Clinical Policy: Donor Lymphocyte Infusion

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Date of Last Revision: 02/26

Coding Implications
Revision Log

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

Description

Donor lymphocyte infusion (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-versus-tumor (GvT) 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 DLI given the absence of coverage criteria provided by the Centers for Medicare and Medicaid Services (CMS) and the applicable Medicare Advantage Contractors. The criteria are sourced from a combination of National Comprehensive Cancer Network (NCCN) guidelines[1,2,3,4,5] and systematic reviews.[6,7,8,9]

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-versus-host disease (GvHD) with uncertain benefit.[10] In addition, various techniques to manipulate the donor lymphocyte graft (e.g., enrichment, depletion, activation) to enhance GvT effect 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.[8]

Note: For criteria applicable to non-Medicare plans, please see CP.MP.101 Donor Lymphocyte Infusion.

Policy/Criteria

I. It is the policy of Medicare health plans affiliated with Centene Corporation® that donor lymphocyte infusion (DLI) is **medically necessary** following an allogeneic hematopoietic stem cell transplantation (HSCT) for the treatment of relapsed or refractory hematologic malignancy or to decrease the risk of relapse of a hematologic malignancy.[9]

Note: DLI should not be used for the sole purpose of increasing donor chimerism without the risk of relapse.[9]

II. It is the policy of Medicare health plans affiliated with Centene Corporation that current evidence does not support the use of donor lymphocyte infusion for any other indication, including, but not limited to the following:

A. Genetic modification or *ex vivo* manipulation of donor lymphocytes;[10]

B. In the presence of higher than grade 2 acute graft-versus-host-disease (GvHD).[7]

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, infection, graft-versus-host disease (GVHD), and relapse of the original malignancy remain considerable clinical challenges.[11] Therefore, salvage therapies to combat the refractory disease are required. 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.[9]

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).[6] 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-versus-tumor (GvT) 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.[12]

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 GvT effect of DLI.[11,12,7]

In striving to eradicate the tumor cell population from the host, complications may persist in patients treated with DLI. 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.[11,7,13] 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.[14] However, there is a strong correlation observed with the onset of GvHD and the intended GvT 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 out of 45 of these patients, and chronic GvHD occurred in 36/41 of these patients.[15] Carlens et al. determined that the three year leukemia free survival was greater for patients who develop chronic GvHD than for those who do not.[16] Therefore, the ultimate goal of DLI is to maximize the GvT 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.[17] 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.[17]

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.[12] 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.[18] Among varying reports, the response rate of relapsed multiple myeloma to DLI is approximately 22 to 52%.[19,20] The propensity of multiple myeloma patients to receive autologous and not allogeneic transplants could have a role in this outcome.[12] 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.[4]

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 three out of 44 were disease-free.[15]

Lastly, chimerism is an important element that develops after the engraftment of a HSCT.[20] 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.[21] One example of the GvT effects observed from the conversion to full chimerism was described by Orisini, in which four patients with relapsed multiple myeloma received DLI specifically with $CD4^+$ T cells. It was observed that three out of four patients saw a clinical response in the absence of GvHD with complete hematopoietic conversion.[22]

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 GvT response.

Coding Implications

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from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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
Policy developed.	08/23	08/23
Annual review. Minor rewording in Description with no impact on criteria. Background updated with no impact on criteria. References reviewed and updated. Reviewed by external specialist.	04/24	04/24
Annual review. Added clarifying language to Criteria II. References reviewed and updated. Reviewed by internal specialist.	02/25	02/25
Updated description to note the absence of coverage criteria from CMS.	12/25	
Annual review. Coding and descriptions reviewed. References reviewed and updated. Reviewed by internal specialist and external specialist.	02/26	02/26

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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Note: For Medicaid members/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.