Clinical Policy: Donor Lymphocyte Infusion

Reference Number: LA.CP.MP.101 Coding Implications
Date of Last Revision: ~~2~~10~~[EG1]~~/122 Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
This policy describes the medical necessity requirements for a donor lymphocyte infusion (DLI). DLI is an immune therapy approach to decrease the risk of relapse for many hematologic malignancies following allogeneic hematopoietic stem cell transplantation (HSCT), or to convert a patient's mixed to full donor chimerism, a state where both donor and recipient stem cells coexist. In this procedure, donor lymphocytes from the original stem cell donor are infused into the patient to cause an immune-mediated graft vs. tumor response. The hematologic malignancies treated by DLIs can include, but are not ~~be~~ limited to, chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), lymphomas, multiple myeloma, and myelodysplastic syndrome.

Policy/Criteria

I. It is the policy of Louisiana Healthcare Connections that donor lymphocyte infusion (DLI) is **medically necessary** following an allogeneic hematopoietic stem cell transplantation (HSCT) for any of the following indications:
- **A.** To decrease the risk of relapse of hematologic malignancy;
- **B.** To convert the recipient stem cells of the donor from mixed to full donor chimerism if there is a concern for relapse. DLI should not be used for the sole purpose of increasing donor chimerism without the risk of relapse.

II. It is the policy of Louisiana Healthcare Connections that current evidence does not support the use of donor lymphocyte infusion for any of the following:
- **A.** For the treatment of all other conditions than those specified above;
- **B.** Genetic modification or *ex vivo* manipulation of donor lymphocytes;
- **C.** In the presence of higher than grade 2 acute graft-versus-host-disease (GvHD);
- **D.** In the presence of total host chimerism.

Background
In addition to chemotherapy, hematopoietic stem cell transplantation (HSCT) has become a mainstream clinical therapy for a variety of hematologic malignancies. Even though the anti-tumor effects of HSCT can be durable for some patients, relapse of the original malignancy presents considerable clinical challenges for 40 to 75% of patients who undergo autologous HSCT and 10 to 40% of those who undergo allogeneic HSCT.[1] Therefore, salvage therapies to combat the refractory disease are required. Donor lymphocyte infusion (DLI) is one such post-transplant immunotherapy.

DLI ~~onor lymphocyte infusion~~, otherwise known as buffy coat infusion, was originally described in 1990 by Kolb and colleagues as a treatment protocol for three patients who relapsed after bone marrow transplantation for chronic myeloid leukemia (CML).[2] In this procedure, mononuclear cells collected by apheresis from the related or unrelated donor who provided the original hematopoietic stem cell graft are infused into the patient to harness the graft vs. tumor effect.

While there is some variety in published reports concerning the dose of donor cells infused, Deol and Lum's review surveyed several articles and reported ~~an effective cellular range of~~ 0.01 to 8.8 × 10^8 T cells/kg as an effective cellular range.[3]

The precise mechanism of action, including the tumor-specific antigens as well as the critical effector cells that mediate the anti-tumor immune response, has not yet been fully elucidated. However, recent evidence suggests that both donor T cells and host-derived immune compartments, including antigen presenting cells and B cells, among others, are critical for facilitating the graft vs. tumor effect of DLI.[1,3,4]

In striving to eradicate the tumor cell population from the host, complications may persist in patients treated with DLI. Graft vs. host disease (GvHD), the most common and significant toxicity attributable to DLI, occurs in approximately in 40-60% of patients, according to a range of several published reports.[1,4,5] GvHD ensues when the transplanted donor cells recognize the host as foreign and initiate an immune reaction that usually affects the patient's skin, gastrointestinal tract, and/or liver.[6] However, there is a strong correlation observed with the onset of GvHD and the intended graft vs. tumor effect. The onset of GvHD is independent of the type of hematologic malignancy. In a retrospective study, Collins et al. observed ~~that of~~ 140 patients treated with DLI for relapsed disease after stem cell transplant, and approximately 60% of these patients presented with GvHD; Acute GvHD developed in 42/45 of these~~, 42/45~~ patients, ~~in complete response of disease developed acute GvHD and~~ and chronic GvHD occurred in 36/41 of these patients ~~in complete response of disease displayed chronic GvHD~~.[7] ~~Nevertheless,~~ Carlens et al. determined that the 3 year leukemia free survival was greater for patients who develop chronic GvHD than for those who do not.[8] Therefore, the ultimate goal of DLI is to maximize the graft vs. tumor response while minimizing the complications that arise from the related GvHD.

In addition to GvHD, bone marrow aplasia is another major complication that can occur in 2 to ~~-~~5% of patients following DLI.[9] Infection and bleeding are compounding risks associated with the onset of aplasia following DLI. The infusion of subsequent donor stem cells can reverse marrow aplasia.

Since Kolb's initial study describing the utility of DLI, focus has been placed on evaluating the clinical benefit of DLI in the context of treating relapsed CML. Multiple studies have revealed that DLI can establish complete remissions in 70-80% of patients with relapsed CML, and the response is durable in the majority of these cases.[9]

DLI is less effective for achieving remission in patients with relapsing acute myeloid leukemia (AML) following HSCT. According to Deol and Lum, there is approximately a 15 to 20% possibility that ~~the ability of~~ DLI will~~to~~ induce remission in relapsed AML ~~is approximately 15-20%~~.[3] However, unlike the observations made for CML, it is often necessary to combine DLI with a chemotherapy regimen to elicit an anti-tumor effect against AML.

Multiple myeloma is another hematologic malignancy with the potential to respond to DLI. Among varying reports, the response rate of relapsed multiple myeloma to DLI is approximately 22 to ~~-~~52%.[10,11] The propensity of multiple myeloma patients to receive autologous and not

allogeneic transplants could have a role in this outcome .[3] National Comprehensive Cancer Network (NCCN) guidelines state that in patients whose disease does not respond to or relapses after allogeneic stem cell grafting may receive DLI to stimulate a beneficial graft-versus-myeloma effect or other myeloma therapies on or off a clinical trial.[18]

Furthermore, DLI is a treatment possibility for relapsed acute lymphoblastic leukemia (ALL). However, the outcomes for relapsed ALL have been less robust compared to CML and AML. Collins et al analyzed outcomes in both retrospective and prospective studies in patients with relapsed ALL treated with chemotherapy and DLI, and found that only 3/44 were disease free.[7]

Lastly, chimerism is an important element that develops after the engraftment of a HSCT.[11] Mixed chimerism is defined when < 90% donor cells are detected, whereas full or complete chimerism is defined as 100% donor cells detected, suggesting completed hematopoietic replacement.[12] One example of the graft vs. tumor effects observed from the conversion to full chimerism was described by Orisini, in which 4 patients with relapsed multiple myeloma received DLI specifically with $CD4^+$ T cells. It was observed that 3/4 patients saw a clinical response in the absence of GvHD with complete hematopoietic conversion.[13]

In summary, ~~donor lymphocyte infusion~~DLI is an effective clinical treatment for an array of relapsed hematologic malignancies. For this adoptive immunotherapy, T lymphocytes from the original stem cell donor are infused into the patient with the intent of inducing a graft vs. tumor response.

Coding Implications

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CPT®* Codes	Description
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38242	Allogeneic lymphocyte infusions
86950	Leukocyte transfusion

HCPCS Codes	Description
S2150	Bone marrow or blood-derived stem-cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy;

HCPCS Codes	Description
	drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition

~~ICD-10-CM Diagnosis Codes that Support Coverage Criteria~~

~~ICD-10-CM Code~~	~~Description~~
~~C81.00 - C81.99~~	~~Hodgkin lymphoma~~
~~C85.10 - C85.99~~	~~Other specified and unspecified types of non-Hodgkin lymphoma~~
~~C90.00 - C90.02~~	~~Multiple myeloma~~
~~C91.00 - C91.Z2~~	~~Lymphoid leukemia~~
~~C92.00 - C92.Z2~~	~~Myeloid leukemia~~
~~D46.0 - D46.Z~~	~~Myelodysplastic syndrome~~
~~Z94.81~~	~~Bone marrow transplant status~~
~~Z94.84~~	~~Stem cells transplant status~~

[EG2]

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Converted corporate to local policy.	08/15/2020	
Annual review. References reviewed and updated. Changed "review date" in the header to "date of last revision" and "date" in the revision log header to "revision date." "Experimental/investigational" verbiage replaced with policy statement verbiage that "current evidence does not support" the use of DLI for the stated indications. Replaced "hematological" with "hematologic" throughout the policy. Added "and may not support medical necessity" in coding implications.	2/22	2/22[EG3] [EG4]
Annual review. Background updated with no impact on criteria. ICD-10 codes removed. References reviewed and updated[EG5]. Changed members to enrollees.	11~~0~~/22	

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Important Reminder

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