



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Effective Date 1/15/2010
Next Review Date.....1/15/2011
Coverage Policy Number0261

Subject Donor Leukocyte Infusion

Table of Contents

Coverage Policy	1
General Background	2
Coding/Billing Information	5
References	6
Policy History.....	12

Hyperlink to Related Coverage Policies

- Stem-Cell Transplant for Acute Lymphocytic/Lymphoblastic Leukemia
- Stem-Cell Transplant for Acute Myelogenous Leukemia
- Stem-Cell Transplantation for Chronic Lymphocytic Leukemia
- Stem-Cell Transplantation for Chronic Myelogenous Leukemia
- Stem-Cell Transplantation for Chronic Myelomonocytic Leukemia (CMML) and Juvenile Myelomonocytic Leukemia (JMML)
- Stem-Cell Transplant for Multiple Myeloma and Poems Syndrome
- Stem-Cell Transplantation for Myelodysplastic Syndromes
- Stem-Cell Transplantation for Non-Hodgkin Lymphoma

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA covers donor leukocyte 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 leukocyte infusion (DLI), also called donor lymphocyte 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 a stem-cell transplantation from the same donor (National Cancer Institute [NCI], 2009). This therapy is based on the premise that the donor white blood cells 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 a donor lymphocyte infusion, at a time remote from the transplant conditioning regimen, can treat relapse successfully after allogeneic hematopoietic stem-cell transplantation (HSCT) in selected patients.

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; in most studies GVHD correlates with the GVL response (Porter, 2006). 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 the 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 been shown to be disease-specific (Soiffer, 2008; Shattenberg, 2005). Three-year disease-free survival (DFS) rates for all patients with chronic myelogenous leukemia equal 60%, while DFS rates exceed 90% in patients with CML in only molecular or cytogenetic relapse only. Other hematologic malignancies appear less responsive with rates $\leq 50\%$, although durable remissions have been achieved.

Chronic Myelogenous Leukemia (CML)

The best responses to DLI occur in patients with CML (Soiffer, 2008). 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 with CML (Huff, 2006; Weisser, 2006; Michallet, 2005; Ferrara, 2004). Patients transplanted in chronic phase have better outcomes than those with advanced disease (Levine, 2002; Luznik and Fuchs, 2002; Dazzi, 2000; Porter, 2000). DLI is highly efficacious 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).

Several studies have compared the use of DLI with another type of chemotherapy or DLI in combination with another 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. The median duration of imatinib therapy was 365 days. The median number of DLI was 1.5 per patient, with escalating cell doses at intervals of four to six weeks, provided there were no clinical signs of GVHD. After DLI therapy, 95% of patients achieved a complete molecular remission, while 90%, 70%, and 70%, respectively, receiving imatinib achieved hematologic, complete molecular cytogenetic, and complete molecular genetic remission. 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 at five years was 100% in the imatinib group and 76% in the DLI 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)

The outlook for patients who relapse after transplantation is extremely poor; no single therapy consistently results in durable remission. The existence of a graft-versus-leukemia effect in the setting of clinical allogeneic

transplantation has been demonstrated for patients with acute leukemia; however, the benefit of donor leukocyte infusion (DLI) for relapsed acute leukemia is limited; overall survival rates (OS) are 15%–20% at one month to three years (Arellano, 2007). In a study involving 310 consecutive patients with relapsed acute leukemia following HLA-matched donor allogeneic hematopoietic stem-cell transplantation (HSCT) (acute myelogenous leukemia [AML], n=229; acute lymphocytic leukemia [ALL], n=81) who received DLI, overall survival was 32% (Arellano, 2007). Multivariate analysis indicated that a longer time to relapse after transplant, peripheral blood source for stem cells, and initial post-relapse therapy with cytokines, DLIs, or second transplant 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. Several smaller studies involving <25 patients have demonstrated remission rates of four to thirty-eight months with the use of DLI after allogeneic 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 ($p < 0.04$).

Levine et al. (2008) reported the outcomes of 45 children who received DLI for relapse after allogeneic HSCT compared with 1229 children selected from the Center for International Blood and Marrow Transplant Research (CIBMTR) database who had similar characteristics, and received allogeneic HSCT but whose relapse was not treated with DLI. Diseases represented by both cohorts were acute myelogenous leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, juvenile myelomonocytic leukemia (JMML), and myelodysplastic syndrome/MDS. None of the patients who relapsed within six months from HSCT responded to DLI. Twenty-six percent who relapsed >six months from transplantation were disease-free at one year ($p = 0.04$). Survival for a cohort of patients who developed mild acute graft-versus-host disease (GVHD) was superior to patients who developed severe GVHD ($p < 0.002$). After adjusting the time from relapse to DLI, there was no difference in survival between the patients who received DLI and those who did not ($p = 0.30$). One-year disease-free survival (DFS) was 30% in patients who received DLI as consolidation following chemotherapy.

Depil et al. (2004) studied the use of 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.

Chronic Lymphocytic Leukemia (CLL)

Several case reports of individuals with relapsed CLL after allogeneic HSCT have documented both remission of disease and severe (and sometimes fatal) graft-versus-host disease (GVHD) (Espanol, 2003; Luznik and Fuchs, 2002; Mehta, 1996; Rondon, 1996).

Chronic Myelomonocytic Leukemia (CMML)

Currently, allogeneic HSCT is the only known curative therapeutic option for patients with CMML; however, data regarding this option are limited (Elliott, 2006). There is also scarce data regarding the use of DLI for this disease in the peer-reviewed published scientific literature. Elliott et al. (2006) reviewed the results of 17 patients with CMML who underwent allogeneic HSCT. Five patients underwent DLI for morphologic relapse and one for mixed donor chimerism. Two patients achieved durable remission of 15 months each. Both patients developed extensive chronic GVHD. Overall survival at three years was 18%. A GVL effect was demonstrated; however, overall outcomes remain less than optimal and unpredictable.

Hodgkin Disease (HD)

Anderlini et al. (2004) studied nine patients with persistent or progressive HD who received DLI following allogeneic HSCT. Seven of the patients had also failed prior autologous HSCT. The median time from HSCT to DLI was seven months. The response rate was 44%. Median duration of response after DLI was seven months. At the time of report publication three patients remained alive, and six had expired. The authors noted that despite the obvious study limitations related to the small sample size, patient heterogeneity and concomitant chemotherapy administration, these data suggest that DLI for immunotherapy of recurrent HL following allogeneic HSCT has significant activity. The authors also noted that these data also suggest that DLI leads to complete or near-complete donor chimerism, as well as, in the majority of cases, GVHD.

Peggs et al. (2007) retrospectively compared the characteristics and outcomes of 67 consecutive sibling donor transplantations following reduced intensity conditioning in multiply relapsed patients with HD. Fifty-three patients had previously undergone autologous hematopoietic stem-cell transplantation (HSCT). Patients received cyclosporine/alemtuzumab (MF-A) or cyclosporine/methotrexate (MF) as prophylaxis for graft-versus-host disease (GVHD). MF-A resulted in significantly lower incidences of non-relapse mortality, acute and chronic GVHD, but no significant excess of relapse/progression. Post donor lymphocyte infusion disease responses occurred in 57% and 55% patients in the MF-A and MF groups, respectively. Progression-free survival was superior with MF-A, with durable responses to donor leukocyte infusion (DLI) contributing to the favorable overall survival (43% vs. 25%, $p=0.0356$).

Idiopathic Myelofibrosis

There is scarce data regarding the use of DLI following allogeneic HSCT. A case report from the University of Barcelona (Cervantes, 2000) documents a complete remission in one patient with idiopathic myelofibrosis in the osteosclerotic phase that received an allogeneic stem-cell transplant but relapsed a few months later. The patient was treated with DLI, which induced chronic GVHD and resulted in a complete remission that lasted to the time of report, 20 months after the procedure.

Inherited Immunodeficiency

A small case series of patients with primary immunodeficiency disorders were treated with allogeneic HSCT followed by DLI for incomplete or decreasing immune constitution (Slatter, et al., 2005). Twelve of 19 patients demonstrated evidence of improved function related to host immunity. Seven of twelve patients were able to discontinue immunoglobulin replacement. One patient developed grade III acute GVHD and one developed severe pneumonitis; both recovered. DLI shows promise for patients with incomplete or failing immune constitution subsequent to allogeneic HSCT; however, there is currently insufficient evidence to support the use of DLI in this patient population.

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; however, many remissions are not durable. 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 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 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 GVHD (38.1%) and chronic GVHD (42.9%). The only significant prognostic factors for response to DLI were the occurrence of acute or chronic GVHD.

Non-Hodgkin's Lymphoma (NHL)

For recurrent childhood NHL, standard treatment may include stem-cell transplant followed by donor lymphocyte infusion or an infusion of T-cell lymphocytes that have been treated in the laboratory (NCI, 2009e). 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. The patients received a total of 68 infusions of donor leukocytes, with a median of two infusions per patient. The 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 (CR) 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 92.0%. 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 donor leukocyte infusion (DLI) for patients treated for indolent lymphomas with disease progression post-hematopoietic stem-cell transplantation (HSCT), resulting in a cumulative complete remission rate (CR) of >75%. The authors note that these data support the existence of a clinically significant graft-versus-tumor (GVT) effect in indolent non-Hodgkin lymphoma (NHL) and 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) (2009a) note that DLI is effective in inducing remissions in patients with relapsed CML following allogeneic stem-cell transplantation (SCT), though it is more effective in chronic phase than advanced phase. Regarding the use of DLI for the treatment of adult patients with multiple myeloma (MM) the NCCN (2009b) notes that DLI may be appropriate for progressive disease following allogeneic HSCT.

National Cancer Institute (NCI): According to the NCI (2009a) 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 (2009b) notes that for children with recurrent childhood acute lymphoblastic leukemia (ALL), “Donor leukocyte infusion has limited benefit for patients with ALL who relapse after allogeneic HSCT.” For relapsing CML, the NCI (2009d) 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 (2009e) notes that a definite graft-versus-myeloma effect has been demonstrated, including regression of myeloma relapses following the infusion of donor lymphocytes.

British Committee on Standards in Haematology (BCSH): BCSH Guidelines on the Diagnosis and Management of Multiple Myeloma (2005) note that DLI should be given to patients with persistent or progressive disease following allogeneic HSCT.

Summary

Evidence in the peer-reviewed literature as well as specialty societies support the safety and effectiveness of donor leukocyte infusion 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 – 202.98	Other malignant neoplasms of lymphoid and histiocytic tissue
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
V42.82	Peripheral stem cells replaced by transplant

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

References

1. Anderlini P, Acholoni SA, Okoroji GJ, Andersson BS, Couriel DR, Delima MJ, et al. Donor leukocyte infusions in relapsed Hodgkin's lymphoma following allogeneic stem cell transplantation: CD3+ cell dose, GVHD and disease response. *Bone Marrow Transplant*. 2004 Sep;34(6):511-4.
2. Arellano ML, Langston A, Winton E, Flowers CR, Waller EK. Treatment of relapsed acute leukemia after allogeneic transplantation: a single center experience. *Bio Blood Marrow Transplant*. 2007 Jan;13(1):116-23.
3. Barrett AJ, Rezvani K, Solomon S, Dickinson AM, Wang XN, Stark G, et al. New developments in allotransplant immunology. *Hematology*. 2003 Jan;2003:350-71.
4. Bethge WA, Hegenbart U, Stuart MJ, Storer BE, Maris MB, Flowers ME, et al. Adoptive immunotherapy with donor lymphocyte infusions after allogeneic hematopoietic cell transplantation following nonmyeloablative conditioning. *Blood*. 2004 Feb 1;103(3):790-5.
5. Bishop MR. The graft-versus-lymphoma effect: fact, fiction, or opportunity? *J Clin Oncol*. 2003 Oct 15;21(20):3713-5. Epub 2003 Sep 8.
6. Bishop MR, Dean RM, Steinberg SM, Odom J, Pavletic SZ, Chow C, et al. Clinical evidence of a graft-versus-lymphoma effect against relapsed diffuse large B-cell lymphoma after allogeneic hematopoietic stem-cell transplantation. *Ann Oncol*. 2008 Nov;19(11):1935-40. Epub 2008 Aug 5.
7. Bishop M, Pavletic SZ. Hematopoietic stem cell transplantation. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, editors. *Abeloff's clinical oncology*. 4th ed. Philadelphia, PA:Churchill Livingstone;2008.

8. Blair A, Goulden NJ, Libri NA, Oakhill A, Pamphilon DH. Immunotherapeutic strategies in acute lymphoblastic leukaemia relapsing after stem cell transplantation. *Blood Rev.* 2005 Nov;19(6):289-300. Epub 2005 Apr 7.
9. Bloor AJ, Thomson K, Chowdhry N, Verfuert S, Ings SJ, Chakraverty R, et al. High response rate to donor lymphocyte infusion after allogeneic stem-cell transplantation for indolent non-Hodgkin lymphoma. *Biol Blood Marrow Transplant.* 2008 Jan;14(1): 50-8.
10. Bonnanomi S, Connor P, Webb D, Ancliff P, Amrolia P, Rao K, et al. Successful outcome of allo-SCT in high-risk pediatric AML using chemotherapy-only conditioning and post transplant immunotherapy. *Bone Marrow Transplant.* 2008 Aug;42(4):253-7. Epub 2008 Jun 16.
11. Campregher PV, Gooley T, Scott BL, Moravec C, Sandmaier B, Martin PJ, et al. Results of donor lymphocyte infusions for relapsed myelodysplastic syndrome after hematopoietic cell transplantation. *Bone Marrow Transplant.* 2007 Nov;40(10):965-71. Epub 2007 Sep 10.
12. Cervantes F, Rovira M, Urbano-Ispizua A, Rozman M, Carreras E, Montserrat E. Complete remission of idiopathic myelofibrosis following donor lymphocyte infusion after failure of allogeneic transplantation: demonstration of a graft-versus-myelofibrosis effect. *Bone Marrow Transplant.* 2000 Sep;26(6):697-9.
13. Cesco-Gaspere M, Morris E, Stauss HJ. Immunomodulation in the treatment of haematological malignancies. *Clin Exp Med.* 2009 Jun;9(2):81-92. Epub 2009 Feb 24.
14. Choi SJ, Lee JH, Lee JH, Kim S, Seol M, Lee YS, et al. Treatment of relapsed acute myeloid leukemia after allogeneic bone marrow transplantation with chemotherapy followed by G-CSF-primed donor leukocyte infusion: a high incidence of isolated extramedullary relapse. *Leukemia.* 2004 Nov;18(11):1789-97.
15. Cudillo L, Cerretti R, Baliva G, De Angelis G, Postorino M, Picardi A, et al. Sezary syndrome in relapse after reduced intensity allogeneic transplant successfully treated with donor lymphocyte infusion. *Bone Marrow Transplant.* 2008 Oct 13.
16. Cummins M, Cwynarski K, Markt S, Dazzi F, Cavenagh J, Clark RE, et al. Management of chronic myeloid leukaemia in relapse following donor lymphocyte infusion induced remission: a retrospective study of the clinical trials committee of the British Society of Blood & Marrow Transplantation (BSBMT). *Bone Marrow Transplant.* 2005;1-5.
17. Dazzi F, Szydlo RM, Cross NC, Craddock C, Kaeda J, Kanfer E, et al. Durability of responses following donor lymphocyte infusions for patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. *Blood.* 2000 Oct 15;96(8):2712-6.
18. Depil S, Deconinck E, Milpied N, Sutton L, Witz F, Juet JP, et al. Donor lymphocyte infusion to treat relapse after allogeneic bone marrow transplantation for myelodysplastic syndrome. *Bone Marrow Transplant.* 2004 Mar;33(5):531-4.
19. Dey BR, McAfee S, Colby C, Sackstein R, Saidman S, Tarbell N, et al. Impact of prophylactic donor leukocyte infusions on mixed chimerism, graft-versus-host disease, and antitumor response in patients with advanced hematologic malignancies treated with nonmyeloablative conditioning and allogeneic bone marrow transplantation. *Biol Blood Marrow Transplant.* 2003 May;9(5):320-9.
20. Dominietto A, Pozzi S, Miglino M, Albarracin F, Piaggio G, Bertolotti F, et al. Donor lymphocyte infusions for the treatment of minimal residual disease in acute leukemia. *Blood.* 2007 Jun 1;109(11):5063-4.
21. Elliott MA, Tefferi A, Hogan WJ, Letendre L, Gastineau DA, Ansell SM, et al. Allogeneic stem cell transplantation and donor lymphocyte infusions for chronic myelomonocytic leukemia. *Bone Marrow Transplant.* 2006 Jun;37(11):1003-8.

22. Espanol I, Buchler T, Ferra C, Gallardo D, Reyes P, Sarra J, et al. Richter's syndrome after allogeneic stem cell transplantation for chronic lymphocytic leukaemia successfully treated by withdrawal of immunosuppression, and donor lymphocyte infusion. *Bone Marrow Transplant*. 2003 Feb;31(3):215-8.
23. Frey NV, Porter DL. Graft-versus-host-disease after donor leukocyte infusions: presentation and management. *Best Pract Res Clin Haematol*. 2008 Jun;21(2):205-22.
24. Huang XJ, Liu DH, Liu KY, Xu LP, Chen H, Han W. Donor lymphocyte infusion for the treatment of leukemia relapse after HLA-mismatched/haploidentical T-cell replete hematopoietic stem cell transplantation. *Haematologica*. 2007 March;92(3):414-7.
25. Huff CA, Fuchs EJ, Smith BD, Blackford A, Garrett-Mayer E, Brodsky RA, et al. Graft-versus-host reactions and the effectiveness of donor lymphocyte infusions. *Biol Blood Marrow Transplant*. 2006 Apr;12(4):414-21.
26. Kolb HJ. Graft-versus-leukemia effects of transplantation and donor lymphocytes. *Blood*. 2008 Dec;112(12):4371-83.
27. Kolb HJ, Schattenberg A, Goldman JM, Hertenstein B, Jacobsen N, Arcese W, et al. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. *Blood*. 1995 Sep 1;86(5):2041-50.
28. Kroger N, Shimoni A, Zagrivnaja M, Ayuk F, Lioznov M, Schieder H, et al. Low-dose thalidomide and donor lymphocyte infusion as adoptive immunotherapy after allogeneic stem cell transplantation in patients with multiple myeloma. *Blood*. 2004 Nov 15;104(10):3361-3.
29. Leukemia and Lymphoma Society. Chronic myelogenous leukemia. Updated 2009 Nov 13. Accessed Nov 24, 2009. Available at URL address: http://www.leukemia-lymphoma.org/all_page?item_id=8501
30. Levenga H, Levison-Keating S, Schattenberg AV, Dolstra H, Schaap N, Raymakers RA. Multiple myeloma patients receiving pre-emptive donor lymphocyte infusion after partial T-cell-depleted allogeneic stem cell transplantation show a long progression-free survival. *Bone Marrow Transplant*. 2007 Aug;40(4):355-9. Epub 2007 Jun 11.
31. Levine JE, Barrett AJ, Zhang MJ, Arora M, Pulsipher MA, Bunin N, et al. Donor leukocyte infusions to treat hematologic malignancy relapse following allo-SCT in a pediatric population. *Bone Marrow Transplant*. 2008 Aug;42(3):201-5. Epub 2008 May 19.
32. Levine JE, Braun T, Penza SL, Beatty P, Cornetta K, Martino R, et al. Prospective trial of chemotherapy and donor leukocyte infusions for relapse of advanced myeloid malignancies after allogeneic stem-cell transplantation. *J Clin Oncol*. 2002 Jan 15;20(2):405-12.
33. Lockhorst HM, Wu K, Verdonck LF, Laterveer LL, van de Donk NW, van Oers MH, et al. The occurrence of graft-versus-host disease is the major predictive factor for response to donor lymphocyte infusions in multiple myeloma. *Blood*. 2004;103(11):4362-4.
34. Loren AW, Porter DL. Donor leukocyte infusions after unrelated donor hematopoietic stem cell transplantation. *Curr Opin Oncol*. 2006 Mar;18(2):107-14.
35. Luznik L, Fuchs EJ. Donor lymphocyte infusions to treat hematologic malignancies in relapse after allogeneic blood or marrow transplantation. *Cancer Control*. 2002 Mar/Apr;9(2):123-37.
36. Marks DI, Lush R, Cavenagh J, Milligan DW, Schey S, Parker A, et al. The toxicity and efficacy of donor lymphocyte infusions given after reduced-intensity conditioning allogeneic stem cell transplantation. *Blood*. 2002 Nov 1;100(9):3108-14.

37. McSweeney PA, Niederwiesser D, Shizuru JA, Sandmaier BM, Molina AJ, Maloney DG, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood*. 2001 Jun 1;97(11):3390-400.
38. Mehta J, Powles R, Singhal S, Iveson T, Treleaven J, Catovsky D. Clinical and hematologic response of chronic lymphocytic and prolymphocytic leukemia persisting after allogeneic bone marrow transplantation with the onset of acute graft-versus-host disease and the possible role of graft-versus-leukemia. *Bone Marrow Transplant*. 1996 Mar;17(3):371-5.
39. Michallet AS, Nicolini F, Furst S, Le QH, Dubois V, Hayette S, et al. Outcome and long-term follow-up of alloreactive donor lymphocyte infusions given for relapse after myeloablative allogeneic hematopoietic stem cell transplantations (HSCT). *Bone Marrow Transplant*. 2005;35:601-8.
40. Miller J, Negrin RS. Experimental cell therapy. In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Silberstein LE, McGlave P, et al., editors. *Hematology: basic principles and practice*. 5th ed. Orlando, FL: Churchill Livingstone; 2008.
41. Munshi NC, Anderson KC. Plasma cell neoplasms. In: Devita VT, Lawrence TS, Rosenberg SA, editors. *Cancer: principles and practice of oncology*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
42. National Cancer Institute (a). Adult acute myeloid leukemia treatment (PDF[®]). Updated 2009 Sep 8. Accessed Nov 24, 2009. Available at URL address: <http://www.cancer.gov/cancertopics/pdq/treatment/adultAML/HealthProfessional/page7>
43. National Cancer Institute (b). Childhood acute lymphoblastic leukemia treatment (PDQ[®]). Updated 2009 Aug 7. Accessed Nov 24, 2009. Available at URL address: <http://www.cancer.gov/cancertopics/pdq/treatment/childALL/healthprofessional>
44. National Cancer Institute (c) Childhood non-Hodgkin lymphoma treatment (PDQ[®]). Updated 2009 Aug 4. Accessed Nov 24, 2009. Available at URL address <http://www.cancer.gov/cancertopics/pdq/treatment/child-non-hodgkins/healthprofessional>
45. National Cancer Institute (d). Chronic myelogenous leukemia treatment (PDQ[®]). Updated 2009 Jul 2. Accessed Dec 2, 2009. Available at URL address: <http://www.cancer.gov/cancertopics/pdq/treatment/CML/healthprofessional>
46. National Cancer Institute (e). Multiple myeloma and other plasma cell neoplasms treatment (PDQ[®]). Updated 2009 Nov 23. Accessed Dec 2, 2009. Available at URL address: <http://www.cancer.gov/cancertopics/pdq/treatment/myeloma/healthprofessional/allpages>
47. National Comprehensive Cancer Network (a). Practice guidelines in oncology-v.2.2010: chronic myelogenous leukemia. Updated 2009 Aug 7. Accessed Nov 24, 2009. Available at URL address: http://www.nccn.org/professionals/physician_gls/PDF/cml.pdf
48. National Comprehensive Cancer Network (b). Practice guidelines in oncology-v.2.2010: multiple myeloma. Updated 2009 Jul 1. Accessed Nov 24, 2009. Available at URL address: http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf
49. National Donor Marrow Program. Reduced intensity transplants. Accessed Dec 2, 2009. Available at URL address: http://www.marow.org/PATIENT/Undrstnd_Disease_Treat/Undrstnd_Treat_Opt/Lrn_BMT_Cord/R_Intensity_Tx/index.html
50. Or R, Hadar E, Bitan M, Resnick IB, Aker M, Ackerstein A, et al. Safety and efficacy of donor lymphocyte infusions following mismatched stem cell transplantation. *Biol Blood Marrow Transplant*. 2006 Dec;12(12):1295-301.

51. Peggs KS, Sureda A, Qian W, Caballero D, Hunter A, Urbano-Isizua A, et al. Reduced-intensity conditioning for allogeneic haematopoietic stem cell transplantation in relapsed and refractory Hodgkin lymphoma: impact of alemtuzumab and donor lymphocyte infusions on long-term outcomes. *Br J Haematol*. 2007 Oct;139(1):70-80.
52. Peggs KS, Thomson K, Hart DP, Geary J, Morris EC, Yong K, et al. Dose-escalated donor lymphocyte infusions following reduced intensity transplantation: toxicity, chimerism, and disease responses. *Blood*. 2004 Feb 15;103(4):1548-56.
53. Pollyea DA, Artz DA, Stock W, Daugherty C, Godley L, Odenike OM, et al. Outcomes of patients with AML and MDS who relapse or progress after reduced intensity allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2007 Dec;40(11):1027-1032. Epub 2007 Sep 10.
54. Porter DL, Antin JH. Donor leukocyte infusions in myeloid malignancies: new strategies. *Best Pract Res Clin Haematol*. 2006;19(4):737-55.
55. Porter DL, Collins RH, Hardy C, Kernan NA, Drobyski WR, Giral S, et al. Treatment of relapsed leukemia after unrelated donor marrow transplantation with unrelated donor leukocyte infusions. *Blood*. 2000 Feb 15;95(4):1214-21.
56. Posthuma EF, Marijit EW, Barge RM, van Soest RA, Baas RO, Starrenberg CW, et al. Alpha-interferon with very-low-dose donor lymphocyte infusion for hematologic or cytogenetic relapse of chronic myeloid leukemia induces rapid and durable complete remissions and is associated with acceptable graft-versus-host disease. *Biol Blood Transplant*. 2004 Mar;10(3):204-12.
57. Reddy P, Ferrara JVM. Graft-versus-host disease and graft-versus-leukemia responses. In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Silberstein LE, McGlave P, et al., editors. *Hematology: basic principles and practice*. 5th ed. Orlando, FL: Churchill Livingstone; 2008.
58. Rizzieri DA, Dev P, Long GD, Gasparetto C, Sullivan KM, Horwitz M, et al. Response and toxicity of donor lymphocyte infusions following T-cell depleted non-myeloablative qlogene3ic hematopoietic SCT from 3-6/6 HLA matched donors. *Bone Marrow Transplant*. 2008 Oct 13.
59. Roback JD. Vaccine-Enhanced Donor Lymphocyte Infusion (veDLI). *Hematology Am Soc Hematol Educ Program*. 2006:486-91.
60. Rondelli D, Barosi G, Bacigalupo A, Prchal JT, Popat U, Alessandrino EP, et al. Allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning in intermediate- or high-risk patients with myelofibrosis with myeloid metaplasia. *Blood*. 2005 May 15;105(10):4115-9. Epub 2005 Jan 25.
61. Rondon G, Giral S, Huh Y, Khouri I, Andersson B, Andreef M, et al. Graft-versus-leukemia effect after allogeneic bone marrow transplantation for chronic lymphocytic leukemia. *Bone Marrow Transplant*. 1996 Sep;18(3):669-72.
62. Rowe JM. Graft-versus-disease effect following allogeneic transplantation for acute leukaemia. *Best Pract Res Clin Haematol*. 2008 Sep;21(3):485-502.
63. Russell NH, Bryne JL, Faulkner RD, Gilyead M, Das-Gupta EP, Haynes AP. Donor lymphocyte infusions can result in sustained remissions in patients with residual or relapsed lymphoid malignancy following allogeneic haemopoietic stem cell transplantation. *Bone Marrow Transplant*. 2005 Sep;36(5):437-41.
64. Saito TI, Rubio MT, Sykes M. Clinical relevance of recipient leukocyte infusion as antitumor therapy following nonmyeloablative allogeneic hematopoietic cell transplantation. *Exp Hematol*. 2006 Sep;34(9):1271-7.

65. Salama M, Nevill T, Marcellus D, Parker P, Johnson M, Kirk A, et al. Donor leukocyte infusions for multiple myeloma. *Bone Marrow Transplant*. 2000;26:1179-84.
66. Savani BN, Srinivasan R, Espinoza-Delgado I, Dorrance C, Takahashi Y, Igarashi T, et al. Treatment of relapsed blast-phase Philadelphia-chromosome-positive leukaemia after non-myeloablative stem-cell transplantation with donor lymphocytes and imatinib. *Lancet Oncol*. 2005 Oct;6:809-12.
67. Schattenberg AV, Dolstra H. Cellular adoptive immunotherapy after allogeneic stem cell transplantation. *Curr Opin Oncol*. 2005 Nov;17(6):617-21.
68. Schmid C, Labopin M, Nagler A, Bornhauser M, Finke J, Fassas A, et al. Donor lymphocyte infusion in the treatment of first hematological relapse after allogeneic stem-cell transplantation in adults with acute myeloid leukemia: a retrospective risk factors analysis and comparison with other strategies by the EBMT Acute Leukemia Working Party. *J Clin Oncol*. 2007 Nov1;25(31):4938-45. Epub 2007 Oct 1.
69. Simula MP, Markt S, Fozza C, Kaeda J, Szydlo RM, Nadal E, et al. Response to donor lymphocyte infusions for chronic myeloid leukemia is dose-dependent: the importance of escalating the cell dose to maximize therapeutic efficacy. *Leukemia*. 2007 May;21(5):943-8. Epub 2007 Mar 15.
70. Slatter MA, Bhattacharya A, Abinun M, Flood TJ, Cant AJ, Gennery AR. Outcome of boost haemopoietic stem cell transplant for decreased donor chimerism or graft dysfunction in primary immunodeficiency. *Bone Marrow Transplant*. 2005;35:683-9.
71. Slavin S. Immunotherapy of cancer with alloreactive lymphocytes. *Lancet Oncol*. 2001 Aug;2(8):491-8.
72. Slavin S, Morecki S, Weiss L, Or R. Donor lymphocyte infusion: the use of alloreactive and tumor-reactive lymphocytes for immunotherapy of malignant and nonmalignant diseases in conjunction with allogeneic stem cell transplantation. *J Hematother Stem Cell Res*. 2002 Apr;11(2):265-76.
73. Soiffer RJ. Donor lymphocyte infusions for acute myeloid leukaemia. *Best Pract Res Clin Haematol*. 2008 Sep;21(3):455-66.
74. Takami A, Okumura H, Yamazaki H, Kami M, Kim SW, Asakura H, et al. Prospective trial of high-dose chemotherapy followed by infusions of peripheral blood stem cells and dose-escalated donor lymphocytes for relapsed leukemia after allogeneic stem cell transplantation. *Int J Hematol*. 2005 Dec;82(5):449-55.
75. Tomblyn M, Lazarus HM. Donor lymphocyte infusions: the long and winding road: how should it be traveled? *Bone Marrow transplant*. 2008 Nov;42(9):569-79. Epub 2008 Aug 18.
76. Van de Donk NW, Kroger N, Hegenbart U, Corradini P, San Miguel JF, Goldschmidt H, et al. Prognostic factors for donor lymphocyte infusions following non-myeloablative allogeneic stem cell transplantation in multiple myeloma. *Bone Marrow Transplant*. 2006 Jun;37(12):1135-41.
77. Verhopen F, Stalder M, Helg C, Chalandon Y. Resistant pure red cell aplasia after allogeneic stem cell transplantation with major ABO mismatch treated by escalating dose donor leukocyte infusion. *Eur J Haematol*. 2004;73:441-6.
78. Vose JM. Bone marrow transplantation. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, editors. *Abeloff's clinical oncology*. 4th ed. Philadelphia, PA:Churchill Livingstone;2008.
79. Weiser M, Tischer J, Schnittger S, Schoch C, Ledderose G, Kolb HJ. A comparison of donor lymphocyte infusions or imatinib mesylate for patients with chronic myelogenous leukemia who have relapsed after allogeneic stem cell transplantation. *Haematologica*. 2006 May;91(5):663-6. Epub 2006 Apr 19.
80. Yoshimi A, Bader P, Matthes-Martin S, Starv J, Sedlacek P, Duffner U, et al. Donor leukocyte infusion after hematopoietic stem cell transplantation in patients with juvenile myelomonocytic leukemia. *Leukemia*. 2005 Jun;19(6):971-7.

Policy History

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

“CIGNA” and the “Tree of Life” logo are registered service marks of CIGNA Intellectual Property, Inc., licensed for use by CIGNA Corporation and its operating subsidiaries. All products and services are provided exclusively by such operating subsidiaries and not by CIGNA Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, CIGNA Behavioral Health, Inc., Intracorp, and HMO or service company subsidiaries of CIGNA Health Corporation and CIGNA Dental Health, Inc. In Arizona, HMO plans are offered by CIGNA HealthCare of Arizona, Inc. In California, HMO plans are offered by CIGNA HealthCare of California, Inc. and Great-West Healthcare of California, Inc. In Connecticut, HMO plans are offered by CIGNA HealthCare of Connecticut, Inc. In North Carolina, HMO plans are offered by CIGNA HealthCare of North Carolina, Inc. In Virginia, HMO plans are offered by CIGNA HealthCare Mid-Atlantic, Inc. All other medical plans in these states are insured or administered by Connecticut General Life Insurance Company.

Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.