

Clinical Policy: Donor Lymphocyte Infusion

Reference Number: PA.CP.MP.101

Effective Date: 01/18

Last Review Date: 11/16

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Description

This policy describes the medical necessity requirements for a donor lymphocyte infusion (DLI). DLI is a treatment for many hematological malignancies that have relapsed following allogeneic hematopoietic stem cell transplantation (HSCT) or bone marrow transplant, or to convert a patient's mixed to full donor chimerism in the absence of relapse. 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 hematological malignancies treated by DLIs include chronic myeloid leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, lymphomas, multiple myeloma, and myelodysplastic syndrome.

Policy/Criteria

- I. It is the policy of Pennsylvania Health and Wellness® that donor lymphocyte infusion is **medically necessary** following an allogeneic HSCT or bone marrow transplant for any of the following indications:
 - A. To treat a relapsed hematological malignancy;
 - B. To convert a member, who has not relapsed, from mixed to full donor chimerism.

- II. It is the policy of Pennsylvania Health and Wellness that donor lymphocyte infusion for the following are considered **experimental/investigational**:
 - A. For the treatment of all other conditions than those specified above;
 - B. Genetic modification or *ex vivo* manipulation of donor lymphocytes;
 - C. Repeat donor leukocyte infusion when positive health benefit responses are not documented.

Background

In addition to chemotherapy, HSCT has become a mainstream clinical therapy for a variety of hematological 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. DLI is one such post-transplant salvage adoptive immunotherapy.

Donor 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 had relapsed after bone marrow transplantation for chronic myeloid leukemia.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 survey several articles and report an effective cellular range of 0.01 to 8.8×10^8 T cells/kg.³

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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 hematological malignancy. In a retrospective study, Collins *et al.* observed that of 140 patients treated with DLI for relapsed disease after stem cell transplant, approximately 60% patients present with GvHD; of these, 42/45 patients in complete response of disease developed acute GvHD and 36/41 patients in complete response of disease displayed chronic GvHD.⁷ Nevertheless, Carlens *et al.* determined that the 3 year leukemia free survival is 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 2-5% 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 chronic myeloid leukemia (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, the ability of DLI 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 hematological malignancy with the potential to respond to DLI. Among varying reports, the response rate of relapsed multiple myeloma to DLI is approximately 22-52%.^{10,11} The propensity of multiple myeloma patients to receive autologous and not allogenic transplants could have a role in this outcome.³

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.

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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. 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 such 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 is an effective clinical treatment for an array of relapsed hematological 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®*	Description
38215	Transplant preparation of hematopoietic cells; cell concentration in plasma, mononuclear, or buffy coat layer
38242	Allogeneic lymphocyte infusions
86950	Leukocyte transfusion

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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

ICD-10-CM Diagnosis Codes that Support Coverage Criteria

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ICD-10-CM Code	Description
C81-C81.99	Hodgkin lymphoma
C85-C85.99	Other specified and unspecified types of non-Hodgkin lymphoma
C90-C90.02	Multiple myeloma and malignant plasma cell neoplasms
C91-C91.92	Lymphoid leukemia
C92-C92.92	Myeloid leukemia
D46-D46.9	Myelodysplastic syndrome

Reviews, Revisions, and Approvals	Date	Approval Date

References

1. Negrin, RS. "Biology of the graft-versus tumor effect following hematopoietic cell transplantation." In: UpToDate, Chao NJ (Ed), UpToDate, Waltham, MA. Accessed on October 19, 2016.
2. Kolb, H. J., et al. "Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients." *Blood* 76.12 (1990): 2462-2465.
3. Deol, Abhinav, and Lawrence G. Lum. "Role of donor lymphocyte infusions in relapsed hematological malignancies after stem cell transplantation revisited." *Cancer treatment reviews* 36.7 (2010): 528-538.
4. Frey, Noelle V., and David L. Porter. "Graft-versus-host disease after donor leukocyte infusions: presentation and management." *Best Practice & Research Clinical Haematology* 21.2 (2008): 205-222.
5. Luznik, Leo, and Ephraim J. Fuchs. "Donor lymphocyte infusions to treat hematologic malignancies in relapse after allogeneic blood or marrow transplantation." *Cancer Control* 9.2 (2002): 123-137.
6. Chao, NJ. "Clinical manifestations, diagnosis, and grading of acute graft-versus-host disease." In: UpToDate, Negrin RS (Ed), UpToDate, Waltham, MA. Accessed on October 19, 2016.
7. Collins, R. H., et al. "Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation." *Journal of clinical oncology* 15.2 (1997): 433-444.
8. Carlens, Stefan, et al. "The role of disease stage in the response to donor lymphocyte infusions as treatment for leukemic relapse." *Biology of Blood and Marrow Transplantation* 7.1 (2001): 31-38.
9. Loren, A. W., and D. L. Porter. "Donor leukocyte infusions for the treatment of relapsed acute leukemia after allogeneic stem cell transplantation." *Bone marrow transplantation* 41.5 (2008): 483-493.
10. Salama, M., et al. "Donor leukocyte infusions for multiple myeloma." *Bone marrow transplantation* 26.11 (2000): 1179-1184.
11. Khan, F., A. Agarwal, and S. Agrawal. "Significance of chimerism in hematopoietic stem cell transplantation: new variations on an old theme." *Bone marrow transplantation* 34.1 (2004): 1-12.

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12. Lokhorst, H. M., et al. "Donor lymphocyte infusions for relapsed multiple myeloma after allogeneic stem-cell transplantation: predictive factors for response and long-term outcome." *Journal of Clinical Oncology* 18.16 (2000): 3031-3037.
13. Orsini, Enrica, et al. "Conversion to full donor chimerism following donor lymphocyte infusion is associated with disease response in patients with multiple myeloma." *Biology of Blood and Marrow Transplantation* 6.4 (2000): 375-386.
14. Negrin RS. Immunotherapy for the prevention and treatment of relapse following hematopoietic cell transplantation. In: UpToDate, Chao NJ (Ed), UpToDate, Waltham, MA. Accessed on October 19, 2016.
15. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Acute Lymphoblastic Leukemia. Version 2.2016. Updated 9/29/16.
16. National Comprehensive Cancer Network (NCCN). NCCN Guidelines in Clinical Guidelines in Oncology. Acute Myeloid Leukemia. Version 2.2016. Updated 6/29/16.
17. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Chronic Myelogenous Leukemia. Version 1.2016. Updated 9/9/15.
18. National Comprehensive Cancer Network (NCCN). NCCN Guidelines in Clinical Guidelines in Oncology. Multiple myeloma. Version 1.2017. Updated 9/29/16
19. National Comprehensive Cancer Network (NCCN). NCCN Clinical Guidelines in Oncology. Non-Hodgkin's lymphomas. Version 3.2016. Updated 5/3/16.
20. National Comprehensive Cancer Network (NCCN). NCCN Guidelines in Clinical Guidelines in Oncology. Myelodysplastic Syndromes. Version 1.2017. Updated 8/18/16.