I. POLICY

Donor lymphocyte infusion may be considered medically necessary following an 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, or to prevent relapse in the setting of a high risk relapse (see policy guidelines), or to convert a patient from mixed to full donor chimerism.

The following procedures are considered investigational:

- Donor lymphocyte transfusion as a treatment of nonhematologic malignancies that have relapsed after a prior allogeneic SCT; and
- Genetic modification of donor lymphocytes
- Donor lymphocyte infusion following allogeneic hematopoietic stem-cell transplantation (HSCT) that was originally considered investigational for the treatment of hematologic malignancy.

There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these procedures.

Policy Guidelines

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

Cross-reference:

MP-9.037 Autologous and Allogeneic Stem Cell Transplantation
II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

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*Refer to FEP Medical Policy Manual MP-2.03.03 Donor Lymphocyte Infusion for Hematologic Malignancies Treated with Allogeneic Hematopoietic Stem-Cell Transplant. The FEP Medical Policy manual can be found at: www.fepblue.org

III. DESCRIPTION/BACKGROUND

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.

Approximately 40-60% 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. A Blue Cross and Blue Shield Technology Evaluation Assessment on this subject was published in 1997. (1, 2) Treatment-related mortality after DLI is 5-20%. 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. (1, 2) The risk of development of GVHD is related, in part, to DLI dose and therapy prior to DLI.

The timing of the use of DLI depends upon the disease indication and may be used in the setting of relapse after an allogeneic HSCT, as a planned strategy to prevent disease relapse in the setting of T cell depleted grafts or non-myeloablative 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. (3)

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. (2) In
addition, many studies include multiple diseases with little information regarding disease-specific outcomes; however, DLI is used in nearly all hemato logic malignancies for which allogeneic HSCT is performed, including chronic myeloid leukemia, acute myeloid and lymphoblastic leukemias, myelodysplastic syndromes, multiple myeloma and Hodgkin’s (HL) and non-Hodgkin’s lymphoma (NHL).

IV. RATIONALE

This policy is updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period of April 2012 through March 2013.

Several review articles summarize studies that have reported the use of donor lymphocyte infusion (DLI) as therapy for the treatment of hemato logic malignancies after an allogeneic hematopoietic stem-cell transplant (HSCT). (1-3)

Chronic myelogenous leukemia (CML)

DLI has been found to be most effective in CML, inducing a molecular complete remission (CR) in up to 80% of patients who relapse in chronic phase. Only a 12.5-33% 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 the majority of patients.

There are several large series reporting outcomes of patients with relapsed CML after receiving DLI. (4-8) These studies comprise more than 500 patients, approximately half of whom had only molecular or cytogenetic relapse at the time of DLI. (2) 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%. (3)

The role of DLI in CML has recently changed as the use of tyrosine-kinase inhibitors (TKIs) 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 TKIs or are unable to tolerate the adverse effects, HSCT and DLI may be an option to manage the disease.

National Comprehensive Cancer Network (NCCN) recommendations for treating CML (v4.2013) 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). (9)

Acute leukemias, myelodysplasia (MDS), and other myeloproliferative diseases

Acute myelogenous leukemia (AML)

DLI for patients with relapsed AML after allogeneic HSCT has resulted in overall remission rates ranging from 15% to 42%, with an OS of approximately 15-20%. (For comparison, a second HSCT in this group of patients results in 10-35% long-term survival with a treatment-
related mortality of approximately 50%). Patients with lower initial disease burden, reduction in the tumor burden with chemotherapy prior to DLI, and favorable cytogenetics appear to have more benefit with DLI with relapsed AML after HSCT.

A large retrospective analysis from the European Blood and Marrow Transplant Group (EBMT) compared OS in 399 patients with AML with post-transplant relapse who either were treated with DLI (n=171) or were not (n=228). (10) 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 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. (3) However, it appears some patients attain durable remissions with DLI after post-transplant relapse. (3)

Warlick and colleagues reported complete remission (CR) after DLI in 49% of 35 patients with relapsed nonchronic myelogenous leukemia, including AML and MDS, after allogeneic HSCT. (11) Overall survival 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 to 66% with higher-dose DLI.

NCCN guidelines do not address the use of DLI in the treatment of AML.

**Acute lymphoblastic leukemia (ALL)**

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%. (2) By comparison, a second allogeneic HSCT provides a 5-year OS of approximately 15-20%, with a treatment-related mortality rate of approximately 50%. (2)

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 prior to 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. (3)

NCCN recommendations for treating ALL (v1.2013) state that DLI can be considered an option for patients in relapse after allogeneic HSCT (category 2A). (12)

**The Lymphomas**

Studies in which patients received DLI for lymphomas consist of small numbers of patients and various histologies (both Hodgkin lymphoma [HL] and high- and low-grade non-Hodgkin lymphomas [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. (3)

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. (13)

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%. (14)

NCCN guidelines do not address the use of DLI in the treatment of Hodgkin or non-Hodgkin lymphomas.

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. (3)

Allogeneic HSCT is currently considered investigational for this indication (see 8.01.17 HSCT for Multiple Myeloma). 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 (15-19) with the highest response to DLI being reported as 62%, (12) with approximately half of the responders attaining a CR. (3) 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. (2)

NCCN recommendations for treating multiple myeloma (v2.2013) state that DLI can be considered an option for patients who do not respond or are in relapse after allogeneic HSCT (category 2A). (20)

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. (21) 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 whom developed acute or chronic GVHD, which was successfully treated with ganciclovir.
Ongoing Clinical Trials

A search of online site ClinicalTrials.gov on April 12, 2013 identified 31 open and active Phase II studies that list donor lymphocyte infusion as an intervention component.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from 1 academic medical center and 5 Blue Distinction Centers for Transplant while this policy was under review in 2011. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was general agreement with the policy statements, although 2 reviewers disagreed with the policy statement on the use of DLI in non-hematopoietic malignancies; one thought it was investigational and also medically necessary and the other did not think this was investigational or medically necessary. One reviewer suggested adding Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disease as another medically necessary indication for DLI. One reviewer commented on an evolving technique for use of ex-vivo expansion of donor lymphocytes.

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. (2) Other than CML, clinical responses are most effective when chemotherapy induction is used to reduce the tumor burden prior to 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. (2)

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 non-hematologic 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.

V. DEFINITIONS

ALLOGENEIC refers to having a different genetic constitution but belonging to the same species i.e., involves a donor and a recipient.

CHIMERISM A state in bone marrow transplantation in which bone marrow and host cells exist compatibly without any signs of graft-versus-host rejection disease.

HEMATOLOGIC refers to the science concerned with blood and the blood-forming tissues.

IMMUNOTHERAPY refers to treatment of disease by stimulating the body’s own immune system.

LYMPHOCYTE is a white blood cell.

LEUKAPHERESIS refers to the separation and storage of leukocytes from donor blood, which is then transfused back into the recipient patient.

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.
VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.
The following ICD-10 diagnosis codes will be effective October 1, 2014:

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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Donor Leukocyte Infusion for Hematologic Malignancies that Relapse after Allogeneic Bone Marrow Transplantation. TEC Assessments 1997; Volume 12, Tab 22.


X. Policy History

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<td>CAC 11/22/11 Adopt BCBSA. Policy title revised to “Donor Lymphocyte Infusion for Hematologic Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant. Policy statements modified to indicate that donor lymphocyte infusion would be considered medically necessary following an allogeneic-hematopoietic stem cell transplantation 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. References revised.</td>
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<td>CAC 3/26/13 Minor. Changed the word “leukocyte” to “lymphocyte” in policy statements for consistency with BCBSA. Policy statements modified to indicate that donor lymphocyte infusion would be considered medically necessary “following an allogeneic-hematopoietic stem cell transplantation (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. Added a statement indicating Donor lymphocyte infusion following allogeneic hematopoietic stem-cell transplantation (HSCT) that was originally considered investigational for the treatment of hematologic malignancy is investigational. Policy Guideline added - “Settings considered high risk for relapse include T cell depleted grafts or nonmyeloablative (reduced-intensity conditioning) allogeneic HSCT. FEP variation added to reference FEP Medical Policy Manual MP-2.03.03 Donor Lymphocyte Infusion for Hematologic Malignancies Treated with Allogeneic Hematopoietic Stem-Cell Transplant. References updated. Codes reviewed skb</td>
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