Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual

Topic: Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant

Date of Origin: September 2011

Section: Transplant

Last Reviewed Date: August 2013

Policy No: 45.03

Effective Date: November 1, 2013

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Donor lymphocyte infusion (DLI), also called donor leukocyte or buffy-coat infusion, is a type of therapy in which T lymphocytes from the blood of a donor are given to a patient who has already received a hematopoietic stem cell transplant (HSCT) from the same donor. The DLI therapeutic effect results from a graft-versus-leukemic or graft-versus-tumor effect due to the recognition of certain antigens on the cancer cells by the donor lymphocytes and the resultant elimination of the tumor cells. Approximately 40-60% of patients who receive a DLI develop graft-versus-host disease (GVHD), and the development of GVHD predicts a response to the DLI.[1,2] Treatment-related mortality after DLI is 5-20%. There does not seem to be a correlation between the type of hematologic malignancy for which the DLI was given and the development of GVHD.[1,2] The risk of development of GVHD is related, in part, to DLI dose and therapy prior to DLI.

The timing of the use of DLI depends upon the disease indication and may be used in the setting of:

- Management of relapse after an allogeneic HSCT. Relapse occurs in approximately 40% of all hematologic malignancy patients and is the most common indication for DLI.[3]
- As a planned strategy to prevent disease relapse in the settings considered high risk for relapse:
    - T cell depleted grafts

- Non-myeloablative (reduced-intensity) conditioning regimens
- As a method to convert mixed to full donor chimerism.

DLI is used in nearly all hematologic malignancies for which allogeneic HSCT is performed, including chronic myeloid leukemia, acute myeloid and lymphoblastic leukemias, myelodysplastic syndromes, multiple myeloma and Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL).

MEDICAL POLICY CRITERIA

I. Donor lymphocyte infusion may be considered **medically necessary** following allogeneic-hematopoietic stem cell transplantation (HSCT) that was originally considered medically necessary for the treatment of:

   A. A hematologic malignancy that has relapsed or is refractory.

   B. To prevent relapse in the setting of a high risk of relapse (i.e., T-cell depleted grafts, non-myeloablative conditioning regimens).

   C. To convert a patient from mixed to full donor chimerism.

II. Donor lymphocyte infusion is considered **investigational** following allogeneic HSCT that was originally considered investigational for the treatment of a hematologic malignancy.

III. Donor lymphocyte infusion is considered **investigational** as a treatment of nonhematologic malignancies following a prior allogeneic HSCT.

IV. Genetic modification of donor lymphocytes is considered **investigational**.

SCIENTIFIC EVIDENCE

The principal outcomes associated with treatment of hematologic malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease may be another primary outcome among patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Ideally, in order to understand the impact of donor lymphocyte infusion (DLI) on health outcomes following allogeneic-HSCT for treatment of hematologic malignancies, well-designed randomized controlled trials (RCTs) that compare this therapy with standard medical treatment without DLI provide the most reliable evidence. In the absence of such information, sufficiently large comparative or observational studies may be sufficient to isolate a potential treatment effect. Further, for treatment of malignant cancers, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

Chronic Myelogenous Leukemia (CML)

The role of DLI in CML has recently changed as the use of tyrosine-kinase inhibitors (TKIs) has revolutionized the treatment of CML by keeping the disease under control instead of proceeding to HSCT. However, for patients who develop resistance to the TKIs or are unable to tolerate the adverse effects, HSCT and DLI may be an option to manage the disease.

Literature on the use of DLI in CML consists of large series reporting outcomes of patients with relapsed CML after receiving DLI.[4-8] These studies comprise over 500 patients, approximately half of whom had only molecular or cytogenetic relapse at the time of DLI.[2] The cell doses varied among patients, with some patients receiving multiple DLI infusions and others receiving planned dose escalations. Despite these variations, a molecular complete remission (CR) was achieved in 77% of patients (405 of 527) with OS at 3 or more years ranging from 53% to 95%.[3] Although interpretation of this evidence is limited by the non-randomized, non-comparative nature of available studies, it is sufficient to suggest treatment benefit with DLI among some patients with CML.

Clinical Practice Guidelines

The 2013 National Comprehensive Cancer Network (NCCN) Chronic Myelogenous Leukemia guideline recommends treating CML with DLI as an option for patients who do not achieve remission, are in cytogenetic relapse, or have an increasing level of molecular relapse.[9]

Acute Myelogenous Leukemia (AML)

The studies of myeloproliferative diseases treated with DLI either after relapse or for mixed chimerism are characterized by small sample sizes, inconsistent pre-DLI therapy, and varied DLI cell doses, making it difficult to draw definite conclusions on outcomes.[3] However, it appears some patients attain durable remissions with DLI after post-transplant relapse. For example:

- A large retrospective analysis from the European Blood and Marrow Transplant Group (EBMT) compared OS in 399 patients with AML with post-transplant relapse who either were treated with DLI (n=171) or were not (n=228).[10] Patients who received DLI had an improved 2-year OS compared with those who did not, (21+/-3% versus 9 +/- 2%, respectively; p<0.001).

- Warlick and colleagues reported on a case series of 35 patients with relapsed nonchronic myelogenous leukemia, including AML and myelodysplastic syndrome, after allogeneic HSCT.[11] Overall survival at 1 year was 30% and 19% at 2 years; complete remission (CR) after DLI was achieved in 49% of patients. The authors reported a lower dose regimen of DLI was more tolerable and reduced graft-versus-host disease (GVHD) occurrence to 25% compared to 66% with higher-dose DLI.

Based on a lack of effective treatment alternatives, the available evidence on DLI in AML is sufficient to suggest potential for treatment benefit, with low-risk of treatment harm.

Clinical Practice Guidelines

Current NCCN guidelines do not specifically address the use of DLI in AML.[12]

Acute Lymphoblastic Leukemia (ALL)

The graft versus tumor effect is thought to be less robust in patients with ALL than in the myeloid leukemias. The clinically evident graft-versus-leukemia effect of DLI requires weeks to months to become apparent, and, as ALL is a rapidly proliferating disease, DLI only is unable to control the disease without a significant reduction in leukemia burden prior to DLI. Small studies have reported response rates to DLI ranging from 0% to 20% and OS rates of less than 15% in patients with ALL.[2] By comparison, a second allogeneic HSCT provides a 5-year OS of approximately 15-20%, with a treatment-related mortality rate of approximately 50%.

Available evidence to date consists of case series. Although it is not clear whether DLI adds benefit to salvage chemotherapy, there are reports of long-term survivors with relapsed ALL who received both chemotherapy and DLI.[3]

Clinical Practice Guidelines

Current NCCN guidelines cite the lack of high quality data on the use of DLI in relapse of ALL, although based on available data, they currently recommend the use of DLI in patients who have relapsed following allogeneic HSCT.[13]

Lymphomas

Studies in which patients received DLI for lymphomas consist of small numbers of patients and various histologies (both Hodgkin lymphoma [HL] and high- and low-grade non-Hodgkin lymphomas [NHL]). In general, the highest response rates have been seen in the indolent lymphomas. For NHL, there are too few patients reported with any single histologic subtype of lymphoma to give adequate information of the benefit of DLI for a specific lymphoma subtype.[3] Examples of available studies include the following:

- Morris and colleagues reported on one of the largest case series of patients with NHL (n=21) and found that DLI showed response rates in 3 of 9 patients with high-grade NHL, 1 of 2 patients with mantle cell lymphoma, and 6 of 10 patients with low-grade disease.[14]
- Peggs and colleagues reported on a series of 14 patients with multiply relapsed HL who received reduced-intensity conditioning allogeneic HSCT and DLI showed a CR of 57% and survival at 2 years of 35%.[15]

Although current evidence is not sufficient to form conclusions, in the absence of other effective treatment options, it is suggestive that DLI may have a treatment benefit among patients with some types of lymphomas.

Clinical Practice Guidelines

NCCN Guidelines

- Current NCCN guidelines for Hodgkin Lymphoma[16] do not specifically address the use of DLI.
- Current NCCN guidelines for non-Hodgkin's lymphomas (NHL)[17] summarizes a small case series[18] that showed that DLI induction of graft-versus-Adult T-cell Leukemia/Lymphoma (ATLL) effect "may provide long-lasting remission in select patients with relapsed ATLL. However, prospective clinical trials are needed to confirm these findings." DLI was not addressed for any other NHL subtypes.

Multiple Myeloma

Available evidence on the use of DLI in multiple myeloma consists of case series. Observational data suggest a graft-versus-tumor effect in multiple myeloma, as the development of GVHD has correlated with response in several analyses. For example, five studies (n=5-63) investigating the role of DLI in relapsed multiple myeloma reported the highest response to DLI as 62%,[19] with approximately half of the responders attaining a complete response.[3,19-23] One confounding factor for high response rates for multiple myeloma treated with DLI is that corticosteroids used for treating GVHD have a known antimyeloma effect which could potentially enhance response rates in these patients.[2]

Available evidence is therefore suggestive of a treatment benefit with DLI, although the quality of the evidence cannot exclude the role of potential confounders in reported treatment outcomes.

Clinical Practice Guidelines

Current NCCN guidelines for treating multiple myeloma (v2.2013) state that DLI can be considered an option for patients who do not respond or are in relapse after allogeneic HSCT.[24]

Genetic Modification of Donor Lymphocytes

In an effort to control GVHD, a group in Italy explored using genetically modified lymphocytes engineered to express the suicide gene thymidine kinase of herpes simplex virus.[25] These lymphocytes were infused into 23 patients with various hematologic malignancies who relapsed after an allogeneic HSCT. Six patients died of progressive disease within 4 weeks of infusion. Eleven patients experienced disease response (CR in 6 and partial remission in 5). Three patients remained alive in CR at a median of 471 days. Twelve patients were evaluable for GVHD, of which 3 developed acute or chronic GVHD which was successfully treated with ganciclovir.

Due to the heterogenous nature of this study sample, and lack of additional evidence from the peer-reviewed literatures, the treatment effect of genetically modified DLI is not known. Additional evidence, applicable to a carefully selected target population, is needed before conclusions regarding the use of genetic modification of donor lymphocytes can be made.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified which specifically recommend the use of genetically modified DLI for treatment of any hematologic malignancy.

Summary

Donor leukocyte infusion (DLI) is used in nearly all hematologic malignancies that relapse after a prior allogeneic HSCT as a planned strategy to prevent disease relapse in a setting of high-risk of disease relapse (e.g., after a reduced-intensity allogeneic hematopoietic stem cell transplant [HSCT]), and to convert mixed to full donor chimerism.

Therefore, DLI may be considered medically necessary following an allogeneic-HSCT that was considered medically necessary for the treatment of a relapsed or refractory hematologic malignancy, to prevent relapse in the setting of a high risk of relapse, or to convert a patient from mixed to full donor

chimerism. Insufficient evidence exists to support the use of DLI in any other context, including the use of DLI with genetically modified donor lymphocytes; such uses are therefore considered investigational.

REFERENCES

1. TEC Assessment 1997. "Donor Leukocyte Infusion for Hematologic Malignancies that Relapse After Allo-BMT." BlueCross BlueShield Association Technology Evaluation Center, Vol. 12, Tab 22.
2. Deol, A, Lum, LG. Role of donor lymphocyte infusions in relapsed hematological malignancies after stem cell transplantation revisited. *Cancer Treat Rev*. 2010 Nov;36(7):528-38. PMID: 20381970
3. 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. PMID: 18711351
4. van den Brink, MR, Porter, DL, Giralt, S, et al. Relapse after allogeneic hematopoietic cell therapy. *Biol Blood Marrow Transplant*. 2010 Jan;16(1 Suppl):S138-45. PMID: 19857588
5. Simula, MP, Marktel, S, Fozza, C, 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. PMID: 17361226
6. Dazzi, F, Szydlo, RM, Cross, NC, 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. PMID: 11023502
7. Guglielmi, C, Arcese, W, Dazzi, F, et al. Donor lymphocyte infusion for relapsed chronic myelogenous leukemia: prognostic relevance of the initial cell dose. *Blood*. 2002 Jul 15;100(2):397-405. PMID: 12091328
8. Fozza, C, Szydlo, RM, Abdel-Rehim, MM, et al. Factors for graft-versus-host disease after donor lymphocyte infusions with an escalating dose regimen: lack of association with cell dose. *Br J Haematol*. 2007 Mar;136(6):833-6. PMID: 17341269
9. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Chronic Myelogenous Leukemia. V.4.2013. [cited 08/02/2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf
10. Schmid, C, Labopin, M, Nagler, 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 Nov 1;25(31):4938-45. PMID: 17909197
11. Warlick, ED, DeFor, T, Blazar, BR, et al. Successful remission rates and survival after lymphodepleting chemotherapy and donor lymphocyte infusion for relapsed hematologic malignancies postallogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2012 Mar;18(3):480-6. PMID: 22155141
12. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Acute Myeloid Leukemia. v.2.2013. [cited 08/17/2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf
13. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Acute Lymphoblastic Leukemia. V.1.2013. [cited 08/17/2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/all.pdf
14. Morris, E, Thomson, K, Craddock, C, et al. Outcomes after alemtuzumab-containing reduced-intensity allogeneic transplantation regimen for relapsed and refractory non-Hodgkin lymphoma. *Blood*. 2004 Dec 15;104(13):3865-71. PMID: 15304395

15. Peggs, KS, Sureda, A, Qian, W, 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. PMID: 17854309
16. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Hodgkin's Lymphoma. v.2.2013. [cited 08/30/2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf
17. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Non-Hodgkin's Lymphomas v.1.2013. [cited 08/17/2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf
18. Ravandi, F, Jorgensen, JL, O'Brien, SM, et al. Eradication of minimal residual disease in hairy cell leukemia. *Blood*. 2006 Jun 15;107(12):4658-62. PMID: 16497968
19. Lokhorst, HM, Schattenberg, A, Cornelissen, JJ, Thomas, LL, Verdonck, LF. Donor leukocyte infusions are effective in relapsed multiple myeloma after allogeneic bone marrow transplantation. *Blood*. 1997 Nov 15;90(10):4206-11. PMID: 9354693
20. Salama, M, Nevill, T, Marcellus, D, et al. Donor leukocyte infusions for multiple myeloma. *Bone Marrow Transplant*. 2000 Dec;26(11):1179-84. PMID: 11149728
21. Collins, RH, Jr., Shpilberg, O, Drobyski, WR, et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. *J Clin Oncol*. 1997 Feb;15(2):433-44. PMID: 9053463
22. Bensinger, WI, Buckner, CD, Anasetti, C, et al. Allogeneic marrow transplantation for multiple myeloma: an analysis of risk factors on outcome. *Blood*. 1996 Oct 1;88(7):2787-93. PMID: 8839877
23. Lokhorst, HM, Schattenberg, A, Cornelissen, JJ, et al. Donor lymphocyte infusions for relapsed multiple myeloma after allogeneic stem-cell transplantation: predictive factors for response and long-term outcome. *J Clin Oncol*. 2000 Aug;18(16):3031-7. PMID: 10944138
24. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Multiple Myeloma. v.2.2013. [cited 08/17/2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
25. Ciceri, F, Bonini, C, Marktel, S, et al. Antitumor effects of HSV-TK-engineered donor lymphocytes after allogeneic stem-cell transplantation. *Blood*. 2007 Jun 1;109(11):4698-707. PMID: 17327416
26. BlueCross BlueShield Association Medical Policy Reference Manual "Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant." Policy No. 2.03.03

CROSS REFERENCES

Hematopoietic Stem Cell Transplantation Index, Transplant, Policy No. 45

CODES	NUMBER	DESCRIPTION
CPT	38242	Allogeneic lymphocyte infusions
HCPCS	None	