

Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant

Effective: December 1, 2023

Next Review: August 2024

Last Review: October 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Donor lymphocyte infusion (DLI) is a type of therapy in which T lymphocytes from the blood of a donor are given to a patient who has already received a hematopoietic cell transplant (HCT) from the same donor. Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

Note: See Appendix I for a glossary of terms.

- I. Donor lymphocyte infusion for a patient who has already received a hematopoietic cell transplantation may be considered **medically necessary** when all of the following Criteria are met (A. – C.):
 - A. A hematologic malignancy that has relapsed or is refractory; and
 - B. To prevent relapse in the setting of a high risk of relapse (i.e., T-cell depleted grafts, non-myeloablative conditioning regimens); and
 - C. To convert a patient from mixed to full donor chimerism.

- II. Donor lymphocyte infusion is considered not medically necessary when Criterion I. is not met.
- III. Donor lymphocyte infusion for all other indications is considered investigational including but not limited to following allogeneic hematopoietic cell transplantation that was originally considered investigational for the treatment of a hematologic malignancy.
- IV. Genetic modification of donor lymphocytes is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Medical Policy Manual: [Transplant Section Table of Contents](#)

BACKGROUND

Donor lymphocyte infusion (DLI), also called donor leukocyte or buffy-coat infusion, is a type of therapy in which T lymphocytes from the blood of a donor are given to a patient who has already received a hematopoietic cell transplant (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]) from the same donor. The DLI therapeutic effect results from a graft-versus-leukemic or graft-versus-tumor effect due to the recognition of certain antigens on the cancer cells by the donor lymphocytes and the resultant elimination of the tumor cells. Approximately 40-60% of patients who receive a DLI develop graft-versus-host disease (GVHD), and the development of GVHD predicts a response to the DLI.^[1, 2] Treatment-related mortality after DLI is 5-20%. There does not seem to be a correlation between the type of hematologic malignancy for which the DLI was given and the development

of GVHD.^[1, 2] The risk of development of GVHD is related, in part, to DLI dose and therapy prior to DLI.

The timing of the use of DLI depends upon the disease indication and may be used in the setting of:

- Management of relapse after an allogeneic HCT. Relapse occurs in approximately 40% of all hematologic malignancy patients and is the most common indication for DLI.^[3]
- As a planned strategy to prevent disease relapse in the settings considered high risk for relapse:
 - T cell depleted grafts
 - Non-myeloablative (reduced-intensity) conditioning regimens
 - As a method to convert mixed to full donor chimerism.

DLI is used in nearly all hematologic malignancies for which allogeneic HCT is performed, including chronic myeloid leukemia, acute myeloid and lymphoblastic leukemias, myelodysplastic syndromes, multiple myeloma and Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL).

EVIDENCE SUMMARY

The principal outcomes associated with treatment of hematologic malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease may be another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of donor lymphocyte infusion (DLI) on health outcomes following allogeneic-HCT for treatment of hematologic malignancies, well-designed randomized controlled trials (RCTs) that compare this therapy with standard medical treatment without DLI provide the most reliable evidence. In the absence of such information, sufficiently large comparative or observational studies may be sufficient to isolate a potential treatment effect. Further, for treatment of malignant cancers, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

CHRONIC MYELOGENOUS LEUKEMIA (CML)

The role of DLI in CML has recently changed as the use of tyrosine-kinase inhibitors (TKIs) has revolutionized the treatment of CML by keeping the disease under control instead of proceeding to HCT. However, for patients who develop resistance to the TKIs or are unable to tolerate the adverse effects, HCT and DLI may be an option to manage the disease.

Literature on the use of DLI in CML consists of large series reporting outcomes of patients with relapsed CML after receiving DLI.^[4-9] These studies comprise over 1000 patients, approximately half of whom had only molecular or cytogenetic relapse at the time of DLI.^[2] The cell doses varied among patients, with some patients receiving multiple DLI infusions and others receiving planned dose escalations. Despite these variations, a molecular or cytogenetic complete remission (CR) was achieved in 74% of patients (746/1007). OS at 3 or more years ranged from 53% to 95%^[3] and was 64% at 5 years and 59% at 10 years after DLI

in another series^[9]. Although interpretation of this evidence is limited by the non-randomized, non-comparative nature of available studies, it is sufficient to suggest treatment benefit with DLI among some patients with CML.

ACUTE LEUKEMIAS, MYELODYSPLASIA, AND OTHER MYELOPROLIFERATIVE DISEASES

Systematic Reviews

A study by Yuan (2021) assessed the preemptive DLI after allogenic hematopoietic cell transplantation (HCT) DLI for late-onset minimal residual disease in acute leukemia or myelodysplastic syndrome.^[10] The study also compared the preemptive DLI to preemptive IL-1 therapy for the same condition. They found that 1-year overall survival (OS) and disease-free survival (DFS) rates were 78.4% and 75.6%, and the cumulative incidence of grades II-IV acute graft versus host disease at 100 days post-preemptive intervention was 12%. The authors concluded that preemptive IL-2 and preemptive DLI yield have comparable outcomes for patients with LMRD receiving allogenic HCT, in terms of acute GVHD, non-relapse mortality, relapse, OS, and DFS.

El-Jurdi (2013) evaluated 39 prospective and retrospective studies on DLI for relapse after HCT for lymphoid malignancies including acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma, non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL).^[11] No randomized controlled studies were identified. The studies were heterogeneous thus limiting interpretation of the review. Reported pooled proportions of CR (95% confidence interval [CI]) were 27% (16% to 40%) for ALL, 55% (15% to 92%) for CLL, 26% (19% to 33%) for multiple myeloma, 52% (33% to 71%) for NHL, and 37% (20% to 56%) for HL.

Nonrandomized Studies

Stadler (2023) published ten-year data on a cohort of 272 consecutive patients with high risk acute leukemia or MDS who were in complete remission at day 120 post-transplant.^[12] Of the cohort, 72 did not have clinical evidence of graft vs. host disease (GVHD) at day 120 and were treated with prophylactic DLI (proDLI). They were compared to 157 patients with clinically relevant GVHD who did not receive DLI and 43 patients who did not receive DLI due to contraindications (e.g., infection, patient refusal, DLI unavailability). Five-year OS and PFS were significantly higher in the proDLI group (77% and 67%) compared to the spontaneous GVHD group (54% and 53%) and the group with contraindications to DLI (46% and 45%) ($p=0.003$). Relapse incidence was highest in the group with DLI contraindications (39%; $p=0.021$) and similar in the proDLI (30%) and GVHD (29%) groups. The study suggests that inducing a graft vs. tumor effect using proDLI in patients without GVHD by transplant day 120 offers similar survival to spontaneous GVHD.

An observational study comparing different treatments for relapse reported on 147 consecutive patients who relapsed after allogeneic HCT for myelodysplastic syndrome.^[13] Sixty-two patients received HCT or DLI, 39 received cytoreductive treatment, and 46 were managed with palliative or supportive care. Two-year rates of OS were 32%, 6%, and 2%, respectively ($p<0.001$). In multivariate analysis, 4 factors adversely influenced 2-year rates of OS: history of acute graft-versus-host disease (hazard ratio [HR], 1.83; 95% CI, 1.26 to 2.67; $p=0.002$), relapse within 6 months (HR=2.69; 95% CI, 0.82 to 3.98; $p<0.001$), progression to acute myelogenous leukemia (HR=2.59; 95% CI, 1.75 to 3.83; $p<0.001$), and platelet count less than

50 g/L at relapse (HR=1.68; 95% CI, 1.15 to 2.44; p=0.007). HCT or DLI was found to be an independent factor that favorably impacts OS (HR=0.40; 95% CI, 0.26 to 0.63; p<0.001).

ACUTE MYELOGENOUS LEUKEMIA (AML)

The studies of myeloproliferative diseases treated with DLI either after relapse or for mixed chimerism are characterized by small sample sizes, inconsistent pre-DLI therapy, and varied DLI cell doses, making it difficult to draw definite conclusions on outcomes.^[3] However, it appears some patients attain durable remissions with DLI after post-transplant relapse.

Nonrandomized Studies

Booth (2023) conducted a retrospective study of pediatric patients with AML that compared post-transplant maintenance therapy using azacytidine (AZA) and prophylactic DLI to historical controls that did not receive maintenance therapy.^[14] A total of 56 patients were included; 39 in the preintervention group and 17 in the postintervention group. Two-year leukemia-free survival (LFS) was improved in the postintervention group but was not significant (p=0.06). Similarly, OS at two years was higher in the postintervention group (88.2% vs 69.2%) but the difference was not significant (p=0.15). The authors conclude that more study is needed to understand the efficacy of post-transplant maintenance therapy with AZA and DLI.

Yan (2016) conducted a non-randomized study in 47 patients with acute leukemia relapsing after an allogeneic HCT^[15]. The patients had achieved complete remission after post-relapse induction chemotherapy and DLI and were compared to a control group who did not receive consolidation chemotherapy and DLI after induction chemotherapy and DLI. The use of consolidation chemotherapy and DLI was guided by results from minimal residual disease testing in addition to whether DLI cause any graft-vs-host disease (GvHD). The one year cumulative incidence of relapse (CIR) was 22% compared to 56% for controls. Leukemia-free survival was 71% compared to 35% for controls. These results suggest that MRD and GvHD guided consolidation chemotherapy and DLI improve outcomes in patients with acute leukemias.

A 2015 large retrospective series from the Center for International Blood and Marrow Transplant Research (CIBMTR) reported outcomes of 1788 AML patients who relapsed after allogeneic HCT in CR1 or CR2, among whom 1231 (69%) received subsequent intensive therapy that included DLI.^[16] Among the 1231 patients who received treatment, 660 (54%) received chemotherapy alone; 202 (16%) received DLI with or without chemotherapy; and, 369 (30%) received a second allogeneic HCT with or without additional chemotherapy or DLI. Among all patients who received DLI, 87 (33%) survived more than 1 year after relapse; median survival was 7 months, with a range of 1 to 177 months. Cell-based therapy (DLI or second HCT) resulted in significantly better post-relapse OS compared with those who received chemotherapy alone. These results are consistent with other reports of DLI in patients who relapse after allogeneic HCT to treat AML.

An analysis from the German Cooperative Transplant Study Group reported outcomes among a cohort of patients (N=154) who relapsed after undergoing allogeneic HCT to treat AML (n=124), MDS (n=28), or myeloproliferative syndrome (n=2).^[17] All patients received a median of 4 courses of azacytidine and DLI was administered to 105 (68%). OS among all patients was 29%±4% at 2-year follow-up, which compares favorably with other reports. The overall incidence of acute GVHD based on the total cohort (N=154) was 23%, and 31% in those given DLI (n=105).

Acute Lymphoblastic Leukemia (ALL)

The graft versus tumor effect is thought to be less robust in patients with ALL than in the myeloid leukemias. The clinically evident graft-versus-leukemia effect of DLI requires weeks to months to become apparent, and, as ALL is a rapidly proliferating disease, DLI only is unable to control the disease without a significant reduction in leukemia burden prior to DLI. Small studies have reported response rates to DLI ranging from 0% to 20% and OS rates of less than 15% in patients with ALL.^[2] By comparison, a second allogeneic HCT provides a 5-year OS of approximately 15-20%, with a treatment-related mortality rate of approximately 50%.

Available evidence to date consists of case series. Although it is not clear whether DLI adds benefit to salvage chemotherapy, there are reports of long-term survivors with relapsed ALL who received both chemotherapy and DLI.^[3] More recent studies compare the use of newer therapies, especially donor-derived chimeric antigen receptor (CAR)-T cell therapy, to DLI.

Liang (2023) compared DLI to donor-derived CAR-T cell therapy in a retrospective study that included 21 patients with refractory or relapsed B-cell lineage (B-ALL) after allogeneic HCT.^[18] Twelve patients were treated with CAR-T therapy and 12 were in a control group treated with DLI. There were three overlaps that received DLI and then CAR-T after subsequent relapse. Median event free survival (EFS) was 516 days in the CAR-T group and 98 days in the DLI group (HR=0.37, 95% CI 0.14-0.96, p=0.0415). However, median OS was not significantly different (412 days vs. 180 days; HR= 0.49, 95% CI 0.17-1.43, p=0.1143). Further study comparing DLI to CAR-T therapy with larger subject sizes is necessary to determine whether CAR-T therapy leads to improved survival compared to DLI.

Tan (2023) conducted a study comparing the efficacy of donor-derived CD19 CAR-T cell therapy to chemotherapy plus DLI for recurrent CD19-positive B-ALL after allogeneic HCT.^[19] The retrospective study involved 43 subjects; comparing 22 patients who were treated with donor-derived anti-CD19 CAR-T cells to 21 patients treated with chemo-DLI. After therapy, 17 patients in the CAR-T group were in morphological remission while eight in the chemo-DLI group were in remission (p=0.008). One and two-year LFS rates in the CAR-T group were 54.5% and 50% compared to 9.5% and 4.8% in the chemo-DLI group (p<0.001). OS at one and two years after CAR-T therapy was 59.1% and 54.5%, while OS in the chemo-DLI group was 19.0% at one year and 9.5% at two years (p<0.05). Rates of graft vs. host disease (p=0.106) and hematologic toxicity (100% in both groups) were similar.

Chauvet (2022) published a retrospective multicenter study comparing blinatumomab (blina) with DLI to blina alone in 72 adult or pediatric patients with relapsed B-ALL.^[20] Fifty patients received blina alone and 22 received blina with DLI. The patient groups were similar regarding patient and disease characteristics, but the treatments they received in addition to blina varied in terms of chemotherapy drugs given as well as the use of local radiation, second transplant, and CAR-T cell therapy. Median follow-up time differed (p=0.03); the blina group follow-up was 38.6 months and the blina with DLI group follow-up was 27.6 months. At two years OS was not significantly different overall (p=0.31), but female sex was associated with better OS (p=0.042). Causes of death were not significantly different (p=0.76). Adverse events and graft vs. host disease incidence were also similar. The authors conclude that prospective trials are needed, but adding DLI to blina therapy does not seem to improve outcomes or toxicities.

LYMPHOMAS

Studies in which patients received DLI for lymphomas consist of small numbers of patients and various histologies (both Hodgkin lymphoma [HL] and high- and low-grade non-Hodgkin lymphomas [NHL]). In general, the highest response rates have been seen in the indolent lymphomas. For NHL, there are too few patients reported with any single histologic subtype of lymphoma to give adequate information of the benefit of DLI for a specific lymphoma subtype.^[3] Examples of available studies include the following:

Morris and colleagues reported on one of the largest case series of patients with NHL (n=21) and found that DLI showed response rates in 3 of 9 patients with high-grade NHL, 1 of 2 patients with mantle cell lymphoma, and 6 of 10 patients with low-grade disease.^[21]

Peggs and colleagues reported on a series of 14 patients with multiply relapsed HL who received reduced-intensity conditioning allogeneic HCT and DLI showed a CR of 57% and survival at 2 years of 35%.^[22]

Although current evidence is not sufficient to form conclusions, in the absence of other effective treatment options, it is suggestive that DLI may have a treatment benefit among patients with some types of lymphomas.

MULTIPLE MYELOMA

Available evidence on the use of DLI in multiple myeloma consists of case series. Observational data suggest a graft-versus-tumor effect in multiple myeloma, as the development of GVHD has correlated with response in several analyses. For example, five studies (n=5-63) investigating the role of DLI in relapsed multiple myeloma reported the highest response to DLI as 62%,^[23] with approximately half of the responders attaining a complete response.^[3, 23-27] One confounding factor for high response rates for multiple myeloma treated with DLI is that corticosteroids used for treating GVHD have a known antimyeloma effect which could potentially enhance response rates in these patients.^[2]

Available evidence is therefore suggestive of a treatment benefit with DLI, although the quality of the evidence cannot exclude the role of potential confounders in reported treatment outcomes.

GENETIC MODIFICATION OF DONOR LYMPHOCYTES

In an effort to control GVHD, a group in Italy explored using genetically modified lymphocytes engineered to express the suicide gene thymidine kinase of herpes simplex virus.^[28] These lymphocytes were infused into 23 patients with various hematologic malignancies who relapsed after an allogeneic HCT. Six patients died of progressive disease within 4 weeks of infusion. Eleven patients experienced disease response (CR in 6 and partial remission in 5). Three patients remained alive in CR at a median of 471 days. Twelve patients were evaluable for GVHD, of which 3 developed acute or chronic GVHD which was successfully treated with ganciclovir.

Due to the heterogenous nature of this study sample, and lack of additional evidence from the peer-reviewed literatures, the treatment effect of genetically modified DLI is not known. Additional evidence, applicable to a carefully selected target population, is needed before conclusions regarding the use of genetic modification of donor lymphocytes can be made.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) *ALL RECOMMENDATIONS ARE CATEGORY 2A UNLESS OTHERWISE INDICATED.

The NCCN guidelines for chronic myelogenous leukemia (CML) include donor lymphocyte infusion (DLI) as an option following allogeneic hematopoietic cell transplant (HCT) in patients who meet criteria for hematologic, cytogenetic, and molecular response and relapse.^[29]

The NCCN guidelines for acute lymphoblastic leukemia (ALL) state that for patients with relapsed disease after allogeneic HCT, a second allogeneic HCT and/or donor lymphocyte infusion (DLI) can be considered.^[30] The NCCN guidelines for pediatric acute lymphoblastic leukemia state that DLI was an early therapy for advanced ALL, but current advances are focused on the use of CAR T to target B-cell lineage (B-ALL) cells.^[30]

The NCCN guidelines for myelodysplastic syndromes state DLI immune-based therapy may be considered for relapse after allogeneic HCT for appropriate patients who had prolonged remission after first transplant.^[31]

The NCCN guidelines for treating multiple myeloma include DLI in the options for additional therapy for relapse or progressive disease after allogeneic HCT.^[32]

SUMMARY

There is enough research to show that donor leukocyte infusion improves outcomes in select patients. Clinical guidelines based on research recommend donor leukocyte infusion for relapse or progressive disease following an allogeneic hematopoietic cell transplantation. Therefore, donor leukocyte infusion may be considered medically necessary when policy criteria are met.

There is not enough research to show that donor leukocyte infusion improves outcomes in patients when policy criteria are not met including but not limited to non-hematologic malignancies. Therefore, the use of donor leukocyte infusion is considered not medically necessary when policy criteria are not met.

There is not enough research to show that donor leukocyte infusion improves outcomes for any other indications including, but not limited to, the use of donor leukocyte infusion with genetically modified donor lymphocytes. No clinical guidelines based on research recommend donor leukocyte infusion in any other indications. Therefore, the use of donor leukocyte infusion is considered investigational for all other indications.

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CODES

Codes	Number	Description
CPT	38242	Allogeneic lymphocyte infusions
HCPCS	None	

Date of Origin: September 2011