

2.03.03	Donor Lymphocyte Infusion for Malignancies Treated with an AllogeneicHematopoietic Stem-Cell Transplant		
Section 2.0 Medicine	Effective Date September 30, 2014		
Subsection 2.03 Oncology	Original Policy Date January 7, 2011	Next Review Date September 2015	

Description

Donor lymphocyte infusion (DLI), also called donor leukocyte or buffy-coat infusion is a type of therapy in which T lymphocytes from the blood of a donor are given to a patient who has already received a hematopoietic stem-cell transplant (HSCT) from the same donor. The DLI therapeutic effect results from a graft-versus-leukemic or graft-versus-tumor effect due to recognition of certain antigens on the cancer cells by the donor lymphocytes and the resultant elimination of the tumor cells.

Related Policies

- Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia
- Hematopoietic Stem-Cell Transplantation for Acute Myelogenous Leukemia
- Hematopoietic Stem-Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia
- Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia
- Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma
- Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphoma
- Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, including Multiple Myeloma and POEMS Syndrome

Policy

Donor lymphocyte infusion may be considered **medically necessary** following allogeneic-hematopoietic stem-cell transplantation (HSCT) that was originally considered medically necessary for the treatment of a hematologic malignancy that has relapsed or is refractory, to prevent relapse in the setting of a high risk of relapse (see Policy Guidelines), or to convert a patient from mixed to full donor chimerism.

Donor lymphocyte infusion is considered **investigational** for **either** of the following indications:

- Following allogeneic HSCT that was originally considered investigational for the treatment of a hematologic malignancy
- As a treatment of nonhematologic malignancies following a prior allogeneic HSCT



Genetic modification of donor lymphocytes is considered investigational.

Policy Guidelines

Settings considered high risk for relapse include T cell depleted grafts or nonmyeloablative (reduced intensity conditioning) allogeneic HSCT.

Coding

There is a specific CPT code to describe allogeneic donor lymphocyte infusions:

• 38242: Allogeneic lymphocyte infusions

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

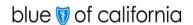
Rationale

Background

The 1997 Blue Cross Blue Shield Technology Evaluation Center (TEC) Assessment and Deol and Lum (2010) published that approximately 40% to 60% of patients who receive a donor lymphocyte infusion (DLI) develop graft-versus-host disease (GVHD), and the development of GVHD predicts a response to the DLI. Treatment-related mortality after DLI is 5% to 20%. There does not seem to be a correlation between the type of hematologic malignancy for which the DLI was given and the development of GVHD. The risk of development of GVHD is related, in part, to DLI dose and therapy before DLI.

Timing of the use of DLI depends upon the disease indication and may be used in the setting of relapse after an allogeneic hematopoietic stem-cell transplantation (HSCT), as a planned strategy to prevent disease relapse in the setting of T cell depleted grafts or nonmyeloablative conditioning regimens, or as a method to convert mixed to full donor chimerism. Management of relapse, which occurs in approximately 40% of all hematologic malignancy patients, is the most common indication for DLI (Tomblyn et al., 2008).

The literature is heterogeneous for reporting methods of cell collection, timing of infusion (e.g., after chemotherapy, in early relapse), cell dose infused and cell subtype used (Deol & Lum, 2010). In addition, many studies include multiple diseases with little information regarding disease-specific outcomes; however, DLI is used in nearly all hematologic malignancies for which allogeneic HSCT is performed, including chronic myeloid



leukemia, acute myeloid and lymphoblastic leukemia's, myelodysplastic syndromes, multiple myeloma, and Hodgkin (HL) and nonHodgkin lymphoma (NHL). Several review articles summarize studies that have reported the use of donor lymphocyte infusion (DLI) as therapy for the treatment of hematologic malignancies after an allogeneic hematopoietic stem-cell transplant (HSCT) (TEC 2010; Deol & Lum, 2010; Tomblyn et al., 2008).

Chronic Myelogenous Leukemia

DLI has been found to be most effective in chronic myelogenous leukemia (CML), inducing a molecular complete remission (CR) in up to 80% of patients who relapse in chronic phase. Only a 12.5% to 33% response rate has been reported in patients in accelerated or blast phase. Response duration to DLI in patients with relapsed CML after HSCT is long-standing in most patients.

There are several large series reporting outcomes of patients with relapsed CML after receiving DLI (Van den Brink et al., 2010; Simula et al., 2007; Dazzi et al., 2000; Guglielmi et al., 2002; Fozza et al., 2007). These studies comprise more than 500 patients, approximately half of whom had only molecular or cytogenetic relapse at the time of DLI (Deol & Lum, 2010). The cell doses varied among patients, with some patients receiving multiple DLI infusions and others planned dose escalations. Despite these variations, a molecular CR was achieved in 77% of patients (405 of 527) with overall survival (OS) at 3 or more years ranging from 53% to 95% (Tomblyn et al., 2008).

The role of DLI in CML has recently changed as the use of tyrosine-kinase inhibitors has revolutionized the treatment of CML by keeping the disease under control instead of proceeding to HSCT. However, for patients who develop resistance to the tyrosine-kinase inhibitors or are unable to tolerate the adverse effects, HSCT and DLI may be an option to manage the disease.

National Comprehensive Cancer Network (NCCN) (V.3.2014) recommendations for treating CML state that DLI can be considered an option for patients who do not achieve remission, are in cytogenetic relapse, or have an increasing level of molecular relapse (category 2A).

Acute Leukemias, Myelodysplasia, and other Myeloproliferative Diseases

El-Jurdi et al. (2013) performed a systematic review, evaluating 39 prospective and retrospective studies on DLI for relapse after HSCT for lymphoid malignancies including acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma, nonHodgkin lymphoma (NHL), and Hodgkin lymphoma (HL). No randomized controlled studies were identified. The studies were heterogeneous thus limiting interpretation of the review. Reported pooled proportions of CR (95% confidence interval [CI]) were 27% (16% to 40%) for ALL, 55% (15% to 92%) for CLL, 26% (19% to 33%) for multiple myeloma, 52% (33% to 71%) for NHL, and 37% (20% to 56%) for HL.

Acute Myelogenous Leukemia

DLI for patients with relapsed acute myelogenous leukemia (AML) after allogeneic HSCT has resulted in overall remission rates ranging from 15% to 42%, with an OS of approximately 15% to 20% (For comparison, a second HSCT in this group of patients results in 10% to 35% long-term survival with a treatment-related mortality of approximately 50%). Patients with lower initial disease burden, reduction in the tumor burden with chemotherapy before DLI, and favorable cytogenetics appear to have more benefit with DLI with relapsed AML after HSCT. In 2007, a large retrospective analysis from the European Blood and Marrow Transplant Group compared OS in 399 patients with AML with post-transplant relapse who either were treated with DLI (n=171) or were not (n=228)

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Medical Policy

(Schmid et al., 2007). Patients who received DLI had an improved 2-year OS compared with those who did not, (21 +/- 3% versus 9 +/- 2%, respectively; p<0.001). The literature for myelodysplasia (MDS) and other myeloproliferative diseases treated with DLI either after relapse or for mixed chimerism consists of small sample sizes, inconsistent pre-DLI therapy, and varied DLI cell doses, making it difficult to draw definite conclusions on outcomes. However, it appears some patients attain durable remissions with DLI after post-transplant relapse (Tomblyn et al., 2008).

Warlick et al. (2012) reported CR after DLI in 49% of 35 patients with relapsed nonchronic myelogenous leukemia, including AML and MDS, after allogeneic HSCT. OS at 1 year was 30% and 19% at 2 years. The authors reported a lower-dose regimen of DLI was more tolerable and reduced graft-versus-host disease (GVHD) occurrence to 25% compared with 66% with higher-dose DLI.

NCCN guidelines do not address the use of DLI in the treatment of AML (V.1.2014).

Acute Lymphoblastic Leukemia

The graft-versus-tumor effect is thought to be less robust in patients with ALL than in the myeloid leukemias. Small studies have reported response rates to DLI ranging from 0% to 20% and OS rates of less than 15%. By comparison, a second allogeneic HSCT provides a 5-year OS of approximately 15% to 20%, with a treatment-related mortality rate of approximately 50% (Deol & Lum, 2010).

The clinically evident graft-versus-leukemia effect of DLI requires weeks to months to become apparent, and, as ALL is a rapidly proliferating disease, DLI only is unable to control the disease without a significant reduction in leukemia burden before DLI. Management of patients with relapsed ALL leading to the best OS is with a combination of salvage chemotherapy and DLI. Although it is not clear whether DLI adds benefit to salvage chemotherapy, there are reports of long-term survivors with relapsed ALL who received both chemotherapy and DLI (Tomblyn et al., 2008).

NCCN (V.1.2014) recommendations for treating ALL state that DLI can be considered an option for patients in relapse after allogeneic HSCT (category 2A).

Lymphomas

Studies in which patients received DLI for lymphomas consist of small numbers of patients and various histologies (both HL and high- and low-grade NHL). In general, the highest response rates have been seen in the indolent lymphomas. For NHL, there are too few patients reported with any single histologic subtype of lymphoma to give adequate information of the benefit of DLI for a specific lymphoma subtype (Tomblyn et al., 2008).

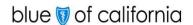
The largest series reported for NHL (n=21) using DLI showed response rates in 3 of 9 patients with high-grade NHL, 1 of 2 patients with mantle cell lymphoma, and 6 of 10 patients with low-grade disease (Morris et al., 2004).

A series of 14 patients with multiply relapsed HL who received reduced intensity conditioning allogeneic HSCT and DLI showed a CR of 57% and survival at 2 years of 35% (Peggs et al., 2007).

NCCN guidelines do not include the use of DLI in the treatment of Hodgkin or non-Hodgkin lymphomas (V.2.2014).

Multiple Myeloma

Observational data suggest a graft-versus-tumor effect in multiple myeloma, as the development of



GVHD has correlated with response in several analyses (Tomblyn et al., 2008).

Allogeneic HSCT is currently considered investigational for this indication (see Blue Shield of California Medical Policy: Hematopoietic Stem-Cell Transplantation for <u>Plasma Cell Dyscrasias</u>, including Multiple Myeloma and <u>POEMS Syndrome</u>). Most patients with multiple myeloma who undergo HSCT receive an autologous HSCT. In addition, the overall role of HSCT for multiple myeloma is currently changing with the advent of new, highly active drugs like lenalidomide and bortezomib.

Five studies reporting the role of DLI in relapsed multiple myeloma consist of patients ranging in number from 5 to 63 (Lokhorst et al., 1997; Salama et al., 2000; Collins et al., 1997; Bensinger et al., 1996; Lokhorst et al., 2000) with the highest response to DLI being reported as 62% by Warlick et al. (2012) with approximately half of the responders attaining a CR (Tomblyn et al., 2008). One confounding factor for high response rates for multiple myeloma treated with DLI is that corticosteroids used for treating GVHD have a known antimyeloma effect, which could potentially enhance response rates in these patients (Deol & Lum, 2010).

NCCN (V.2.2014) recommendations for treating multiple myeloma state that DLI can be considered an option for patients who do not respond or are in relapse after allogeneic HSCT (category 2A).

Genetic Modification of Donor Lymphocytes

There are inadequate data to permit conclusions regarding the use of genetic modification of donor lymphocytes. In an effort to control GVHD, a group in Italy explored using genetically modified lymphocytes engineered to express the suicide gene thymidine kinase of herpes simplex virus (Ciceri et al., 2007). These lymphocytes were infused into 23 patients with various hematologic malignancies who relapsed after an allogeneic HSCT. Six patients died of progressive disease within 4 weeks of infusion. Eleven patients experienced disease response (CR in 6 and partial remission in 5). Three patients remained alive in CR at a median of 471 days. Twelve patients were evaluable for GVHD, 3 of who developed acute or chronic GVHD, which was successfully treated with ganciclovir.

Ongoing Clinical Trials

A search of online site <u>ClinicalTrials.gov</u> on April 22, 2014 identified 30 open and active phase II studies that list donor lymphocyte infusion as an intervention component.

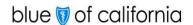
Summary

Donor lymphocyte infusion (DLI), also called donor leukocyte or buffy-coat infusion, is a type of therapy in which T lymphocytes from the blood of a donor are given to a patient who has already received a hematopoietic stem-cell transplant (HSCT) from the same donor. The DLI therapeutic effect results from a graft-versus-leukemic or graft-versus-tumor effect due to the recognition of certain antigens on the cancer cells by the donor lymphocytes and the resultant elimination of the tumor cells.

The response rates to DLI for relapsed hematologic malignancies following an allogeneic HSCT are best in chronic myelogenous leukemia (CML), followed by the lymphomas, multiple myeloma, and acute leukemias, respectively (Deol & Lum, 2010).

Other than CML, clinical responses are most effective when chemotherapy induction is used to reduce the tumor burden before DLI.

DLI is used in nearly all hematologic malignancies that relapse after a prior allogeneic HSCT, as a planned strategy to prevent disease relapse in a setting of high-risk of disease



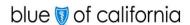
relapse (e.g., after a reduced intensity allogeneic HSCT), and to convert mixed to full donor chimerism. Future directions are focused on enhancing the antitumor effect of the donor T cells while decreasing the toxicities related to GVHD from DLI (Deol & Lum, 2010).

Therefore, DLI may be considered medically necessary following an allogeneic HSCT that was considered medically necessary for the treatment of a hematologic malignancy that has relapsed or is refractory, to prevent relapse in the setting of a high risk of relapse, or to convert a patient from mixed to full donor chimerism. DLI is considered investigational following an allogeneic HSCT for the treatment of a hematologic malignancy that was originally considered investigational.

Data on the use of DLI in the treatment of nonhematologic malignancies following a prior allogeneic HSCT are limited, and therefore, use of DLI in this circumstance is considered investigational. Data on the genetic modification of donor lymphocytes are also limited. Therefore, genetic modification of donor lymphocytes is considered investigational.

References

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Documentation Required for Clinical Review

- Referring physician history and physical
- Bone marrow transplant consultation report and/or progress notes documenting:
 - o Diagnosis (including disease staging) and prognosis
 - o Synopsis of alternative treatments performed and results
 - o Specific transplant type being requested

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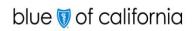
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
 - o Clinical history
 - o Specific issues identified during the transplant evaluation
 - o Consultation reports/letters (when applicable)
 - o Correspondence from referring physicians (when applicable)
 - Identification of donor for allogeneic related bone marrow/stem cell transplant (when information available)
- Medical social service/social worker and/or psychiatric (if issues are noted)
 evaluations including psychosocial assessment or impression of patient's ability to
 be an adequate candidate for transplant
- Radiology reports including:
 - o Chest x-ray (CXR)
 - o PET scan, CT scan and bone survey (as appropriate)
- Cardiology procedures and pulmonary function reports:
 - o EKG
 - o Echocardiogram
 - o Pulmonary function tests (PFTs)
- Biopsy/Pathology reports including:
 - o Bone marrow biopsy
 - o Lymph node biopsy (as appropriate)
- Laboratory reports

Coding

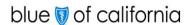
This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following service/procedure may be considered medically necessary in certain instances and investigational in others. Services may be medically necessary when policy criteria are met. Services are considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.



Туре	Code	Description	
CPT®	38242	Allogeneic lymphocyte infusions	
НСРС	None		
ICD-9 Procedure	99.09	Transfusion of other substance	
	99.72	Therapeutic leukopheresis	
	For dates of service on or after 10/01/2015		
ICD-10 Procedure	30233Q1	Transfusion of Nonautologous White Cells into Peripheral Vein, Percutaneous Approach	
	30243Q1	Transfusion of Nonautologous White Cells into Central Vein, Percutaneous Approach	
	30253Q1	Transfusion of Nonautologous White Cells into Peripheral Artery, Percutaneous Approach	
	30263Q1	Transfusion of Nonautologous White Cells into Central Artery, Percutaneous Approach	
	6A050Z1	Leukopheresis, single or multiple	
	6A051Z1	Leukopheresis, single or multiple	
	202.00 - 202.98	Nodular lymphoma, code range	
	203.00 - 203.82	Multiple myeloma, code range	
	204.00 - 204.92	Acute lymphoid leukemia, code range	
	205.10 - 205.11	Chronic myeloid leukemia, code range	
	206.00 - 208.92	Acute monocytic leukemia, code range	
	99.09 - 201.98	Hodgkin's disease code range	
	V59.09	Other blood donors	
ICD-9 Diagnosis	All Diagnoses		
ICD-10	For dates of service on or after 10/01/2015		
Diagnosis	All Diagnoses		



Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
1/7/2011	BCBSA Medical Policy adoption	Medical Policy Committee
9/30/2014	Policy title change from Donor Lymphocyte Infusion	Medical Policy Committee
	Policy Revision without position change	

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

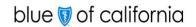
Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.



Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.