



# Medical Coverage Policy

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## Donor Lymphocyte Infusion and Hematopoietic Progenitor Cell (HPC) Boost

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### Overview

This Coverage Policy addresses donor lymphocyte infusion (DLI) and hematopoietic progenitor cell (HPC) boost. These therapies may be given following hematopoietic stem cell transplantation (HSCT). The donor source for DLI and HPC boost is the same as that for the HSCT.

A DLI is a type of therapy in which lymphocytes from the blood of a donor are given to an individual whose disease does not respond or relapses following an allogeneic HSCT for a hematologic cancer. DLI is used to treat relapsed, persistent or refractory hematologic malignancy or when there is high risk of relapse of a hematologic malignancy.

Hematopoietic progenitor cell (HPC) boost is an infusion of stem cells given following autologous and allogeneic HSCT to promote engraftment or enhancement of chimerism.

### Coverage Policy

**Donor lymphocyte infusion (DLI) is considered medically necessary following an allogeneic hematopoietic stem cell transplantation (HSCT) for the treatment of a relapsed, persistent or refractory hematologic malignancy or when there is high risk of relapse of a hematologic malignancy.**

**Hematopoietic progenitor cell (HPC) boost is considered medically necessary following autologous and allogeneic HSCT for EITHER of the following indications:**

- promote engraftment
- enhancement of chimerism when studies reveal <100% donor cells

**DLI is considered experimental, investigational or unproven for any other condition.**

## General Background

### Donor Lymphocyte Infusion (DLI)

Donor lymphocyte infusion (DLI), also called donor leukocyte infusion, or buffy coat infusion, is a type of therapy in which lymphocytes from the blood of the donor are given to a patient who has already received allogeneic hematopoietic stem cell transplantation (HSCT) from the same donor. This therapy is based on the premise that the donor lymphocytes will recognize and kill the recipient's cancer cells in a process known as the graft-versus-leukemia (GVL) or graft-versus-tumor (GVT) effect. It is now accepted that DLI, at a time remote from the transplant conditioning regimen, can treat infections and relapse successfully after allogeneic HSCT in selected patients with hematologic malignancies; however significant complications may result including acute and chronic graft-versus-host disease (GVHD), anemia, and infection. DLI is not used to promote engraftment or enhancement of chimerism. The intent is not to restore hematopoiesis. The recipient does not receive a preparative regimen, but may require concomitant therapy for the underlying problem (LeMaistre et al., 2013).

Timing of DLI varies according to indication; for example, to treat tumor recurrence as a planned strategy to prevent disease relapse in the setting of T-cell-depleted grafts or non-myeloablative conditioning regimens (Tomblyn, 2008; Porter, 2006). The success of DLI to treat a relapse has also been shown to be disease-specific (Soiffer, 2008; Shattenberg, 2005). Better outcomes have been noted with chronic myelogenous leukemia (CML); although remissions have also been achieved with other hematologic malignancies, including acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML)/myelodysplastic syndrome (MDS), multiple myeloma, non-Hodgkin lymphoma, Hodgkin disease, chronic myelomonocytic leukemia (CMML), and idiopathic myelofibrosis. The more common indications for which DLI may be used in selected individuals are discussed below.

### Literature Review

**Chronic Myelogenous Leukemia (CML):** DLI is an effective means of restoring sustained, complete cytogenetic or molecular remissions in patients with relapsed CML and has been shown to induce complete remission (CR) in 60–80% of patients (Soiffer, 2008; Huff, 2006; Weisser, 2006; Michallet, 2005; Ferrara, 2004). Individuals transplanted in chronic phase have better outcomes than those with advanced disease (Levine, 2002; Luznik, 2002; Dazzi, 2000; Porter, 2000). DLI is highly effective if an appropriate number of cells are used. Factors affecting the optimal cell dose include the number of leukemic cells at the time of DLI and the alloreactive T-cell frequency contained in the donor lymphocyte preparation (Simula, 2007). Several small case series have demonstrated similar outcomes for the use of unrelated-donor DLI compared with matched sibling donor DLI (Loren and Porter, 2006).

A number of studies have examined outcomes of DLI alone compared with chemotherapy or DLI in combination with a chemotherapy agent. Authors noted that imatinib, in contrast to DLI, does not provide definite cure for relapsed CML after allogeneic HSCT. For patients with relapsing CML who received DLI after allogeneic HSCT 95% of patients achieved a complete molecular remission, while 90%, 70%, and 70% of those receiving imatinib achieved hematologic, complete molecular cytogenetic, and complete molecular genetic remission, respectively. One-, three-, and five-year probability of overall survival was 100%, 85%, and 76%-100%.

**Acute Lymphocytic Leukemia (ALL):** The existence of a GVL effect in the setting of clinical allogeneic transplantation has been demonstrated for patients with acute leukemia; however, the benefit of DLI for relapsed acute leukemia is limited. OS rates are 15%–20% at one month to three years (Arellano, 2007). In a study involving 310 consecutive patients with relapsed acute leukemia who received DLI following human leukocyte antigen (HLA)-matched-donor allogeneic HSCT, OS was 32% (Arellano, 2007). Multivariate analysis indicated that longer time to relapse after HSCT, peripheral blood source for stem cells, and initial post-relapse therapy with cytokines, DLI, or second HSCT were associated with improved post-relapse survival ( $p < .001$ ,  $p < .001$ , and  $p < .25$ , respectively). Study outcomes suggest that therapies aimed at enhancing the GVL effect of allogeneic transplantation, including the use of DLI, may be beneficial for improving post-transplantation survival. Smaller studies involving <25 patients have demonstrated remission rates of four to thirty-eight months with the use of donor lymphocyte infusion (DLI) after allogeneic hematopoietic stem cell transplantation (HSCT) (Savani, 2005; Takami, 2005).

**Acute Myelogenous Leukemia (AML)/Myelodysplastic Syndrome (MDS):** A graft-versus-leukemia (GVL) effect has been identified in patients with relapsed AML or MDS undergoing DLI after allogeneic HSCT. Survival is reported in several small retrospective studies as 24%-42% at a range of one year to 49 months (Campregher, 2007; Pollyea, 2007; Orr, 2006; Choi, 2004; Depril, 2004; Porter, 2000). In a study by Schmid et al. (2008) comparing 399 patients with AML in first hematological relapse after HSCT whose treatment did (n=171), or who did not (n=228) include DLI, estimated survival at two years was 21% and 9%, respectively, for the cohort receiving DLI compared with the non-DLI group. Better outcome was noted for age >37 years ( $p < 0.008$ ), relapse occurring more than five months after HSCT ( $p < 0.0001$ ), and use of DLI ( $p < 0.04$ ).

Depil et al. (2004) studied outcomes with donor lymphocyte infusion (DLI) for 14 patients with myelodysplastic syndrome (MDS) in relapse following allogeneic hematopoietic stem cell transplantation (HSCT). The median time from HSCT to relapse was 319 days, and median time from relapse to DLI was 35 days. Patients received a median dose of 2.5 infusions per patient. Treatment-related mortality (TRM) was 0%. At median follow-up interval of 49 months, six patients (42%) were alive. Overall estimated survival from time of DLI was 528 days. The authors noted that DLI is well-tolerated and seems to be effective in a small number of patients; however, DLI alone should not be considered as standard treatment for remission induction in patients relapsing after HSCT for MDS.

**Multiple Myeloma (MM):** The use of DLI has also been proposed for the treatment of relapsed MM following allogeneic HSCT. According to Tomblyn (2008), patients with MM have overall response rates of 40–45% after DLI with remission rates of 30% suggesting benefit in relapsed disease. Many remissions are not durable, however. The strongest prognostic factor predicting response is the occurrence of graft-versus-host disease (GVHD) (Kolb, 2008; Lockhorst, 2004). Lavenga et al. (2007) studied a cohort of 24 patients with MM who were preemptively treated with DLI following partial T-cell depleted allogeneic HSCT. Thirteen patients received DLI after HSCT. The median time from transplant to DLI was 7.5 months. Eleven patients did not receive DLI because of GVHD, rejection, rapid progressive disease, poor performance status, donor-related problems, or death. Overall, 10 patients achieved a clinical complete remission after DLI. Therapeutic DLI was given for progression or relapse in four patients; two of these patients entered partial remission and were alive at 64 and 58 months after HSCT, respectively.

Van de Donk et al. (2006) retrospectively reviewed 63 patients with relapsed or persistent myeloma who were given DLI following non-myeloablative allogeneic HSCT. Overall response rate was 38.1%. Overall survival (OS) after DLI was 23.6 months. Median OS for patients not responding to DLI was 23.6 months and had not been reached for patients responding to DLI. In responders, progression-free survival (PFS) was 27.8 months. Major toxicities were acute (38.1%) and chronic GVHD (42.9%). The only significant prognostic factor for response to DLI was the occurrence of acute or chronic GVHD.

**Non-Hodgkin Lymphoma (NHL):** For recurrent childhood NHL, standard treatment may include HSCT followed by DLI or an infusion of T-cell lymphocytes that have been treated in the laboratory (National Cancer Institute [NCI], 2018). Bloor et al. (2008) reported the results of 28 patients with low-grade lymphoid malignancies previously treated with a reduced intensity (n=26) or fully myeloablative (n=2) allogeneic HSCT. Indications for DLI were progressive disease with or without mixed chimerism and persistent mixed chimerism alone six months from the date of transplantation, without significant GVHD. Thirteen patients responded to DLI. The cumulative

response rates after DLI to treat progressive disease and persistent mixed chimerism were 76.5% and 91.6%, respectively. All thirteen patients achieved complete remission which was ongoing in nine patients at a median duration of 967 days from last DLI. Of the 17 patients treated for disease progression, the projected five-year OS and progression-free survival (PFS) rates after the last treatment with DLI were 87.8% and 76.2%, respectively. A total of 25 patients received DLI for mixed chimerism. The cumulative response to DLI for mixed chimerism was 92 %. All of the responding patients converted to stable full chimerism; the median time to response was 6.7 months. Results of this study demonstrate a significant response to DLI for patients treated for indolent lymphomas with disease progression post-HSCT. Cumulative complete remission rate was >75%. These results suggest that this is an effective treatment for progressive disease after allogeneic HSCT.

### **Hematopoietic Progenitor Cell (HPC) Boost**

A boost of hematopoietic progenitor cells (HPC) (also known as stem cells) from the original HCST donor is intended to restore hematopoiesis or augment poor graft function after hematopoietic stem cell transplantation (HSCT). Poor graft function is a severe complication of HSCT which is defined as persistent cytopenias and/or transfusion dependence. The cell product used for a HPC boost may be a previously cryopreserved cell product, or alternatively, the donor may need to undergo additional evaluation, stem cell mobilization, and cell harvest. A boost is not preceded by a preparative regimen. A potential source of confusion is that a boost is often required when additional conventional chemotherapy is given to treat relapse and reestablish remission after transplantation. Prolonged cytopenias and immunosuppression may result, requiring additional HPC boost, which is typically given days to weeks after reinduction chemotherapy (LeMaistre, 2013).

### **Literature Review**

Although data are not robust, several prospective and retrospective clinical trials demonstrate beneficial effects of HPC boost after HSCT.

Ghobadi et al. (2017) reported on outcomes of a study utilizing either fresh or cryopreserved peripheral blood stem cell products to create CD34+ selected boost infusions to treat patients (n=26) with poor graft function more than 60 days following allogeneic HSCT. Seventeen donor-recipient pairs were enrolled onto the prospective study; an additional nine patients treated off protocol were reviewed retrospectively. Three different donor products were used for CD34+ selection: fresh mobilized product using G-CSF only, fresh mobilized products using G-CSF and plerixafor, and cryopreserved cells mobilized with G-CSF. The primary objective was hematologic response rate and secondary objectives included CD34+ yields, incidence and severity of acute and chronic graft-versus-host disease (GVHD), overall survival (OS), and relapse-free survival (RFS). The complete response rate was 62% and overall response (i.e., hematologic recovery rate) was 81%. Treatment was well tolerated; there was no treatment-related mortality and no grade III or IV acute GVHD. Data suggest improved graft function using fresh or cryopreserved peripheral stem cells.

Mainardi et al. (2017) reported retrospective study results involving 50 children with acute lymphatic leukemia, acute myeloid leukemia and severe aplastic anemia who received 61 boosts with CD34+ selected peripheral blood stem cells after transplantation from matched unrelated (n = 25) or mismatched related (n = 25) donors. No conditioning was performed prior and no immunosuppressive therapy was administered post the allogeneic HSCT. Within 8 weeks, a significant increase in median neutrophil counts ( $p < 0.05$ ) and a decrease in red blood cell and platelet transfusion requirement ( $p < 0.0001$  and  $< 0.001$ ) respectively, were observed. 78.8% of patients resolved one or two of their cytopenias and 36.5% had a complete hematological response. The rate of de novo acute graft-versus-host disease (GVHD) grade I–III was only 6% and resolved completely. No GVHD grade IV or chronic GVHD occurred. Patients who responded to HPC displayed a trend toward better overall survival (OS) ( $P = 0.07$ ). Data suggest improved graft function with HPC boost in this cohort of patients.

Klyuchnikov et al. (2013) retrospectively analyzed outcomes of a CD34<sup>b</sup>-selected stem cell boost (SCB) without prior conditioning in 32 patients with poor graft function. The median interval between allogeneic HSCT and SCB was five months. Hematological improvement was observed in 81% of patients and noted after a median of 30 days after SCB. The recipients of related grafts responded faster than recipients of unrelated grafts ( $p = .04$ ). The cumulative incidence of acute (grade II to IV) and chronic graft-versus-host disease (GVHD) after SCB was 17% and 26%, respectively. Patients with acute GVHD received a higher median CD3<sup>b</sup> cell dose. The two-year probability of overall survival was 45%. Data suggest that SCB represents an effective approach to improve poor

graft function post transplantation. The authors note that optimal timing of SCB administration, anti-infective, and GVHD prophylaxis needs further evaluation.

### Professional Societies/Organizations

**National Cancer Institute ([NCI], 2018):** Regarding treatment with donor lymphocytes, the NCI notes the following:

- Acute myelogenous leukemia (AML): Adult patients who relapse following an allogeneic HSCT may undergo an infusion of lymphocytes from the donor.
- Relapsing chronic myelogenous leukemia (CML): Infusions of buffy coat leukocytes or isolated T cells obtained by pheresis from the transplant donor have induced long-term remissions in more than 50% of patients who relapse following allogeneic transplantation. The efficacy of this treatment is thought to be the result of an immunologic graft-versus-leukemia effect. This treatment is most effective for patients whose relapse is detectable only by cytogenetics or molecular studies and is associated with significant graft-versus-host disease.
- Multiple myeloma: A definite graft-versus-myeloma effect has been demonstrated, including regression of myeloma relapses following the infusion of donor lymphocytes.
- Non-Hodgkin lymphoma (NHL) in children: Adoptive immunotherapy with donor lymphocytes has been effective in treating post transplantation lymphoproliferative disease (PTLD) after blood or bone marrow transplant. Although this approach has been demonstrated to be feasible in patients with PTLD after solid organ transplantation, it has not been demonstrated to be as effective or practical.
- Non-Hodgkin lymphoma (NHL) in adults: Anecdotal durable remissions have been reported after allogeneic HSCT and after subsequent donor lymphocyte infusion for relapses after transplantation.

**National Comprehensive Cancer Network (NCCN™):** Practice Guidelines for Oncology (2019) note the following regarding donor lymphocyte infusion (DLI):

- chronic myelogenous leukemia (CML): effective in inducing durable molecular remissions in the majority of patients with relapsed CML following allogeneic hematopoietic stem cell transplantation (HSCT), though it is more effective in chronic phase than advanced phase relapse.
- multiple myeloma: DLI may be given to stimulate a beneficial graft-versus-myeloma effect in patients whose disease either does not respond to, or relapses after allogeneic stem cell grafting.
- acute lymphoblastic leukemia: DLI can be considered for an individual with relapsed disease
- acute myeloid leukemia: as pre-emptive treatment post allogeneic transplantation

### Centers for Medicare & Medicaid Services (CMS)

- National Coverage Determinations (NCDs): No NCD found
- Local Coverage Determinations (LCDs) No LCD found

### Use outside the US

No relevant information

## Coding/Billing Information

**Note:** 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

CPT®* Codes	Description
38242	Allogeneic lymphocyte infusions
38243	HPC boost

\*Current Procedural Terminology (CPT®) ©2018 American Medical Association: Chicago, IL.

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