



CIGNA MEDICAL COVERAGE POLICY

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Subject Donor Lymphocyte Infusion

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Coverage Policy

CIGNA covers donor lymphocyte infusion (DLI) as medically necessary following an allogeneic hematopoietic stem-cell transplantation (HSCT) for the treatment of relapsed, persistent or refractory hematologic malignancies or when there is high risk of relapse of hematologic malignancies.

CIGNA does not cover DLI for any other condition because it is considered experimental, investigational or unproven.

General Background

Donor lymphocyte infusion (DLI), also called donor leukocyte infusion, or buffy coat infusion, is a type of therapy in which lymphocytes from the blood of a donor are given to a patient who has already received allogeneic stem-cell transplantation from the same donor. This therapy is based on the premise that the donor lymphocytes will recognize and kill the recipient's cancer cells in a process known as the graft-versus-leukemia (GVL) or graft-versus-tumor (GVT) effect. DLI represents the only form of curative immunotherapy based on adoptive transfer of immunocompetent cells (Cesco-Gaspere, 2009). It is now accepted that DLI, at a time remote from the transplant conditioning regimen, can treat relapse successfully after allogeneic hematopoietic stem-cell transplantation (HSCT) in selected patients with hematologic malignancies.

The most significant and common complications after DLI are acute and chronic graft-versus-host disease (GVHD). Acute or chronic GVHD will occur in 40–60% of evaluable patients. Other adverse effects of DLI include bone-marrow suppression, leading to anemia and infection. These effects result in up to 20% mortality from the procedure (Tomblyn, 2008; Slavin, 2002). The risks of these complications appear related, in part, to donor source, cell dose and therapy prior to DLI (Tomblyn, 2008).

Timing of DLI varies according to indication, for example, to treat tumor recurrence, 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 (Tomblyn, 2008; Porter, 2006). The success of DLI to treat a relapse has also been shown to be disease-specific (Soiffer, 2008; Shattenberg, 2005). Better outcomes have been noted with chronic myelogenous leukemia (CML); remissions have also been achieved with other hematologic malignancies, including acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML)/myelodysplastic syndrome (MDS), multiple myeloma, non-Hodgkin lymphoma, Hodgkin disease, chronic myelomonocytic leukemia (CMML), and idiopathic myelofibrosis. The more common indications for which DLI may be used in selected individuals are discussed below.

Chronic Myelogenous Leukemia (CML): DLI is an effective means of restoring sustained, complete cytogenetic or molecular remissions in patients with relapsed CML and has been shown to induce complete remission (CR) in 60–80% of patients (Soiffer, 2008; Huff, 2006; Weisser, 2006; Michallet, 2005; Ferrara, 2004). Individuals transplanted in chronic phase have better outcomes than those with advanced disease (Levine, 2002; Luznik, 2002; Dazzi, 2000; Porter, 2000). DLI is highly effective if an appropriate number of cells are used. Factors affecting the optimal cell dose include the number of leukemic cells at the time of DLI and the alloreactive T-cell frequency contained in the donor lymphocyte preparation (Simula, 2007). Several small case series have demonstrated similar outcomes for the use of unrelated-donor DLI compared with matched sibling donor DLI (Loren and Porter, 2006).

A number of studies have examined outcomes of DLI alone compared with chemotherapy or DLI in combination with a chemotherapy agent. In a study by Weisser et al. (2006) DLI was compared with imatinib mesylate for patients with relapsing CML after allogeneic HSCT in chronic or accelerated phase. Twenty-one patients received DLI, and ten patients received imatinib. After DLI therapy, 95% of patients achieved a complete molecular remission, while 90%, 70%, and 70% of those receiving imatinib achieved hematologic, complete molecular cytogenetic, and complete molecular genetic remission, respectively. Probability of relapse was significantly higher in the imatinib group than in the patients receiving DLI ($p=0.006$). The rate of leukemia-free survival was significantly higher in the DLI group than in the imatinib group ($p=0.016$), although the rate of treatment-related mortality (TRM) was higher in the DLI group compared to patients receiving imatinib (10% versus 0%). The probability of overall survival (OS) at five years was 76% in the DLI group and 100% in the imatinib group ($p=0.183$). The authors noted that imatinib, in contrast to DLI, does not provide definite cure for relapsed CML after allogeneic HSCT. In a small study involving 21 patients with relapsed CML following allogeneic HSCT the use of DLI alone was compared with DLI in combination with alpha interferon. One-, three-, and five-year survival rates were 100%, 85%, and 76%, respectively for patients receiving DLI plus alpha interferon. With a median follow-up of 20 months, survival for patients receiving DLI alone was 100%.

Acute Lymphocytic Leukemia (ALL): Outcomes for patients who relapse after transplantation are poor; no single therapy consistently results in durable remission. The existence of a GVL effect in the setting of clinical allogeneic transplantation has been demonstrated for patients with acute leukemia; however, the benefit of DLI for relapsed acute leukemia is limited. OS rates are 15%–20% at one month to three years (Arellano, 2007). In a study involving 310 consecutive patients with relapsed acute leukemia who received DLI following human

leukocyte antigen (HLA)-matched-donor allogeneic hematopoietic stem-cell transplantation (HSCT), overall survival (OS) was 32% (Arellano, 2007). Multivariate analysis indicated that longer time to relapse after transplantation, peripheral blood source for stem cells, and initial post-relapse therapy with cytokines, donor lymphocyte infusions (DLI), or second transplantation were associated with improved post-relapse survival ($p < .001$, $p < .001$, and $p < .25$, respectively). This study suggests that therapies aimed at enhancing the graft-versus-leukemia (GVL) effect of allogeneic transplantation, including the use of DLI, may be beneficial for improving post-transplantation survival. Smaller studies involving <25 patients have demonstrated remission rates of four to thirty-eight months with the use of DLI after allogeneic hematopoietic stem-cell transplantation (HSCT) (Savani, 2005; Takami, 2005).

Acute Myelogenous Leukemia (AML)/Myelodysplastic Syndrome (MDS): A GVL effect has been identified in patients with relapsed AML or MDS after allogeneic HSCT undergoing DLI; survival is reported in several retrospective studies involving a total of 99 patients as 24%-42% at a range of one year to 49 months (Campregher, 2007; Pollyea, 2007; Orr, 2006; Choi, 2004; Depril, 2004; Porter, 2000). In a study by Schmid et al. (2008) comparing 399 patients with AML in first hematological relapse after HSCT whose treatment did (n=171), or who did not (n=228) include DLI, estimated survival at two years was 21% and 9%, respectively, for the cohort receiving DLI compared with the non-DLI group. Better outcome was noted for age >37 years ($p < 0.008$), relapse occurring more than five months after HSCT ($p < 0.0001$), and use of DLI ($p < 0.04$).

Depil et al. (2004) studied outcomes with DLI for 14 patients with MDS in relapse following allogeneic HSCT. The median time from HSCT to relapse was 319 days, and median time from relapse to DLI was 35 days. Patients received a median dose of 2.5 infusions per patient. Treatment-related mortality (TRM) was 0%. At median follow-up interval of 49 months, six patients (42%) were alive. Overall estimated survival from time of DLI was 528 days. The authors noted that DLI is well-tolerated and seems to be effective in a small number of patients; however, DLI alone should not be considered as standard treatment for remission induction in patients relapsing after HSCT for MDS.

Multiple Myeloma (MM): The use of DLI has also been proposed for the treatment of relapsed MM following allogeneic HSCT. According to Tomblyn (2008), patients with MM have overall response rates of 40–45% after DLI with remission rates of 30% suggesting benefit in relapsed disease. Many remissions are not durable, however. The strongest prognostic factor predicting response is the occurrence of GVHD (Kolb, 2008; Lockhorst, 2004). Lavenga et al. (2007) studied a cohort of 24 patients with MM who were preemptively treated with DLI following partial T-cell depleted allogeneic HSCT. Thirteen patients received DLI after HSCT. The median time from transplant to DLI was 7.5 months. Eleven patients did not receive DLI because of GVHD, rejection, rapid progressive disease, poor performance status, donor-related problems, or death. Overall, 10 patients achieved a clinical CR after DLI. Therapeutic DLI was given for progression or relapse in four patients; two of these patients entered partial remission and were alive at 64 and 58 months after HSCT, respectively.

Van de Donk et al. (2006) retrospectively reviewed 63 patients with relapsed or persistent myeloma who were given donor lymphocyte infusion (DLI) following non-myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT). Overall response rate was 38.1%. Overall survival (OS) after DLI was 23.6 months. Median OS for patients not responding to DLI was 23.6 months and had not been reached for patients responding to DLI. In responders, progression-free survival (PFS) was 27.8 months. Major toxicities were acute graft-versus-host disease (GVHD) (38.1%) and chronic GVHD (42.9%). The only significant prognostic factor for response to DLI was the occurrence of acute or chronic GVHD.

Non-Hodgkin Lymphoma (NHL): For recurrent childhood NHL, standard treatment may include stem-cell transplantation followed by DLI or an infusion of T-cell lymphocytes that have been treated in the laboratory (NCI, 2010e). Bloor et al. (2008) reported the results of 28 patients with low-grade lymphoid malignancies previously treated with a reduced intensity (n=26) or fully myeloablative (n=2) allogeneic HSCT. Indications for DLI were progressive disease with or without mixed chimerism and persistent mixed chimerism alone six months from the date of transplantation, without significant GVHD. Thirteen patients responded to DLI. The cumulative response rates after DLI to treat progressive disease and persistent mixed chimerism were 76.5% and 91.6%, respectively. All thirteen patients achieved complete remission which was ongoing in nine patients at a median duration of 967 days from last DLI. Of the 17 patients treated for disease progression, the projected five-year overall survival (OS) and progression-free survival (PFS) rates after the last treatment with DLI were 87.8% and 76.2%, respectively. A total of 25 patients received DLI for mixed chimerism. The cumulative response to DLI for mixed chimerism was 92%. All of the responding patients converted to stable full

chimerism; the median time to response was 6.7 months. Results of this study demonstrate a significant response to DLI for patients treated for indolent lymphomas with disease progression post-hematopoietic stem-cell transplantation (HSCT). Cumulative complete remission rate was >75%. These results suggest that this is an effective treatment for progressive disease after allogeneic HSCT.

Professional Societies/Organizations

National Comprehensive Cancer Network (NCCN): Practice Guidelines for Chronic Myelogenous Leukemia (CML) (2010a) note “DLI is effective in inducing remissions in patients with relapsed CML following allogeneic HSCT, though it is more effective in chronic phase than advanced phase. DLI induces complete remissions in majority of patients with CML in early-stage relapse.” Regarding the use of DLI for the treatment of adult patients with multiple myeloma (MM) the Guidelines note “Patient’s whose disease either does not respond to or relapses after allogeneic stem cell grafting may receive donor lymphocyte infusions in order to stimulate a beneficial graft-versus-myeloma effect (2010).”

National Cancer Institute (NCI): According to the NCI (2010a) adult patients who relapse following an allogeneic bone marrow transplant for AML may undergo an infusion of lymphocytes from the donor, similar to the therapy patients with relapsing chronic myelogenous (CML) undergo. The NCI (2010b) notes that for children with recurrent childhood acute lymphoblastic leukemia (ALL), “There are a number of new options for documenting and preventing subsequent relapse after transplantation, including withdrawal of immune suppression or donor lymphocyte infusion and targeted immunotherapies, such as monoclonal antibodies and NK cell therapy.” For relapsing CML, the NCI (2010d) notes “Infusions of buffy coat leukocytes or isolated T cells obtained by pheresis from the bone marrow transplant donor have induced long-term remissions in more than 50% of patients who relapse following allogeneic transplant.” Regarding the use of DLI for individuals with multiple myeloma, the NCI (2010e) notes that a definite graft-versus-myeloma effect has been demonstrated, including regression of myeloma relapses following the infusion of donor lymphocytes.

British Committee for Standards in Haematology (BCSH): On behalf of the BCSH Guidelines on the Diagnosis and Management of Multiple Myeloma, Cummins et al. (2005) notes that DLI should be considered for patients with relapsed/persistent disease following allogeneic HSCT.

Summary

Data in the peer-reviewed literature as well as specialty societies support the safety and effectiveness of donor lymphocyte infusion (DLI) following allogeneic hematopoietic stem-cell transplantation (HSCT) for the treatment of select individuals with relapsed, persistent or refractory hematologic malignancies, or when there is high risk of relapse of hematologic malignancies. The role of DLI for any other condition has not been established.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT [®] * Codes	Description
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

ICD-9-CM Diagnosis Codes	Description
200.00 – 200.88	Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue
201.00 – 201.98	Hodgkin's disease
202.00 –	Other malignant neoplasms of lymphoid and histiocytic tissue

202.98	
203.00 – 203.82	Multiple myeloma and immunoproliferative neoplasms
204.00 – 204.92	Lymphoid leukemia
205.00 – 205.92	Myeloid leukemia
206.00 – 206.92	Monocytic leukemia
207.00 – 207.82	Other specified leukemia
208.00 – 208.92	Leukemia of unspecified cell type
238.75	Myelodysplastic syndrome, unspecified
238.76	Myelofibrosis with myeloid metaplasia
V42.82	Peripheral stem cells replaced by transplant

***Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	1/15/2008	0261	Donor Leukocyte Infusion

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