by the Kimmel Cancer Center Core grant (P30 CA006973).

Abbreviations

ANC	Absolute neutrophil count
BM	Bone marrow
BMT	Bone marrow transplant
DLI	Donor lymphocyte infusion
GVHD	Graft vs host disease
GVL	Graft vs leukemia effect
HSCT	Hematopoietic stem cell transplant
MMF	mycophenolate mofetil
MRD	Minimal residual disease
T-ALL	T-cell acute lymphoblastic leukemia
TNTC	Too Numerous to Count

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Table I

Timeline of disease course, interventions, and disease assessments

<u>Age</u>	<u>Event</u>	<u>Bone Marrow</u>	<u>Treatment</u>
4 yr 2 mo.	Diagnosis T-ALL / CNS3	90% blasts	Induction as per COG AALL0434
4 yr 3 mo.	End Induction CNS neg	MRD+ 0.016%	Consolidation as per COG AALL0434 Arm C
4 yr 6 mo.	End Consolidation CNS3 relapse	MRD+ 0.02%	reinduction as per TACL-2008-002, dose level 2
			nelarabine 650 mg/m ² IV qday D 1–5
			etoposide 100 g/m ² IV qday D1–5
			cyclophosphamide 330 mg/m ² IV qday D 1–5
			IT MTX 12mg, hydrocortisone 12mg, Ara-C 24 mg
			D+8,+15,+22,+29
	End reinduction	MRD– / CNS –	Methotrexate 5,000 mg/m ² IV qday D 1
			nelarabine 650 mg/m ² IV qday D 8–12
4 yr 8 mo.	Matched Sibling BMT		D –14,–13,–12 Cranial XRT 600 cGy qday
			D –8 to –6 TBI 200 cGy bid
			D –5,–4 thiotepa 5mg/kg IV qday
			D –3,–2 cyclophosphamide 60mg/kg IV qday
			D –2 start tacrolimus PO
			D zero BM infusion
			D +1,+3,+6 methotrexate 5mg/m ² IV qday
	D+31,+59,+87	MRD–	off tacrolimus D+98
	D+176 – Dx recurrence	MRD+ 0.06%	
	D+195	MRD+ 0.08%	
5 yr 3 mo.	Matched Sibling DLI		Day–1 cyclophosphamide 50 mg/kg IV qday
			Day zero 1×10^6 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 ² IV qday D+1,+8,+15,+22
			doxorubicin 60 mg/m ² IV qday D+1
			prednisone 20 mg/m ² PO BID D 1–28
			bortezomib 1.3 mg/m ² IV qday D+1,+4,+8,+11
			peg-asparaginase 2,500 IU/m ² IV qday D+2,+8
			(peg-asp D+15,+22 doses held for LFTs)
			IT MTX 12mg qday D+20*,D+29
			*–D+15 IT delayed because of uncertain tap
	Pre-2nd transplant	MRD+ 0.02%	
5 yr 8 mo.	Parental Haploidentical BMT		D –6 to –3 busulfan 32 mg/m ² IV q6hr

Age	Event	Bone Marrow	Treatment
	(KIR B haplotype)		(adjust to AUC 900-1400 micro mol/L*min)
			D -2,-1 cyclophosphamide 50 mg/kg IV qday
			D zero haplo BM infusion
			D +3,+4 cyclophosphamide 50mg/kg IV qday
			D +5 start tacrolimus, MMF
			IT MTX 10mg qday weekly x5, starting D+45
	D+28	MRD-	off MMF D+35
	D+59,+90,+139,+178,+286	MRD-	off tacrolimus D+155
	D+425 – Dx recurrence	MRD+ 0.06%	
	D+433	MRD+ 0.09%	
6 yr 11 mo.	Parental Haplo DLI #1		Day -1 cyclophosphamide 50mg/kg IV qday
			Day zero 1×10^6 BM CD3+ cells/kg
	D+33	MRD+ 0.035%	
	D+77,+120,+200	MRD-	
	D+373 – Dx recurrence	MRD+ 0.07%	
8 yr 0 mo.	Parental Haplo DLI #2		Day -1 cyclophosphamide 50mg/kg IV qday
			Day zero 1×10^6 BM CD3+ cells/kg
	D+37	MRD+ 0.015%	
	D+65,+96,+156, +267, +312	MRD-	

Additional abbreviations: MTX – methotrexate. Ara-C - cytarabine. XRT – radiation. cGy – centigray. BM – bone marrow. LFT – liver enzymes. AUC – area under the curve.