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Clinical applications of donor lymphocyte infusion from an HLA-haploidentical donor: consensus recommendations from the Acute Leukemia Working Party of the EBMT

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ABSTRACT

Donor lymphocyte infusion has been used in the management of relapsed hematologic malignancies after allogeneic hematopoietic cell transplantation. It can eradicate minimal residual disease or be used to rescue a hematologic relapse, being able to induce durable remissions in a subset of patients. With the increased use of haploidentical

hematopoietic cell transplantation, there is renewed interest in the use of donor lymphocytes to either treat or prevent disease relapse post transplant. Published retrospective and small prospective studies have shown encouraging results with therapeutic donor lymphocyte infusion in different haploidentical transplantation platforms. In this consensus paper, finalized on behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation, we summarize the available evidence on the use of donor lymphocyte infusion from haploidentical donor, and provide recommendations on its therapeutic, pre-emptive and prophylactic use in clinical practice.

Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) remains an important therapeutic option for a wide number of both hematologic malignancies and non-hematologic disorders. With improvements in conditioning regimens, graft-*versus*-host disease (GvHD) prophylaxis and supportive care, leading to a reduced risk of transplant-related mortality, disease relapse has become the foremost cause of mortality after allo-HCT. The cumulative incidence of relapse (CIR) after allo-HCT for acute leukemia can be as high as 40-50% with only 10-15% long-term survival in patients experiencing leukemia recurrence.[1-3] Strategies aimed at preventing and/or treating disease relapse have the greatest potential to improve transplant outcomes. Donor-lymphocyte infusion (DLI) has an established role in the management of disease relapse after allo-HCT. Unmanipulated DLI is a form of immunotherapy, which can induce durable remissions by enhancing the graft-*versus*-tumor (GvT) effect.[4-6] Efficacy of DLI varies by type and burden of the disease.[7] DLI is more effective in chronic myeloid leukemia (CML), leading to complete remission (CR) in 70-80% of patients in hematologic or cytogenetic CML relapse, whereas less than 40% of acute leukemia patients respond to DLI.[8,9] A study by Schmid *et al.* using the European Society for Blood and Marrow Transplantation (EBMT) registry showed DLI was associated with improved survival of patients with AML in the first hematologic relapse after allo-HCT, but 2-year overall survival (OS) was only 15% if DLI was given in the setting of active disease.[10] Pre-emptive DLI for mixed chimerism or molecular disease relapse and prophylactic DLI for high-risk hematologic malignancies have also been studied with promising results in the setting of human leukocyte antigen (HLA)-matched allo-HCT.[11-13]

Allo-HCT from an HLA-haploidentical related donor (haplo-HCT) has emerged as a suitable alternative for those patients who need an allograft but who lack an HLA-matched related or unrelated donor.[14,15] Several T-cell depleted and T-cell replete haploidentical transplant strategies are applied today. In T-cell replete haploidentical stem cell transplantation, the use of post-transplant cyclophosphamide (PTCy) has rapidly increased across the globe due to its logistical simplicity and efficacy.[2] Another T-cell replete haplo-HCT platform is granulocyte colony stimulating factor (GCSF)-antithymocyte globulin (ATG)-based or "GIAC" protocol' [GCSF-stimulation of the donor; intensified immunosuppression through post-transplantation cyclosporine (CSA), mycophenolate mofetil (MMF), and short-course methotrexate (MTX); anti-thymocyte globulin (ATG); and combination of peripheral blood stem cells (PBSC) and bone marrow (BM) allografts] initially developed at the Peking University.[16] Today's T-cell depleted strategies derive from the mega-dose CD34$^+$ protocol developed at the Perugia University[17] and represent a historical standard in T-cell depletion. From this platform, several other T-cell depleted strategies have evolved, such as CD3/CD19 cell depletion[18] and α-β-T/CD19-B cell depletion.[19] The adoptive transfer of selectively allo-depleted[20] or gene-modified T cells with a suicide switch[21,22] after T-cell depleted transplantation have further optimized this transplant form and are now being investigated in large randomized trials in comparison with PTCy.

Haplo-HCT with PTCy has shown comparable clinical outcomes to matched unrelated donor allo-HCT in retrospective analyses with a significantly lower risk of chronic GvHD in myeloid and lymphoid malignancies, regardless of whether the graft was obtained from BM or mobilized PBSC.[23-26] There is concern that DLI from a haploidentical donor (haplo-DLI) may pose an increased risk for GvHD, given the higher degree of HLA disparity between the donor and recipient. However, a greater HLA-disparity may also be beneficial in promoting a stronger GvT effect.[27] Another advantage is that a related haploidentical donor is, in most cases, readily available and collection is faster than a registry-based unrelated donor. While the experience with haplo-DLI is limited, and there are many uncertainties around its clinical application, it can be a powerful tool to manage a disease relapse after haplo-HCT. Nonetheless, it should be emphasized that haplo-DLI after T-cell depleted transplantation without full immune reconstitution may have very different effects than after T-cell replete transplantation and may require completely different dosing strategies. Therefore, in the absence of data from prospective clinical trials, general recommendations cannot be made.

In this review, we summarize the published experience with haplo-DLI and provide recommendations regarding its use in various clinical settings (therapeutic *vs.* pre-emptive *vs*. prophylactic DLI), use of chemotherapy before DLI, optimal cell dose, and concurrent immunosuppression management. Newer strategies using cellular engineering, donor-derived natural killer (NK) cells and pharmacological immunomodulation are also discussed.

Therapeutic haplo-donor-lymphocyte infusion: hematologic relapse

Previously published retrospective studies have suggested that outcomes of haplo-DLI in patients with hematologic relapse are comparable to standard DLI from an HLA-matched donor. The incidence of DLI-associated GvHD also appears to be similar regardless of donor type.[28-30] Possible explanations, at least when used late post transplant, are the use of lower cell dose and presence of donor-derived tolerogenic cells in the recipient,

which may reduce their alloreactivity and, thus, the risk of GvHD. The type of haplo-HCT protocol may influence outcomes of subsequent haplo-DLI. The current therapeutic haplo-DLI experience is limited to haplo-HCT/PTCy or a 'GCSF-ATG-based protocol'. Table 1 summarizes the published studies using DLI from a haploidentical donor.

Therapeutic donor-lymphocyte infusion in T-cell replete haplo-hematopoietic cell transplantation

Zeidan *et al*. retrospectively reported results of haplo-DLI in 40 patients [minimal residual disease (MRD)/loss of chimerism (LOC): n=5; hematologic relapse: n=35] after a haplo-HCT/PTCy with BM graft. At the median follow up of seven months, CR was achieved in 30% of patients (CR after a hematologic relapse: 26%) and acute GvHD (aGvHD) occurred in 25% of them. At time of last follow up, six patients were alive in CR for over a year after the intervention. The cell dose in most DLI was $1x10^6$ $CD3^+$ cells/kg and the majority of patients received cytoreductive chemotherapy before DLI.[28] Subsequently, two similar reports showed that haplo-DLI after chemotherapy successfully resulted in CR in approximately 30% of the patients with a subset of long-term survivors.[29,30] The incidence of grade 2-4 aGvHD was approximately 30%, and only 5% of patients developed grade 3-4 aGvHD. No patient (0%) developed extensive chronic GvHD (cGvHD).[29,30] None of these studies used immunosuppression for GvHD prophylaxis after haplo-DLI. Disease responses and GvHD rates were comparable between patients who received BM *versus* a PBSC graft.[30] Patients with relapsed Hodgkin lymphoma appear to have relatively better disease responses to haplo-DLI compared to those with acute leukemia (40% *vs.* 33%).[29] In a smaller retrospective study (n=21) published by Goldsmith *et al.*, the authors showed that patients with extra-medullary disease relapse had a better relapse-free survival (RFS) compared to those with marrow relapse (4-month RFS 43% *vs*. 8%).[30] The group at Peking University has developed a haplo-DLI protocol using GCSF-primed peripheral blood progenitor cells (GBPC) with short-term immunosuppression. They have used a higher cell dose ($1x10^7$ to $1x10^8$ $CD3^+$ cells/kg) than that used in haplo-DLI in the setting of allo-HCT/PTCy ($1x10^5$ to $1x10^6$ $CD3^+$ cells/kg).[31-37] An earlier prospective study using GBPC without immunosuppression resulted in a high incidence of severe GvHD (grade 3-4 aGvHD 30%, extensive cGvHD 30%), resulting in 2-year disease-free survival (DFS) of 40% and non-relapse mortality (NRM) of 25%.[38] Subsequent studies used cytoreductive chemotherapy before GBPC infusion (chemo-DLI) followed by GvHD prophylaxis with low-dose weekly MTX or CSA for 6-8 weeks. A retrospective report by Yan *et al.* on 55 patients with relapsed acute leukemia showed 3-year DFS, NRM, and OS of 24%,13%, and 25%, respectively. A total of 76% of patients achieved CR (MRD negative CR: 55%).[39] Relapse after achieving CR following chemo-DLI was a major problem, resulting in poor long-term survival. In spite of the limitations of cross-study comparison, outcomes of chemo-GBPC infusion with short-course immunosuppression are comparable to unmanipulated haplo-DLI after haplo-HCT/PTCy.

Pre-emptive haplo-donor-lymphocyte infusion: minimal residual disease, mixed-donor chimerism

Impact of minimal residual disease and mixed-chimerism on haplo-hematopoietic cell transplantation outcomes

Strategies are being explored to reliably predict the risk of disease relapse after an allo-HCT in the hope of implementing pre-emptive treatments. The presence of MRD before or after allo-HCT is associated with significantly increased risk of relapse and reduced survival in both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML).[40,41] Canaani *et al.* looked at pre-haplo-HCT MRD positivity in AML patients and showed its negative correlation with leukemia-free survival.[42] Low donor T-cell chimerism [mixed-chimerism (MC)] after an allo-HCT is also associated with poor donor-derived immune reconstitution and increased risk of disease relapse, especially after myeloablative conditioning. In patients with AML/MDS who underwent myeloablative allo-HCT, donor T-cell chimerism <85% at day (d)+90 and d+120 was associated with increased risk of 3-year disease progression (HR=2.1, P=0.04).[43] Koreth *et al.* reported that d+100 total donor chimerism <90% was associated with increased risk of relapse (HR= 2.54, P<0.001) and lower OS (HR=1.50, P=0.009) in patients after a reduced-intensity allo-HCT.[44] Pre-emptive DLI from a full matched donor for MRD and MC appears to be safe and effective in improving disease-specific outcomes.[45,46]

Pre-emptive donor-lymphocyte infusion in T-cell replete haplo-hematopoietic cell transplantation

In the previously mentioned retrospective study by Zeidan *et al.*, 3 of 4 patients who received haplo-DLI for MRD entered CR.[28] Similarly, other reports showed higher response rates in patients who received haplo-DLI for MRD or MC compared to the administration at the time of hematologic relapse.[29,30] Yan *et al.* reported comparative outcomes of prospective studies of standard-risk acute leukemia and MDS patients with persistent MRD after allo-HCT (haploidentical donor, n=29; matched donor, n=27), who received low-dose interleukin-2 (IL-2) or pre-emptive DLI. The latter was associated with reduced 3-year CIR compared to IL-2 alone (28% *vs*. 64%; P=0.001).[31] In another retrospective study by Mo *et al.*, 101 patients (haplo-HCT, n=56) received chemo-DLI for persistent MRD after an allo-HCT. Three-year CIR, NRM, and OS were 40%, 10%, and 52%, respectively. Patients who cleared their MRD within 30 days after pre-emptive chemo-DLI had lower relapse rates compared to those with persistent MRD beyond 30 days (20% *vs*. 47%; P=0.001).[36] It should be noted that the published data on pre-emptive haplo-DLI for MC is limited to a few patients[28,30] and further studies are needed to establish its role in preventing disease relapse.

It is important to monitor for MRD after allo-HCT as DLI is probably more effective when administered for MRD only compared overt hematologic relapse.[47] Retrospective studies have shown that persistent MRD post-transplant is associated with high relapse rate and poor outcomes,[48] and the eradication of MRD improves survival.[46] Comparative studies are needed between DLI and other systemic therapies in order to develop disease-

Table 1. Donor-lymphocyte infusion from a haploidentical donor.

Study	N. of patients (prospective/ retrospective)	Diagnosis	Indication for DLI	Treatments before DLI	$CD3^+$ dose/kg	N. of DLI (median)	Disease response	Rate of GvHD	Survival	Notes
T-cell depleted haplo-HCT										
Lewalle *et al.* (2003)[65]	12 (prospective)	AML=5 ALL=3 CML=1 Other=3	Prophylactic=12	None	1-4x10^4			58%	1-yr RFS=50%, 1-yr OS=50%, NRM=0%	T-/B-cell depleted graft
Dodero *et al.* (2009)[62]	23 (prospective)	Lymphoma CLL ALL MM AML	Prophylactic-23	None	2-15x10^4	2	NA	aGvHD=26% (grade 3-4=9%) cGvHD=15% (extensive=12%)	2-yr PFS=45% 2-yr OS=44% NRM=26%	$CD8^+$ T-cell depleted DLI
Martelli *et al.* (2014)[61]	43 (prospective)	AML=33 ALL=10	Prophylactic-43	None	T_{reg}=2.5x10^6±1.1 T_{con}=1.1x10^6±0.6	1	NA	aGvHD (grade ≥2)=15% cGvHD=16% (extensive=7%)	CI NRM=40% 46-m relapse =5%	T_{reg} on day-4, T_{con} on day 0
Gilman *et al.* (2018)[60]	34 (prospective)	AML/MDS=13 ALL=10 Other=11	Prophylactic-34	None	3-5x10^4	1	NA	aGvHD (grade 3-4)=4% cGvHD=16% (extensive=7%)	2-yr OS=63% 2-yr NRM=25%	Post-DLI-GvHD ppx=100%
T-cell replete haplo-HCT										
Or *et al.* (2006)[106]	28 (haplo-26,MMUD-2) (retrospective)	AML=12 ALL=7 CML=5 Other=3	Prophylactic-6 Therapeutic- 22	None	1x10^2 to 15x10^8	1-7 (1)	CR=18%	46%	NRM=11%	
Huang *et al.* (2007)[38]*	20 (prospective)	AML=7 ALL=10 CML=3	Therapeutic=20	CT=9 TKI=2	0.07-4.39x10^8	1-3 (1)	CR=75%	aGvHD=55% (grade 3-4=30%) cGvHD=64% (extensive=30%)	2-yr DFS=40% NRM=25%	Post-DLI-GvHD ppx=55%
Yan *et al.* (2012)[31]*	56 (haplo-29, matched related-26, MUD-1) (prospective)	AML=32 ALL=21 MDS=3	Pre-emptive=56 (MRD)	CT=32	0.75-2x10^8	1	NA	aGvHD=31% (grade 3-4=8%) cGvHD=43% (extensive=34%)	3-yr DFS=56% 3-yr OS=58% 3-yr NRM=14%	Post-DLI-GvHD ppx=100%
Yan *et al.* (2012)[69]*	124 (retrospective)	AML=49 ALL=59 MDS=5 CML=11	Prophylactic=74 Therapeutic/ pre-emptive= 50(MRD)	CT=27 (MRD+) All relapsed pts received CT.	0.13-2.11x10^8	1-4(1)	NA	aGvHD=53% (grade 3-4=28%)	2-yr CIR=35% 2-yr OS=47% 2-yr NRM=34% In disease relapse, 2-yr CIR=45% 2-yr OS=19% 2-yr NRM=37%	Post-DLI-GvHD ppx=100%
Wang *et al.* (2012)[66]*	61 (retrospective)	AML=42 ALL=19	Prophylactic=61	CT=0%	0.9-7.2x10^8	1	NA	aGvHD=48% (grade 3-4=10%) cGvHD=39% (extensive=31%)	3-yr DFS=22% 3-yr OS=31% 2-yr NRM=38%	Post-DLI-GvHD ppx=100%
Yan *et al.* (2013)[33]*	50 (retrospective)	AML=29 ALL=21	Therapeutic=50	CT=100%	0.11-2.07x10^{08}	NA	CR=64%	aGvHD=66% (grade 3-4=40%) cGvHD=44% (extensive=42%)	1-yr DFS=36% 1-yr OS=36% 1-yr NRM=14%	Post-DLI-GvHD ppx=100%
Yan *et al.* (2015)[39]*	55 (retrospective)	AML=18 ALL=23	Therapeutic=55	CT=100%	0.19-0.74x10^8	NA	CR=76% MRD negative CR=55%	aGvHD=44% (grade 3-4=11%) cGvHD=49% (extensive=42%)	3-yr DFS=24% 3-yr OS=25% 3-yr NRM=13%	Post-DLI-GvHD ppx=100%
Mo *et al.* (2016)[36]*	101 (haplo=58) (retrospective)	AML/MDS=69 ALL=32	Pre-emptive =101(MRD)	CT=100%	1.7-7.4x10^7	NA	CR=76%	aGvHD=9% (grade 3-4=4%) cGvHD=59%	AML/MDS, 3-yr DFS=57% 3-yr NRM=7% ALL, 3-yr DFS=49% 3-yr NRM=11%	Post-DLI-GvHD ppx=100%

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Study T-cell depleted haplo-HCT	N of patients (prospective/ retrospective)	Diagnosis	Indication for DLI	Treatments before DLI	CD3+ dose/kg	N. of DLI (median)	Disease response	Rate of GvHD	Survival	Notes
Yan *et al.* (2016)[57*#]	47 (haplo=31) (prospective)	AML=25 ALL=22	Pre-emptive=47 (MRD)	CT=100%	1.5-6.4x10^7	1-4	NA	aGvHD =19% (grade 3-4=6%) cGvHD=79% (≥moderate=66%)	1-yr DFS=71% 1-yr NRM=9% 1-yr OS=78%	Post-DLI-GvHD ppx=100%
Yan *et al.* (2017)[32*]	100 (haplo=62) (prospective)	AML=59 ALL=41	Prophylactic=100	CT=0%	1.8-6.6x10^7	NA	NA	Haplo-HCT, aGvHD =47% (grade 3-4=10%) cGvHD=63% (≥moderate=59%)	Haplo-HCT, 3-yr DFS=51% 3-yr NRM=18% 3-yr OS=49%	Post-DLI-GvHD ppx=100%
Ma *et al.* (2017)[34*]	36 (retrospective)	AML/ALL/ MDS/CML	Therapeutic=36	CT/TKI =100%	NA	NA	CR=56%	Grade 3-4 aGvHD=25%) Extensive cGvHD=36%	3-yr DFS=11% 3-yr OS=14%	Post-DLI-GvHD ppx=100%
Gao *et al.* (2018)[54*]	31 (retrospective)	AML=21 ALL=5 CML=2 Other=3	Prophylactic=31	CT=0%	0.4-6.9x10^7	1	NA	aGvHD=58% (Grade 3-4=7%) cGvHD=39% (Mod-severe=29%)	2-yr RFS=32% 2-yr NRM=33% 2-yr OS=40%	Post-DLI-GvHD ppx=100%
Zeidan *et al.* (2014)[28+]	40 (retrospective)	AML=16 ALL=3 CML=1 Lymphoma=11 Other=9	Therapeutic=35 Pre-emptive=5 (MRD+/MC)	CT/RT= 70%	1x10^5 to 1x10^8	1-4(1)	CR=30% (MRD=75%, Relapse=26%)	aGvHD=25% (grade 3-4=15%) cGvHD=8% (extensive=5%)	8/12 responders (67%) alive, in CR at 17.5 months	
Ghiso *et al.* (2015)[29+]	42 (retrospective)	AML=22 ALL=9 HL=10 MM=1	Therapeutic=22 Pre-emptive=20 (MRD)	CT/RT= 100%	1x10^3 to 1x10^7	1-6 (mean-2.5)	CR=36% CR in MRD =45%	aGvHD=33% (grade 3-4=5%) cGvHD=0%	Leukemia, median response=4m(2-10), median survival =7m(1-15) HL, median response =9m(3-28), median survival =18m(4-34)	
Jaiswal *et al.* (2016)[56§]	21 (prospective)	AML=21	Prophylactic=21	CT=0%	9.2-110x10^7	1-3	NA	Cum incident aGvHD =31% cGvHD=41%	1.5-yr PFS=62% 1.5-yr CIR=21% 1.5-yr OS=71%	Post-DLI-GvHD ppx=100%
Goldsmith *et al.* (2017)[30+]	21 (retrospective)	AML/MDS=16 ALL=2 CML=2 Lymphoma=11 Other=9	Therapeutic=19 Pre-emptive=2(MC)	CT=76%	0.01-3x10^7	1-5	CR=32%	aGvHD=33% (grade 3-4=5%) cGvHD=26% (extensive=0%)	Hematologic relapse, 4-m RFS=8% 4-m OS=29% EM relapse, 4-m RFS=43% 4-m OS=71%	PBSC haplo-HCT
Cauchois *et al.* (2018)[67+]	36 (retrospective)	AML/MDS=25 ALL=2 Lymphoma=6 Other=3	Prophylactic=36	CT=0%	0.1-2.5x10^6	1-3	NA	1-yr CI of mod-severe GvHD=33%	1-yr PFS=83% 1-yr NRM=9% 1-yr OS=76%	PBSC graft=31

N: number; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; MDS: myelodysplastic syndromes; MMUD: mismatched unrelated donor; GvHD ppx: graft-*versus*-host disease prophylaxis; aGvHD: acute GvHD; cGvHD: chronic GvHD; OS: overall survival; DFS: disease-free survival; PFS: progression-free survival; NRM: non-relapse mortality; CT: chemotherapy; TKI: tyrosine kinase inhibitor; MRD: minimal residual disease; MC: mixed-chimerism; NA: not available; RT: radiation therapy; PBSC: peripheral blood stem cell; EM: extra-medullary relapse; RFS: relapse-free survival; haplo-HCT: haploidentical-hematopoietic cell transplant; matched: HLA-matched allo-HCT; MUD: HLA-matched unrelated donor; T_{reg}: regulatory T-cell; T_{con}: conventional T-cells; CI: cumulative incidence; yr: year; m: months; NA: not available. *Granulocyte colony-stimulating factor (GCSF)-anti-thymocyte globulin (ATG)-based protocol and G-CSF-primed peripheral blood progenitor cell (GBPC). §Haplo-HCT with post-transplant cyclophosphamide (PTCy) and GBPC. +Haplo-HCT with PTCy and standard donor-lymphocyte infusion (DLI). #Patients had salvage chemotherapy + therapeutic DLI for hematologic relapse, followed by pre-emptive DLI for persistent minimal residual disease (MRD). pt: patient; mod: moderate; cum: cumulative; HL: Hodgkin lymphoma.

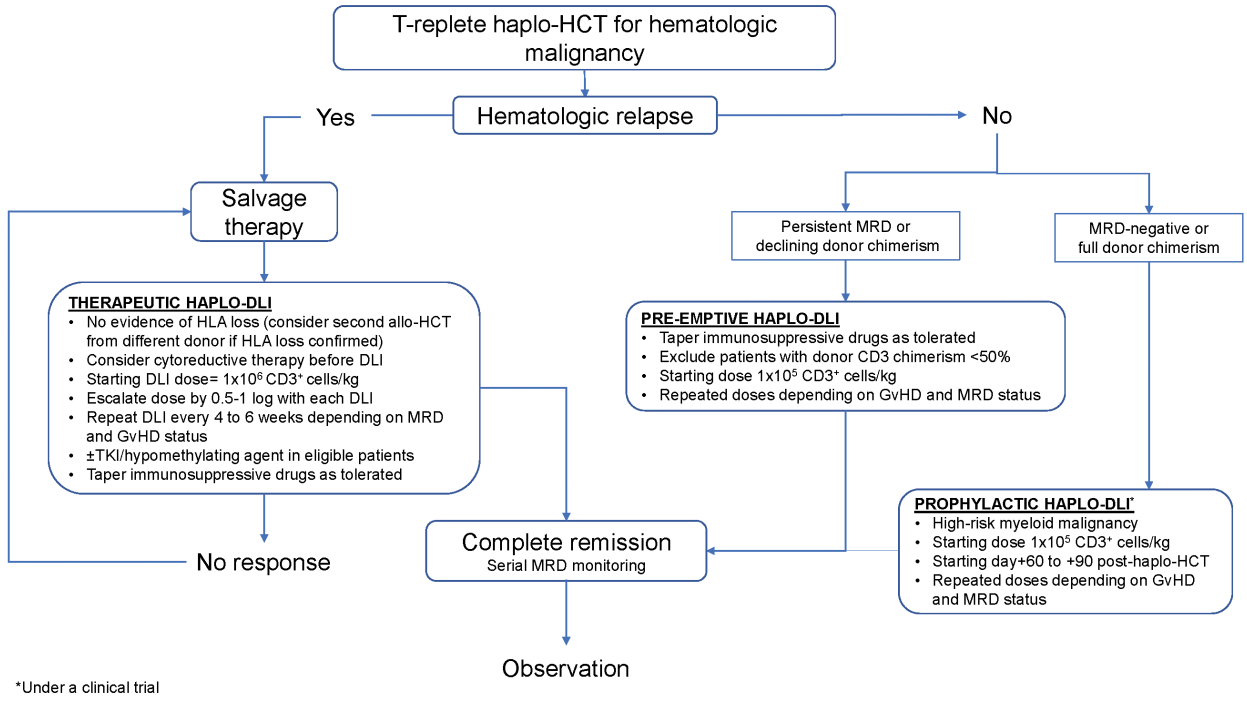

Figure 1. Proposed treatment algorithm of therapeutic, pre-emptive and prophylactic donor-lymphocyte infusion (DLI) following T-cell replete haploidentical hematopoietic cell transplantation (HCT). HLA: human leukocyte antigen; MRD: minimal residual disease; GvHD: graft-*versus*-host disease; TKI: tyrosine kinase inhibitor.

specific MRD management strategies. DLI should not be used in patients who have converted to host chimerism due to increased risk of marrow aplasia.[49] An alternative strategy for such patients would be to undergo a second allo-HCT from the same or from a different donor. It is important to weigh the risk of GvHD and marrow aplasia *versus* the potential benefit of reducing the disease relapse when considering pre-emptive DLI for MRD or MC.

Prophylactic haplo-donor-lymphocyte infusion

Prophylactic DLI from a matched donor has been studied in patients with high-risk myeloid malignancies and was associated with improved disease-specific outcomes and low NRM.[11,50,51] It can contribute to immune reconstitution and reduce the risk of infection,[52] which is a major challenge after a T-cell depleted haplo-HCT. A matched-pair analysis by the EBMT showed improved OS in high-risk AML recipients who received prophylactic DLI from a matched donor (70% *vs.* 40% in controls; P=0.027).[53] Inclusion criteria differ among published studies in their definition of high-risk disease. Most reports included patients with primary induction failure acute leukemia, high disease risk index, active disease before allo-HCT or the presence of high-risk mutations (i.e. TP53, ASXL1, RUNX1) in myeloid malignancies.[54-57] One of the first experiences with prophylactic haplo-DLI was in the setting of autologous-HCT. Nagler *et al.* reported outcomes of 26 patients who received multiple haplo-DLI (with/without IL-2) after an autologous-HCT. This approach was feasible in inducing GvHD, but higher cell doses led to increased toxicity.[58] The timing of prophylactic-DLI is also important as decreasing the interval between allo-HCT and DLI will likely increase the risk of aGvHD.[13] The activity of ATG, given as a part of conditioning, may persist for weeks, and residual ATG may negatively impact prophylactically infused donor lymphocytes.[59] At the same time, the administration of haplo-DLI as early as d+45 was feasible in single center studies.[32,56] It may be reasonable to administer prophylactic haplo-DLI before d+90 given that median time to relapse after allo-HCT is approximately three months.

Prophylactic donor-lymphocyte infusion in T-cell depleted haplo-hematopoietic cell transplantation

Early experience with prophylactic haplo-DLI was with T-cell-depleted haplo-HCT where donor lymphocytes were infused after a CD34⁺ cell-selected graft to enhance immune reconstitution.[60-62] Perruccio *et al.* showed that infusion of donor-derived non-alloreactive T cells specific for cytomegalovirus (CMV) and aspergillus resulted in the rapid development of T-cell responses against these pathogens without inducing GvHD.[63] Another prospective study utilized CD8⁺ T-cell depleted DLI, which resulted in aGvHD in 26% of patients with 2-year PFS of 45%.[62] Donor-derived T regulatory cells (T_{regs}), co-infused with conventional T cells (T_{cons}) were shown to protect recipients against GvHD.[64] In a prospective study, patients received T_{regs} (d -4) followed by a megadose of CD34⁺cells and T_{cons} on d0 from a haploidentical donor without any post-transplant immunosuppression. Only 15% of the patients developed ≥grade 2 aGvHD and DFS was 56% at 18 months.[61] In another prospective study by Gilman *et al.*, 34 pediatric patients were infused an unmanipulated prophylactic haplo-DLI with MTX between d+30 and d+42 after a T-cell depleted/CD34⁺ selected haplo-HCT. The intervention was safe and 2-year NRM

and OS were 25% and 63%, respectively.[60] Lewalle *et al.* reported the outcomes of 12 patients who received prophylactic haplo-DLI starting on d+28 after T-/B-cell depleted haplo-HCT in a prospective study. One-year RFS, NRM, and OS were 50%, 0%, and 50%, respectively.[65] Despite the encouraging results with prophylactic infusion of T-cell subset after a T-cell deplete/CD34$^+$ selected haplo-HCT, its widespread adoption has been challenging as cell selection remains a labor-intensive and expensive process.

Prophylactic donor-lymphocyte infusion in T-cell replete haplo-hematopoietic cell transplantation

The Chinese group has led the way by incorporating prophylactic GBPC in high-risk malignancies after a haplo-HCT with the GCSF-ATG-based protocol. In a retrospective study by Wang *et al.*, [61] patients with high-risk leukemia who underwent GBPC infusion were compared to 27 patients who received routine care after an haplo-HCT. Prophylactic GBPC was associated with lower relapse rate (36% *vs*. 55%; *P*=0.017) and superior estimated 3-year survival (31% *vs*. 11%; *P*=0.001) compared to routine care. There was no difference in NRM between the two groups.[66] A prospective study by the same group enrolled 62 patients with high-risk acute leukemia. All patients received prophylactic GPBC between d+45 and d+60 and further DLI were guided by MRD and GvHD status. Three-year DFS, NRM, and OS were 51%, 18%, and 49%, respectively. Acute and chronic GvHD were seen in 47% and 63% patients, respectively. Outcomes were similar between recipients of haploidentical (n=62) *versus* matched donor (n=38) prophylactic DLI.[32]

Jaiswal *et al.* reported their prospective experience with prophylactic GBPC in the T-cell replete haplo-HCT/PTCy setting. Twenty-one patients with AML (not in remission) received up to three doses of haplo-GPBC (d+21, d+35 and d+60). They were compared with 20 patients who received routine monitoring after haplo-HCT. At 18 months, CIR, PFS, and OS were 21% *versus* 66%; 62% *versus* 25% and 71% *versus* 35% in DLI and routine care cohorts, respectively. Incidence of aGvHD was 31%, while incidence of chronic GvHD was 41% after GBPC infusions. NRM was equivalent between the groups.[56] Recently, Cauchios *et al.* reported outcomes of 36 patients who received prophylactic haplo-DLI after a haplo-HCT/PTCy. One-year PFS and OS were 76% and 83%, respectively. The cumulative incidence of relapse was 16% and the incidence of DLI-associated GvHD was 33%.[67]

Practical aspects of haplo-donor-lymphocyte infusion

Cell dose

The CD3$^+$ T-cell dose ranged from 0.01 to 8.8x10^8 mononuclear cells/kg in reports on therapeutic DLI from a matched donor.[7] A study reported a relatively lower rate of GvHD with an escalating cell dose regimen *versus* a single bulk infusion of DLI from HLA-matched donors. Disease responses were similar between the two approaches.[68] There was no dose-response relationship with GvHD or disease response rates in haplo-DLI in the setting of T-cell depleted haplo-HCT.[28,29] The average starting dose for therapeutic haplo-DLI in the T-cell replete haplo-HCT/PTCy setting was 1 or 2 log lower than the standard DLI dose (1x10^7 CD3$^+$ cells/kg) from HLA-matched donors. In a report on 40 patients, a cell dose of 1x10^6 CD3$^+$ cells/kg was associated with grade 2-4 aGvHD in 17% of patients, and a CR rate of 27%.[28] Goldsmith *et al.* used the same dose in 21 patients; only seven (33%) developed aGvHD (grade 3-4 aGvHD in 1 patient).[30] These incidences of aGvHD were lower than those reported by the Chinese group using haplo-GBPC at 1 to 2 log higher cell dose with the GCSF-ATG-based protocol. A starting cell dose of 1x10^7 to 1x10^8 CD3$^+$ cells/kg was associated with grade 2-4 aGvHD in 50-60% (grade 3-4 aGvHD approximately 30%) of patients.[31,38,69] Subsequent reports by Yan *et al.* showed a reduced incidence of aGvHD with the routine use of short-term GvHD prophylaxis after GBPC infusion.[39] Available data suggest that 1x10^6 CD3$^+$cells/kg is a reasonable starting dose with appropriate repeated dose escalation every 4-6 weeks based on disease response and GvHD for therapeutic haplo-DLI in T-replete haplo-HCT with PTCy. Clinical trials are needed to establish the optimal timing and cell dose in prophylactic and T-cell depleted haplo-HCT settings. Published studies have used wide-ranging repeated non-escalating cell doses for pre-emptive or prophylactic DLI.[32,37,54]

The end point of donor-lymphocyte infusion therapy

It is important to establish the goal of DLI therapy beforehand as each DLI is associated with increased risk of GvHD. Patients with DLI-responsive relapse usually respond within 2-3 months.[7] Repeated infusions of escalating doses of therapeutic DLI can be administered until CR is achieved (ideally an MRD-negative status) or the patient develops clinically significant GvHD. Patients should be evaluated for GvHD, donor chimerism and disease response after each DLI. Pre-emptive DLI for MRD persistence after allo-HCT may be stopped once the achievement of MRD negativity, significant GvHD or a hematologic relapse occurs. Donor chimerism should be assessed after each pre-emptive DLI for MC. Pre-emptive DLI may be stopped once ≥90% donor chimerism is achieved. As noted above, DLI can result in marrow aplasia in those patients who have converted to host chimerism. There is no standard duration of prophylactic DLI outside a clinical trial. In these circumstances, each dose of prophylactic haplo-DLI should be used with caution, balancing the risk of disease relapse and GvHD.

Traditional donor-lymphocyte infusion *versus* granulocyte colony-stimulating factor-primed peripheral blood progenitor cell infusion

Standard DLI uses freshly collected unmanipulated donor lymphocytes. This approach privileges tumor alloreactivity over the risk of GvHD. GCSF promotes T-cell hypo-responsiveness in marrow grafts by increasing the number of plasmacytoid dendritic cells and monocytes. It also reduces the expression of co-stimulatory CD28/B7 on monocytes, B and T cells,[70] promotes macrophage[71] and T-cell polarization in the BM graft towards the more tolerogenic pattern. This property is maintained even after *in vitro* mixture of G-CSF primed BM and PBSC grafts.[72,73] The Chinese group has reported their extensive experience with using GBPC instead of unmanipulated DLI. Huang *et al.* reported the outcomes of 20 patients who received therapeutic GBPC from hap-

loidentical donors (the majority of whom received salvage therapy prior to GBPC infusion); CR was achieved in 75% of patients and the rates of acute and chronic GvHD were 55% and 64%, respectively.[38] In another study of pre-emptive GBPC infusion for MRD after an allo-HCT (haploidentical related donor: n=29; matched-related donor: n=26), the incidences of acute and chronic GvHD were 31% and 43%, respectively. Routine debulking chemotherapy and short-term immunosuppression were used in most studies using GBPC.[31] A prospective observational study by Jaiswal *et al.* used prophylactic-GBPC in the setting of T-cell replete haplo-HCT/PTCy.[56] The incidence of aGvHD was comparable but cGvHD was higher than that reported with unmanipulated haplo-DLI in the PTCy setting.[28-30] A recent report from Mexico showed that administration of G-CSF-primed whole blood units (median cell count $6.7x10^6$ $CD3^+$ cells/kg) from haploidentical donors is safe, with disease responses and improvement in MC in a subset of patients.[74] Whole blood units can potentially reduce the cost associated with haplo-DLI in developing countries. Long-term immune tolerance after PTCy may be enough to overcome the immunological barrier of haplo-DLI, and GCSF priming may not be required in this setting. Comparative studies between unmanipulated DLI *versus* GBPC in the setting of haplo-HCT/PTCy are needed.

Role of concurrent immunosuppression

Graft-*versus*-host disease is the main limiting toxicity of DLI, and short-term immunosuppression with DLI may improve the safety of DLI. Yan *et al.* reported aGvHD in 31% of patients after pre-emptive GBPC infusion for MRD persistence after T-cell replete haplo-HCT.[31] All patients received CSA or low-dose MTX for 6-8 weeks after GBPC. There was no difference in acute and chronic GvHD rates between CSA and MTX. MTX was associated with lower relapse rate (38% *vs*. 81%; *P*=0.029) and better DFS (52% *vs*. 16%; *P*=0.06). Patients who received MTX had higher absolute lymphocyte count compared to those who received CSA, which may have contributed to better GvT effect.[39] The same group also showed that patients receiving GvHD prophylaxis for 6-8 weeks had a lower cumulative incidence of grade 3-4 aGvHD than patients receiving prophylaxis for 4-6, 2-4, and <2 weeks (9%, 14%, 32%, and 50%, respectively; *P*=0.018).[69] In a retrospective study, Mo *et al.* used pre-emptive chemo-DLI for MRD persistence along with routine prophylaxis with CSA or MTX (haploidentical donor 6-8 weeks; matched donor 4-6 weeks). The incidence of aGvHD was only 9% (grade 3-4 aGvHD: 4%) in their cohort of 101 patients.[36] It is important to note here that haplo-DLI without concurrent immunosuppression in the T-cell replete haplo-HCT/PTCy setting has been reported to have a similar incidence of GvHD compared to the GCSF-ATG-based haplo-HCT protocol, which routinely uses prophylactic immunosuppression with DLI.[28] The potential impairment of the DLI-mediated GvT effect by CSA or MTX is a concern when managing a hematologic relapse. It is reasonable to add short-term MTX after a pre-emptive or prophylactic haplo-DLI, especially in patients with a history of GvHD.[56] There are no data available on concurrent immunosuppression with therapeutic haplo-DLI in the T-cell replete haplo-HCT/PTCy setting.

Combination of systemic therapies with donor-lymphocyte infusion

Administration of salvage therapy before the infusion of DLI may improve its efficacy by reducing the tumor burden and supporting *in vivo* expansion of infused T cells. In this regard, chemotherapy helps eliminate regulatory donor T cells and create a favorable immunological environment for DLI by increasing serum levels of IL-7 that favors peripheral expansion of T cells.[75] In the retrospective study by Zeidan *et al.*, patients who received a cytoreductive therapy had better CR rates compared to those who received unmanipulated haplo-DLI without any preceding therapy (39% *vs*. 8%).[28] This beneficial effect of pre-DLI chemotherapy was not seen in a similar report by Goldsmith *et al*.[30]

The downside of pre-DLI chemotherapy is tissue injury and inflammatory cytokine surge which may increase the risk of GvHD, especially when used closer to the allo-HCT.[76] Intensive chemotherapy after an allo-HCT is poorly tolerated, and infectious complications are common.[34,76] Recently, hypomethylating agents (i.e. azacitidine, decitabine) have been used with DLI for relapsed AML/MDS. Azacitidine can induce allogeneic $CD8^+$ T-cell response by enhancing the expression of epigenetically silenced tumor-associated antigens.[77] A combination of a hypomethylating agent and DLI is safe with no apparent increase in GvHD or infection risk compared to DLI-alone.[78,79] In a prospective study using azacitidine with DLI for relapsed disease after HLA-matched allo-HCT, the CR rate was 23% and the 2-year OS was 17%.[80] Another retrospective study utilizing decitabine followed by DLI for relapsed myeloid malignancies showed an overall response rate of 25% with 2-year OS of 11%.[81] Drugs targeting specific molecular anomalies (*BCR-ABL1*, *FLT3-ITD*, *IDH1*, *IDH2*) are increasingly being incorporated in the treatment of disease relapse or as maintenance therapy after allo-HCT.[82,83] These drugs are safer compared to traditional salvage chemotherapy and may provide benefit when administered in combination with DLI.[84]

Immune escape after haplo-hematopoietic cell transplantation

Recent data have shed light on mechanisms of immune escape causing disease relapse after haplo-HCT. In haplo-SCT, HLA haplotype mismatched in the donor/recipient pair was replaced by a shared parent haplotype (uniparental disomy) in 5 of 17 patients with relapsed AML post-haplo-HCT.[85] In a subsequent retrospective analysis of 69 patients who relapsed after haplo-HCT, mismatched-HLA haplotype loss accounted for 33% of the relapses.[86] Based on retrospective studies, a second allo-HCT using a donor with a different mismatched haplotype or a mismatched unrelated donor may induce a better GvT effect compared to same donor from the first haplo-HCT.[86,87] At present, there is no standardized method of detecting loss of mismatched HLA haplotype in leukemic cells. HLA-allele specific quantitative polymerase chain reaction is required to quantify recipient- and donor-specific alleles to confirm uniparental disomy in low-burden disease relapse.[86,88]

Historically speaking, most patients receiving therapeutic DLI relapse and succumb to their disease. Close monitoring of MRD and donor chimerism after a successful therapeutic haplo-DLI is important to identify the

patients who are at high-risk of subsequent relapses. Mo *et al.* reported that patients with persistent MRD after DLI had increased relapse risk (P=0.001), resulting in poor DFS (P=0.004).[36] In a prospective study of 47 patients (66% received haplo-HCT), MRD-guided repeated administration of pre-emptive chemo-DLI was effective in reducing the risk of subsequent relapse after achieving initial disease response. The one-year CIR, DFS, and OS were 22%, 71%, and 78%, respectively (Figure 1).[57]

Future directions

Donor-derived natural killer cells

Natural killer cells may play a role in tumor alloreactivity in the setting of mismatched or haploidentical transplant. A recent study showed a marked reduction in donor-derived NK cells in the recipients of PTCy, leading to blunting of NK-cell alloreactivity.[89] In a pilot study, prophylactic infusion of $CD56^+/CD3^+$ cells after haplo-HCT/PTCy in patients with refractory active disease was safe and associated with rapid immune reconstitution.[55] The same group used prophylactic DLI primed with abatacept (CTLA4Ig), which selectively suppresses T-cell alloreactivity without interfering with NK-cell activation. Abatacept with DLI was associated with reduced incidence of aGvHD (10% *vs*. 31%) and improved relapse-free survival compared to prophylactic DLI alone.[90] In a phase I study by Ciurea *et al.*, donor-derived NK cells expanded *ex vivo* were infused prophylactically before and after haplo-HCT in high-risk myeloid malignancies. The intervention was safe and associated with improved NK-cell number and function, lower viral infections, and low relapse rate when compared to a historical control group.[91] Several methods to enhance NK-cell alloreactivity, including combination with immunomodulatory drugs,[92] use of cytokine-activated NK cells,[93] and selection of alloreactive single KIR^+ NK cells,[94] are under investigation.

Engineered donor-lymphocyte infusion

Different strategies are being explored to modify DLI composition and reduce the risk of GvHD while maintaining antitumor activity. ATIR101© is a haplo-DLI product with alloreactive T cells depleted by *ex vivo* photodepletion.[20] In a pooled analysis of two prospective trials, 37 patients received prophylactic ATIR101© after T-cell depleted haplo-HCT. One-year relapse rate, NRM and OS were 8%, 33% and 58%, respectively. Interestingly, aGvHD (grade 3-4) and severe cGvHD were seen in 5% and 0% of the patients, respectively.[95] Alloanergized DLI generated *ex vivo* was infused on d+35 after a $CD34^+$ selected haplo-HCT in a phase I study. These donor lymphocytes with the reduced donor-specific alloreactivity expanded *in vivo* and contributed to immune reconstitution.[96] Another strategy is to insert an inducible suicide gene in donor lymphocytes so that they can be selectively eliminated to treat DLI-associated GvHD.[21,97] A recent analysis on 100 children with acute leukemia given a titrated number of donor T cells transduced with the inducible caspase-9 safety switch after haplo-HSCT showed an 82% probability of relapse-free survival.[98]

Chimeric antigen receptor T-cell (CAR-T) therapy has emerged as a potent form of adoptive cellular therapy. Two CD19 CAR-T-cell therapies have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for relapsed/refractory high-grade B-cell lymphoma and B-ALL.[99,100] Prophylactic infusion of CD19 CAR-T cells from a haploidentical donor was found to be safe with only mild aGvHD in one report.[101] There are reports of therapeutic or pre-emptive donor-derived CAR-T-cell infusion with a small number of patients achieving durable remissions. CAR-T-cell-associated GvHD appears to be rare and of mild severity.[102] Selective depletion of $CD3^+$ $\alpha\beta$-TCR^+ T cells (thought to be the principal mediators of GvHD) to enrich DLI with $CD3^+$ $\gamma\delta$-TCR^+ T cells and $CD3^-$ $CD56^+$ NK cells is also an attractive strategy to reduce the risk of GvHD while maintaining tumor alloreactivity.[103] Maschan *et al.* infused low-dose ($1x10^5$ $CD3^+$cells/kg) CD45RA-depleted DLI (memory T cell) in 25 patients after TCR α/β-depleted haplo-HCT. The intervention was safe and associated with the expansion of cytomegalovirus-specific T cells in the recipients.[52]

Donor-lymphocyte infusion with immunomodulatory drugs

Immunomodulation with checkpoint inhibitors and targeted agents may enhance the efficacy of DLI. This may allow lower $CD3^+$ cell dose while maintaining tumor alloreactivity. Blinatumomab (a CD19-CD3 bispecific T-cell engager) has been used with DLI for relapsed B-ALL. In a recent report of 14 patients, it appears to be safe with high response rates.[104] In a prospective phase II study, DLI was administered with azacitidine and lenalidomide in patients with molecular or hematologic relapse of myeloid malignancies. The combination was relatively safe and the CR rates were 67% in MRD and 43% in hematologic relapse.[80] Interferon-γ (IFNγ) induced re-expression of epigenetically silenced MHC class II antigens in relapsed AML clones after allo-HCT.[105] One could hypothesize that treating a patient with IFNγ before haplo-DLI may result in better tumor alloreactivity, although it may also increase the risk of GvHD.

Conclusions

- Unmanipulated DLI from a haploidentical donor appears to be relatively safe and reasonably effective in patients who relapse after a T-cell replete haplo-HCT. Patients given haplo-DLI should be enrolled in a clinical trial whenever possible, as data regarding optimal cell dose, timing and role of concurrent systemic therapies with haplo-DLI are limited. Information about the application of unmanipulated DLI after T-cell depleted transplantation is limited, which is why dosing should be managed with caution.
- The risk of GvHD after unmanipulated DLI in the haplo-HCT/PTCy setting is comparable to an unmanipulated DLI from an HLA-matched donor.
- Cytoreductive therapy prior to DLI from a haploidentical donor should be considered in patients with a hematologic relapse after haplo-HCT.
- Pre-emptive haplo-DLI may play a role in reducing disease relapse in patients with persistent MRD or mixed-donor chimerism after haplo-HCT; however, more studies are needed.
- Patients with high-risk myeloid malignancies may benefit from a prophylactic haplo-DLI, which should ide-

ally be used in the setting of a clinical trial.

• The administration of manipulated DLI after T-cell depleted or T-cell replete haploidentical transplantation, such as allodepleted or gene-modified T cells, should only be performed in the setting of a clinical trial.

• Patients should be monitored closely with frequent disease-specific MRD testing and donor-chimerism after DLI administration.

• Mismatched-HLA allele loss was detected in one-third of leukemia relapses after a haplo-HCT. Such patients are unlikely to benefit from DLI from the original donor. A second allo-HCT from a related donor with a different mismatched haplotype or a mismatched unrelated donor may be considered if HLA-loss is confirmed.

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