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Escalated dose donor lymphocyte infusion treatment in patients with primary immune deficiencies after HSCT with reducedintensity conditioning regimen

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Escalated Dose Donor Lymphocyte Infusion Treatment in Patients with Primary Immune Deficiencies After HSCT with Reduced-Intensity Conditioning Regimen

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Abstract

Objective/Background: **Mixed chimerism is a major concern after allogenic hematopoietic stem cell transplantation (HSCT) using a reduced-intensity conditioning (RIC) regimen in primary immunodeficiencies (PIDs). A donor lymphocyte infusion (DLI) escalating dose regimen has been developed with the aim of reducing toxicity while preserving efficacy. However, the graft-versus-host disease (GvHD) development remains the most common and adverse effect of DLI and continues to be a limiting factor in its application, especially nonmalignant diseases such as PIDs. We prospectively evaluated PID patients after HSCT using RIC in Children s Medical Center, who were candidates for an escalating dose of DLI for MC from 2016 to 2018.**

Methods: **With the median follow-up of 16.4 months, 12 patients (nine males and three females) with a median age of 3.72 years received DLI. The median number of DLI was 3.2 (range, 1−5), the maximum and total dose of DLIs administered per patient were 3.6×10^7 (range, 1−5) cells/kg $CD3^+$ and 9.3×10^7 (range, 1−15) cells/kg $CD3^+$ cells, respectively.**

Results: **Median donor chimerism at baseline before the DLIs was 41% (range, 11−73%), patients received DLIs at a median of 105 (range, 37−230) days and 52 (range, 3−168) days after the HSCT and onset of the MC, respectively. At the final assessment, six (54.5%) patients improved after DLIs at a median of 47.3 days.**

Conclusion: **PID patients may benefit from DLI with an escalating dose regimen, but the GvHD development remains a concern during the DLI, and the optimum dose and frequency must be standardized.**

Keywords: Donor lymphocyte infusion, Hematopoietic stem cell transplantation, Mixed chimerism, Primary immunodeficiency

1. Introduction

Primary immunodeficiencies (PIDs) are a heterogeneous group of inherited disorders characterized by impairment of innate or adaptive immunity, which results in high susceptibility to infection and commonly leading to lethal complications [1]. Hematopoietic stem cell transplantation (HSCT), despite improvements in supportive care approaches, is currently the only curative procedure for the majority of PIDs [2]. HSCT was restricted initially to severe combined immunodeficiency (SCID) patients [3]. Now there is an expanding list of other PIDs such as chronic granulomatous disease (CGD), leukocyte adhesion deficiency (LAD), major histocompatibility complex class II deficiency

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(MHC-II def.), and defects in cytokine signaling pathways [1].

Many PID children have significant comorbidities at the time of HSCT. The conventional myeloablative preparation may be associated with significant treatment-related toxicity and also a long-term consequence [4]. The use of reduced-intensity conditioning (RIC) enables HSCT in patients with preexisting comorbidities that have precluded it by using conventional approaches. Using RIC for PIDs is now the treatment of choice in many institutions, especially in the presence of severe infections [5,6]. Mixed chimerism (MC) and graft loss occur in a proportion of PID children who receive RIC regimen for HSCT [7]. Moreover, MC, a common condition following the RIC–HSCT, has been under survey for ambiguity surrounding its power to resolve symptoms of the underlying disease [8].

While MC is likely to correct the phenotypic expression of most PID children, the donor lymphocyte infusion (DLI) used to increase donor chimerism or second HSCT procedures may be required [5,6]. The first clinical trial that demonstrated DLI efficacy was reported in relapsing chronic myeloid leukemia (CML) patients post-HSCT by Kolb et al. [9]. DLI then has broadly been used after allogenic HSCT either to enhance donor chimerism after non-myeloablative conditioning/RIC or to treat disease relapse [10]. However, the time and dosage of DLI that can be administered with relative safety, particularly in the reduced-intensity setting, remain defined; its early administration, in combination with persistent host antigen-presenting cells, has an impact on graft-versus-host disease (GvHD) development, which remains the most common and adverse DLI effect [11,12] as well as continuing to be a limiting factor in its application, especially in nonmalignant diseases.

The escalating dose approach has been developed with the aim of reducing toxicity while preserving efficacy, and relies on repeated donor T-cell infusions. It starts from a low T-cell dose and increases at regular intervals, until the patient gets GvHD-free and does not achieve the predefined therapeutic target [13,14]. In this study, we evaluate the efficacy of a graded dosing regimen of $CD3^+$ cells in correcting MC, as well as minimizing the DLI-induced GvHD risk in PID patients receiving HSCT after RIC.

2. Patients and methods

2.1. Study design and data collection

This prospective study evaluates the result of escalating doses of DLI as an intervention for MC in PID patients treated with HSCT at Children's Medical Center from 2016 to 2018. The institutional review board approved this study. A signed consent was obtained from the children's parents, who were the treatment modality's candidates.

2.2. Patient characteristics

Of total 46 PID patients who received HSCT, 12 (26%) were candidates for DLI from the original stem cell donor: five patients with SCID, two with LAD, two with CGD, two with MHC II def., and one with Wiskott–Aldrich syndrome. The majority of the patients were boys (75%), with a median age of 3.72 (range, 0.2–14) years.

2.3. Conditioning regimen protocol

All patients received an equal RIC regimen: a combination of Fludarabine (Emcure – baxter; Delhi, India) 30 mg/m^2 intravenously (IV) for 5 consecutive days (Days −8 to −4), Melphalan (Zytotoxisch, Germany) 70 mg/m^2 IV for 2 consecutive days (Days −3 and −2), and rabbit antihuman thymocyte immunoglobulin (Thymoglobulin 5 mg/mL; Genzyme Polyclonal S.A.S, France) 2.5 mg/kg for 4 consecutive days (Days −4 to −1).

2.4. GvHD prophylaxis regimen

GvHD prophylaxis at the initial HSCT time was performed with Cyclosporin A (Novartis, US) 1.5 mg/kg daily IV starting on Day −1, then 3 mg/kg from Day −7, plus Methylprednisolone (Pfizer Oncology, US) 1 mg/kg/day IV starting on Day −5 (Day −5 to 7), then 0.5 mg/kg/day to Day +14. The CsA level was monitored twice weekly (therapeutic range, 100–250 ng/mL).

2.5. Transplant characteristics

Patients received G-CSF (McMillan, UK)–mobilized peripheral blood (PB) stem cells from an HLA-matched sibling donor (MSD; $n = 4$), HLA-matched other-related donor (MOD; $n = 7$), and single-locus mismatched unrelated donor (MMUD; $n = 1$) (Table 1).

Neutrophil and platelet (Plt) engraftments were defined when the absolute neutrophil and Plt count, without Plt transfusion support, exceeded 500/μL and 20 × 10^3/μL, respectively, on 3 consecutive days.

2.6. Donor chimerism measurement

Whole blood donor chimerism was generally monitored routinely at Days +15, +30, +60, +90,

Table 1. Donor/Recipient Characteristics and Transplant Details of Patients Undergoing Donor Lymphocyte Infusion for Mixed Donor Chimerism.

Patients#	Sex	Type of disease	Time from diagnosis to transplant s(months)	Age at transplant (years)	Donor characteristics		
					Age (years)	Sex	Relationship/matching
1	M	LAD	18	4.5	17	M	MSD
2	M	CGD	8	2	35	M	MOD
3	M	CGD	21.5	5	7	F	MSD
4	M	SCID	10	1	27	F	MOD
5	M	WAS	3	1.3	8	M	MOD
6	M	SCID	1.5	0.2	38	F	MOD
7	F	LAD	6	14	21	M	MSD
8	M	SCID	2	0.3	9	F	MSD
9	F	MHC-II Def.	6	12	30	F	MOD
10	F	SCID	4	0.5	21	M	MOD
11	M	MHC-II Def.	2	14	10	F	MOD
12	M	SCID	4	0.8	25	F	MMUD

Note. CGD = Chronic granulomatous disease, F = female; LAD = leukocyte adhesion deficiency; M = male; MHC-II Def. = major histocompatibility complex II deficiency; MMUD = single-locus mismatched unrelated donor; MOD = HLA-matched other-related donors; MSD = HLA-matched sibling donors; PID = primary immunodeficiency; SCID = severe combined immunodeficiency; WAS = Wiskott–Aldrich syndrome.

+180, +360, and +2 years after HSCT but weekly after the occurrence of MC. In patients with opposite-sex donors, chimerism was monitored by fluorescent in situ hybridization with X and Y chromosome probes. In patients with same-sex donors, donor chimerism was monitored with PCR amplification for one highly variable short tandem repeats, which was followed by capillary electrophoresis for size discrimination, to determine the various alleles at 16 individual loci as well as specific X and Y chromosomes products. All whole blood chimerism studies were performed in the clinical genetics laboratory. The presence of <95% of donor cells in the recipient's bone marrow or PB was defined as MC [7].

2.7. DLI and treatment outcomes evaluation

Patients with PIDs were treated with the escalating DLI dose when their whole blood donor chimerism, despite the immunosuppression's discontinuation, dropped to less than 75%. PB lymphocytes were collected by an Optia continuous apheresis device using CMNC program from the same donor used for the initial transplant and infused into the recipient without any conditioning. The collected cells were aliquot and cryopreserved, except the first dose, which was given freshly to the patient on the same collection day. The escalating $CD3^+$ cell dose was used starting from $1–2 \times 10^7$ cells/kg, depending on the physician's decision. The additional DLI was administered at 3 or 4 weeks of intervals in increasing doses (1×10^7 cells/kg per dose) until either GvHD or a stabilization/reversal of MC was observed, without exceeding five DLI in total. The response to DLI was defined as the donor chimerism increase of at least 20% after DLI. Complete response to DLI was defined as the donor chimerism of ≥95%. Otherwise, a <20% increase or any decline in donor chimerism was considered as no DLI response. Stabilized chimerism was defined if the donor chimerism increased < 20% but not declined after DLI [7,15]. Acute and chronic GvHD (aGvHD and cGvHD) were diagnosed and graded using standard criteria [16,17].

2.8. Statistical analysis, data collection, and statistical methods

Data were analyzed using the Statistica 9.0 software package (StatSoft, Tulsa, OK, USA). Results are presented as medians with ranges for quantitative variables, number and percentage for qualitative variables, and p values where appropriate. Significance was set at $p \leq 0.05$. Variables examined were: underlying diseases, age at HSCT, time from diagnosis to HSCT, donor characteristics (age, relation, HLA matching, ABO blood groups, and sex), age at first DLI, chimerism at Day +15, time for first loss of donor chimerism after HSCT, the time between MC and first DLI, the time between first DLI and HSCT, MC baseline before first DLI, peak chimerism after DLI, number of DLIs, the first dose, maximum dose, total $CD3^+$ T-cell dose ($\times 10^7$ cell/kg), GvHD, and infection after DLI.

3. Results

3.1. Patients, donors, and engraftment characteristics

A total of 46 PID patients received HSCT, 12 children were managed with DLI for MC after PB HSCT, the median age of donors was 21 (range, 7–38) years, the median number of infused white

blood cells, mononuclear cells, $CD34^+$ cells, and $CD3^+$ cells was 9.9×10^8 cells/kg, 8×10^8 cells/kg, 6.2×10^6 cells/kg, and 337×10^6 cells/kg, respectively. Engraftment occurred in all patients; the median times to neutrophils and Plt engraftments were 12 (range, 10–14) days and 16 (range, 15–18) days, respectively.

Full and mixed (a median of 37% [range, 17–49%]) donor chimerisms were seen in eight (66.6%) patients and four (33.3%) patients on Day 15 post-transplant, respectively.

3.2. General characteristics of DLIs

The first DLI infusion dose was 1×10^7 $CD3^+$ cells/kg in seven (58.3%) patients, while five (41.7%) patients received 2×10^7 $CD3^+$ cells/kg. The median number of DLI was 3.2 (range, 1–5), the maximum and the total dose of DLIs administered per patient was 3.6×10^7 (range, 1–5) cells/kg and 9.3×10^7 (range, 1–15) cells/kg, respectively. In total, out of 12 patients, four (33.3%) received four DLIs, and the rest, every two (16.67%) patients received 1, 2, 3, and 5 DLIs, respectively.

3.3. Chimerism response after DLI

Donor chimerism improvement after DLIs was analyzed in 11 patients because one of the patient died before assessing the level of chimerism. The details regarding chimerism and DLI response is displayed in Table 2. Median donor chimerism at baseline before the DLIs was 41% (range, 11–73%); patients received DLIs at a median of 105 (range, 37–230) days and 52 (range, 3–168) days after the HSCT and after the onset of the MC, respectively. At the last assessment, six (54.5%) patients showed improvement after DLIs at a median of 47.3 (range, 23–110) days. In four (36.4%) patients, complete donor chimerism was achieved, while the DLI response was stabilized in two (18.2%) patients, with a median of 44% (range, 35–53%). By contrast, five (45.4%) patients had no improvement in donor chimerism after DLIs and continued with mixed donor chimerism at a median of 29% (range, 10–42%).

3.4. Factors affecting the response to DLI

We classified patients as the DLI responders (at least 20% MC improvement after DLI) and non-responders (MC non-increase or continuous decrease) to analyze the factors affecting the DLI response. No significant role of the examined variables, except the donor chimerism level at Day + 15 post-HSCT and aGvHD (p values: 0.0283 and 0.0084, respectively), were found in the DLI response. Although the time interval between transplant and initial MC was lower in the responder group, it was not significant between the two groups. Table 3 illustrates the

Table 2. Donor Chimerism and Overall Response after DLI.

Patients #	Chimerism in Day + 15	Chimerism before first DLI	Chimerism in last follow-up	Number of DLIs	Time between HSCT and first DLI	Days from DLI to aGVHD	Follow-up time (months)
1	95	31	10	4	210	—	23
2	34	34	99	1	52	12	26
3	49	11	99	2	106	105	24
4	98	58	35	4	230	—	24
5	95	48	49	5	104	—	15
6	99	73	20	4	90	—	15
7	100	47	99	2	131	66	8
8	17	23	53	3	37	60	8
9	99	37	18	5	57	—	8
10	100	68	42	3	92	—	15
11	48	22	35	4	42	84	14

Note. aGvHD = Acute graft-versus-host disease; DLI = donor lymphocyte infusion; HSCT = hematopoietic stem cell transplantation.

Table 3. T-Cell DLI for Mixed Donor Chimerism: Characteristics for Responders Compared to Non-Responders.

	All patients ($n = 11$)	Responders ($n = 6$)	Non-responders ($n = 5$)	p
Donor chimerism at Day + 15	76	57.8	97.4	**0.028**
Mean first $CD3^+$ cell dose ($\times 10^7$ cells/kg)	1.5	1.3	1.6	**0.42**
Day post-transplant for first DLI	104.6	76.3	138.6	**0.10**
Day post-transplant for initial mixed chimerism	49.7	37.5	64.4	**0.07**
Day between chimerism drop and first DLI	52.1	38.7	68.2	**0.32**
Last chimerism before starting DLI (%)	41	34.955	48.4	**0.33**
aGvHD following DLI	5	5	0	**0.008**

Note. aGvHD = Acute graft-versus-host disease; DLI = donor lymphocyte infusion. The significance of data is shown in Bold font.

characteristics of DLI responders compared with non-responders. Although not reaching the significance level, 75% of patients who received HSCT from MSD were responders to the escalated DLI dose versus 42.8% of MOD recipients.

3.5. DLI-associated complications

3.5.1. GvHD after DLI

Five (45.5%) patients developed Grade II–IV aGvHD after DLIs. Involvement of the skin ($n = 2$), liver ($n = 2$), and both organs ($n = 1$) was found in patients with GvHD. The maximum aGvHD rate in children with CGD, SCID, LAD, and MHC II deficiency was 100%, 40%, and 50% of each, respectively. The aGvHD grade II-IV was observed after HSCT and the first DLIs on median 122 (range, 42–211) days and 65 (range, 12–105) days, respectively. All patients who developed aGvHD were responders, of which three achieved full donor chimerism (FDC). The MOD and MSD HSCTs were used in two (40%) patients and three (60%) patients, respectively. The aGvHD resolved in all affected patients after DLI was stopped and the use of 1 mg/kg prednisolone.

Limited cGvHD was noted in one (8.3%) patient with SCID, receiving MOD transplants, with a history of aGvHD after HSCT.

3.5.2. Risk factors for aGvHD after DLI

We analyzed the results of this study comparing patients who developed aGvHD with those without aGvHD after DLI in PID patients to identify the factors affecting GvHD (Table 4). The chimerism level on Day +15, the last chimerism before starting DLI, and the DLI response had a significance level. The patient's age at DLI and the number of days of post-transplant for the first DLI were different, but did not reach a significance level. After DLI, cytomegalovirus reactivation occurred in three patients (27.3%) that showed an appropriate response to treatment by ganciclovir.

3.6. Treatment outcome

Among 12 patients who received DLIs, 11 (91.6%) patients were alive at a median of 16.4 (range, 8–26) months after DLI. The cause of death was disseminated invasive Bacillus Calmette–Guérin (BCGosis) in one (8.3%) patient with SCID who received HSCT from MMUD. Two patients had MC of less than 20%, but still more than 10%. All 11 patients are healthy and without any sign of PIDs.

4. Discussion

Because of increased reduced-intensity preparative regimens use for non-malignant diseases, mixed donor chimerism is increasingly common in the pediatric HSCT setting [15]. DLI is useful for MC treatment potentially. However, the conventional approach is usually associated with GvHD, which can be severe in many cases. The escalating dose approach has been developed with the aim of reducing toxicity while preserving efficacy [14,15].

Our results showed the efficacy of escalated DLI doses in correcting MC in six (54.5%) PID pediatric patients post-HSCT using the RIC regimen, of which four (>95%) patients achieved FDC, while five (45.5%) did not respond to DLI. It is necessary to note that these results were similar to those of other studies with DLI conventional usage. Haines et al. [15] reported regarding DLI treatment outcomes in MC after a similar RIC regimen in children with

Table 4. T-Cell DLI for Mixed Donor Chimerism: Risk Factors for aGvHD after DLI.

	With aGvHD($n = 5$)	Without aGvHD($n = 6$)	p
Donor type			
MSD	3 (60%)	1 (16.6%)	**0.1553**
MOD	2 (28.5%)	5 (71.5%)	**0.1754**
Sex mismatching	4 (80%)	4 (66.6%)	**0.6385**
Blood group mismatch (ABO)	2 (40%)	3 (50%)	**0.7518**
CMV infections after DLI	1 (20%)	2 (66.7%)	**0.6374**
Response to DLI	5 (100%)	1 (16.6%)	**0.0084**
Patient age at time of DLI (months)	85 ± 79	17 ± 19	**0.0696**
Donor chimerism at Day + 15	50 ± 31	97 ± 2	**0.004**
Day post-transplant for first DLI	74 ± 42	131 ± 71	**0.1503**
Day post-transplant for initial mixed chimerism	39 ± 32	63 ± 53	**0.4080**
Day between chimerism drop and first DLI	39 ± 32	62.7 ± 53.3	**0.2484**
Last chimerism before starting DLI (%)	27 ± 14	52 ± 17	**0.0277**

Note. aGvHD = Acute Graft-versus-host disease; CMV = cytomegalovirus; DLI = donor lymphocyte infusion; HSCT = hematopoietic stem cell transplantation; MOD = HLA-matched other-related donors; MSD = HLA-matched sibling donors. The significance of data is shown in Bold font.

nonmalignant diseases and indicated that donor chimerism increased by >20% in 56% of patients; of these, with 37% achieved FDC, while 44% had no significant chimerism improvement after DLI. In another study, Umeda et al. [18] demonstrated that 50% of pediatric patients with nonmalignant diseases (PID, inherited metabolic disease, bone marrow failure syndrome, or histiocytosis) with MC converted to complete chimerism after DLI. In contrast, based on our previous experience, 80% of pediatric nonmalignant disorders achieved sustained mixed or converted to FDC [19]. This difference in success rate may be due to the type of underlying diseases and conditioning regimen.

Also, these results are with the concordance of many studies comparing the efficacy of escalating DLI with the conventional DLI, which reported that both groups had the same probability of achieving the therapeutic target [14]. Regarding the DLI-induced GvHD risk, in the conventional approach, approximately 40–60% of patients who received DLI developed GvHD [10,20,21]. By contrast, GvHD was much lower in CML patients receiving the escalating doses than in patients treated with a single DLI infusion (10% vs. 44%, $p = .01$), while 60% of patients with non-Hodgkin lymphoma developed GvHD after dose-escalated DLI with 14.7% aGvHD [22].

Fozza et al. [23] reported that 15% of CML patients had Grade II–IV aGvHD after DLI with an escalating dose regimen. Although cell dose did not correlate with aGvHD development, the interval from HSCT to last DLI and male recipients of female donor cells have demonstrated a positive correlation with aGvHD incidence. By contrast, in our study, 45.5% of PID patients developed aGvHD. Risk factors of aGvHD were the level of chimerism at Day +15 because of the better DLI response of the patients with lower donor chimerism, which may be related to earlier initiation of this treatment modality in this situation.

The DLI number and mean total $CD3^+$ dose are significantly lower in the responder group than in the non-responder group. Therefore, it seems that the most DLI response will occur after the initial doses, and there is no significant change in the treatment response with the increasing frequency of DLI.

It appears that patients who responded not only had lower donor chimerism but also a faster drop and received DLI sooner; however, it is difficult to make any interpretation from these data with only a few patients. Also, none of the patients in our study showed signs of PID regardless of DLI response because the DLI stabilized the lymphocyte chimerism and prevented rejection in the non-responder group. We are not able to justify this point because of our restrictions on the lymphocyte chimerism analysis.

5. Conclusions

Despite the small number of patients, our study results demonstrate that using DLI with an escalating dose regimen is successful in correcting or stabilization MC in pediatric patients with PIDs. The response rate peaks were seen after the initial doses. The lower the chimerism level, the better the DLI response, especially on Day +15, so it is recommended to closely monitor the chimerism for several months after RIC-based HSCT in PID patients.

However, the DLI optimum dose and frequency must be standardized. A multicenter study with a large sample size and analytical analysis needs to define the safe donor T-cell dose and the optimal administration time.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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