Clinical Policy: Donor Lymphocyte Infusion

Description
This policy describes the medical necessity requirements for a donor lymphocyte infusion (DLI). DLI is an immune therapy approach to decrease the risk of relapse for many hematological malignancies following allogenic hematopoietic stem cell transplantation (HSCT), or to convert a patient’s mixed to full donor chimerism, a state where both donor and recipient stem cells coexist. In this procedure, donor lymphocytes from the original stem cell donor are infused into the patient to cause an immune-mediated graft vs. tumor response. The hematological malignancies treated by DLIs can include, but not limited to, chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), lymphomas, multiple myeloma, and myelodysplastic syndrome.

Policy/Criteria
I. It is the policy of health plans affiliated with Centene Corporation® that donor lymphocyte infusion is medically necessary following an allogenic hematopoietic stem cell transplantation (HSCT) for any of the following indications:
   A. To decrease the risk of relapse of hematological malignancy;
   B. To convert the recipient stem cells of the donor from mixed to full donor chimerism if there is a concern for relapse. DLI should not be used for the sole purpose of increasing donor chimerism without the risk of relapse.

II. It is the policy of health plans affiliated with Centene Corporation that donor lymphocyte infusion is considered experimental/investigational for any of the following:
   A. For the treatment of all other conditions than those specified above;
   B. Genetic modification or ex vivo manipulation of donor lymphocytes;
   C. In the presence of higher than grade 2 acute graft-versus-host-disease (GvHD);
   D. In the presence of total host chimerism.

Background
In addition to chemotherapy, HSCT has become a mainstream clinical therapy for a variety of hematological malignancies. Even though the anti-tumor effects of HSCT can be durable for some patients, relapse of the original malignancy presents considerable clinical challenges for 40 to 75% of patients who undergo autologous HSCT and 10 to 40% of those who undergo allogenic HSCT. Therefore, salvage therapies to combat the refractory disease are required. DLI is one such post-transplant immunotherapy.

Donor lymphocyte infusion, otherwise known as buffy coat infusion, was originally described in 1990 by Kolb and colleagues as a treatment protocol for three patients who had relapsed after bone marrow transplantation for CML. In this procedure, mononuclear cells collected by apheresis from the related or unrelated donor who provided the original hematopoietic stem cell graft are infused into the patient to harness the graft vs. tumor effect. While there is some variety
in published reports concerning the dose of donor cells infused, Deol and Lum survey several articles and report an effective cellular range of 0.01 to $8.8 \times 10^8$ T cells/kg.³

The precise mechanism of action, including the tumor-specific antigens as well as the critical effector cells that mediate the anti-tumor immune response, has not yet been fully elucidated. However, recent evidence suggests that both donor T cells and host-derived immune compartments, including antigen presenting cells and B cells, among others, are critical for facilitating the graft vs. tumor effect of DLI.¹,³,⁴

In striving to eradicate the tumor cell population from the host, complications may persist in patients treated with DLI. Graft vs. host disease (GvHD), the most common and significant toxicity attributable to DLI, occurs in approximately in 40-60% of patients, according to a range of several published reports.¹,₄,⁵ GvHD ensues when the transplanted donor cells recognize the host as foreign and initiate an immune reaction that usually affects the patient’s skin, gastrointestinal tract, and/or liver.⁶ However, there is a strong correlation observed with the onset of GvHD and the intended graft vs. tumor effect. The onset of GvHD is independent of the type of hematological malignancy. In a retrospective study, Collins et al. observed that of 140 patients treated with DLI for relapsed disease after stem cell transplant, approximately 60% patients present with GvHD; of these, 42/45 patients in complete response of disease developed acute GvHD and 36/41 patients in complete response of disease displayed chronic GvHD.⁷ Nevertheless, Carlens et al. determined that the 3 year leukemia free survival is greater for patients who develop chronic GvHD than for those who do not.⁸ Therefore, the ultimate goal of DLI is to maximize the graft vs. tumor response while minimizing the complications that arise from the related GvHD.

In addition to GvHD, bone marrow aplasia is another major complication that can occur in 2-5% of patients following DLI.⁹ Infection and bleeding are compounding risks associated with the onset of aplasia following DLI. The infusion of subsequent donor stem cells can reverse marrow aplasia.

Since Kolb’s initial study describing the utility of DLI, focus has been placed on evaluating the clinical benefit of DLI in the context of treating relapsed CML. Multiple studies have revealed that DLI can establish complete remissions in 70-80% of patients with relapsed CML, and the response is durable in the majority of these cases.⁹

DLI is less effective for achieving remission in patients with relapsing AML following HSCT. According to Deol and Lum, the ability of DLI to induce remission in relapsed AML is approximately 15-20%.³ However, unlike the observations made for CML, it is often necessary to combine DLI with a chemotherapy regimen to elicit an anti-tumor effect against AML.

Multiple myeloma is another hematological malignancy with the potential to respond to DLI. Among varying reports, the response rate of relapsed multiple myeloma to DLI is approximately 22-52%.¹⁰,¹¹ The propensity of multiple myeloma patients to receive autologous and not allogeneic transplants could have a role in this outcome.³ NCCN guidelines state that in patients whose disease does not respond to or relapses after allogeneic stem cell grafting may receive
**CLINICAL POLICY**  
**Donor Lymphocyte Infusion**

DLI to stimulate a beneficial graft-versus-myeloma effect or other myeloma therapies on or off a clinical trial.  

Furthermore, DLI is a treatment possibility for relapsed ALL. However the outcomes for relapsed ALL have been less robust compared to CML and AML. Collins et al analyzed outcomes in both retrospective and prospective studies in patients with relapsed ALL treated with chemotherapy and DLI, and found that only 3/44 were disease free.  

Lastly, chimerism is an important element that develops after the engraftment of a HSCT. Mixed chimerism is defined when < 90% donor cells are detected, whereas full or complete chimerism is defined as 100% donor cells detected, suggesting completed hematopoietic replacement. One such example of the graft vs. tumor effects observed from the conversion to full chimerism was described by Orisini, in which 4 patients with relapsed multiple myeloma received DLI specifically with CD4⁺ T cells. It was observed that 3/4 patients saw a clinical response in the absence of GvHD with complete hematopoietic conversion.  

In summary, donor lymphocyte infusion is an effective clinical treatment for an array of relapsed hematological malignancies. For this adoptive immunotherapy, T lymphocytes from the original stem cell donor are infused into the patient with the intent of inducing a graft vs. tumor response.

**Coding Implications**

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2019, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38242</td>
<td>Allogeneic lymphocyte infusions</td>
</tr>
<tr>
<td>86950</td>
<td>Leukocyte transfusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem-cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition</td>
</tr>
</tbody>
</table>
ICD-10-CM Diagnosis Codes that Support Coverage Criteria

<table>
<thead>
<tr>
<th>ICD-10-CM Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C81.00 - C81.99</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>C85.10 - C85.99</td>
<td>Other specified and unspecified types of non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>C90.00 - C90.02</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>C91.00 - C91.Z2</td>
<td>Lymphoid leukemia</td>
</tr>
<tr>
<td>C92.00 - C92.Z2</td>
<td>Myeloid leukemia</td>
</tr>
<tr>
<td>D46.0 - D46.Z</td>
<td>Myelodysplastic syndrome</td>
</tr>
<tr>
<td>Z94.81</td>
<td>Bone marrow transplant status</td>
</tr>
<tr>
<td>Z94.84</td>
<td>Stem cells transplant status</td>
</tr>
</tbody>
</table>

Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Policy developed</th>
<th>Date</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarified in I. that DLI is indicated post <em>allogenic</em> HSCT; also added post bone marrow transplant. Added II C: Repeat DLI not medically necessary if no documented positive response from the first. Made minor wording changes in the background. Added CPT codes 38215 and 86950. Added HCPCS and ICD-10 codes.</td>
<td>10/16</td>
<td>11/16</td>
</tr>
<tr>
<td>References reviewed and updated. Code updates.</td>
<td>10/17</td>
<td>11/17</td>
</tr>
<tr>
<td>Removed “who has not relapsed” from I.B. Background updated. References reviewed and updated.</td>
<td>10/18</td>
<td>10/18</td>
</tr>
<tr>
<td>Description updated. Specified in I.A. that DLI is indicated to reduce the risk of relapse. Added to I.B. that DLI is intended to convert recipient cells from mixed to full chimerism, if there is a risk of relapse. Added to II. “higher than grade 2 acute graft-versus-host-disease (GvHD)” and “total host chimerism.” Removed not medically necessary indication from section II. of a second DLI when benefits were not noted from the first. References reviewed and updated. Specialist review. Replaced “member” with “member/enrollee” in all instances.</td>
<td>10/20</td>
<td>10/20</td>
</tr>
</tbody>
</table>

References


**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.
This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.

**Note: For Medicaid members/enrollees**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

**Note: For Medicare members/enrollees**, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at [http://www.cms.gov](http://www.cms.gov) for additional information.

©2016 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.