Clinical Policy: Donor Lymphocyte Infusion

Reference Number: LA.CP.MP.101

Coding ~~Implications~~

Implemcations

Date of Last Revision: ~~4~~09/23 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 limited to, chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), lymphomas, multiple myeloma, and myelodysplastic syndrome. This policy describes the medical necessity requirements for a donor lymphocyte infusion (DLI). The criteria are sourced from a combination of National Comprehensive Cancer Network (NCCN) guidelines[15, 16, 17, 18,19] and systematic reviews.[2,4,14,27]

This policy allows for DLI post-HSCT to decrease the risk of relapse of hematologic malignancy. It is not recommended in the case of full chimerism, for which DLI does not produce additional benefit. DLI should not be used for the sole purpose of increasing donor chimerism without the risk of relapse due to the risk of exacerbating graft vs. host disease (GvHD) with uncertain benefit.[29] In addition, various techniques to manipulate the donor lymphocyte graft (e.g., enrichment, depletion, activation) to enhance graft vs. tumor (GvT) or lessen GvHD are undergoing investigation. These techniques are not recommended for use outside of a clinical trial since benefits are not established as outweighing risks and further studies are needed before they can be widely utilized for DLI.[14]

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:~~the treatment of relapsed or refractory hematologic malignancy or to decrease the risk of relapse of a hematologic malignancy.[27]

~~A. To decrease the risk of relapse of hematologic malignancy;~~

~~To convert the recipient stem cells of the donor from mixed to full donor chimerism if there is a concern for relapse.~~

~~B.~~ **Note:** DLI should not be used for the sole purpose of increasing donor chimerism without the risk of relapse.[27]

~~C. Does not have ANY of the following absolute contraindications:~~

~~1. Infections with highly virulent and/or resistant microbes that are poorly controlled pre-transplant;~~

~~2. Inability to adhere to the regimen necessary to preserve the transplant, even with caregiver support;~~

~~3. Absence of an adequate or reliable social support system;~~
~~4. Active substance use or dependence including current tobacco use, vaping, marijuana use (unless prescribed by a licensed practitioner), or IV drug use without convincing evidence of risk reduction behaviors (unless urgent transplant timelines are present, in which case a commitment to reducing behaviors is acceptable). Serial blood and urine testing may be used to verify abstinence from substances that are of concern.~~

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.~~A. Genetic modification or *ex vivo* manipulation of donor lymphocytes;[29]
~~C.~~B. In the presence of higher than grade 2 acute graft-versus-host-disease (GvHD~~);~~).[4]
~~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.~~Donor lymphocyte infusion (DLI) is one such post-transplant immunotherapy that can be used for therapeutic purposes (for proven relapsed/progression) or as a pre-emptive/prophylactic therapy in patients considered to be at high risk of relapse. Pre-emptive therapy allows for DLI to be infused in patients having an incipient relapse because of mixed chimerism or detection of minimal residual disease (MRD) by molecular or immunophenotypic methods. Numerous studies suggest that in very high-risk patients, often with mixed chimerism, a high response rate to DLI can be obtained.[27]

DLI, 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 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 to 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 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 patients, and chronic GvHD occurred in 36/41 of these patients.[7] 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 to 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 DLI will induce remission in relapsed AML.[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.[-26] 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, 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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NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis.

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; 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

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	2/22	2/22

Reviews, Revisions, and Approvals	Revision Date	Approval Date
of DLI for the stated indications. Replaced "hematological" with "hematologic" throughout the policy. Added "and may not support medical necessity" in coding implications.		
Annual review. Background updated with no impact on criteria. ICD-10 codes removed. References reviewed and updated. Changed members to enrollees.	12/22	4/3/23
Added contraindication criteria I.C.1. through 4. Background updated with no impact on criteria. Removed HCPCS "S2150" not on LA Fee schedule	4/23	7/21/23
Updated policy description. Updated all criteria in statements I. and II. Note for non-covered codes added.	09/23	

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Important Reminder

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