Subject: Donor Lymphocyte Infusion		Original Effective Date: 11/11/14
Policy Number: MCP-210	**Revision Date(s):**	
Review Date: 12/16/15, 9/15/16, 9/19/17, 7/10/18, 6/19/19, 6/17/20, 2/15/21		
MCPC Approval Date: 7/10/18, 6/19/19, 6/17/20, 2/9/21		

Contents

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Donor lymphocyte infusion (DLI) also called donor leukocyte or buffy-coat infusion is a form of adoptive immunotherapy and is performed following an allogeneic hematopoietic stem cell transplant to induce a graft versus leukemia, or graft versus tumor response without requiring the recipient to undergo additional high-dose chemotherapy. Donor mononuclear cells are collected by apheresis from the related or unrelated donor that provided the original hematopoietic stem cell graft. This collection is an outpatient procedure for the donor. The lymphocytes are then either infused via vein into the recipient or are frozen for use at a later time. The main

complications following DLI are the emergence of graft-versus-host disease (GVHD) and myelosuppression. DLI should be avoided in patients with ongoing active GVHD and in patients who have converted to host (rather than donor) chimerism. [2]

The ideal dose and timing of DLI is not known and clinical practice varies. 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 is the most common indication for DLI. Patients who respond to DLI will usually demonstrate a clinical response within two to three months, but a full response may take one year or longer. Responses can be durable with reports of responses lasting up to 20 years. 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's (HL) and non-Hodgkin's lymphoma (NHL). [2]

POSITION STATEMENT [4-14]

1. Donor lymphocyte infusion (DLI) may be considered medically necessary and authorized following a medically necessary ***allogeneic*** hematopoietic stem cell transplant for a hematologic malignancy when all of the following criteria are met: [ALL]

   - ❑ Management of relapse, refractory or persistent disease; [9 10] or
   - ❑ As a planned strategy to prevent disease relapse in the settings considered high risk for relapse: [6 9 10] [ONE]
     - o T cell depleted grafts; or
     - o Non-myeloablative (reduced-intensity) conditioning regimens;

     OR
   - ❑ As a method to convert mixed to full donor chimerism [9 10]

     AND
   - ❑ Donor lymphocytes must be collected from the original hematopoietic stem cell donor

2. Donor lymphocyte infusion is considered experimental, investigational and unproven as a treatment of non-hematologic malignancies following a prior allogeneic HSCT due to insufficient peer reviewed evidence.

3. Genetic modification of donor lymphocytes is considered experimental, investigational and unproven due to insufficient peer reviewed evidence.

4. All other uses for donor lymphocyte infusions not outlined above are considered experimental, investigational and unproven.

SUMMARY OF MEDICAL EVIDENCE

There are no randomized controlled trials comparing DLI to other methods of treatment for relapse, refractory or persistent disease following allogeneic transplantation for hematological diseases. The literature consists of retrospective reviews and prospective studies. The literature is varied for reporting methods of cell collection, timing of infusion, cell dose infused and cell subtype used and many studies report disease-specific outcomes. There is ongoing research on the genetic modification of donor lymphocytes; however the literature is insufficient to determine any long term benefit on health outcomes when used in the treatment of hematological malignancies. A summary of the most relevant studies showing disease outcomes are outlined below.

The Center for International Blood and Marrow Transplant Research (CIBMTR) reported outcomes of 1788 AML patients who relapsed after allogeneic HCT in CR1 or CR2, among whom 1231 (69%) received subsequent intensive therapy that included DLI. Among the 1231 patients who received treatment, 660 (54%) received chemotherapy alone; 202 (16%) received DLI with or without chemotherapy; and, 369 (30%) received a second allogeneic HCT with or without additional chemotherapy or DLI. Among all patients who received DLI, 87 (33%) survived more than 1 year after relapse; median survival was 7 months, with a range of 1 to 177 months. Cell based therapy (DLI or second HCT) resulted in significantly better post relapse OS compared with those who received chemotherapy alone. These results are consistent with other reports of DLI in patients who relapse after allogeneic HCT to treat AML. [15]

A 2013 systematic review 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). 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. [7]

A large retrospective analysis of 446 patients given hematopoietic cell transplants from HLA-matched related or unrelated donors after conditioning and post grafting immunosuppression following grafting was done. 53 patients received donor lymphocyte infusion (DLI) with a median CD3 dose of 1 × 107 cells/kg. Their diagnoses included myelodysplastic syndrome (n = 10), acute leukemia (n = 10), chronic leukemia (n = 11), multiple myeloma (n = 9), lymphoma (n = 9), and solid tumors (n = 4). Patients received DLI for persistent disease (n = 8), disease relapse (n = 17), progressive disease (n = 12), low donor chimerism with disease (n = 11), or low chimerism with disease remission (n = 5). Seventeen of the 53 patients (32%) are alive with a median follow-up of 30 months; 5 are in complete remission (CR), 2 are in partial remission (PR), and 10 have stable or progressive disease. Nine of 53 patients (17%) developed grades II to IV acute graft-versus-host disease. Of 48 patients receiving DLI for treatment of disease, 7 achieved CR and 5 PR, with an overall response rate of 25%. Six of 16 patients who received DLI for chimerism had increases in donor chimerism leading to sustained engraftment, whereas 10 eventually rejected their grafts. The reviewers concluded that DLI

is a potential treatment strategy, with acceptable toxicity, for patients with persistent, relapsed, or progressive disease after nonmyeloablative hematopoietic cell transplantation. [11]

Outcomes were retrospectively reported on 35 patients with chronic myelogenous leukemia (CML) hematologic malignancies, acute myelogenous leukemia (AML) or myelodysplastic syndromes/myeloproliferative disorders (MDS/MPD) (n = 22) receiving lymphodepleting chemotherapy followed by donor lymphocyte infusion (DLI) at 2 T cell dose levels (0.5 and 1.0 × 10(8) CD3/kg). Forty-nine percent of patients achieved complete remission (CR), with a median duration of remission of 6 months (range: 2-71+). CR rates were similar between the 2 groups. The incidence of acute graft-versus-host disease (aGVHD) of any grade was 49%. Overall survival at 1 and 2 years was 30% however, for those achieving CR, 1- and 2-year survival was improved at 44%, respectively. These results demonstrate that DLI after lymphodepleting chemotherapy for relapsed hematologic malignancies results in frequent CRs. The lower DLI dose regimen improved the tolerability of this therapeutic approach, with modest rates of severe aGVHD. [5]

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). Patients who received DLI had an improved two year OS compared with those who did not, (21+/-3% versus 9 +/- 2%, respectively; p<0.001). [8]

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

HCPCS	Description
	N/A

ICD-10	Description: [For dates of service on or after 10/01/2015]
	Any/All

REFERENCES

Government Agency

1. Centers for Medicare & Medicaid Services. NCD for Stem Cell Transplantation [former (110.8.1) 2010.] Current version 110.23. Effective 1/27/2016. Accessed at: http://www.cms.gov/medicare-coverage-database/

Professional Society Guidelines and Other Resources

2. UpToDate: [website]. Waltham, MA: Walters Kluwer Health; 2021. Negrin C. Immunotherapy for the prevention and treatment of relapse following hematopoietic cell transplantation.
3. NCCN Clinical Practice Guidelines in Oncology™. © 2017-2021 National Comprehensive Cancer Network, Inc. Accessed at: https://www.nccn.org/professionals/physician_gls/default.aspx

- Chronic Myelogenous Leukemia
- Multiple Myeloma
- Non-Hodgkin Lymphoma: T-Cell Lymphomas
- Acute Lymphoblastic Leukemia
- Acute Myeloid Leukemia.

Peer Reviewed Literature

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REVIEW/REVISION HISTORY:

11/11/14: New Policy
12/16/15, 9/15/16, 9/19/17, 7/10/18, 6/19/19, 6/17/20, 2/9/21: Policy reviewed, no changes.