Molina Clinical Policy
Donor Lymphocyte Infusion: Policy No. 210

Last Approval: 2/14/2024
Next Review Due By: February 2025

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 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 date unknown).

DLI is a form of adoptive immunotherapy that is performed following an allogeneic hematopoietic stem cell transplant (HSCT) to induce a graft-versus- leukemia response. 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 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 acute 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:

1. In the setting of relapse after an allogeneic HSCT.
2. As a planned strategy to prevent disease relapse in the setting of T cell depleted grafts or non-myeloablative conditioning regimens.
3. 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, acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndromes, multiple myeloma, and Hodgkin's and non-Hodgkin's lymphoma (Negrin 2022).

COVERAGE POLICY

Donor lymphocyte infusion **may be considered medically necessary** and authorized following a medically necessary *allogeneic* hematopoietic stem cell transplantation for a hematologic malignancy when **ALL** of the following criteria are met:

1. Donor lymphocytes must be collected from the original hematopoietic stem cell donor.
2. The donor lymphocyte infusion must be used for **ONE** of the following indications:
    a. For the management of refractory or persistent disease or relapse.
    b. As a method to convert mixed to full donor chimerism.

c. As a planned strategy to prevent disease relapse in settings considered high-risk for relapse with **ONE** of the following:
   - T-cell depleted grafts.
   - Non-myeloablative (reduced intensity) conditioning regimens.

Limitations and Exclusions

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

1. As a treatment of non-hematologic malignancies following a prior allogeneic hematopoietic stem cell transplantation due to insufficient peer reviewed evidence.
2. Genetic modification of donor lymphocytes.
3. All other uses for donor lymphocyte infusions 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.

Yang et al. (2024) completed a multicenter retrospective study to determine "the superiority of prophylactic modified DLI and preemptive modified DLI in patients with high-risk relapse features [with] acute leukemia." High-risk features were defined as 1) failure to achieve complete remission following two cycles of induction chemotherapy, 2) advanced disease at transplantation, 3) minimal residual disease positive at transplantation, and 4) acute leukemia with unfavorable genetic abnormalities according to National Comprehensive Cancer Network guidelines. Patients included in the study had already undergone myeloablative conditioning and allogeneic HSCT prior to receiving DLI. Peripheral blood stem cells and/or bone marrow cells obtained for DLI were infused without ex vivo T cell depletion. All patients received cyclosporin A, methotrexate, and low-dose mycophenolate mofetil for GVHD prophylaxis. Patients receiving prophylactic DLI received DLI "three months after HSCT for patients with high-risk acute leukemia in continuous complete remission with undetectable minimal residual disease and complete chimeric if they had no history of acute GVHD greater than grade II." Patients receiving preemptive DLI "stopped immunosuppressive drugs and received [DLI] immediately after [minimal residual disease] turning positive with morphology remission." A total of 271 patients were included in data analysis with 95 in the prophylactic DLI cohort and 176 in the preemptive DLI cohort. Results showed a higher progression-free survival (63.4% vs. 53.0%, p=0.026) and overall survival (OS) (65.2% vs. 57.0%, p=0.14) for the prophylactic DLI cohort. The prophylactic DLI cohort also had a lower cumulative incidence of relapse compared to the preemptive DLI cohort (25.3% vs. 36.7%, p=0.02). Both cohorts had comparable cumulative rates of grade III-IV acute and chronic GVHD and non-relapse mortality. Overall results demonstrated reduced post-transplant relapse and improved long-term survival for "early scheduled prophylactic DLI rather than preemptive DLI after detectable minimal residual disease" in high-risk patients with acute leukemia.

Rashidi et al. (2023) completed a multicenter phase 2 clinical trial to determine the efficacy of a 10-day decitabine and ruxolitinib in reducing the toxicity and improving the efficacy of dose-escalated DLI in patients with relapsed acute myeloid leukemia and myelodysplastic syndromes. The primary outcome measured was OS at 6 months. Secondary outcomes included the cumulative incidence of grade II-IV acute GVHD at 6 months and the rate of nonrelapse mortality and progression free survival at 1 year. The trial was terminated early due to the observable futility of the treatment. A total of 14 patients were included in data analysis. Results from the available data showed a 6-month OS of 36%, a 6-month cumulative incidence of grade II-IV acute GVHD of 57%, a 1-year progression free survival of 7%,

and a 1-year nonrelapse mortality of 14%.

Ros-Soto et al. (2022) completed a retrospective study to determine patient and donor factors affecting achievement of full donor chimerism (defined as ≥ 95% cells of donor origin) and disease remission along with observed complications following DLI. A total of 100 patients with either 1) acute myelogenous leukemia, 2) acute lymphoblastic leukemia, 3) myelodysplastic syndrome, 4) Hodgkin's and non-Hodgkin's lymphomas, 5) multiple myeloma, or 6) myeloproliferative neoplasms were included in the study. Indications for DLI included T-cell mixed chimerism (present in 61 patients) and relapsed disease (present in 39 patients) with both indications also serving as study cohorts for analysis. All patients included in the study received reduced intensity conditioning and 93% of patients received T-cell depletion with Alemtuzumab. DLI was administered based on institutional-specific protocols. Chimerism was "assessed at days 30 and 100 after transplantation and then repeated every 3 months until 3 years after transplantation." Repeat samples were obtained monthly if full donor chimerism was not achieved. Results were based on a median follow-up period of 36 months (range 1.4-160.1 months). Forty patients (65.6%) with mixed chimerism attained full donor chimerism. Fifteen out of 61 patients (24.6%) experienced disease relapse following initial DLI. OS, relapse following DLI, and disease-free survival (DFS) at 1-*year post-transplant was 85%, 14.8%, and 77% for the mixed chimerism cohort and 54%, 12.8%, and 44% for the relapse cohort. OS, relapse following DLI, and DFS at 2 years post-transplant was 74%, 16.4%, and 69% for the mixed chimerism cohort and 44%, 17.9%, and 33% for the relapse cohort. OS, relapse following DLI, and DFS at 5 years post-transplant was 65%, 24.9%, and 57% for the mixed chimerism cohort and 24%, 21.3%, and 21% for the relapse cohort. Twenty-nine patients developed acute GVHD (8 grade I, 12 grade II, 6 grade III, 3 grade IV) with a cumulative incidence of 23% at day 100. The incidence of acute GVHD was noted to be higher in patients whose donors were ≥ 30 years of age. Twenty-four patients developed chronic GVHD (9 mild, 12 moderate, 3 severe) with a cumulative incidence of 22% at 1 year. Graft failure occurred in 2 patients; however, both patients remained alive at the time of censoring. GVHD-free/relapse-free survival was reported on the mixed chimerism cohort at 1-year post-transplant and was noted to be 71%. Factors associated with improved overall survival, disease control, and GVHD-free/relapse-free survival during multivariate analysis included patients achieving and remaining in full donor chimerism and patients whose donors were < 30 years of age.

Merker et al. (2019) completed a retrospective study to compare the administration of DLI and cytokine-induced killer cell therapy "for the treatment of relapsing hematologic malignancies after allogeneic HSCT." A total of 91 patients were included in the study, with 55 included in the DLI cohort and 36 included in the cytokine-induced killer cell therapy cohort. Included patients were diagnosed with either 1) acute myelogenous leukemia, 2) chronic myelogenous leukemia, 3) acute lymphoblastic leukemia, 4) biphenotypic leukemia, or 5) T cell non-Hodgkin's lymphoma. Chimerism and minimal residual disease in peripheral blood and bone marrow samples were assessed at days 30, 60, and 90 following transplantation and then at months 6, 12, and 18 following transplantation. Mixed chimerism was defined as "1% autologous cells in 2 consecutive samples and patients with > 1% of autologous cells in a single sample post-transplantation." Chimerism monitoring was completed using peripheral blood testing on a weekly basis and minimal residual disease testing was completed monthly using bone marrow samples. Pre-emptive cellular immunotherapy (DLI or cytokine-induced killer cell therapy) was offered to patients with detectable minimal residual disease, mixed chimerism, and/or overt hematologic relapse with a maximum of grade I acute GVHD. Prophylactic treatment was provided to patients with refractory disease at the time of HSCT. DLI and cytokine-induced killer cell therapy was stopped if minimal residual disease cleared or mixed chimerism converted to full donor chimerism. Of the patients receiving DLI, 36 had molecular hematologic relapse, 10 had overt hematologic relapse, and 9 had active disease at the time of transplantation. Of the patients receiving cytokine-induced killer cell therapy, 17 had molecular relapse following transplantation, 11 had refractory disease, and 8 experienced hematologic relapses. Results were based on a median follow-up period of 27.9 months (range 0.9-149.2 months). Approximately 29% of patients receiving DLI achieved complete remission compared to 53% of patients receiving cytokine-induced killer cell therapy. Relapse occurred in approximately 71% of patients receiving DLI compared to 47% of patients receiving cytokine-induced killer cell therapy. All patients with overt hematologic relapse in both groups died. The 6-month OS was 57% for those in the DLI cohort compared to 77% for those in the cytokine-induced killer cell therapy cohort. The 6-month relapse rates were 55% for the DLI cohort and 22% for the cytokine-induced killer cell therapy cohort. Acute GVHD occurred in 19 (35%) of patients in the DLI cohort compared to 9 (25%) of patients in the cytokine-induced killer cell therapy cohort. The majority of patients (n=12) in the DLI cohort developed grade I acute GVHD compared to the majority of patients (n=5) in the cytokine-induced killer cell therapy cohort developing grade II acute GVHD. Researchers noted that patients in the cytokine-induced killer cell therapy cohort had a much more "unfavorable situation at the time of HSCT" compared to those in the DLI cohort, yet those in the cytokine-induced killer cell therapy cohort had better overall outcomes, suggesting that cytokine-induced killer cell therapy was superior to DLI.

Bejanyan et al. (2015) reported outcomes of 1788 acute myelogenous leukemia patients who relapsed after allogeneic HSCT in complete remission 1 or complete remission 2, 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 acute myelogenous leukemia.

National and Specialty Organizations

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

- *Acute Lymphoblastic Leukemia* ([1]2023) – DLI may be considered for patients with relapsed disease following allogeneic HSCT.
- *Pediatric Acute Lymphoblastic Leukemia* ([2]2023) – DLI is **not** recommended as a treatment for advanced acute lymphoblastic leukemia in pediatric patients due to significant risk of GVHD.
- *Acute Myeloid Leukemia* ([3]2023) – No official recommendation for DLI, although the NCCN references a study suggesting DLI "may be a treatment option for therapy in patients who have acute myeloid leukemia that relapses after allogeneic HSCT."
- *Chronic Myelogenous Leukemia* ([4]2023) – A tyrosine kinase inhibitor may be considered with or without DLI as an additional treatment option if there is a positive quantitative RT-PCR test following allogeneic HSCT. DLI may encourage "durable molecular remissions in the majority of patients with relapsed chronic myelogenous leukemia following allogeneic HSCT." Studies show higher efficacy in the chronic phase compared to the advanced phase of relapse.
- *Multiple Myeloma* ([5]2023) – DLI may stimulate a graft-versus-myeloma effect which may benefit patients whose disease does not respond to (or relapses) following allogeneic HSCT.
- *Myelodysplastic Syndromes* ([6]2023) – DLI or a second allogeneic HSCT may be considered "for appropriate patients who had a prolonged remission after [initial allogeneic HSCT]" or if there is no response following the initial allogeneic HSCT.
- *T-Cell Lymphomas* ([7]2023) – No official recommendation for DLI, but the NCCN references a study showing induction of "long-term remissions in a few patients with [progressive disease] or disease relapse after allogeneic HSCT."

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology) Code

Code	Description
38242	Allogeneic lymphocyte infusions

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

02/14/2024	Policy reviewed, no changes to criteria. Updated Overview, Summary of Medical Evidence, and References. IRO Peer Review on January 22, 2024, by a practicing, board-certified physician with a specialty in Hematology.
02/08/2023	Policy reviewed, no changes to criteria.
02/09/2022	Policy reviewed; no changes made to coverage section; updated Summary of Medical Evidence and Reference sections.
02/09/2021	Policy reviewed, no changes.
06/17/2020	Policy reviewed, no changes.
06/19/2019	Policy reviewed, no changes.

07/10/2018	Policy reviewed, no changes.
09/19/2017	Policy reviewed, no changes.
09/15/2016	Policy reviewed, no changes.
12/16/2015	Policy reviewed, no changes.
11/11/2014	New policy.

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