Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant

Policy Number: 2.03.03  
Last Review: 8/2014

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for donor lymphocyte infusion for malignancies treated with an allogeneic hematopoietic stem-cell transplant when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

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 Considerations), or to convert a patient from mixed to full donor chimerism.

When Policy Topic is not covered

Donor lymphocyte infusion is considered investigational following allogeneic-hematopoietic stem cell transplantation (HSCT) that was originally considered investigational for the treatment of a hematologic malignancy.

Donor lymphocyte infusion is considered investigational as a treatment of nonhematologic malignancies following a prior allogeneic HSCT.

Genetic modification of donor lymphocytes is considered investigational.

Considerations

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

Donor lymphocyte infusions (DLI) may be used following allogeneic HSCT that are considered investigational, such as following allogeneic HSCT for multiple myeloma. The policy statement considers DLI use in this case investigational.

Reimbursement for stem cell collection and storage are considered payable under the Transplant Benefit when billed as a one-time, all-inclusive charge.

Transplant Benefit

The date on which the Transplant Benefit starts accumulating is determined by the transplant coordinator. The Transplant Benefit ends when the Transplant Lifetime Maximum benefit (if applicable) has been exhausted.

Benefits include:

- hospitalization of the recipient for medically recognized transplants from a donor to a transplant recipient;
• evaluation tests requiring hospitalization to determine the suitability of both potential (member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor) and actual donors, when such tests cannot be safely and effectively performed on an outpatient basis (Note: The member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor);
• hospital room, board and general nursing in semi-private rooms;
• special care units, such as coronary and intensive care;
• hospital ancillary services;
• physicians' services for surgery, technical assistance, administration of anesthetics, and medical care;
• acquisition, preparation, transportation, and storage of organ / tissue / cells;
• diagnostic services;
• drugs which require a prescription by federal law;
• medical and surgical care of the donor (related to the procurement of the organ / tissue / cells) if coverage is not available to the donor from any other source. (Covered services provided to a donor will be applied against the recipient's transplant maximum benefit, if applicable)

If the donor and recipient are both listed on the same (family) policy, BCBSKC charges only one deductible and one coinsurance, if applicable.

In addition to the specific organ criteria, transplant candidates must also meet the following general criteria, including, but not limited to:
• Since compliance is a major factor in transplant graft survival, the patient (or legal guardian) must have the ability to accept and understand the transplant procedure and to maintain compliance with long-term medical management and immunosuppression.
• If applicable, patients with a history of malignancy must have passed the recommended length of time to be considered cured for that specific cancer. A complete metastatic evaluation must be performed before a patient will be considered an acceptable transplant candidate.
• Patients with a history of alcohol or substance abuse must have a six month history of abstinence as evidenced by negative urine or serum drug screens taken randomly.
• The patient must have adequate cardiopulmonary status.
• The patient must be free from active infection.

A covered person is eligible for retransplantation as deemed medically necessary and appropriate by BCBSKC. Review of a retransplantation request will include review of the covered person’s compliance with relevant transplant selection criteria including, but not limited to, adherence to medication regimens, follow-up examinations and abstinence from the use of alcohol and drugs.

Coverage will not be provided for:
• Transplant services when the cost is covered by government, foundation or charitable grants
• The purchase price of organs which are sold rather than donated to the recipient.
• An artificial organ

Clinical trials for conditions other than those allowed in this policy may be available in the research setting. However, these trials are considered investigational and/or experimental and therefore contract exclusions.

Note: There are some state mandates in place that require insurance carriers to cover certain clinical trials under very specific guidelines. Please contact your BCBSKC representative for more information

Description of Procedure or Service
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.

Background
Approximately 40-60% of patients who receive a 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 hematologic 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).

Rationale
This policy was originally created in 1998 and was updated regularly with searches of the MEDLINE database. The most recent literature review was performed for the period of March 2013 through April 22, 2014.

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). (1-3)

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. (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 (405/527) 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 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) recommendations for treating CML (v3.2014) 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, and other myeloproliferative diseases

In a 2013 systematic review, El-Jurdi et al evaluated 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, non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL).(10) 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.

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).(11) 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.(3) However, it appears some patients attain durable remissions with DLI after post-transplant relapse.(3)

Warlick et al reported CR after DLI in 49% of 35 patients with relapsed nonchronic myelogenous leukemia, including AML and MDS, after allogeneic HSCT.(12) 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.

**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% to 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 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.(3)

NCCN recommendations for treating ALL (v3.2013) state that DLI can be considered an option for patients in relapse after allogeneic HSCT (category 2A).(13)

**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.(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.(14)

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%.(15)

NCCN guidelines do not include the use of DLI in the treatment of HL or NHL.

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 Policy No. 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(16-20) 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 antmyeloma effect, which could potentially enhance response rates in these patients.(2)

NCCN recommendations for treating multiple myeloma (v2.2014) state that DLI can be considered an option for patients who do not respond or are in relapse after allogeneic HSCT (category 2A).(21)

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.(22) 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 22, 2014 identified 30 open and active phase 2 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 nonhematopoietic malignancies; 1 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-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 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 (eg, 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 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.

Medicare National Coverage

No national coverage determination was identified. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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.


Billing Coding/Physician Documentation Information

38242 Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
Policy Implementation/Update Information

<table>
<thead>
<tr>
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<td>New policy.</td>
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<td>8/1/06</td>
<td>Policy statement revised to indicate that donor leukocyte infusion would be considered medically necessary for a broader group of hematologic malignancies.</td>
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<tr>
<td>8/1/11</td>
<td>Title changed to “Donor Lymphocyte Infusion for 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 (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 (see Considerations), or to convert a patient from mixed to full donor chimerism.”</td>
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