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 in both the adult and pediatric populations. 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 and HPC boost are considered not medically necessary for any other indication.

Health Equity Considerations

In a review by Kirtane and Lee (2017), it was estimated that there would be 172,910 new cases of hematologic malignancies diagnosed in 2017 and of these, 58,300 deaths. Data from 2010 to 2014 for Acute myeloid leukemia (AML) suggest that whites have a higher incidence (4.3 per 100,000 persons) compared to Blacks, Asian/Pacific Islanders, and Hispanics (3.5, 3.4, and 3.6 per 100,000 respectively). However, despite a lower incidence, Black and Hispanic patients with AML had an increased risk of death (12 and 6% respectively) compared with non-Hispanic whites. Statistically significant improvements in overall five-year survival and outcomes have been seen in the last several years among non-Hispanic whites (12–16%), Blacks (8–12%, and Asian/Pacific Islanders (11–17%) however, the improvement for Hispanics was not statistically significant (13–14%). Acute Lymphocytic Leukemia (ALL) accounts for approximately 25% of childhood malignancies and data from 1999–2008 suggested that the probability of death for Black and Hispanic patients was about 45–46% higher respectively than for white and Asian/Pacific Islander

patients. Multiple myeloma is one of the most diagnosed hematologic malignancies in Black people with an incidence of 11.0 per 100,000 compared to 4.9 per 100,000 for whites. It is suggested that the higher incidence rate for Blacks may be due to an increased prevalence of monoclonal gammopathy. Five-year survival for individuals aged 50–69 years was significantly higher for Blacks compared to whites (42% vs 36%; p<0.001) and patients aged 70 years or older (31% vs 26%; p<0.001). In an analysis of 37,000 MM patients, it was observed that Hispanics had significantly worse overall survival rates compared to whites (2.4 vs 2.6 years; p=0.006). Compared with whites, Black and Hispanic adolescents and young adults have a 62% and 35% higher risk of death due to Hodgkin's Lymphoma (HL) and are also more likely to be diagnosed at an advanced stage. Five-year overall survival rates for Blacks (76%) and Hispanics (75%) were found to be inferior to whites (82%) and Asian/Pacific Islanders (81%). Patients in the lowest socioeconomic status (SES) were found to have a 64% increased risk of death related to HL compared to patients in the highest SES. The authors suggested that further research into social determinants and biologic hypotheses is needed to identify the basis for these disparities.

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. Overall survival (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).

Patriarca et al. (2020) reported on a retrospective multicenter study including pediatric and adult patients with acute leukemia (AL) who received donor lymphocyte infusions (DLIs) after allogeneic hematopoietic stem cell transplantation (HCT) (n=252). Forty-six patients (18%) received a second HCT after a median of 232 days (32-1,390) from the first DLI. With a median follow-up of 461 days after the first DLI, 1-, 3-, and 5- year overall survival (OS) of the whole group from start of DLI treatment was 55, 39, and 33%, respectively. In multivariate analysis, older recipient age, and transplants from haploidentical donors significantly reduced OS, whereas DLI for mixed chimerism or as pre-emptive/prophylactic treatment compared to DLI for AL relapse and a schedule including more than one DLI significantly prolonged OS. The authors concluded that the study confirms that DLI administration in absence of overt hematological relapse and multiple infusions are associated with a favorable outcome in AL patients and that DLI from haploidentical donors had a poor outcome and may represent an area of further investigation.

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. (2007) 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): 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.

Shahzad et al. (2021) conducted a systematic review and meta-analysis of six retrospective studies and one prospective study to assess the safety and efficacy of stem cell boost (SCB) for poor graft function (PGF) in adult allo-HSCT recipients. There were a total of 209 patients (61% were male) with a median age of 49 years and a range of 18–69 years. The number of participants in each study ranged from 10–62. Hematologic disorders included: acute lymphoblastic leukemia/acute myelogenous leukemia, myelofibrosis, chronic myelogenous leukemia, myelodysplastic syndromes, non-Hodgkin lymphoma, lymphoproliferative disorders, severe aplastic anemia, multiple myeloma, and others. Data on race and ethnicity was not provided. Studies were included if they were case-control, retrospective, or prospective cohort studies; studies reporting data for adult patients; studies reporting allo-HSCT with PGF in the absence of infection, GVHD, or mixed donor chimerism (<95% donor cells); and studies in which CD34-selected SCB was the sole intervention. The intervention was CD34-selected stem cell boost (SCB) administered for poor graft function (PGF) in adult allo-HSCT recipients. The median time frame from allo-HSCT to SCB was 138 days with a range of 113–450 days. Overall response rate (ORR) (i.e., included CR and PR), rates of complete response (CR) (i.e., hematologic improvement in all three cell lineages without transfusion dependence), partial response (PR) (i.e., hematologic improvement in one or two lineages), acute and chronic graft versus host disease (GVHD), relapse, death, non-relapse mortality (NRM), relapse-free survival (RFS), and overall survival (OS). Data was pooled for the experimental arm of the studies only. CR was achieved in 72% of participants (95% CI, 63%–79%; p=0.23; n=209). ORR was achieved in 80% of participants (95% CI, 74%–85%; p=0.66; n=209). PR was achieved in 13% of participants (95% CI, 7%–24%; p=0.24; n=171). OS ranged from 80% at one year to 40% at nine years. Acute GVHD was reported in 17% of participants (95% CI, 13%–23%; p=0.43; n=209). Chronic GVHD was reported in 18% of participants (95% CI, 8%–34%; p<0.01; n=189). NRM was reported in 27% of participants (95% CI, 17%–40%; p=0.06; n=155). Death due to relapse was reported in 17% of participants (95% CI, 11%–23%; p=0.66; n=155). Author noted limitations of the study included poor study design (i.e., retrospective studies and studies without randomization and blinding), small patient populations, and heterogenous nature of the studies. Additional limitations of the study were the failure to pool and compare control arm data and failure to report follow-up intervals for several outcome measures. Data suggest that CD34-selected SCB for PGF in adults status post all-HSCT could result in improved outcomes.

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 CD34þ-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 CD3þ 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): Regarding treatment with donor lymphocytes, the NCI includes the following:

- Multiple myeloma: "A definite graft-versus-myeloma effect has been demonstrated, including regression of myeloma relapses following the infusion of donor lymphocytes (NCI, 2023b)."
- Non-Hodgkin lymphoma (NHL) in children: "Adoptive immunotherapy with either donor lymphocytes or ex vivo–generated EBV-specific cytotoxic T-lymphocytes (EBV-CTLs) has been effective in treating patients with post transplantation lymphoproliferative disease (PTLD) after blood or bone marrow transplantation (NCI, 2024a)."
- Non-Hodgkin lymphoma (NHL) in adults: "Anecdotal durable remissions have been reported after allogeneic SCT and even after subsequent donor lymphocyte infusion for relapses after transplant (NCI, 2023a)."
- Pediatric allogeneic hematopoietic stem cell transplantation: "Investigators have defined two approaches to treat the increased risks of relapse and rejection associated with increasing recipient chimerism: rapid withdrawal of immune suppression and donor lymphocyte infusions (DLI). These approaches are frequently used to address this issue, and they have been shown to decrease relapse risk and stop rejection in some cases. The timing of tapers of immune suppression and doses and approaches to administration of DLI to increase or stabilize donor chimerism vary among transplant approaches and institutions (NCI, 2024b)".

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

- Guideline for chronic myeloid leukemia (CML): "Donor lymphocyte infusion (DLI) is effective in inducing durable molecular remissions in the majority of patients with relapsed CML following allogeneic HCT, though it is more effective in patients with chronic phase relapse than advanced phase relapse (NCCN, 2023)."
- Guideline for multiple myeloma: "Patients whose disease either does not respond to or relapses after allogeneic hematopoietic cell grafting may receive donor lymphocyte infusions to stimulate a beneficial graft-versus-myeloma effect" (NCCN, 2024a).
- Guideline for acute lymphoblastic leukemia: "For patients with relapsed disease after allogeneic HCT, a second allogeneic HCT and/or donor lymphocyte infusion (DLI) can be considered (NCCN, 2024b)."

Use outside the US
No relevant information

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	No National Coverage Determination found	
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:
1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare and Medicaid Services (CMS) code updates may occur more frequently than policy updates.
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	Hematopoietic progenitor cell (HPC); HPC boost

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Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	No clinical policy statement changes.	5/15/2024