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 a relapsed, persistent or refractory hematologic malignancy or when there is high risk of relapse of a hematologic malignancy.

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 hematopoietic stem-cell transplantation (HSCT) 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. It is now accepted that DLI, at a time remote from the transplant conditioning regimen, can treat relapse successfully after allogeneic HSCT in selected patients with hematologic malignancies; however significant complications may result including acute and chronic graft-versus-host disease (GVHD), anemia, and infection.

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); although 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. Authors noted that imatinib, in contrast to DLI, does not provide definite cure for relapsed CML after allogeneic HSCT. For patients with relapsing CML who received DLI after allogeneic HSCT 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. One-, three-, and five-year probability of overall survival was 100%, 85%, and 76%-100%.

Acute Lymphocytic Leukemia (ALL): 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 HSCT, OS was 32% (Arellano, 2007). Multivariate analysis indicated that longer time to relapse after HSCT, peripheral blood source for stem cells, and initial post-relapse therapy with cytokines, DLI, or second HSCT were associated with improved post-relapse survival ($p<.001$, $p<.001$, and $p<.25$, respectively). Study outcomes suggest that therapies aimed at enhancing the 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 donor lymphocyte infusion (DLI) after allogeneic hematopoietic stem-cell transplantation (HSCT) (Savani, 2005; Takami, 2005).

Acute Myelogenous Leukemia (AML)/Myelodysplastic Syndrome (MDS): A graft-versus-leukemia (GVL) effect has been identified in patients with relapsed AML or MDS undergoing DLI after allogeneic HSCT. Survival is reported in several small retrospective studies 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 donor lymphocyte infusion (DLI) for 14 patients with myelodysplastic syndrome (MDS) in relapse following allogeneic hematopoietic stem-cell transplantation (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 graft-versus-host disease (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 complete remission 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 DLI following non-myeloablative allogeneic 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 (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 HSCT followed by DLI or an infusion of T-cell lymphocytes that have been treated in the laboratory (NCI, 2011e). 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 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-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 Cancer Institute (NCI): According to the NCI (2014) adult patients who relapse following an allogeneic bone marrow transplant for acute myelogenous leukemia (AML) may undergo an infusion of lymphocytes from the donor, similar to the therapy patients with relapsing chronic myelogenous (CML) undergo. For relapsing CML, the NCI (2013c) 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. The efficacy of this treatment is thought to be the result of an immunologic graft-versus-leukemia effect. This treatment is most effective for patients whose relapse is detectable only by cytogenetics or molecular studies and is associated with significant graft-versus-host disease. ” Regarding individuals with multiple myeloma, the NCI (2013d) notes “A definite graft-versus-myeloma effect has been demonstrated, including regression of myeloma relapses following the infusion of donor lymphocytes.”

National Comprehensive Cancer Network Network™ (NCCN™): Practice Guidelines for Chronic Myelogenous Leukemia (CML) (2014) note "Donor lymphocyte infusion (DLI) is effective in inducing durable molecular remissions in the majority of patients with relapsed CML following allogeneic hematopoietic stem-cell transplantation (HSCT), though it is more effective in chronic phase than advanced phase 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 (2013a)."

Use outside the US
No relevant information

Summary
Donor lymphocyte infusions (DLI) have been shown to induce durable molecular remissions in an individual with relapsed, persistent or refractory hematologic malignancy, or when there is high risk of relapse. Data in the peer-reviewed literature as well as several professional societies/organizations support the safety and effectiveness of DLI following allogeneic hematopoietic stem-cell transplantation (HSCT) for the treatment of select individuals with hematologic malignancy. The role of DLI for any other indication has not been established.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Covered when medically necessary:

CPT®* Codes	Description
38242	Allogeneic lymphocyte infusions

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