Anthem

Clinical UM Guideline

Subject: Donor Lymphocyte Infusion for Hematologic Malignancies after Allogeneic Hematopoietic Progenitor Cell Transplantation
Guideline #: CG-TRANS-03 **Publish Date:** 06/28/2023
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Description

This document addresses the use of donor lymphocyte infusions after an allogeneic hematopoietic progenitor cell transplant to treat a hematologic malignancy (e.g., cancer of the blood or bone marrow, such as leukemia or lymphoma). Donor lymphocyte infusion (DLI) is a form of adoptive immunotherapy in which a transplant recipient is infused with lymphocytes obtained in a leukapheresis procedure from the original allogeneic hematopoietic progenitor cell donor. This procedure attempts to induce a beneficial graft-versus-leukemia (GVL) response without the need for additional bone marrow harvest from the donor or further high-dose chemotherapy for the recipient.

Clinical Indications

Medically Necessary:

Donor* lymphocyte infusion is considered **medically necessary** for individuals following a medically necessary allogeneic (myeloablative or non-myeloablative) hematopoietic progenitor cell transplant used to treat a hematologic malignancy.

***Note:** The donor for the lymphocytes is the same individual whose hematopoietic progenitor cells were used for the transplant procedure.

Collection and cryopreservation of donor lymphocytes is considered **medically necessary** prior to, at the time of, or after a medically necessary allogeneic or non-myeloablative allogeneic hematopoietic progenitor cell transplant.

Not Medically Necessary:

Donor lymphocyte infusion is considered **not medically necessary** in all other cases.

Genetic modification of donor lymphocytes as an adjunct to donor lymphocyte infusion is considered **not medically necessary.**

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Donor lymphocyte infusion
When services may be Medically Necessary when criteria are met:

CPT	
38242	Allogeneic lymphocyte infusions

ICD-10 Diagnosis	
C81.00-C81.99	Hodgkin lymphoma
C82.00-C82.99	Follicular lymphoma
C83.00-C83.99	Non-follicular lymphoma
C84.00-C84.99	Mature T/NK-cell lymphomas
C85.10-C85.99	Other specified and unspecified types of non-Hodgkin lymphoma
C86.0-C86.6	Other specified types of T/NK-cell lymphoma
C88.0-C88.9	Malignant immunoproliferative diseases and certain other B-cell lymphoma
C90.00-C90.32	Multiple myeloma and malignant plasma cell neoplasms
C91.00-C91.92	Lymphoid leukemia
C92.00-C92.92	Myeloid leukemia
Z85.6-Z85.79	Personal history of leukemia, other malignant neoplasms of lymphoid, hematopoietic and related tissues
Z94.81	Bone marrow transplant status
Z94.84	Stem cells transplant status

When services are Not Medically Necessary:
For the procedure codes listed above when criteria are not met or for all other diagnoses not listed.

Genetic modification of donor lymphocytes
When services are Not Medically Necessary:
When the code describes a procedure designated in the Clinical Indications section as not medically necessary.

CPT	
86999	Unlisted transfusion medicine procedure [when specified as genetic modification of donor lymphocytes]

ICD-10 Diagnosis	
	All diagnoses

Discussion/General Information

Infusing lymphocytes from the original hematopoietic cell donor can be used to treat transplant recipients with hematologic malignancies in relapse following allogeneic hematopoietic progenitor cell transplantation. DLI, which is also referred to as donor leukocyte or buffy coat transfusion, is a form of adoptive immunotherapy and attempts to induce a beneficial GVL or graft-versus-tumor (GVT) response without the need for an additional bone marrow harvest from the donor or further high-dose chemotherapy for the recipient. Collection of donor leukocytes requires the original donor to undergo a leukapheresis procedure. After collection, these cells are infused into the recipient either immediately or after frozen storage.

Leukapheresis is the removal of white blood cells from blood that is drawn directly from a blood vessel in the arm or through a small tube (catheter) placed in a single vein. The blood goes through a centrifuge where white blood cells, along with some platelets and a small amount of red blood cells, are removed. The remainder of the cells and plasma will pass through the centrifuge and will then be returned to the donor through a needle or catheter that is placed in the opposite arm. The procedure is performed in the outpatient setting and takes 2 to 3 hours to complete. DLI is used as an alternative to a second hematopoietic cell transplant.

DLI has been researched as a treatment for a variety of hematologic malignancies, including most prominently chronic myeloid leukemia (CML), but also acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), multiple myeloma, myelodysplastic syndromes, chronic lymphocytic leukemia, Hodgkin disease, and non-Hodgkin lymphoma. Studies are limited due to small numbers but they have provided evidence that DLI can establish a graft-versus-leukemia/lymphoma effect.

There is clear clinical evidence that DLI can eradicate and cure relapsed CML. In addition, infusions using lymphocytes obtained from the original hematopoietic progenitor cell donor can induce long-term, complete, hematological, cytogenetic, and molecular genetic remissions in individuals treated for relapsing CML after an allogeneic hematopoietic cell transplant (HCT). The National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines (CPG, V.1.2023) for CML state “Donor lymphocyte infusion (DLI) is effective in inducing durable molecular remissions in the majority of patients with relapsed CML following allogeneic HCT, though it is more effective in patients with chronic phase relapse than advanced phase relapse.” These recommendations were based on 2A category of evidence and uniform consensus. The results from CML may be extrapolated to individuals with relapsed AML, since there is evidence of a graft-versus-leukemia effect in individuals with AML treated with allogeneic transplants.

Therapy is also effective for relapse of hematologic malignant diseases other than CML, although response rates are lower. The medical evidence currently available for the use of DLI in individuals with relapsed disease from other hematologic malignancies including, but not limited to, ALL, multiple myeloma, Hodgkin disease and non-Hodgkin lymphoma, consists mostly of multiple small case series. However, there is a preponderance of these smaller studies that in conjunction, demonstrate that DLI may induce an anti-tumor response in individuals who have relapsed disease following an allogeneic hematopoietic progenitor cell transplant.

Beitinjaneh and colleagues (2012) reported a higher response rate and longer overall survival when DLI was used preemptively in individuals treated with allogeneic HCT as a treatment for multiple myeloma. Between July 1996 and June 2008, 23 individuals with multiple myeloma received DLI, 8 as preemptive DLI for residual disease (RD) and 15 as DLI for the treatment of recurrent or progressive disease (PD). With a median follow-up of 24 months, 5 of 23 individuals (22%) achieved a complete response (CR) or a very good partial response (2 CR, 3 very good partial response [VGPR]), and stable disease (SD) in 8 individuals (34%) after DLI. A higher response rate (≥ VGPR 50% vs. 7%, p=0.03), a longer overall survival (28.3 vs. 7.6 months, p=0.03) and a trend toward longer progression-free survival (11.9 vs. 5.2 months, p=0.1) were reported in individuals who received DLI for RD. Five individuals (22%) had Grade II-IV acute graft-versus-host disease (GVHD). The authors concluded the preemptive use of DLI after an allogeneic HSCT for multiple myeloma may be associated with improved outcomes. Additional clinical trials are encouraged to identify the optimal timing for DLI.

The NCCN CPGs for multiple myeloma (V.3.2023) include the use of DLI in individuals with unresponsive or relapsed disease after allogeneic hematopoietic cell grafting in order to stimulate a beneficial graft-versus-myeloma effect. Similarly, the NCCN CPGs for Acute Lymphoblastic Leukemia (V1.2022) state that, “For patients with relapsed disease after allogeneic HCT, a second HCT and/or donor lymphocyte infusion (DLI) can be considered.”

Sala and colleagues (2014) reported results from a retrospective series of 18 individuals with relapsed and/or refractory Hodgkin lymphoma after allogeneic HSCT that were treated with a combination of bendamustine followed by DLI. Nine of the participants were eligible for DLI after bendamustine, based on the pre-specified criteria. A median of two DLIs were infused into the individuals. Adverse events from the DLI included 3 individuals with chronic GVHD and 3 cases of Grade IV acute GVHD. Acute hospitalization was required for 3 individuals with acute GVHD. Of those treated with DLI, CR was seen in 3 individuals and PR in 7 individuals, for an overall response rate (ORR) of 55% with a 9-month (range 1-26 months) median duration of response. For the 18 participants, the median overall survival was 11 months (range 1-52 months) and the progression-free survival (PFS) was 6 months (range, 1-28 months). The authors noted the combination of bendamustine followed by DLI demonstrated a response. However, a randomized trial is needed to determine if the treatment effect was due to the bendamustine compared to the DLI or the combination.

Thomson and colleagues (2010) reported multicenter results of 82 individuals with follicular lymphoma that were treated with allogeneic stem cell transplantation. All individuals with mixed chimerism or residual or progressive disease were eligible for DLI. Thirteen participants received 25 DLIs with remission in 10 individuals (77%). At a median of 44 months after the last DLI, the ongoing complete response seemed durable. There was no response in 3 individuals treated with DLI. The authors concluded the frequency and duration of response demonstrated was an “encouraging strategy to treat follicular lymphoma.”

GVHD is a common occurrence with DLI. As a result, studies continue to investigate various dosing, timing of DLI infusions, and new approaches, including modifications to T-lymphocytes to minimize GVHD complications. The level of evidence is insufficient to permit conclusions in terms of uses of DLI for other than hematologic malignancies that have relapsed following a prior allogeneic hematopoietic progenitor cell transplant or to permit conclusions regarding the use of genetic modification (e.g., modified T-lymphocytes) of donor lymphocytes in the treatment of hematologic malignancies.

However, in a study by Alho and colleagues (2016), the authors observed that the “development and maintenance of immune tolerance after allogeneic hematopoietic stem cell transplantation requires the balanced reconstitution of donor-derived CD4 regulatory T cells (CD4Tregs) as well as effector CD4 (conventional CD4 T cells [CD4Tcons]) and CD8 T cells.” They studied 107 adult subjects who received “T-replete stem cell grafts after reduced-intensity conditioning who were monitored” over a 2-year period. The authors found that the imbalances assisted in the “production, expansion, and persistence of effector T cells over CD4Tregs and were associated with the development of chronic GVHD.”

There is also research interest in the genetic modification of donor lymphocytes. For example, it has been proposed that donor lymphocytes can be modified by insertion of a thymidine kinase gene, rendering the cells susceptible to ganciclovir therapy. If the infusion of the genetically modified donor lymphocytes results in severe graft vs. host disease, the transplant recipient can then be treated with ganciclovir to selectively destroy the donor lymphocytes. Other editing techniques may involve disrupting the GVHD process by targeting T-cell receptors and cell surface expression or the genetic editing to evade host-mediated rejection (Qasim, 2023). However, further investigation and data regarding the safety and efficacy of genetic modifications of DLI on GVHD and/or graft-versus-leukemia (GVL) are needed.

Definitions

Allogeneic: Genetically dissimilar; involves a donor and recipient.

Bone marrow: A soft, spongy tissue that fills the cavities inside most bones in the human body. Bone marrow is a source of stem cells that manufacture red blood cells, white blood cells, and platelets.

Graft-versus-host disease (GVHD): A potential complication of transplants associated with the use of blood or tissue from a different person (allogeneic). The transplanted cells recognize the recipient's tissue as foreign and attack the recipient.

Graft-versus-leukemia/lymphoma effect (GVL): Transplanted white blood cells that recognize residual cancer cells (cells that survived chemotherapy and radiation therapy and continue to grow in the body) and attack them.

Hematologic malignancy: A cancer of the blood or bone marrow, such as leukemia or lymphoma.

Hematopoietic progenitor cells: Primitive cells capable of replication and formation into mature blood cells in order to repopulate the bone marrow. Cells may be obtained from bone marrow, peripheral blood or umbilical cord blood.

Leukocytes: Another term for white blood cells. There are several types of leukocytes: granulocytes (neutrophils, eosinophils, and basophils), monocytes, and lymphocytes.

Lymphocyte: Cells present in the blood and lymphatic tissue derived from stem cells. Comprised of T cells and B cells.

Non-myeloablative allogeneic hematopoietic stem cell transplant: Also called reduced intensity or mini-allogeneic transplant. The conditioning regimen is less intense and does not completely ablate the stem cells in the individual's bone marrow.

Peripheral blood: Blood derived from the circulatory system (as opposed to blood in the bone marrow where it is made).

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Government Agency, Medical Society, and Other Authoritative Publications:

1. NCCN Clinical Practice Guidelines in Oncology™. © 2023. National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on March 22, 2023.
    - Acute Lymphoblastic Leukemia. (V.1.2022). April 4, 2022.
    - Chronic Myeloid Leukemia (V.1.2023). Revised August 5, 2022.
    - Multiple Myeloma (V.3.2022). Revised December 8, 2022.
    - T-Cell Lymphomas. (V.1.2023). Revised January 5, 2023.

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	05/11/2023	Medical Policy & Technology Assessment (MPTAC) review. Updated Description, Discussion, Definitions and References sections.
Reviewed	05/12/2022	MPTAC review. Updated Description, Discussion, References and Websites sections.
Reviewed	05/13/2021	MPTAC review. Updated Discussion, References and Websites sections. Reformatted Coding section.
Reviewed	05/14/2020	MPTAC review. Updated Discussion, References and Websites sections.
Reviewed	06/06/2019	MPTAC review. Updated References section.
New	07/26/2018	MPTAC review.
New	07/18/2018	Hematology/Oncology Subcommittee review. Initial document development. Moved content of TRANS.00018 Donor Lymphocyte Infusion for Hematologic Malignancies after Allogeneic Hematopoietic Progenitor Cell Transplantation to new clinical utilization management guideline document with the same title.

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services generally across all providers delivering services to Plan's or line of business's members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.