Molina Clinical Policy
Donor Lymphocyte Infusion: Policy No. 210

Last Approval: 2/8/2023
Next Review Due By: February 2024

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. 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 (e.g., 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 MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Donor lymphocyte infusion (DLI) (also called donor leukocyte or buffy-coat infusion) is a therapy in which lymphocytes from a donor's blood are given to a patient who has received a stem cell transplant from the same donor. Lymphocytes from the donor may kill remaining cancer cells in the patient. This therapy treats chronic myelogenous leukemia (CML) that has returned as well as multiple myeloma. Research is being done to study the efficacy of DLI for the treatment of other cancer types. (NCI, n.d.).

DLI is a form of adoptive immunotherapy that is performed following an allogeneic hematopoietic stem cell transplant (HSCT) to induce a graft versus leukemia. It can also be performed for 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. (The collection is an outpatient procedure for the donor). The lymphocytes are infused via vein into the recipient or are frozen for use at another date. 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. (Negrin, 2022).

The use of DLI depends upon the disease indication and may be used in the following scenarios:

- 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.

The ideal dose and timing of DLI is unknown and clinical practice varies. Management of relapse is the most common indication for DLI. Patients who respond to DLI usually demonstrate a clinical response within two to three months, however a full response may take one year or more. Responses can be durable with reports of responses lasting up to 20 years. DLI is used in most hematologic malignancies where allogeneic HSCT is performed including chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndromes, multiple myeloma, and Hodgkin's and non-Hodgkin's lymphoma. (Negrin, 2022).

COVERAGE POLICY

Donor Lymphocyte Infusion (DLI) **may be considered medically necessary** and authorized following a medically necessary *allogeneic* HSCT for a hematologic malignancy when **ALL** of the following criteria are met:

1. Management of relapse, refractory, or persistent disease (Tomblyn et al., 2008; Porter et al., 2006); **OR**
2. As a planned strategy to prevent disease relapse in the settings considered high risk for relapse with **ONE** of the following (Van den Brink et al., 2010; Tomblyn et al., 2008; Porter et al., 2006);
   a. T cell depleted grafts; **OR**
   b. Non-myeloablative (reduced intensity) conditioning regimens.

OR

3. As a method to convert mixed to full donor chimerism (Tomblyn et al., 2008; Porter et al., 2006); **AND**

4. Donor lymphocytes must be collected from the original hematopoietic stem cell donor.

Limitations and Exclusions

The following **are considered experimental, investigational, and unproven** due to a lack of evidence:

- As a treatment of non-hematologic malignancies following a prior allogeneic HSCT due to insufficient peer reviewed evidence.
- Genetic modification of donor lymphocytes.
- All other uses for DLI not outlined above.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

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 and is varied for reporting methods of cell collection, timing of infusion, cell dose infused, and cell subtype used. Many studies report disease-specific outcomes. Research continues for genetic modification of donor lymphocytes however the literature is insufficient to determine long-term benefits on health outcomes when used in the treatment of hematological malignancies.

Deol et al. (2010) analyzed studies that focused on DLI for treating hematological disorders that are refractory to or that relapse after allogeneic HSCT. Efficacy of treatment may depend on the patient's type of disease, the dose of lymphocytes that are infused, and development of GVHD. Highest response was found in patients with CML followed by lymphomas, multiple myeloma and acute leukemias.

The Center for International Blood and Marrow Transplant Research (CIBMTR) reported outcomes of 1788 AML patients who relapsed after allogeneic HSCT in CR1 or CR2, among whom 1231 (69%) received subsequent intensive therapy that included DLI. Of 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 HSCT 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 HSCT) resulted in significantly better post relapse OS compared with those who received chemotherapy alone. Results are consistent with other reports of DLI in patients who relapse after allogeneic HSCT for AML. (Bejanyan et al., 2015).

El-Jurdi et al. (2013) published a systematic review that 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.

Bethge et al. (2004) performed a large retrospective analysis of 446 patients who were given hematopoietic cell transplants from HLA-matched related or unrelated donors following conditioning with 2 Gy total body irradiation with or without fludarabine and post-grafting immunosuppression with mycophenolate mofetil and cyclosporine following grafting. A total of 53 patients received DLI with a median CD3 dose of 1 × 107 cells/kg.

Diagnoses ranged from 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). At time of publication, 17 of the 53 patients (32%) were living with a median follow-up of 30 months; 5 patients were in complete remission (CR); 2 are in partial remission (PR); and 10 have stable or progressive disease. Of the 53 patients, 9 (17%) developed grades II to IV acute GVHD. Of the 48 patients receiving DLI for treatment of disease, 7 achieved CR and 5 PR (overall response rate 25%). Of the 16 who received DLI for chimerism, 6 had increases in donor chimerism leading to sustained engraftment, whereas 10 eventually rejected their grafts. DLI is a possible treatment strategy for patients with persistent, relapsed, or progressive disease following nonmyeloablative hematopoietic cell transplantation; the authors note that there are levels of acceptable toxicity.

Warlick et al. (2012) retrospectively reported on outcomes of 35 patients with nonchronic CML hematologic malignancies, AML, or myelodysplastic syndromes/myeloproliferative disorders (MDS/MPD) (n = 22) receiving lymphodepleting chemotherapy followed by DLI at 2 T cell dose levels (0.5 and 1.0 × 10(8) CD3/kg). Forty-nine percent of patients attained complete remission (CR) – the median duration of remission was 6 months and CR rates were similar between the two groups. Acute aGVHD incidence of any grade was 49%. Overall survival at one and two years was 30% however, for those achieving CR, 1- and 2-year survival was improved at 44%, respectively. The study also showed that DLI following lymphodepleting chemotherapy for relapsed hematologic malignancies results in frequent CRs. Also, improved tolerability was found with a lower DLI dose regimen; there were modest rates of severe aGVHD.

National and Specialty Organizations

The **National Comprehensive Cancer Network (NCCN)** (2023, 2022) published *Clinical Practice Guidelines in Oncology* for the following topics:

- *Acute Lymphoblastic Leukemia (ALL)* – considered for patients with relapsed disease
- *Acute Myeloid Leukemia (AML)*
- *Chronic Myelogenous Leukemia (CML)* – may encourage durable molecular remissions in a large percentage of patients with relapsed CML following allogeneic HSCT (studies show higher efficacy in the chronic phase compared to the advanced phase of relapse).
- *Multiple Myeloma* – DLI may stimulate a graft-versus-myeloma effect which may benefit patients whose disease does not respond to (or relapses) following allogeneic stem cell grafting
- *T-Cell Lymphomas*

SUPPLEMENTAL INFORMATION

None.

CODING & BILLING INFORMATION

CPT Code

CPT	Description
38242	Allogeneic lymphocyte infusions

HCPCS Codes – N/A

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

2/8/2023 Policy reviewed, no changes to criteria.
2/9/2022 Policy reviewed; no changes made to coverage section; updated Summary of Medical Evidence and Reference sections.
12/16/2015, 9/15/2016, 9/19/2017, 7/10/2018, 6/19/2019, 6/17/2020, 2/9/2021 Policy reviewed, no changes.
11/11/2014 New policy.

REFERENCES

Government Agency

1. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database. National coverage determination (NCD) – Stem cell transplantation (110.23). Available from CMS. Effective January 27, 2016. Accessed January 27, 2023.

National and Specialty Organizations

1. National Cancer Institute (NCI). Donor lymphocyte infusion. Available from NIH. Accessed January 27, 2023.
2. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Acute lymphoblastic leukemia (version 1.2022). Published April 4, 2022. Available from NCCN. Accessed January 27, 2023. Registration (free) and login required.
3. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Acute myeloid leukemia (version 3.2022). Published January 13, 2023. Available via the NCCN. Accessed January 27, 2023. Registration (free) and login required.
4. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Chronic myeloid leukemia (version 1.2023). Available via the NCCN. Published August 5, 2022. Accessed January 27, 2023. Registration (free) and login required.
5. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Multiple myeloma (version 3.2023). Published December 8, 2022. Available via the NCCN. Accessed January 27, 2023. Registration (free) and login required.
6. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: T-cell lymphomas (version 1.2023). Published January 5, 2023. Available via the NCCN. Accessed January 27, 2023. Registration (free) and login required.

Evidence Based Reviews and Publications

1. Negrin RS. Immunotherapy for the prevention and treatment of relapse following hematopoietic cell transplantation. Available from UpToDate. Updated August 24, 2022. Accessed January 27, 2023. Registration and login required.

Peer Reviewed Publications

1. Bejanyan N, Weisdorf DJ, Logan BR, Wang HL, Devine SM, de Lima M, et al. Survival of patients with acute myeloid leukemia relapsing after allogeneic hematopoietic cell transplantation: A Center for International Blood and Marrow Transplant Research Study. Biol Blood Marrow Transplant. 2015 Mar;21(3):454-9. doi: 10.1016/j.bbmt.2014.11.007. PMID: 25460355. PMCID: PMC4329076.
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4. El-Jurdi N, Reljic T, Kumar A, Pidala J, Bazarbachi A, Djulbegovic B, et al. Efficacy of adoptive immunotherapy with donor lymphocyte infusion in relapsed lymphoid malignancies. Immunotherapy. 2013 May;5(5):457-66. doi: 10.2217/imt.13.31. PMID: 23638742.
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8. Warlick ED, DeFor T, Blazar BR, Burns L, Verneris MR, Ustun C, et al. Successful remission rates and survival after lymphodepleting chemotherapy and donor lymphocyte infusion for relapsed hematologic malignancies post allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2012 Mar;18(3):480-6. doi: 10.1016/j.bbmt.2011.11.030. PMID: 22155141. PMCID: PMC4107638.