Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

Title: Donor Lymphocyte Infusion For Malignancies Treated With An Allogeneic Hematopoietic Cell Transplant

Description/Background

Donor lymphocyte infusion is a type of therapy in which lymphocytes (a type of white blood cells) from the blood of a donor are given to the recipient who has already received a stem cell transplant from the same donor. Donor lymphocyte infusion may help bone marrow transplant recipients, whose cancer has returned, by killing the remaining cancer cells. Donor lymphocyte infusion is being studied in the treatment of many types of cancer.

Approximately 40-60% of patients who receive donor lymphocyte infusion develop graft-versus-host disease (GVHD), and the development of GVHD predicts a response to the donor lymphocyte infusion. Treatment-related mortality after donor lymphocyte infusion is 5-20%. There does not seem to be a correlation between the type of hematologic malignancy for which the donor lymphocyte infusion was given and the development of GVHD.(1) The risk of development of GVHD is related, in part, to donor lymphocyte infusion dose and therapy before donor lymphocyte infusion.

Donor lymphocyte infusion may be used for various indications such as relapse after an allogeneic hematopoietic cell transplantation (HCT), to prevent disease relapse in the setting of T cell-depleted grafts or non-myeloablative conditioning regimens, or to convert mixed to full donor chimerism. Management of relapse, which occurs in approximately 40% of all hematologic malignancy patients, is the most common indication for donor lymphocyte infusion.(2)

The literature is heterogeneous when reporting methods of cell collection, indication (e.g., planned after chemotherapy, in early relapse), cell dose infused and cell subtype used.(1) In addition, many studies include multiple diseases with little information on disease-specific

outcomes; however, donor lymphocyte infusion is used in nearly all hematologic malignancies for which allogeneic HCT is performed, including chronic myeloid leukemia, acute myeloid and lymphoblastic leukemias, myelodysplastic syndromes, multiple myeloma and Hodgkin (HL) and non-Hodgkin lymphoma (NHL).

Regulatory Status:

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic cells are included in these regulations.

Medical Policy Statement

Donor lymphocyte infusion may be considered established following allogeneic-hematopoietic cell transplantation (HCT) in specified situations. It is considered a useful therapeutic option for individuals meeting specific selection criteria.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions

Donor lymphocyte infusion may be considered established following allogeneic-hematopoietic cell transplantation (HCT) that was originally considered medically necessary for the following indications:

- Treatment of a hematologic malignancy that has relapsed or is refractory to treatment.
- Prevention of relapse in the setting of a high risk of relapse**
- To convert a patient from mixed to full donor chimerism.

****Note**: *Settings considered high-risk for relapse include T cell depleted grafts or nonmyeloablative (reduced-intensity conditioning) allogeneic HCT.*

Exclusions

- Donor lymphocyte infusion following allogeneic hematopoietic cell transplantation (HCT) that was originally considered experimental/investigational for the treatment of a hematologic malignancy.
- Donor lymphocyte infusion as a treatment of nonhematologic malignancies following a prior allogeneic HCT.
- Genetic modification of donor lymphocytes.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

38242

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

DONOR LYMPHOCYTE INFUSION

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is the only curative treatment option for many malignant high-risk hematological diseases.(3)The Graft-vs.-Tumor (GvT) effect is the major hallmark of this treatment approach. However, disease relapse remains a major limitation. Boosting the GvT effect by checkpoint inhibitors (CI) is an attractive option in this desperate situation although potentially triggering Graft-vs.-Host Disease (GvHD). Early reports in individuals with Hodgkin's lymphoma support the idea that CI therapy after HCT is feasible and effective. We have retrospectively analyzed CI therapy for treatment of disease recurrence after allo-HCT other than Hodgkin's lymphoma including 21 patients from 8 German transplant centers. The median follow-up was 59 days. The overall response rate (ORR) was 43%. Individuals receiving donor lymphocyte infusion (DLI) in combination with CI had superior response (ORR 80%). Severe acute GvHD grade III-IV and moderate to severe chronic GvHD were observed in 29% of all individuals. Taken together, CI therapy in relapsed patients after HCT, especially in combination with DLI, is effective but induces severe GvHD in a considerable proportion of patients. Thus, prospective trials or EBMT registry-based validation of different dosing and application schedules including immunosuppressive regimens in those individuals are urgently needed.

Chronic Myelogenous Leukemia

Donor lymphocyte infusion has been most effective in chronic myelogenous leukemia (CML), inducing a molecular complete remission (CR) in up to 80% of subjects who relapse in chronic phase. Only a 12% to 33% response rate has been reported in subjects in accelerated or blast phase. Response duration to donor lymphocyte infusion in subjects with relapsed CML after HCT is long-standing in most subjects.

Several large series have reported outcomes of subjects with relapsed CML after receiving donor lymphocyte infusion.(5-10) These studies comprise more than 1000 subjects, approximately half of whom had only molecular or cytogenetic relapse at the time of donor lymphocyte infusion.(2) The cell doses varied among subjects, with some receiving multiple donor lymphocyte infusions and other planned dose escalations. Despite these variations, a molecular or cytogenetic CR was achieved in 74% of patients (746/1007). Overall survival (OS) at 3 or more years ranged from 53% to 95% (3), was 64% at 5 years and 59% at 10 years after donor lymphocyte infusion in another series.(10)

The role of donor lymphocyte infusion in CML has changed since the introduction of tyrosine-kinase inhibitors (TKIs) in CML treatment, which keeps the disease under control instead of proceeding to HCT. However, for subjects who develop resistance to the TKIs or are unable to tolerate the adverse effects, HCT and donor lymphocyte infusion may be a disease management option.

Acute Leukemias, Myelodysplasia (MDS), and Other Myeloproliferative Diseases
A systemic review by El-Jurdi et al (2013) evaluated 39 prospective and retrospective studies, using donor lymphocyte infusions to treat relapse after HCT for lymphoid malignancies including acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma, non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL).(11) No randomized controlled studies were identified. Studies selected were heterogeneous thus limiting interpretation of the review. Reported pooled proportions of CR (95% confidence interval [CI]) were 27% (16% to 40%) for ALL, 55% (15% to 92%) for CLL, 26% (19% to 33%) for multiple myeloma, 52% (33% to 71%) for NHL, and 37% (20% to 56%) for HL.

An observational study compared different treatments for 147 consecutive subjects who relapsed after receiving allogeneic HCT for myelodysplastic syndrome.(12) Sixty-two subjects received HCT or donor lymphocyte infusion, 39 received cytoreductive treatment, and 46 were managed with palliative or supportive care. Two-year rates of OS were 32%, 6%, and 2%, respectively (p<.001). In multivariate analysis, 4 factors adversely influenced 2-year OS rates: history of acute graft-versus-host disease (hazard ratio [HR], 1.83; 95% CI, 1.26 to 2.67; p=0.002), relapse within 6 months (HR=2.69; 95% CI, 0.82 to 3.98; p<0.001), progression to acute myelogenous leukemia (HR=2.59; 95% CI, 1.75 to 3.83; p<0.001), and platelet count less than 50 g/L at relapse (HR=1.68; 95% CI, 1.15 to 2.44; p=0.007). HCT or donor lymphocyte infusion was an independent factor that favorably impacted OS (HR=0.40; 95% CI, 0.26 to 0.63; p<0.001).

Acute Myelogenous Leukemia
Use of donor lymphocyte infusion for subjects with relapsed acute myelogenous leukemia (AML) after allogeneic HCT has yielded overall remission rates ranging from 15% to 42%, with an OS of 15-20%. (For comparison, a second HCT in this group of subjects results in 10% to 35% long-term survival with a treatment-related mortality of approximately 50%). Subjects with lower initial disease burden, reduction in the tumor burden with chemotherapy prior to donor lymphocyte infusion, and favorable cytogenetics appear to have more benefit with donor lymphocyte infusion.

A large retrospective analysis from the European Blood and Marrow Transplant Group compared OS in 399 subjects with AML with post-transplant relapse who either were treated with (n=171 donor lymphocyte infusion or without (n=228) donor lymphocyte infusion.(12) Subjects who received donor lymphocyte infusion had an improved 2-year OS (21%) compared with those who did not (9%; p<0.001).

A large retrospective series from the Center for International Blood and Marrow Transplant Research (2015) reported outcomes of 1788 AML subjects who experienced a first or second relapse after allogeneic HCT, among whom 1231 (69%) received subsequent intensive therapy that included donor lymphocyte infusion.(14) Among the 1231 subjects who received treatment, 660 (54%) received chemotherapy alone; 202 (16%) received donor lymphocyte infusion with or without chemotherapy; and, 369 (30%) received a second allogeneic HCT with or without additional chemotherapy or donor lymphocyte infusion. Among all subjects who received donor lymphocyte infusion, 87 (33%) survived more than 1 year after relapse; median survival was 7 months (range 1 to 177 months). Cell-based therapy (donor lymphocyte infusion or second HCT) resulted in significantly better post-relapse OS than chemotherapy alone. These results are consistent with other reports of donor lymphocyte infusion in subjects who had an AML relapse after allogeneic HCT.

The literature for myelodysplasia (MDS) and other myeloproliferative diseases treated with donor lymphocyte infusion either after relapse or for mixed chimerism consists of small sample sizes, inconsistent pre-donor lymphocyte infusion therapy, and varied donor lymphocyte infusion cell doses, making it difficult to draw definite conclusions about outcomes.(3) However, it appears some subjects attain durable remissions with donor lymphocyte infusion after post-transplant relapse.(3)

Warlick et al (2012) reported complete remission (CR) after donor lymphocyte infusion in 49% (17/35) subjects with relapsed nonchronic myelogenous leukemia, including AML and MDS, after allogeneic HCT. Overall survival (OS) at 1 year was 30% and 19% at 2 years. The authors reported that a lower dose regimen of donor lymphocyte infusion was more tolerable and reduced graft-versus-host disease (GVHD) occurrence to 25% compared to 66% with higher-dose donor lymphocyte infusion.

An analysis from the German Cooperative Transplant Study Group reported outcomes among a cohort of subjects (N=154) who relapsed after undergoing allogeneic HCT to treat AML (n=124), MDS (n=28), or myeloproliferative syndrome (n=2).(16) All subjects received a median of 4 courses of azacitidine and donor lymphocyte infusion was administered to 105 (68%). OS among all subjects was 29% at 2-year follow-up, which compares favorably with other reports. The overall incidence of acute GVHD based on the total cohort (N=154) was 23%, and 31% in those given donor lymphocyte infusion (n=105).

Acute Lymphoblastic Leukemia (ALL)
The graft-versus-tumor effect is thought to be less robust in patients with ALL than in the myeloid leukemias. Small studies have reported donor lymphocyte infusion response rates ranging from 0% to 20% and OS rates of less than 15%.(2) By comparison, a second allogeneic HCT provides a 5-year OS of approximately 15% to 20%, with a treatment-related mortality rate of approximately 50%.(2)

The clinically evident graft-versus-leukemia effect of donor lymphocyte infusion requires weeks to months to manifest. ALL is a rapidly proliferating disease and donor lymphocyte infusion alone does not control the disease; a significant reduction in leukemia burden prior to donor lymphocyte infusion is necessary. Management of subjects with relapsed ALL leading to the best OS is through a combination of salvage chemotherapy and donor lymphocyte infusion. Although it is unclear whether donor lymphocyte infusion adds benefit to salvage chemotherapy, long-term survival has been reported with relapsed ALL treated with chemotherapy plus donor lymphocyte infusion.(3)

Lymphomas
Studies in which individuals received donor lymphocyte infusion for lymphomas consist of small numbers of individuals 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, too few individuals reported with any single histologic subtype of lymphoma to provide adequate information of the benefit of donor lymphocyte infusion for a specific subtypes.(3)

The largest series reported for NHL (n=21) using donor lymphocyte infusion showed response rates in 3 of 9 individuals with high-grade NHL, 1 of 2 individuals with mantle cell lymphoma, and 6 of 10 individuals with low-grade disease.(17)

A series of 14 individuals with multiply relapsed HL who received reduced-intensity conditioning allogeneic HCT and donor lymphocyte infusion showed a CR of 57% and 2-year survival of 35%.(18)

Multiple myeloma
Observational data suggest a graft-versus-tumor effect in multiple myeloma because the development of GVHD has correlated with response in several analyses.(3) Most individuals with multiple myeloma who undergo HCT receive an autologous HCT. In addition, the overall role of HCT for multiple myeloma is changing with the advent of new, highly active novel agents like lenalidomide and bortezomib.

Five studies (sample size range, 5-63 individuals) have reported the role of donor lymphocyte infusion in relapsed multiple myeloma,(19-23) with the highest response to donor lymphocyte infusion being reported as 62%, with approximately half of the responders attaining a CR.(3) One confounding factor for high response rates for multiple myeloma treated with donor lymphocyte infusion is that corticosteroids used for treating GVHD have a known antimyeloma effect, which could potentially enhance response rates in these individuals.(2)

Section Summary: Donor Lymphocyte Infusion
There are a few nonrandomized comparative studies and numerous case series of donor lymphocyte infusion treatment for various hematologic malignancies and other myeloproliferative disorders. The nonrandomized studies, in individuals with acute leukemia and myelodysplastic syndrome, have reported higher response rates for individuals treated with donor lymphocyte infusion than with alternatives. The case series report higher response rates than expected for relapsed disease compared with historical controls. Although there are no high-quality RCTs for donor lymphocyte infusion treatment, this evidence permits the conclusion that response rates improve with donor lymphocyte infusion treatment for individuals with previous HCT treatment and relapsed disease.

MODIFIED DONOR LYMPHOCYTE INFUSION
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.(24) These lymphocytes were infused into 23 individuals with various hematologic malignancies who relapsed after allogeneic HCT. Six individuals died of progressive disease within 4 weeks of infusion. Eleven patients experienced disease response (CR in 6, partial remission in 5). Three individuals were still in CR at a median of 471 days. Twelve individuals were evaluable for GVHD, 3 of whom developed acute or chronic GVHD, which was successfully treated with ganciclovir.

In a phase II study, donor lymphocytes were treated with rapamycin ex vivo to produce rapamycin-resistant donor lymphocyte infusions.(25) Forty individuals undergoing low-intensity HCT for hematologic malignancy were treated preemptively with chemotherapy and donor lymphocyte infusion. There were no infusional toxicities or serious events attributable to donor lymphocyte infusion. Classical acute GVHD occurred in 4 of 40 patients. By the end of the study (follow-up range, 42-84 months), 18 of 40 patients remained in sustained remission.

A phase I study evaluated individual response to donor lymphocyte infusion expressing the herpes simplex virus thymidine kinase suicide gene.(26) Three patients were enrolled in the trial and received a single donor lymphocyte infusion. No local or systemic toxicity related to

the gene-transfer procedure was observed. Two individuals achieved stable disease. No individual had severe GVHD requiring systemic steroid and/or ganciclovir administration. Tyrosine kinase cells were detected in the peripheral blood of all 3 individuals by polymerase chain reaction but did not persist more than 28 days.

Section Summary: Modified Donor Lymphocyte Infusion
These early phase studies are insufficient to determine the efficacy of modified donor lymphocyte infusion in the treatment of hematologic malignancies. Randomized studies comparing modified donor lymphocyte infusion to standard treatment would be necessary to determine efficacy.

Summary of Evidence
For individuals who have had an allogeneic hematopoietic cell transplant, (HCT) who receive donor lymphocyte infusion, the evidence includes nonrandomized comparative studies and case series. Relevant outcomes are overall survival and change in disease status. In various hematologic malignancies and for various indications such as planned or preemptive donor lymphocyte infusion, treatment of relapse, or conversion of mixed to full donor chimerism, individuals have shown evidence of responding to donor lymphocyte infusion. Response rates to donor lymphocyte infusion for relapsed hematologic malignancies following an allogeneic HCT are best in chronic myelogenous leukemia (CML), followed by the lymphomas, multiple myeloma, and acute leukemias, respectively. Other than CML, clinical responses are most effective when chemotherapy induction is used to reduce the tumor burden before donor lymphocyte infusion. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have had an allogeneic HCT who receive a modified (genetic or other ex vivo modification) donor lymphocytes infusion, the evidence includes case series. Relevant outcomes are overall survival and change in disease status. The case series have demonstrated the feasibility of the technique and no serious adverse effects. Without a comparison to standard treatment, the efficacy of administering modified donor lymphocytes is unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

CLINICAL INPUT RECEIVED FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, Blue Cross Blue Shield Association received input from 1 academic medical center and 5 Blue Distinction Centers for Transplant while this policy was under review in 2011. There was general agreement with the policy statements, although 2 reviewers disagreed with the policy statement on the use of donor lymphocyte infusion in non-hematopoietic malignancies; 1 thought it was investigational and also medically necessary and the other did not think this was investigational or medically necessary. One reviewer

suggested adding Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disease as another medically necessary indication for donor lymphocyte infusion. One reviewer commented on an evolving technique for use of ex-vivo expansion of donor lymphocytes.

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

NCCN guidelines discuss the use of lymphocyte infusions in acute myeloid leukemia (AML).(27) A prospective phase II trial of 28 patients suggests that azacitidine followed by donor lymphocyte infusions (DLIs) may be a treatment option for therapy in individuals who have AML that relapses after allogeneic HCT.

NCCN guidelines discuss the use of lymphocyte infusions in post-transplant relapse of chronic myeloid leukemia.(28) Donor lymphocyte infusion is effective in inducing durable molecular remission in the majority of individuals with relapsed CML following allo-HCT. It is more effective in chronic phase relapse than advanced phase relapse.

National Comprehensive Cancer Network (NCCN) guidelines do not address the use of donor lymphocyte infusions in the treatment of Hodgkin lymphoma (29) or non-Hodgkin lymphomas (Chronic lymphocytic leukemia/small lymphocytic lymphoma, B-Cell lymphoma, hairy cell leukemia and primary cutaneous lymphomas).(30-33)

The NCCN guidelines do not address the use of donor lymphocyte infusions in the treatment of T-Cell lymphomas (non-Hodgkin lymphoma) but there is some discussion surrounding the topic. Donor lymphocyte infusion induces long-term remissions in a few patients with progressive disease or disease relapse after allogeneic HCT.(34)

NCCN recommendations for treating acute lymphoblastic leukemia state that donor lymphocyte infusion can be considered an option for patients in relapse after allogeneic HCT.(35)

NCCN recommendations for treating multiple myeloma state that donor lymphocyte infusion can be considered an option for patients who are in relapse after allogeneic HCT. There is discussion surrounding patients who do not respond to allogeneic hematopoietic cell grafting.(36)

Acute Leukemia Working Party of the EBMT

The Acute Leukemia Working Party of the EBMT (2020) released the following consensus regarding the use of donor lymphocyte infusion from a human leukocyte antigen (HLA) haploidentical donor:

- Unmanipulated donor lymphocyte infusion (DLI) from a haploidentical donor appears to be relatively safe and reasonably effective in patients who relapse after a T-cell replete haplo-HCT. Patients given haplo-DLI should be enrolled in a clinical trial whenever possible, as data regarding optimal cell dose, timing and role of concurrent systemic therapies with haplo-DLI are limited. Information about the application of unmanipulated DLI after T-cell depleted transplantation is limited, which is why dosing should be managed with caution.

- The risk of graft versus host disease (GvHD) after unmanipulated DLI in the haplo-HCT/PTCy setting is comparable to an unmanipulated DLI from an HLA-matched donor.
- Cytoreductive therapy prior to DLI from a haploidentical donor should be considered in patients with a hematologic relapse after haplo-HCT.
- Pre-emptive haplo-DLI may play a role in reducing disease relapse in patients with persistent minimal residual disease or mixed-donor chimerism after haplo-HCT; however, more studies are needed.
- Patients with high-risk myeloid malignancies may benefit from a prophylactic haplo-DLI, which should ideally be used in the setting of a clinical trial.
- The administration of manipulated DLI after T-cell depleted or T-cell replete haploidentical transplantation, such as allo-depleted or gene-modified T cells, should only be performed in the setting of a clinical trial.
- Patients should be monitored closely with frequent disease-specific MRD testing and donor-chimerism after DLI administration.
- Mismatched-HLA allele loss was detected in one- third of leukemia relapses after a haplo-HCT. Such patients are unlikely to benefit from DLI from the original donor. A second allo-HCT from a related donor with a different mismatched haplotype or a mismatched unrelated donor may be considered if HLA-loss is confirmed.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

Government Regulations
National:
Indications and Limitations of Coverage
No national coverage determination on donor lymphocyte infusions was identified. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Local:
There is no local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Cell Lymphocytic Lymphoma – Autologous or Allogeneic
- BMT – Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer

- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias (Allogeneic)
- BMT – Hematopoietic Cell Transplantation for Germ-Cell Tumors
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Malignant Astrocytomas and Gliomas (Autologous)
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

References

1. Deol A, Lum LG. Role of donor lymphocyte infusions in relapsed hematological malignancies after stem cell transplantation revisited. Cancer Treat Rev 2010; 36(7):528-38.
2. Tomblyn M, Lazarus HM. Donor lymphocyte infusions: the long and winding road: how should it be traveled? Bone Marrow Transplant 2008; 42(9):569-79.
3. Holderried TAW, Fraccaroli A, Schumacher M, et al. The role of checkpoint blockade after allogeneic stem cell transplantation in diseases other than Hodgkin's lymphoma. Bone Mar Trans 2019, doi: 10.1038/s41409-019-0498-0. PMID: 30833743
4. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Donor leukocyte infusion for hematologic malignancies that relapse after Allo-BMT. TEC Assessments 1997; Volume 12, Tab 22.
5. van den Brink MR, Porter DL, Giralt S et al. Relapse after allogeneic hematopoietic cell therapy. Biol Blood Marrow Transplant 2010; 16(1 Suppl):S138-45.
6. 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; 21(5):943-8.
7. 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; 96(8):2712-6.
8. 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; 100(2):397-405.
9. 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; 136(6):833-6.
10. Radujkovic A, Guglielmi C, Bergantini S, et al. Donor lymphocyte infusions for chronic myeloid leukemia relapsing after allogeneic stem cell transplantation: may we predict

graft-versus-leukemia without graft-versus-host disease? Biol Blood Marrow Transplant. Mar 19, 2015.
11. El-Jurdi N, Reljic T, Kumar A et al. Efficacy of adoptive immunotherapy with donor lymphocyte infusion in relapsed lymphoid malignancies. Immunotherapy 2013; 5(5):457-66.
12. Guieze R, Damaj G, Pereira B, et al. Management of myelodysplastic syndrome relapsing after allogeneic hematopoietic stem cell transplantation: a study by the French Society of Bone Marrow Transplantation and Cell Therapies. Biol Blood Marrow Transplant. Aug 6 2015. PMID 26256942
13. 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; 25(31):4938-45.
14. Bejanyan N, Weisdorf DJ, Logan BR, et al. Survival of patients with acute myeloid leukemia relapsing after allogeneic hematopoietic cell transplantation: a center for international blood and marrow transplant research study. Biol Blood Marrow Transplant. Mar 2015;21(3):454-459.
15. Warlick ED, DeFor T, Blazar BR et al. Successful remission rates and survival after lymphodepleting chemotherapy and donor lymphocyte infusion for relapsed hematologic malignancies post allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2012; 18(3):480-6.
16. Shroeder T, Rachlis E, Bug G, et al. Treatment of acute myeloid leukemia or myelodysplastic syndrome relapse after allogeneic stem cell transplantation with azacitidine and donor lymphocyte infusions-a retrospective multicenter analysis from the German cooperative transplant study group. Biol Blood Marrow Transplant. Apr 2015;21(4):653-660.
17. 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; 104(13):3865-71.
18. 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; 139(1):70-80.
19. Lokhorst HM, Schattenberg A, Cornelissen JJ et al. Donor leukocyte infusions are effective in relapsed multiple myeloma after allogeneic bone marrow transplantation. Blood 1997; 90(10):4206-11.
20. Salama M, Nevill T, Marcellus D et al. Donor leukocyte infusions for multiple myeloma. Bone Marrow Transplant 2000; 26(11):1179-84.
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; 15(2):433-44.
22. Bensinger WI, Buckner CD, Anasetti C et al. Allogeneic marrow transplantation for multiple myeloma: an analysis of risk factors on outcome. Blood 1996; 88(7):2787-93.
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; 18(16):3031-7.
24. Ciceri F, Bonini C, Marktel S et al. Antitumor effects of HSV-TK-engineered donor lymphocytes after allogeneic stem-cell transplantation. Blood 2007; 109(11):4698-707.

25. Fowler DH, Mossoba ME, Steinberg SM, et al. Phase 2 clinical trial of rapamycin-resistant donor CD4+ Th2/Th1 (T-Rapa) cells after low-intensity allogeneic hematopoietic cell transplantation. Blood. Apr 11 2013;121(15):2864-2874. PMID 23426943
26. Hashimoto H, Kitano S, Ueda R, et al. Infusion of donor lymphocytes expressing the herpes simplex virus thymidine kinase suicide gene for recurrent hematologic malignancies after allogeneic hematopoietic stem cell transplantation. Int J Hematol. Jul 2015;102(1):101-110. PMID 25948083
27. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. v. 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed May 31, 2024.
28. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Chronic Myeloid Leukemia. v. 2.2024. http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Accessed May 31, 2024.
29. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Hodgkin Lymphoma. v. 3.2024; https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. Accessed May 31, 2024.
30. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. v 3.2024; https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed May 31, 2024.
31. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. B-Cell Lymphomas. v. 2.2024; https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed May 31, 2024.
32. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Hairy Cell Leukemia. v. 2.2024; https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf. Accessed May 31, 2024.
33. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Primary Cutaneous Lymphomas. v. 2.2024; https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf. Accessed May 31, 2024.
34. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. T-Cell Lymphomas. v. 4.2024; https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed May 31, 2024.
35. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Acute Lymphoblastic Leukemia. v.4.2023; http://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed May 31, 2024.
36. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Multiple Myeloma v.4.2024; http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed May 31, 2024.
37. Dholaria, B, Savani, BN., et al. Clinical applications of donor lymphocyte infusion from an HLA-haploidentical donor: consensus recommendations from the Acute Leukemia Working Party of the EBMT. *Haematologica*. 2020. 105(1):47-58.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 31, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/13	10/16/12	10/16/12	This topic is split out from former combined policies: • Allogeneic Bone Marrow or Stem Cell Transplants (Investigational) • Allogeneic (Allogenic) Bone Marrow/Stem Cell Umbilical Cord Blood Transplants Donor Lymphocyte Infusion (Established) • Policy formatted to mirror BCBSA. • Added "relative contraindications" to inclusionary/exclusionary section.
11/1/14	8/19/14	8/25/14	Routine maintenance. Added an inclusion, "…or to convert a patient from mixed to full donor chimerism." References updated.
11/1/15	8/24/15	9/14/15	Routine maintenance
11/1/16	8/16/16	8/16/16	Routine maintenance
11/1/17	8/15/17	8/15/17	Stem removed from "hematopoietic cell transplant"
11/1/18	8/21/18	8/21/18	Routine maintenance
11/1/19	8/20/19		• Routine maintenance • Unable to retire based on occasional use
11/1/20	8/18/20		Routine maintenance
11/1/21	8/17/21		Routine maintenance
11/1/22	8/16/22		Routine maintenance
11/1/23	8/15/23		Routine maintenance (slp) Vendor managed: N/A
11/1/24	8/20/24		Routine maintenance (slp) Vendor managed: N/A

Next Review Date: 3rd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: DONOR LYMPHOCYTE INFUSION FOR MALIGNANCIES TREATED WITH AN ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.