Donor leucocyte infusion

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ABSTRACT

Donor-derived cellular therapies play a pivotal role in optimizing outcomes after allogeneic hematopoietic stem-cell transplantation (HCT). This article reviews three key post-transplant interventions: donor lymphocyte infusion (DLI), hematopoietic stem-cell boost, and mesenchymal stromal cell (MSC) infusion. DLI remains a cornerstone strategy for enhancing graft-*versus*-leukemia effects, preventing or treating relapse, and promoting immune reconstitution, while also carrying risk of graft-*versus*-host disease. Stem-cell boosts, typically performed using $CD34^+$ selected products, offer an effective approach for managing poor graft function or mixed chimerism without significantly increasing alloimmune toxicity. MSC infusion has emerged as a promising immunomodulatory therapy for steroid-refractory graft-*versus*-host disease and for facilitating engraftment, owing to its anti-inflammatory and tissue-regenerative properties.

Keywords: Lymphocyte Transfusion. Graft *vs* Host Disease. Mesenchymal Stem Cells.

INTRODUCTION

Since the 1990s donor leucocyte infusion (DLI), has been used for the prevention and treatment of relapse after HCT, to the reversal of mixed chimerism particularly in non-malignant diseases after reduced-intensity conditioning, and as an adjuvant therapy for persistent viral infections[1,2].

Several strategies involving donor T cell manipulation have been developed to enhance the graft-*versus*-leukemia (GvL) effect while minimizing graft-*versus*-host disease (GvHD), such as activation of specific cell subsets with cytokines or growth factors, selection, and expansion of T cell subpopulations, infusion of NK cells, among others. Nevertheless, unmanipulated DLI, dosed based on the number of $CD3^+$ T cells, remains the standard approach across centers[3,4].

FACTORS INFLUENCING DONOR LEUCOCYTE INFUSION RESPONSE

- Minimal residual disease (MRD) positivity and decreasing donor chimerism are risk factors for relapse[1,5];

- Disease sensitivity to DLI: high in chronic myeloid leukemia (CML), myelofibrosis, and indolent non-Hodgkin lymphoma; intermediate in acute myeloid leukemia (AML), myelodysplastic syndrome, myeloma, and Hodgkin lymphoma; and low in acute lymphocytic leukemia and aggressive lymphomas[1];
- Donor-receptor human leukocyte antigen (HLA) disparities: inversely associated with required DLI dose[1];
- Graft source and manipulation: higher DLI doses are tolerated after bone marrow or *in-vivo* T-depleted graft (*e.g.*, with antithymocyte globulin or alemtuzumab), whether for prophylactic, pre-emptive or therapeutic purposes[1];
- DLI schedule: escalating dose and intervals (Table 1);

Table 1. Donor leucocyte infusion schedule according to indication, timing, and donor type.

DLI	Timing for the first dose	MRD (CD3/kg)	MUD (CD3/kg)	MMUD/Haplo (CD3/kg)	Number of doses	Second to fourth doses	Interval between doses
Prophylactic *If there are no signs of GvHD*	Three months *If* ex-vivo *TCD and any risk*	1×10^5/kg	1×10^5/kg	1×10^5/kg	1–3	0.5–1 log increase*	6–8 weeks
	Six months *If no* ex-vivo *TCD and HR disease*	1×10^6/kg	1×10^6/kg	5×10^5/kg	1–3	0.5–1 log increase*	6–8 weeks
Pre-emptive *If there are no signs of GvHD*	Three months	$1–5 \times 10^5$/kg	1×10^5/kg	1×10^5/kg	1–4*	0.5–1 log *	4–6 weeks
	Six months	$1–3 \times 10^6$/kg	1×10^6/kg	1×10^6/kg	1–4*	0–5-1 log *	4–6 weeks
Therapeutic	After systemic therapy	1×10^7/kg	1×10^7/kg	1×10^6/kg	1–4	Increase 1 log max 1×10^8/kg	4–6 weeks
G-DLI + CsA# *If no GvHD*	D+21, D+35 and D+60	-	-	1×10^6/kg 5×10^6/kg	1 2	Increase 0.5 log *if no GvHD*	14 to 25 days

DLI: donor leucocyte infusion; MRD: minimal residual disease; MUD: matched unrelated donor; MMUD: mismatched unrelatad donor; HAPLO: haploidentical; GvHD: graft-*versus*-host disease; TCD: T cell depletion; HR: risk disease; CsA: cyclosporine; *chimerism/MRD/GvHD guided; #DLI granulocyte-stimulating factor (G-CSF)-mobilized, keeping cyclosporine until D+60 and then start tapering over four weeks[17]. Source: modified from Pagliuca S, 2024[1].

- Combination with specific targeted or immunomodulatory drugs (*e.g.*, hypomethylating agents, tyrosine kinase inhibitors, blinatumomab, interferon, granulocyte-macrophage colony-stimulating factor): may enhance efficacy but require close monitoring for toxicity and dose adjustment[1];
- HLA loss by leukemic cells (in 10–30% of relapses after HLA-mismatched HCT): renders DLI ineffective and increases GvHD risk[6]. Molecular HLA typing is recommended before DLI[1].

SOURCE OF DONOR LEUCOCYTE INFUSION

- Conventional DLI: unstimulated apheresis. The first dose is usually given fresh, and subsequent aliquots are cryopreserved. It is worth noting that cryopreservation reduces lymphocyte effect[1];
- DLI collected after mobilization with granulocyte colony-stimulating factor (G-DLI), usually at the same time of stem cell collection. It may enhance the GvL activity without increasing the risk of GvHD[7];
- Fresh whole blood DLI: collected in small aliquots from the donor's peripheral blood without apheresis, counted e infused[8].

INDICATIONS FOR DONOR LEUCOCYTE INFUSION[1,9–12]

Prophylactic donor leucocyte infusion

- After *ex-vivo* T-depletion grafts, to restore GvL effect and reduce relapse risk;
- Leukemias with very high-risk cytogenetic and molecular alterations;

- Diseases that have failed more than two lines of treatment;
- Positive MRD pre-HCT or disease status ≥ second complete remission;
- Second HCT, after immunosuppressor suspension (if GvHD is absent by D+60);
- Previous rituximab for Epstein Barr virus reactivation or post-transplant lymphoproliferative disease[13–16];
- In general, it starts at least ≥ 90 days after HCT (accordingly disease *versus* GvHD risks);
- Early administration of G-DLI after HCT for high-risk leukemia[17,18].

Preemptive donor leucocyte infusion

- Mixed chimerism (for non-malignant or malignant diseases);
- Persistent or recurrent MRD;
- Clinical option in severe viral infections.

Therapeutic donor leucocyte infusion

- Hematological and/or extramedullary relapse.

PREREQUISITES FOR DONOR LEUCOCYTE INFUSION[12]

- Resolution of tissue damage and inflammatory conditions (severe infections or endothelitis);
- No systemic immunosuppressive medications for at least three to six weeks (may be longer in the setting of mismatched donor transplantation).

Exceptions:

- In high-risk disease, early DLI infusion may be considered even if the patients are still on immunosuppression;
- Therapeutic DLI may be offered earlier;
- Absence of active acute and chronic GvHD;
- No prior clinically significant GvHD;
- No graft rejection (loss of donor chimerism).

CLINICAL DATA SUPPORTING DONOR LEUCOCYTE INFUSION[1,9,19,20-25]

- Pediatric AML patients show higher remission rates after first DLI compared to adults. Prophylactic DLI outperforms preemptive or therapeutic use, especially in AML and CML, with complete response rates up to 80% and five-year overall survival near 70%[21];
- Prophylactic DLI plus azacitidine has been associated with two-year leukemia-free survival up to 88%, improved immune reconstitution, and no increase in GvHD[22,23];
- Conversion from mixed to full donor chimerism is more frequent in leukemia than in non-malignant diseases, and more likely with matched sibling or haploidentical donors than unrelated donors;
- Early scheduling of prophylactic DLI rather than preemptive DLI in high-risk acute leukemia may reduce post-transplant relapse and improve long-term survival[24];
- In pediatric acute leukemia, DLI can successfully treat relapse, with remission rates ranging from 20 to 80%;
- It is worth noting that relapse rates are higher in Brazil than in higher income[25].

TOXICITIES

The most important complications of DLI are GvHD and pancytopenia. GvHD risk increases with early DLI post-HCT, higher cell doses (> 1 × 10^8 T cells/kg), HLA mismatch, and lack of immunosuppression. Dose escalation every 4–12 weeks may reduce GvHD risk, especially in indolent disease or molecular relapse.

Aplasia is more common with mixed chimerism and may occur even with G-CSF–mobilized cells. Monitoring includes weekly clinical and laboratory assessments; if GvHD develops, perform severity score assessment, including lung function tests every three to six months, even in asymptomatic patients.

STEM CELL BOOST[26–35]

Indications: Patients with poor graft function or declining donor chimerism after allogeneic HCT may benefit from a stem cell boost (SCB).

Limitations in Brazil: Although $CD34^+$-selected products are commonly described in the international literature, this strategy remains highly restricted in Brazil. As a result, SCB is rarely used in Brazilian clinical practice.

- Administration and risks of boost without CD34+ selection: When SCB is used, it is typically performed with apheresis of G-CSF–mobilized peripheral blood stem cells. This unselected approach is associated with a higher $CD3^+$ T cell content, which may increase the risk of acute GvHD, and its efficacy remains controversial. If performed, careful attention must be given to the $CD3^+$ T cell dose infused, to minimize the risk of GvHD.

- Supportive measures: Other supportive strategies to improve graft function should also be considered, such as appropriate iron chelation and the use of agents like eltrombopag[31].

- Cryopreserved autologous stem cells boost: Boost of previously cryopreserved autologous stem cells can be used to treat prolonged cytopenias after autologous HCT or after CAR-T cell therapy. In both settings, it is important to identify patients at highest risks, so a backup collection can be planned[35].

MESENCHYMAL STROMAL CELL[36–43]

Definition and mechanisms

- Non-hematopoietic mesoderma-derived cells with regenerative and immunomodulatory properties;
- Sourced from bone marrow, adipose tissue, or umbilical cord;
- Inhibit T, B, NK, and monocyte activity, reducing inflammation and promoting immune tolerance[37,38].

Indications

- Used for tissue repair (*e.g.*, osteonecrosis) and treatment of immune-mediated complications[36];
- Mostly used for acute or chronic steroid-refractory GvHD post-HCT.

Evidence and administration

- Studies demonstrate safety and efficacy, especially in pediatrics[40–42], with approximately 50% of children achieving clinical response;
- Dosing: 2–4 × 10^6 mesenchyal cells (MSC)/kg twice weekly; source and protocol vary by center[42];
- European Society for Blood and Marrow Transplantation recommends MSC as second-line (category 2A) for acute GvHD[39];
- Food and Drug Administration approved Remestemcel-L in 2024 for steroid-refractory^{aGvHD} in children ≥ 2 months old[43].

LIMITATIONS IN BRAZIL

Not yet commercially approved; the Brazilian Health Regulatory Agency must be notified for use.

Post-transplant cellular therapies—including DLI, SCB, and MSC—offer important immunomodulatory and supportive strategies after HCT. While DLI is the most established, with proven benefit in relapse prevention, SCB may aid in graft function recovery, and MSC shows promise in steroid-refractory GvHD, especially in pediatrics.

However, all approaches face challenges such as limited availability, especially in Brazil, and lack of standardized protocols. Broader access to feasible options like fresh whole blood DLI, and further studies to define optimal indications, combinations, and emerging immune targets, are essential to improve outcomes in diverse transplant settings.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Sousa AM, Tavares RCB, Santis GC and Seber A. **Conception and design:** Sousa AM, Seber A and Tavares RCB. **Technical procedures:** Sousa AM and Seber A. **Manuscript writing:** Sousa AM, Tavares RCB, Santis GC and Seber A. **Final approval:** Sousa AM and Seber A.

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