Clinical Policy: Donor Lymphocyte Infusion

Reference Number: CP.MP.101
Date of Last Revision: 10/23

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 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 (MM), and myelodysplastic syndrome (MDS). This policy describes the medical necessity requirements for DLI. 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 vs. host disease (GvHD) with uncertain benefit.[10] 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.[8]

Policy/Criteria

I. It is the policy of 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 health plans affiliated with Centene Corporation that current evidence does not support the use of donor lymphocyte infusion for any of the following:
A. Genetic modification or *ex vivo* manipulation of donor lymphocytes;[10]
B. In the presence of grade 2 or higher acute graft versus host disease (GvHD).[7,8]

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.[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 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.[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 graft vs. tumor effect of DLI.[7,11,12]

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 40 to 60% of patients, according to a range of several published reports.[7,11,13] 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 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.[15] Carlens et al. determined that the three year leukemia free survival is greater for patients who develop chronic GvHD than for those who do not.[16] 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.[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 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 3/44 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 graft vs. tumor 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 3/4 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 graft vs. tumor response.

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2022, American Medical Association. All rights reserved. CPT codes and CPT descriptions are 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 posttransplant care in the global definition

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed	11/15	11/15
References reviewed and updated. Specialist review.	09/19	10/19
Description updated. Specified in I.A. that DLI is indicated to reduce the risk of relapse. Added to I.B. that DLI is intended to convert recipient cells from mixed to full chimerism, if there is a risk of relapse. Added to II. "higher than grade 2 acute graft-versus-host-disease (GvHD)" and "total host chimerism." Removed not medically necessary indication from section II. of a second DLI when benefits were not noted from the first. References reviewed and updated. Specialist review. Replaced "member" with "member/enrollee" in all instances.	10/20	10/20
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.	10/21	10/21
Annual review. Background updated with no impact on criteria. ICD-10 codes removed. References reviewed and updated. Specialist review.	10/22	10/22
Added contraindication criteria I.C.1. through 4.	02/23	02/23
Updated policy description. Updated all criteria in statements I. and II.	08/23	08/23
Annual review. Minor rewording in Description with no impact on criteria. Criteria II.B. updated to state grade 2 or higher acute graft versus host disease (GvHD). Background updated with no impact on criteria. References reviewed and updated. Reviewed by internal specialist.	10/23	10/23

References

1. Brown PA, Shah B, Advani A, et al. Acute Lymphoblastic Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2021;19(9):1079 to 1109. Published 2021 Sep 20. doi:10.6004/jnccn.2021.0042
2. National Comprehensive Cancer Network®. NCCN Guidelines Version 4.2023 Acute Myeloid Leukemia. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Published July 11, 2023. Accessed September 11, 2023.
3. National Comprehensive Cancer Network®. NCCN Guidelines Version 1.2024 Chronic Myeloid Leukemia. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Published August 01, 2023. Accessed September 11, 2023.
4. National Comprehensive Cancer Network®. NCCN Guidelines Version 1.2024 Multiple Myeloma. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Published September 22, 2023. Accessed September 11, 2023.
5. National Comprehensive Cancer Network®. NCCN Guidelines Version 1.2023 Myelodysplastic Syndromes. https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Published September 12, 2022. Accessed September 11, 2023.
6. Kolb HJ, Mittermüller J, Clemm C, et al. Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients. *Blood*. 1990;15;76(12):2462 to 2465.
7. Frey NV, Porter DL. Graft-versus-host disease after donor leukocyte infusions: presentation and management. *Best Pract Res Clin Haematol*. 2008;21(2):205 to 22. doi: 10.1016/j.beha.2008.02.007
8. Negrin RS. Immunotherapy for the prevention and treatment of relapse following allogenic hematopoietic cell transplantation. UpToDate. www.uptodate.com. Updated August 24, 2022. Accessed September 01, 2023.
9. Castagna L, Sarina B, Bramanti S, Perseghin P, Mariotti J, Morabito L. Donor lymphocyte infusion after allogeneic stem cell transplantation. *Transfus Apher Sci*. 2016;54(3):345 to 355. doi:10.1016/j.transci.2016.05.011
10. Kolb HJ, Schmid C, Barrett AJ, Schendel DJ. Graft-versus-leukemia reactions in allogeneic chimeras. *Blood* 2004;103(3):767 to 776. doi:10.1182/blood-2003-02-0342
11. Negrin RS. Biology of the graft-versus-tumor effect following hematopoietic cell transplantation. UpToDate. www.uptodate.com. Updated May 04, 2022. Accessed August 31, 2023.
12. Deol A, Lum LG. Role of donor lymphocyte infusions in relapsed hematologic malignancies after stem cell transplantation revisited. *Cancer Treat Rev*. 2010;36(7):528 to 538. doi: 10.1016/j.ctrv.2010.03.004
13. Luznik L, Fuchs EJ. Donor lymphocyte infusions to treat hematologic malignancies in relapse after allogeneic blood or marrow transplantation. *Cancer Control*. 2002;9(2):123 to 137. doi:10.1177/107327480200900205
14. Chao, NJ. Clinical manifestations, diagnosis, and grading of acute graft- versus-host disease. UpToDate. www.uptodate.com. Updated September 09, 2022. Accessed September 01, 2023.
15. Collins RH Jr, Shpilberg O, Drobyski WR, et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. *J Clin Oncol*. 1997;15(2):433 to 444. doi: 10.1200/JCO.1997.15.2.433

16. Carlens S, Remberger M, Aschan J, Ringdén O. The role of disease stage in the response to donor lymphocyte infusions as treatment for leukemic relapse. *Biol Blood Marrow Transplant*. 2001;7(1):31 to 38. doi:10.1053/bbmt.2001.v7.pm11215696
17. Loren AW, Porter DL. Donor leukocyte infusions for the treatment of relapsed acute leukemia after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2008;41(5):483 to 493. doi:10.1038/sj.bmt.1705898
18. Kumar S. Multiple myeloma: Use of allogeneic hematopoietic cell transplantation. UpToDate. www.uptodate.com. Updated June 07, 2023. Accessed September 22, 2023.
19. Salama M, Nevill T, Marcellus D et al. Donor leukocyte infusions for multiple myeloma. *Bone Marrow Transplant*. 2000;26(11):1179 to 1184. doi: 10.1038/sj.bmt.1702685
20. Khan F, Agarwal A, Agrawal S. Significance of chimerism in hematopoietic stem cell transplantation: new variations on an old theme. *Bone Marrow Transplant*. 2004;34(1):1 to 12. doi: 10.1038/sj.bmt.1704525
21. Lokhorst HM, Schattenberg A, Cornelissen JJ, et al. Donor lymphocyte infusions for relapsed multiple myeloma after allogeneic stem-cell transplantation: predictive factors for response and long-term outcome. *J Clin Oncol*. 2000;18(16):3031 to 3037. doi:10.1200/JCO.2000.18.16.3031
22. Orsini E, Alyea EP, Chillemi A, et al. Conversion to full donor chimerism following donor lymphocyte infusion is associated with disease response in patients with multiple myeloma. *Biol Blood Marrow Transplant*. 2000;6(4):375 to 386. doi: 10.1016/s1083-8791(00)70014-0
23. Tsirigotis P, Byrne M, Schmid C, et al. Relapse of AML after hematopoietic stem cell transplantation: methods of monitoring and preventive strategies. A review from the ALWP of the EBMT. *Bone Marrow Transplant*. 2016;51(11):1431 to 1438. doi: 10.1038/bmt.2016.167
24. Larson RA. Treatment of relapsed or refractory acute myeloid leukemia. UpToDate. www.uptodate.com. Updated March 31, 2023. Accessed September 12, 2023.
25. Negrin RS. Hematopoietic cell transplantation in chronic myeloid leukemia. UpToDate. www.uptodate.com. Updated June 03, 2022. Accessed September 11, 2023.
26. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood*. 2017;129(13):1753 to 1762. doi: 10.1182/blood-2016-06-724500
27. Guièze R, Damaj G, Pereira B, et al. Management of Myelodysplastic Syndrome Relapsing after Allogeneic Hematopoietic Stem Cell Transplantation: A Study by the French Society of Bone Marrow Transplantation and Cell Therapies. *Biol Blood Marrow Transplant*. 2016;22(2):240 to 247. doi: 10.1016/j.bbmt.2015.07.037
28. Scarisbrick JJ, Dignan FL, Tulpule S, et al. A multicentre UK study of GVHD following DLI: rates of GVHD are high but mortality from GVHD is infrequent. *Bone Marrow Transplant.* 2015;50(1):62 to 67. doi:10.1038/bmt.2014.227
29. Toprak SK. Donor lymphocyte infusion in myeloid disorders. *Transfus Apher Sci*. 2018;57(2):178 to 186. doi: 10.1016/j.transci.2018.04.018

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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This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

 Providers, members/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.

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.