

07.03.13 Donor Lymphocyte Infusion (DLI) and Hematopoietic Progenitor Cell (HPC) Boost

Original Effective Date: November 2020

Review Date: March 2026

Revised: March 2023

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Related Policies:

- [07.03.11 Hematopoietic Stem Cell Transplantation Autologous and Allogeneic*](#)

Summary

Description

This evidence review will address the following:

- Infusing lymphocytes from the original hematopoietic cell donor can be used to treatment recipients with a hematologic malignancy (e.g., cancer of the blood or bone marrow) in relapse following allogeneic hematopoietic stem cell transplantation. Donor lymphocyte infusion (DLI) is a form of adoptive immunotherapy and attempts to induce a beneficial graft-versus-tumor (GVT) response without the need for additional bone marrow harvest from the donor or further high-dose chemotherapy for the recipient. Collection of donor lymphocytes requires the original donor to

undergo a leukapheresis procedure. After collection, these cells are infused into the recipient either immediately or after frozen storage.

- A hematopoietic progenitor cell (HPC) (also known as stem cells) boost from the original hematopoietic stem cell transplant (HSCT) donor is intended to restore hematopoiesis or augment poor graft function after HSCT.

Summary of Evidence

For individuals who have had an allogeneic hematopoietic stem cell transplant (HSCT) who receive donor lymphocyte infusion (DLI), the evidence includes meta-analysis, systematic reviews, nonrandomized studies, observational and case series studies. Relevant outcomes are overall survival and change in disease status. In various hematologic malignancies and for various indications such as planned or preemptive DLI, treatment of relapse, or conversion of mixed to full donor chimerism, patients have shown evidence of responding to DLI. Response rates to DLI 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 DLI. The evidence is sufficient to determine the effects of the technology on net health outcomes

For individuals who have had a HSCT who receive a boost of hematopoietic progenitor cell (HPC) (also known as stem cells), the evidence includes systematic review-meta-analysis and observational studies. Relevant outcomes are overall survival and change in disease status. Poor graft function is a severe complication of HSCT and HPC boost has been studied in a variety of hematologic malignancies to restore hematopoiesis or augment poor graft function (promote engraftment) after HSCT. Although the evidence is not robust as there are no high-quality RCTs regarding HPC boost following HSCT the available evidence has demonstrated beneficial effects for individuals with non-engraftment or delayed engraftment after HSCT. Also, most institutional and consensus guidelines recommend that at the time of first HSCT, enough hematopoietic stem cells (HSCs) should be collected to perform two stem cell transplants. The boost stem cells (BSCs) may be used for a second transplant or less commonly for stem cell boost in case of non-engraftment or delayed engraftment. The evidence is sufficient to determine the effects of the technology on net health outcomes.

For individuals who have had an allogeneic HSCT who receive a modified (genetic or other ex vivo modification) DLI, 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.

OBJECTIVE

The first objective of this evidence review is to evaluate the safety and efficacy of the use of donor lymphocyte infusions (DLI) from the original donor or utilizing genetically modified lymphocytes on the net health outcome of individuals following a medically necessary allogeneic (myeloablative or non-myeloablative) hematopoietic stem cell transplant (HSCT).

The second objective of this evidence review is to evaluate the safety and efficacy of the use of hematopoietic progenitor cell (HPC) boost on the net health outcome of individuals following a medically

necessary allogeneic (myeloablative or non-myeloablative) or autologous hematopoietic stem cell transplant (HSCT).

PRIOR APPROVAL

Not applicable.

POLICY

Donor Lymphocyte Infusion

Donor lymphocyte infusion (DLI) is considered **medically necessary** following an allogeneic (myeloablative or non-myeloablative) hematopoietic stem cell transplant (HSCT) that was originally considered medically necessary for the treatment of hematologic malignancy for the following:

- Hematologic malignancy has relapsed or is refractory;
- Prevent hematologic malignancy relapse in the setting of T-cell depleted grafts or non-myeloablative conditioning regimens;
- Convert an individual from a mixed to full donor chimerism.

Note: *The donor for the lymphocytes is the same individual whose stem cells (hematopoietic progenitor cells) were used for the medically necessary transplant procedure.*

Collection and Cryopreservation of donor lymphocytes is considered **medically necessary** prior to, at the time of, or after a medically necessary allogeneic (myeloablative or non-myeloablative) HSCT.

DLI is considered **investigational** including but not limited to the following because the evidence is insufficient to determine the effects of the technology on health outcomes:

- DLI as a treatment of nonhematologic malignancies.
- DLI following allogeneic (myeloablative or non-myeloablative) HSCT that was originally considered investigational for the treatment of hematologic malignancy.
- Genetic modification of donor lymphocytes (e.g., modified by insertion of a thymidine kinase gene) as an adjunct to DLI.

Hematopoietic Progenitor Cell Boost

Hematopoietic progenitor cell (HPC) boost is considered **medically necessary** following autologous or an allogeneic (myeloablative or non-myeloablative) HSCT that was originally considered medically necessary for the treatment of hematologic malignancy for either of the following indications:

- Promote engraftment.
- Enhancement of chimerism when studies reveal <100% donor cells.

HPC boost is considered **investigational** for all other indications because the evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY GUIDELINES

Definitions

Allogeneic: Genetically dissimilar; involves a donor and recipient.

Bone marrow: A soft, spongy tissue that fills the cavities inside most bones in the human body. Bone marrow is a source of stem cells that manufacture red blood cells, white blood cells, and platelets.

Graft-versus-host disease (GVHD): A potential complication of transplants associated with the use of blood or tissue from a different person (allogeneic). The transplanted cells recognize the recipient's tissue as foreign and attack the recipient.

Graft-versus-leukemia/lymphoma effect (GVL): Transplanted white blood cells that recognize residual cancer cells (cells that survived chemotherapy and radiation therapy and continue to grow in the body) and attack them.

Hematologic malignancy: A cancer of the blood or bone marrow, such as leukemia or lymphoma.

Hematopoietic progenitor cells: Primitive cells capable of replication and formation into mature blood cells in order to repopulate the bone marrow. Cells may be obtained from bone marrow, peripheral blood or umbilical cord blood.

Leukocytes: White blood cells.

Lymphocyte: Cells present in the blood and lymphatic tissue derived from stem cells.

Non-myeloablative allogeneic hematopoietic stem cell transplant: Also called reduced intensity or mini-allogeneic transplant. The conditioning regimen is less intense and does not completely ablate the stem cells in the individual's bone marrow.

Peripheral blood: Blood derived from the circulatory system (as opposed to blood in the bone marrow where it is made).

Refractory Disease: In the treatment of cancer in which the individual does not respond to treatment.

Relapsed Disease: The return of or the signs or symptoms of the cancer after a period of improvement.

Coding

See the [Codes table](#) for details.

BACKGROUND

Graft-Versus-Host-Disease

Graft-versus-host disease (GVHD) is a potential serious complication of allogeneic myeloablative or non-myeloablative HSCT. GVHD occurs when donor cells attack healthy cells in the individual and there are two main categories: acute graft-versus-host disease or chronic graft versus-host disease. Each type affects different organs and tissues and has different signs and symptoms. An individual may develop one, both or neither type.

Acute GVHD usually develops within the first 100 days after transplantation but can occur later. It can affect the skin, the liver and the gastrointestinal tract (stomach, intestines, and colon), between 30% to 70% of transplant recipients develop acute GVHD. Physicians classify the severity of acute GVHD according to the number of organs involved and the degree to which they are affected. Each organ is staged individually with each stage ranging between 1 (mildest) to 4 (most severe).

Chronic GVHD may occur at any time after transplantation but typically develops at least 100 days after the day of transplant. Chronic GVHD may involve a single organ or possibly many organs, 40% to 50% of individuals receiving allogeneic SCT. Since this is a chronic condition, it can last for years or even a lifetime.

Donor Lymphocyte Infusion

DLI may be used for various indications such as relapse after allogeneic hematopoietic stem cell transplantation (HSCT), to prevent disease relapse in the setting of T cell-depleted grafts or nonmyeloablative 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 DLI.

DLI which is also referred to as donor leukocyte or buffy coat transfusion, is a form of adoptive immunotherapy and attempts to induce a beneficial graft-versus-leukemia/lymphoma effect (GVL) or graft-versus-tumor (GVT) response without the need for an additional bone marrow harvest from the donor or further high-dose chemotherapy for the recipient. Collection of donor leukocytes requires the original donor to undergo a leukapheresis procedure. After collection, these cells are infused into the recipient either immediately or after frozen storage. A DLI is used as an alternative to a second hematopoietic cell transplant.

DLI has been researched as a treatment for a variety of hematologic malignancies, including most prominently chronic myeloid leukemia, but also acute myeloid leukemia, acute lymphocytic leukemia, multiple myeloma, myelodysplastic syndromes, chronic lymphocytic leukemia, Hodgkin disease, and non-Hodgkin lymphoma.

Hematopoietic Progenitor Cell (HPC) Boost

A boost of HPC (also known as stem cells) from the original HSCT donor is intended to restore hematopoiesis or augment poor graft function after HSCT. Poor graft function is a severe complication of HSCT which is defined as persistent cytopenia's and/or transfusion dependence. The cell product used for a HPC boost may be a previously cryopreserved cell product, or alternatively, the donor may need to undergo additional evaluation, stem cell mobilization, and cell harvest. A boost is not preceded by a preparative regimen. A potential source of confusion is that a boost is often required when additional conventional chemotherapy is given to treat relapse and reestablish remission after transplantation. Prolonged cytopenia's and immunosuppression may result, requiring additional HPC boost, which is typically given days to weeks after reinduction chemotherapy.

Regulatory Status

The U.S. Food and Drug Administration regulate certain human cells, tissues, and cellular and tissue-based products under the legal authority of section 361 of the Public Health Service Act (42 USC 264). This section authorizes the Surgeon General, with the approval of the Secretary of the U.S. Department of Health and Human Services, to make and enforce such regulations as judged necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the United States or from state to state. According to Addendum 7342.007—Imported Human Cells, Tissues, and

Cellular and Tissue-based Products (HCT/Ps), umbilical cord blood stem cells, peripheral blood stem cells, lymphocytes (donor lymphocytes for infusion, T cells) are identified by product code 57M.P.

RATIONALE

This evidence review was created in November 2020 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through March 2026.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Donor Lymphocyte Infusion (DLI)

Clinical Context and Therapy Purpose

The purpose of donor lymphocyte infusion (DLI) in individuals who are transplant recipients with hematologic malignancies in relapse following allogeneic hematopoietic progenitor cell transplantation (myeloablative or non-myeloablative) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are transplant recipients following allogeneic hematopoietic progenitor cell transplantation (myeloablative or non-myeloablative) with one of the following:

- Hematologic malignancy has relapsed or is refractory;
- Prevent hematologic malignancy relapse in the setting T-cell depleted grafts or non-myeloablative conditioning regimens;
- Convert an individual from a mixed to full donor chimerism.

Interventions

The therapy being considered is DLI from the original donor or utilizing genetically modified lymphocytes.

Comparators

The following therapies are currently being used to treatment hematologic malignancies: chemotherapy and/or immunotherapy.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, change in disease status, treatment-related mortality, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Meta-Analysis

Poonsombudlert et. al. (2020) performed a comprehensive meta-analysis with a literature search completed in MEDLINE, Cochrane library and Embase database through May 2019 which evaluated the association between prophylactic donor lymphocyte infusion (pDLI), primary disease relapse (PDR), acute graft-versus-host disease (aGVHD) and overall survival (OS). PDR and GVHD remain the two most challenging complications in the setting allogeneic hematopoietic stem cell transplantation (aHSCT) and new transplant strategies are being developed to lesson these complications. Therapeutic donor lymphocyte infusion (tDLI) has been one of the main treatments in patients who have relapsed after aHSCT, utilized to restart the graft-versus-tumor (GVT) effect without needing to repeat the HSCT. Previous studies regarding tDLI “have been discouraging due to a high rate of aGVHD and limited outcomes.” However, patients needing HSCT as treatment often carry high-risk mutations and have usually been heavily treated, “therefore, achievement of any degree in disease control is considered meaningful.” One of the new strategies is the use of DLI in a prophylactic or pre-emptive state (pDLI) when the tumor burden is still low instead of waiting for relapse of the disease to occur. The initial use of pDLI from various studies have shown inconsistent results and have a limited of number of participants from each study. In the evidence review the primary outcomes were the pooled odd ratio (OD) of PDR, aGVHD, and OS among the pDLI group versus the control group. Nine studies were included, two were retrospective case–control studies, and the rest were prospective case–control studies resulting in a total of 748 patients who underwent pDLI (398 patients) as a case group and those that did not use pDLI (350 patients) as a control group and reported the pooled odd ratio (OR) for the association of pDLI use, PDR, aGVHD, and OS. The results showed “a significant decreased odd of PDR in the pDLI group (pooled OR = 0.42, 95% CI 0.30–0.58, I² = 0%), but there was no significant increased odd of aGVHD (pooled OR of 0.98, 95% CI 0.56–1.72, I² = 0.8%). The authors also found that there was an increased odd of overall survival (OS) (pooled OR 3.17, 95% CI 1.85–5.45, I² = 50.2%). Limitations of this study included: in the

nine studies utilized all were conducted in adult patients with advanced high-risk malignant hematologic diseases and could have limited the external validity of the meta-analysis to patients in other groups, patients with various indications for transplant, diverse pre-transplant comorbidities as well as various disease statuses likely accounted for the heterogeneity of the outcomes, but were able to identify pDLI strategy, administration time and pDLI CD3+cell dose as the sources of heterogeneity. Selection bias may have occurred as some studies often exclude patients with a history of GVHD from the treatment group. The authors concluded “this meta-analysis observational study demonstrated that pDLI is a potentially valuable method for PDR prevention in patients with high-risk hematologic malignancies as it offers the benefit of relapse prevention and increased overall survival. From our analysis, pDLI use does not significantly increased odd of aGVHD as proposed by previous studies. However, this is still an area of active development, and there is a need for additional research to optimize the transplant protocols and pDLI use strategies. Further large, prospective, controlled trials are warranted to investigate the finer details of the proposed association between pDLI use and PDR prevention, OS as well as aGVHD.”

Observational Study

Uchibori et al (2025) performed a retrospective comprehensive analysis at a single-center institution on 75 patients (29 females [38.7% and 46 males 61.3%]) who underwent donor lymphocyte infusion (DLI) for disease relapse between April 1994 and March 2024 following allogeneic transplant. The most common underlying diseases in all 75 cases was acute myeloid leukemia (AML, n = 46) and myelodysplastic syndromes (MDS, n = 12). Until 2014, DLI was only performed in patients with AML (n = 14), MDS (n = 2), or chronic myeloid leukemia (n = 5). However, since 2015, patients with various diseases, including lymphoid malignancies, also underwent DLI. The primary end point was 3-year overall survival (OS) rate after DLI. The secondary endpoints included the 100-day complete remission (CR) rate and incidence of graft-versus-host disease (GVHD). The 3-year OS rate was 29.1% (95% CI, 18.8–40.2%). The 100-day CR rate was 52.1%, and acute GVHD occurred in 25.3% of the patients, with no strong correlation between GVHD incidence and CR achievement. Limitations included 30-year retrospective study inconsistency in timing and cell dose of administration, and combined cases with and without subsequent allogeneic transplant. The authors noted that “Future efforts should validate these findings and optimize DLI protocols to improve outcomes.”

Acute Leukemias, Lymphomas, Myelodysplastic Syndromes, and other Myeloproliferative Disorders

Systematic Reviews

Kreldle et. al. (2022) provided an overview regarding the prevention and treatment of relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in acute myeloid leukemia (AML) which included cell-based (donor lymphocyte infusion [DLI]) and pharmacologic options. Despite therapeutic progress in the treatment of AML, relapse post- allo-HSCT remains a major challenge. Relapse of AML after allo-HSCT can be related to the escape of tumor cells from the effect of pre-transplant conditioning chemotherapy and/or escape from post-transplant immune control. In turn, these two mechanisms limit the expected immune response against malignant cells, thus contributing to relapse post-allo-HSCT. For therapeutic DLI and prophylactic or pre-emptive DLI the studies included concluded the following: “Post-transplant maintenance therapy is usually deployed in patients who are MRD negative in complete remission, while pre-emptive treatment refers to therapy administered upon detection of MRD. Both scenarios aim at providing prophylaxis against disease relapse. Although there are several limitations in clinical practice for DLI, it remains a powerful example of adoptive immunotherapy and an established salvage and prophylactic option post-transplant. DLI is most effective in certain conditions, including low tumor burden and loss of chimerism or MRD. As such, DLI use in the prophylactic setting, before

a relapse becomes evident, should be considered. The risk of relapse post-transplant should be taken into consideration. Another important consideration is the time between allo-HSCT and DLI administration, where shorter intervals can represent a greater risk for developing GVHD.”

El-Jurdi et. al. (2013) in a systematic review evaluated 39 prospective and retrospective studies using donor lymphocyte infusion (DLI) 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). No randomized controlled trials 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.

Tomblyn et. al. (2008) in a review regarding donor lymphocyte infusions (DLI) which are often utilized after allogeneic stem cell transplant (SCT) to augment the graft-versus-host (GVHD) effect. The timing of the DLI varies according to indication whether to treat recurrence or as a planned strategy to prevent disease relapse in the setting of T-cell depleted grafts or non-myeloablative conditions regimens, or as a method to convert mixed to full donor chimerism. This review found that DLI may lead to 3-year disease-free survivals (DFS) in excess of 60% for all CML patients and approach 90% in patients with only molecular or cytogenetic relapse. Other hematologic malignancies appear much less responsive, as less than 50% of patients responded and provided, at best, 3-year DFS rates of 20-50%. Multiple myeloma patients have overall response rates of 40-45% after DLI, suggesting benefit in relapsed disease. There are limited experiences for diseases such as Hodgkin's lymphoma, myelodysplasia and ALL regarding use of DLI. The literature for myelodysplasia syndromes (MDS) and other myeloproliferative diseases treated with DLI either after relapse or for mixed chimerism consists of small sample sizes, inconsistent pre-DLI therapy, and varied DLI cell doses, making it difficult to draw definite conclusions about outcomes. However, it appears that some patients attain durable remissions with DLI after posttransplant relapse. The authors concluded “published literature suggest that DLI should be administered early after relapse or as prophylactic strategy in patients receiving T-cell depleted grafts, and patients with bulky or aggressive disease.”

Observational Studies

Hou et al (2024) in a retrospective study assessed the effect of donor lymphocyte infusion (DLI) in pediatric hematologic malignancies after allogeneic hematopoietic stem cell transplant (HSCT) for treatment of relapse. There were 23 patients (male 12, 52.2% and female 11, 47.8%) who received DLI between June 1998 and December 2022 after allogeneic HSCT: 17 patients with acute leukemia, 3 with chronic leukemia and 3 with lymphoma. Patients median age was 9 years. The primary outcomes were overall survival (OS), event-free survival (EFS) and graft-versus-host-disease (GVHD) development. A total of 70 DLIs were performed for the 23 patients. The patients' 5-year EFS and OS were 43.5% $\pm$ 10.9% and 38.3% $\pm$ 10.3%. Ten (43.5%) patients died of their underlying hematologic malignancies, and another three patients (13.0%) died of severe GVHD and infection (NRM). The other 10 patients (43.5%) maintained their disease-free status. The study was limited due to its retrospective design, small sample size and variations in DLI type and patients' underlying malignancies.

Guieze et. al. (2015) in an observational study compared different treatments for 147 consecutive patients who relapsed after allogeneic HCT for myelodysplastic syndrome. 11 Sixty-two patients received HCT or DLI, 39 received cytoreductive treatment, and 46 were managed with palliative or supportive care. Two-year OS rates were 32%, 6%, and 2%, respectively ($p < 0.001$). In multivariate analysis, 4 factors adversely influenced 2-year OS rates: history of acute graft-versus-host disease (GVHD; 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), 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 DLI was an independent factor that favorably impacted OS (HR=0.40; 95% CI, 0.26 to 0.63; p<0.001).

Bejanyan et. al. (2015) in a large retrospective series from the Center for International Blood and Marrow Transplant Research (CIBMTR) reported outcomes for 1788 acute myeloid leukemia (AML) patients who experienced a first or second relapse after allogeneic hematopoietic cell transplantation (HCT), among whom 1231 (69%) received subsequent intensive therapy that included donor lymphocyte infusion (DLI). Among the 1231 patients who received treatment, 660 (54%) received chemotherapy alone; 202 (16%) received DLI with or without chemotherapy; and 369 (30%) received a second allogeneic HCT with or without additional chemotherapy or DLI. Among all patients who received DLI, 87 (33%) survived more than 1 year after relapse; median survival was 7 months (range, 1-177 months). Cell-based therapy (DLI or second HCT) resulted in significantly better post-relapse OS than chemotherapy alone.

Schroeder et. al. (2015) retrospectively analyzed data of 154 patients with acute myeloid leukemia (AML, n = 124), myelodysplastic (MDS, n = 28), or myeloproliferative syndrome (n = 2) to expand the current knowledge regarding azacitidine (Aza) and donor lymphocyte infusions (DLI) as salvage therapy for relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and identify predictors for response and survival. All patients received a median number of 4 courses of Aza (range, 4 to 14) and DLI were administered to 105 patients (68%; median number of DLI, 2; range, 1 to 7). Forty-one patients (27%) achieved complete remission (CR) and 9 patients (6%) achieved partial remission (PR), resulting in an overall response rate of 33%. Clinical responses after Aza and DLI translated into a 2-year overall survival (OS) rate of 29%. This outcome compares well with survival rates observed after other treatment options, such as intensive chemotherapy, DLI, and/or second transplantation. The authors concluded “the combination of Aza and DLI is a valuable treatment alternative for patients relapsing after allo-HST in particular those with MDS or AML with low disease burden.”

Chronic Myelogenous Leukemia

Schmidt et. al. (2020) in a registry based retrospective study using the Center for International Blood & Marrow Transplant Research (CIBMTR) database which included more than 420 transplant centers in the United States from patients with chronic myelogenous leukemia (CML). The registration research data is collected pre-transplantation, at 100 days and 6 months post-transplant and annually thereafter until death or last follow-up. This study used data regarding patients with CML who received TKI, and subsequently underwent hematopoietic cell transplant (HCT) from an allogeneic donor and relapsed following transplantation. The median time to DLI post HCT was 4 weeks, and one-month post HCT relapse was used as a landmark to avoid selection bias against DLI due to early death post HCT relapse. Data from CIBMTR was utilized from 134 centers during the years 2002-2014. Treatment at relapse was determined and grouped into three arms 1) TKI in combination with DLI (Combination arm); 2) TKI without DLI (Primary TKI); and 3) DLI without TKI (Primary DLI). Disease related variables included disease status prior to HCT, time from diagnosis to HCT, time from HCT to relapse, time from diagnosis to relapse. Patients were excluded if they did not receive a TKI prior to HCT. Patients were also assessed for presence of GVHD (acute II-IV/chronic). Two hundred fifteen (215) patients with CML were transplanted between 2002 and 2014 and received TKI prior to HCT and had relapsed following their first allogeneic HCT (Group 1 combination arm [TKI and DLI n=48, Group 2 primary TKI [without DLI] n=128, and Group 3 Primary DLI [without TKI] n= 39). The completeness of follow-up, from 30 days post-HCT relapse in the defined population was 94% at 3 years. The primary endpoint was effect of salvage treatment starting at 30 days post HCT relapse on overall survival (OS) in the three treatment groups. Secondary endpoints examined included evaluation of cause of death, impact of disease status on overall survival, impact of maintenance on overall survival, and impact of GVHD on treatment effect. The median follow-up of survivors was 30 days post-HCT relapse, 58 months for the Combination arm, 64 months for the Primary TKI arm and 46 months for the Primary DLI arm. The median time from HCT to relapse was slightly

longer in the Primary TKI arm at 8 months compared to 6 months in the Combination arm, and 4 months in the Primary DLI arm, $p=0.04$. The year of transplant differed, $p < 0.01$, as more patients that received primary DLI were treated prior to 2007. The biggest impact on overall survival (OS) was disease status prior to HCT. “As expected, the biggest impact on OS was disease status prior to HCT. Compared to those in chronic phase 1 (CP1), recipients that went to transplant in blast phase (BP) had a hazard ratio (HR) of 5.51 (95% confidence intervals [CI] 2.93–10.37; $p=0.007$) and patients in CP2 or higher had a HR 2.64 (95% CI 1.46–4.79; $p = 0.001$). Patients that received Primary DLI compared to Primary TKI had inferior survival HR 2.15 (95% CI 1.27–3.65; $p = 0.004$). Those who received Primary TKI had similar OS compared to those who received Combination therapy ($p=0.81$). In a sensitivity multivariate analysis, after controlling for how relapse was detected [clinical/hematologic vs. subclinical [molecular or cytogenetic]], TKI with or without DLI remained significantly associated with superior OS compared to DLI primary ($p=0.003$). Recipients who did not receive post-HCT maintenance had inferior OS with HR 2.00 (95% CI 1.21–3.31), $p = 0.007$). The presence of GVHD prior to the analysis was not associated with post-relapse OS ($p=0.77$). Adjusted survival shows OS advantage of TKI use at 2 years, with OS of 65%, (95% CI: 0.53–0.77) in the Combination arm, 59%, (95% CI: 0.51–0.67) in the Primary TKI arm, and 41%, (95% CI: 0.27–0.55) in the Primary DLI arm ($p=0.013$).” The limitations noted for this study included the decision made by the clinician to use one strategy versus another was not captured, the registry did not collect dose quantification of DLI allowing a better identification of immunotherapy thresholds/GVHD risk thresholds and did not have the exact disease status (chronic, accelerated or blast phase) at the time of relapse to further define relapse severity. The authors concluded “The decision of which treatment modality to use at disease relapse can be difficult for clinicians as there are no large, prospective studies directing therapy. Each therapy comes with risks and benefits that must be weighed and the patient scenario at relapse may dictate which treatment strategy is used. In the current study pre-relapse GVHD did not affect survival, however clinicians would be hesitant to use DLI in patients that had severe acute GVHD or ongoing chronic GVHD. DLI appears to be most effective in patients with CP, in our study there were relatively more patients with CP1 in the DLI arm. our data suggest that TKI is the most effective treatment strategy at disease relapse following HCT for CML. Combination therapy of TKI plus DLI did not confer additional benefit, and DLI alone showed inferior OS when compared to TKI with or without a DLI. While registration data is not all encompassing, it is unlikely a clinical trial will be conducted to address current therapeutic landscape for CML therapy at relapse with current immunotherapy and TKI treatment options.” See [Practice Guideline and Position Statements](#).

Several large series studies (Dazzi 2000, Guglielmi et. al. 2002, Simula et. al. 2007, Fozza et. al. 2007, van den Brink et. al. 2010, Radujkovic et. al. 2015) have reported outcomes of patients with relapsed CML after receiving DLI. These studies comprise more than 1000 patients, approximately half of whom had only molecular or cytogenetic relapse at the time of DLI. The cell doses varied among patients, with some receiving multiple DLI infusions and others, planned dose escalations. Despite these variations, a molecular or cytogenetic CR was achieved in 74% (746/1007) of patients. Overall survival (OS) at 3 years or more ranged from 53% to 95%, 2 was 64% at 5 years, and was 59% at 10 years after DLI in another series.

Lymphomas

Systematic Review

See above the systematic review for El-Jurdi et. al. (2013) which evaluated 39 prospective and retrospective studies using donor lymphocyte infusion (DLI) 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).

Tomblyn et. al. (2008) reported that studies in which patients received donor lymphocyte infusion (DLI) for lymphomas consist of small numbers of patients and various histologies (both Hodgkin lymphoma [HL] and high- and low-grade non-Hodgkin lymphoma [NHL]). In general, the highest response rates were seen in the indolent lymphomas. For NHL, too few patients have been reported with any single histologic subtype of lymphoma to provide adequate information on the benefit of DLI for specific subtypes.

Observational Studies

Peggs et. al. (2007) compared the results in 67 sibling donor transplantations following reduced- intensity conditioning (RIC) for Hodgkins's lymphoma (HL) in multiple relapsed patients from two national phase II studies conditioned with fludarabine/melphalan. One used cyclosporine/alemtuzumab (MF-A, $n = 31$), the other used cyclosporine/methotrexate (MF, $n = 36$) as graft-versus-host (GvHD) prophylaxis. Fourteen patients received RIC and donor lymphocyte infusion (DLI) which resulted in showing complete remission (CR) rate of 57%- and 2-year survival rate of 35%.

Morris et. al. (2004) reported on the outcomes after alemtuzumab containing reduced-intensity allogeneic transplantation regimen for relapsed and refractory non-Hodgkin lymphoma in 88 patients. Forty-one patients had indolent/low-grade NHL (LG-NHL) (follicular NHL, $n = 29$; chronic lymphocytic leukemia [CLL], $n = 9$; and lymphoplasmacytoid NHL, $n = 3$), 37 patients had aggressive/ high-grade NHL (HG-NHL) (diffuse large B-cell NHL, $n = 22$; transformed LG-NHL, $n = 11$; peripheral T-cell NHL, $n = 4$), and the remaining 10 patients had mantle cell lymphoma (MCL). All patients received the same conditioning regimen: 20 mg/d alemtuzumab by intravenous infusion. Two broad categories of patients were eligible for donor lymphocyte infusion (DLI). Patients who had relapses or showed evidence of progressive disease were given therapeutic DLI. Patients with persistent disease, minimal residual disease, or mixed hematopoietic chimerism at 6 months or more after transplantation were candidates for preemptive DLI. Patients were excluded from DLI if they had active GVHD or other contraindications to the receipt of DLI. Patients had regular follow-ups at 3-month intervals after transplantation to assess disease response and remission status. Major study end points were overall survival, disease-free survival, and response to DLI, in addition to shorter-term end points of engraftment. Seventy-four (84%) patients were evaluated for disease response (14 early transplant related mortality [TRM]). Overall, at 6 months after transplantation, 42 were in CR (57%), 17 were in stable PR (23%), and 15 had progressive disease (20%). Twenty-one patients received DLI, 3 for minimal residual disease (MRD), 1 for persistent disease, and 17 for disease progression or relapse. All 3 patients receiving DLI for MRD had LG-NHL. Within this group, 2 responded and 1 transient response was observed. One patient received DLI for persistent disease and responded. Seventeen patients (HG-NHL $n = 8$; MCL $n = 2$; LG-NHL $n = 7$) received DLI for disease progression or relapse. In the HG-NHL group, 2 responded and 5 had no response observed. The remaining patient was not restaged at the time of follow-up. One of the 2 patients with MCL responded to DLI. Of the 7 patients treated with DLI with LG-NHL, 4 responded, 2 had no response, and 1 was not able to be evaluated due to concurrent local radiotherapy. The authors concluded "with this T cell-depleting conditioning regimen, responses to subsequent DLI are required to achieve overall disease control, similar to that observed by others using non-T cell-depleting regimens."

Multiple Myeloma

LeBlanc et al (2024) investigated the efficacy and safety in a phase II, open label study of lenalidomide (Len) and dexamethasone (Dex) followed by donor lymphocyte infusions (DLI) in relapsed multiple myeloma following allogeneic stem cell transplant. Bone marrow minimal measurable disease (MRD) using flow cytometry (10^{-5}) was performed at enrollment, then every 3 months for 2 years or until disease progression in a subset of patients. The primary endpoint was efficacy measured by progression-free survival (PFS) and overall survival (OS). Secondary measures included incidence of grade $\geq$ III non-

hematologic toxicity and grade $\geq$ IV hematologic toxicity, incidence of acute graft versus host disease (GVHD). A total of 22 patients (54% were male) participated in this study, including 62% with high-risk cytogenetics. The median age was 49 years (range 30-62 years) and received G-CSF mobilized peripheral blood stem cells from 8/8 matched-sibling or unrelated donors. a total of six cycles of lenalidomide, and dexamethasone followed by three DLIs spaced 6 weeks apart. During the follow-up phase, starting after the last DLI, clinical evaluations were performed every 4 weeks for 3 months, then every 3 months up to 5 years after initiation of the first Len/Dex cycle. With a median follow-up of 5.3 years (range: 4.1–6.1), PFS and OS were 26.5% (95% CI: 10.4–45.9%) and 69.2% (95% CI: 43.3–85.1%), respectively. Overall, the best responses achieved post-Len/Dex + DLIs were complete remission in 9.1%, very good partial response in 50%, and progressive disease in 40.9%. Among the nine patients tested for MRD, only two achieved a negative status after receiving DLIs. Six patients died, all due to disease progression. No acute GVHD was observed after DLIs. A very low incidence of moderate/severe chronic GVHD of 18.2% with no need for systemic immunosuppressants one year after diagnosis. No unexpected adverse events were observed. A positive correlation between response to Len/Dex re-induction and response to DLIs was found ($p = 0.0032$). Limitations included a small number of patients, heterogeneity in induction therapy and DLI doses and only a subset of patients that agreed to serial bone marrow exams.

Groger et. al. (2018) examined the efficacy of prophylactic donor lymphocyte infusions (DLI) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in multiple myeloma (MM) patients with a long-term follow-up of more than 5 years. “A total of 61 patients with MM who did not relapse or develop disease progression after allo-HSCT were treated with prophylactic DLI in an escalating fashion (overall 132 DLI procedures) to deepen remission status and prevent relapse. Overall response rate to DLI was 77%. Thirty- three patients (54%) upgraded their remission status, 41 patients (67%) achieved or maintained complete remission, and 26% achieved a molecular remission. Incidence of acute graft-versus-host disease (GVHD) grade II to IV was 33% and no DLI-related mortality was noted. After a median follow-up of 68.7 months from first DLI the estimated 8-year progression-free survival (PFS), and overall survival (OS) in a landmark analysis was 43% (95% confidence interval [CI], 28% to 57%) and 67% (95% CI, 53% to 82%), respectively, with best outcome for patients who acquired molecular remission (8-year PFS was 62% and 8-year OS was 83%). Prophylactic escalating DLI in a selected cohort of MM patients to prevent relapse after allograft resulted in a low incidence of severe GVHD.” The authors concluded for those individuals who could receive DLI had a favorable outcome, especially those patients who received a molecular remission. When using an escalating fashion of DLIs the risk of acute and chronic GVHD was low and no non-relapsed mortality was observed. “Overall, prophylactic escalating DLI post allograft in a selected cohort of MM patients is effective to maintain or upgrade remission in a noncomparative study with a low incidence of severe GVHD and should be included in allogeneic transplant studies on MM patients.”

Five studies (Bensinger et. al (1996), Collins et. al (1997), Lokhorst et. al. (1997), Salama et. al (2000), Lokhorst et. al. (2000) has reported on the role of donor lymphocyte infusion (DLI) in relapsed multiple myeloma (MM) consisting of patients ranging in number of 5 to 63 with the highest response to DLI being reported as 62% with approximately half of the responders attaining complete remission (CR). One confounding factor for high response rates for MM treated with DLI following allogeneic HSCT is that corticosteroids used for treating GVHD have known antimyeloma effect which could potentially enhance response rates in these patients. See [Practice Guideline and Position Statements](#).

Genetic Modification of Donor Lymphocytes

There is ongoing research regarding the genetic modification of donor lymphocytes, it has been proposed that donor lymphocytes can be modified by insertion of a thymidine kinase gene in an approach to prevent T-cell mediated GVHD while preserving GVT effect of an allograft. However, existing techniques

are insufficient in converting T-cell lymphocytes. Further studies are needed to develop more efficient gene transfer protocols and determine the value in the treatment of hematologic malignancies. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Section Summary: Donor Lymphocyte Infusion (DLI)

DLI has been researched as a treatment for a variety of hematologic malignancies following allo-HSCT. Although there are no high-quality RCTs for DLI treatment, consistent findings across multiple comparative nonrandomized studies and systematic reviews of these have reported higher response rates compared to alternative treatments and permits a conclusion that response rates improve with DLI treatment for individuals treated with hematologic malignancy that have relapsed or is refractory, to prevent hematologic malignancy relapse in the setting T-cell depleted grafts or non-myeloablative conditioning regimens and convert an individual from a mixed to full donor chimerism with previous all-HSCT treatment.

Hematopoietic Progenitor Cell Boost

Clinical Context and Therapy Purpose

The purpose of hematopoietic progenitor cell (HPC) (also known as stem cells) boost from the original HSCT donor is intended to restore hematopoiesis or augment poor graft function to a transplant recipient after HSCT, as a treatment option that is an alternative to or an improvement in existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is a transplant recipient after HSCT.

Interventions

The therapy being considered is hematopoietic progenitor cell (HPC) boost.

Poor graft function is a severe complication of HSCT which is defined as persistent cytopenia's and/or transfusion dependence. The cell product used for a HPC boost may be a previously cryopreserved cell product, or alternatively, the donor may need to undergo additional evaluation, stem cell mobilization, and cell harvest. A boost is not preceded by a preparative regimen. A potential source of confusion is that a boost is often required when additional conventional chemotherapy is given to treat relapse and reestablish remission after transplantation. Prolonged cytopenia's and immunosuppression may result, requiring additional HPC boost, which is typically given days to weeks after reinduction chemotherapy.

Comparators

The following therapies are currently being used to treatment hematologic malignancies: chemotherapy and/or immunotherapy.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, change in disease status, treatment-related mortality, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Review and Meta-Analysis

Shahzad et. al. (2021) assessed the outcomes including overall response rate (ORR) and rates of complete response (CR), partial response (PR), acute and chronic GVHD, relapse, death, non-relapse mortality (NRM), relapse-free survival (RFS), and overall survival (OS) following administration of CD34-selected stem cell boost (SCB) for poor graft function (PGF) in adult allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients. PGF after allo-HSCT is associated with high morbidity and mortality. Seven studies were included (6 studies were retrospective and 1 study was prospective) that included 209 patients who received SCB for PGF after allo-HSCT. All studies evaluated CD34-selected SCB as an intervention for PGF, and no study included T cell-depleted allo-HSCT recipients. Underlying hematologic disorders included acute lymphoblastic leukemia/acute myelogenous leukemia (n = 75; 36%), myelofibrosis (n = 31; 15%), chronic myelogenous leukemia (n = 17; 8%), myelodysplastic syndromes (n = 13; 6%), non-Hodgkin lymphoma (n = 14; 7%), lymphoproliferative disorders (n = 30; 14%), severe aplastic anemia (n = 15; 7%), multiple myeloma (n = 2; 1%), and others (n = 12; 5%). Donor types were matched sibling/related donor in 77 patients (37%), matched unrelated donor in 74 (36%), mismatched unrelated donor in 47 (22%), and haploidentical related donor in 11 (5%). The median time from allo-HSCT to SCB was 138 days (range, 113 to 450 days). "CR and ORR were reported in all 7 studies, with an estimated pooled CR of 72% (95% CI, 63% to 79%; I² = 26%; p = .23; n = 209) and a pooled ORR of 80% (95% CI, 74% to 85%; I² = 0%; P = .66; n = 209). A pooled PR of 13% (95% CI, 7% to 24%; I² = 41%; P = .24; n = 171) was estimated based on available data for 5 studies. After a median follow-up of 42 months (range, 30 to 77 months), the actuarial survival rate was 54% (95% CI, 47% to 61%; I² = 0%; P = .62; n = 207). OS ranged from 80% at 1 year to 40% at 9 years. Acute GVHD as a complication of SCB was reported in 33 patients, with a pooled rate of 17% (95% CI, 13% to 23%; I² = 0%; P = .43; n = 209) and chronic GVHD developed in 31 patients, with a pooled rate of 18% (95% CI, 8% to 34%; I² = 76%; P < .01; n = 189). NRM was reported in 42 patients, with a pooled rate of 27% (95% CI, 17% to 40%; I² = 59%; P = 0.06; n = 155). Death due to relapse was reported in 25 patients, with a pooled rate of 17% (95% CI, 11% to 23%; I² = 0%; P = .66; n = 155)." Limitations of this study include six of 7 studies were retrospective, all studies were conducted without randomization and blinding, and studies included small numbers of patients. The authors concluded "to our knowledge, this is the first systematic review and meta-analysis of outcomes in patients with PGF after allo-HSCT. CD-34 selected

SCB infusion could provide a safe and effective treatment option for PGF after an allo-HSCT. A low CD3+ T cell count in stem cell products correlates directly with the low incidence of GVHD. The paucity of haploidentical transplants was noted, likely reflecting the era of the reviewed studies. ab T cell depleted SCB represents a promising strategy for PGF and may expand therapeutic options for patients with infectious complications and mixed donor chimerism. There is an unmet need for prospective studies to address optimal dosing and manipulation of SCB.”

Observational Studies

Liang et. al. (2021) in a retrospective review examined the utilization of back up stem cells (BSCs) in patients with multiple myeloma (MM) undergoing autologous stem cell transplantation (ASCT). ASCT is a standard treatment for MM, most institutional and consensus guidelines recommend that at time of first ASCT, enough hematopoietic stem cells (HSC) should be collected to perform two stem cell transplants. The BSCs may be used for a second transplant or less commonly for stem cell boost in case of non-engraftment or delayed engraftment and can be utilized without additional conditioning. Delayed engraftment or poor graft function is a rare, life-threatening post-transplantation complication associated with infections, bleeding, and secondary iron overload due to transfusions. A total of 393 patients diagnosed with MM were included in this review. Sixty patients (n=60; 15%) had high-risk cytogenetics at diagnosis. One hundred ninety-four (n=194; 49%) of the patients received one line of induction therapy before ASCT; 154 (39%) of patients received doublet regimens; and 16 (55%) received triplet regimens. Maintenance was administered in 110 (28%) of the patients after first ASCT. Overall, 27 (6.9%) of patients utilized BSCs, with 10 patients using them for stem cell boost for delayed or non-engraftment, 18 patients (4.6%) using them for a second salvage ASCT, including one patient undergoing both stem cell both and second ASCT. The decision to utilize BSCs regarding delayed/non-engraftment is the decision of the treating physician as there are no consensus guidelines for this rare complication. Two hundred-forty patients experienced a relapse over a median follow-up time of 3.5 year with 18 patients (7.5%) using BSCs for second transplant. Within this subset of patients, the rate of BSCs utilization for second transplant was based on duration of response after first transplant (progression-free survival) of <2, 2–3, and ≥3 years were 4.7% (n = 6), 4.8% (n = 2), and 13.9% (n = 10), respectively. The main limitations of this study included: single-center design, transplant centers may have different hematopoietic stem cell (HSC) collection targets and protocols for mobilization, apheresis, cryopreservation and storage which can affect the number of HSC available for backup and there was a very low number of patients utilizing BSCs for boost which limits the ability to examine predictors of poor graft function in this cohort. The Authors concluded “the rates of BSCs of backup stem cell utilization for second ASCT and stem cell boost in patients with multiple myeloma undergoing autologous transplant are very low. However, the survival benefit of second ASCT in select patients and particularly need for stem cell boost for poor graft function may necessitate continuing to collect and store backup stem cells in all patients. Future studies should evaluate factors which may a-priori help identify patients who are at risk of poor graft function or who may benefit from a second transplant.”

In 2018, Mainardi et. al. reported retrospective study results involving 50 children with acute lymphatic leukemia, acute myeloid leukemia and severe aplastic anemia who received 61 boosts with CD34+ selected peripheral blood stem cells after transplantation from matched unrelated (n = 25) or mismatched related (n = 25) donors. No conditioning was performed prior, and no immunosuppressive therapy was administered post the allogeneic HSCT. Within 8 weeks, a significant increase in median neutrophil counts ($p < 0.05$) and a decrease in red blood cell and platelet transfusion requirement ($p < 0.0001$ and <0.001) respectively, were observed. 78.8% of patients resolved one or two of their cytopenia's and 36.5% had a complete hematological response. The rate of de novo acute graft-versus-host disease (GVHD) grade I–III was only 6% and resolved completely. No GVHD grade IV or chronic GVHD occurred.

Patients who responded to hematopoietic progenitor cell (HPC) displayed a trend toward better overall survival (OS) ($P = 0.07$). Data suggest improved graft function with HPC boost in this cohort of patients.

In 2017, Ghobadi et. al. performed single institution study at the Washington University School of Medicine. A pilot trial was conducted to study three different sources of CD34+ cells for treatment of poor graft function (PGF): (1) fresh mobilized product using G-CSF only, (2) fresh mobilized products using G-CSF and plerixafor, and (3) cryopreserved cells mobilized with G-CSF. Seventeen donor-recipient pairs were enrolled onto this prospective study. A retrospective review of similar patients treated off protocol with the same regimen was conducted. From June 2010 through June 2015, 17 donor-recipient pairs were enrolled in the prospective study and 9 donor-recipient pairs were treated off protocol. Together 26 donor-patient pair were analyzed and reported in this manuscript. The primary objective was the hematologic response rate. Secondary objectives included: (1) CD34+ yields; (2) incidence and severity of acute and chronic GVHD; (3) Overall survival (OS) and relapse free survival (RFS). The Washington University Institutional Review Board (IRB) approved the study. The prospective trial was registered at ClinicalTrials.gov as NCT01026987. PGF was defined as having cytopenia ($ANC < 0.5k/\mu L$, platelets $< 30k/\mu L$ or platelet transfusion dependence, or red blood cell transfusion dependence) for two consecutive weeks in the absence of relapse/persistent hematologic disorder, incomplete ($< 90\%$) donor chimerism, active infectious diseases, or drug related myelosuppression. Primary PGF was defined as PGF in the absence of full engraftment. Secondary PGF was defined as PGF after full engraftment. Complete response was defined as improvement of all involved cells lineages; partial response was defined as improvement of platelets and/or neutrophils with continuing RBC transfusion dependence. Neutrophil improvement was defined as an absolute neutrophil count $> 500/\mu L$ without growth factor support for > 7 days; platelet improvement was defined as platelet count $\geq 50,000/\mu L$ without platelet transfusion support for > 7 days; and RBC improvement was defined as hemoglobin > 9 g/dL and transfusion independence. CD34+ yield was defined as the number of CD34+ cells after selection/CD34+ cells in the mobilized product prior to CD34+ selection. Overall survival (OS) was defined as time from SCB to death. Relapse-free survival (RFS) was defined as time from stem cell boost (SCB) to relapse or death. Eligible patients were those who were at least 18 years old, had an ECOG performance status of 2 or below, and had poor graft function (PGF) following allo-HSCT (more than 60 days post allo-HSCT). Patients with poor graft function secondary to relapse/persistent disease, incomplete ($< 90\%$) donor chimerism, or active infectious diseases were excluded, as were patients with significant medical, psychiatric, or social conditions that contraindicated the procedure. Previous allo-HSCT may have been performed using a related or unrelated donor; however, the original donor was required to undergo additional PBSC collection or authorize that cryopreserved cells from a previous PBSC collection be used. Blood counts were performed at least weekly through Day +14 then at least every other week through Day +100, monthly thereafter for patients on the prospective trial; patients reviewed retrospectively were followed per institutional guidelines. Incidence and severity of acute GVHD was defined according to Glucksberg criteria, chronic GVHD as limited or extensive. Patients were monitored for acute GVHD through Day +100 and for chronic GVHD through Day +365 following SCB. The median age at SCB was 52.5 years (range 25–68) and 16 of 26 were male. Twelve patients underwent allo-HSCT for acute myelogenous leukemia, 6 for myelodysplastic syndrome, 4 for acute lymphoblastic leukemia, 2 for aplastic anemia, and 1 for Hodgkin's lymphoma, and 1 for Diamond-Blackfan Anemia. Sixteen patients had related donors (11 HLA-matched siblings, 5 haplo-identical donors). Ten had unrelated donors (9 HLA-matched and 1 HLA-mismatch). All received peripheral blood stem cell products. Sixteen patients had primary PGF, 10 secondary. The median time from allo-HSCT to SCB was 4.6 months (range 2.1–23.6). At time of SCB 6 had PGF involving neutrophils, 25 platelets, and 23 red blood cells. Twenty-six recipients of SCB for the treatment of PGF following allo-HSCT. The complete response rate was 62% and overall response rate was 81%. Six of the 10 patients who failed to achieve a complete response suffered from disease relapse while only one of 17 patients with complete hematologic response suffered from disease relapse within 3 months of SCB; Treatment was well tolerated; there was no TRM and no grade III–IV acute GVHD. The

authors concluded our data suggests that cryopreserved products can be an effective and viable source of cells for SCB (stem cell boost).

Section Summary: Hematopoietic Progenitor Cell (HPC) Boost

Although the evidence is not robust as there are no high-quality RCTs regarding HPC boost following HSCT, the evidence does include systematic review meta-analysis and several prospective and retrospective studies which have demonstrated beneficial effects of HPC boost after HSCT by reporting higher response rates compared to alternative treatments for restoring hematopoiesis or augment poor graft function.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network (NCCN)

Treatment by Cancer Type	Current Clinical Practice Guideline
Acute Lymphoblastic Leukemia Version 2.2025	For patients with relapsed disease after initial allogeneic HCT, a second allogeneic HCT and/or donor lymphocyte infusion (DLI) can be considered.
Acute Myeloid Leukemia Version 2.2026	A study suggests that azacitidine followed by donor lymphocyte infusions (DLIs) may be a treatment option for therapy in patients who have AML that relapses after allogeneic HCT. These data are based on a prospective phase II trial of 28 patients with AML. In this study, 22 patients received DLIs and an ORR of 30% was achieved. This included 7 CRs and 2 PRs. At publication, 5 patients remained in CR with a median of 777 days (range, 461–888 days). Neutropenia and thrombocytopenia grade III/IV were the most common adverse events (65% and 63%, respectively). Acute and chronic graft-versus-host disease (GVHD) were seen in 37% and 17% of patients, respectively. Correlations suggest a better response in patients with myelodysplasia-related changes ($P = .011$) and lower blast count ($P = .039$) or patients with high-risk cytogenetics ($P = .035$). However, interpretation of results is limited by the small size of the study.

B-Cell Lymphomas Version 2.2026	Does not include or indicate the use of donor lymphocyte infusion (DLI) in the treatment of B-cell lymphomas.
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 2.2026	Does not include or indicate the use of donor lymphocyte infusion (DLI) in the treatment of CLL or SLL.
Chronic Myeloid Leukemia Version 1.2026	Donor lymphocyte infusion (DLI) is an effective in inducing durable molecular remissions in the majority of patients with relapsed CML following an allogeneic HCT, although it is more effective in individuals with chronic phase relapse than advanced phase relapse. However, DLI is associated with complications such as graft-versus-host-disease (GVHD), susceptibility to infections and immunosuppression.
Hairy Cell Leukemia Version 2.2026	Does not include or indicate the use of donor lymphocyte infusion (DLI) in the treatment of hairy cell leukemia.
Histiocytic Neoplasms Version 2.2025 • Adult Langerhans Cell Histiocytosis • Erdheim-Chester Disease • Pediatric Langerhans Cell Histiocytosis • Rosai-Dorfman Disease	Does not include or indicate the use of donor lymphocyte infusion (DLI) in the treatment of histiocytic neoplasms.
Hodgkin Lymphoma Version 1.2026 • Classic Hodgkin Lymphoma (age 18-60 years) • Hodgkin Lymphoma • Management of CHL in Adults > 60 or Adults Unfit for Intensive Therapy • Management of CHL in Pregnancy • Nodular Lymphocyte-Predominant Hodgkin Lymphoma (Age ≥ 18 years)	Does not include or indicate the use of donor lymphocyte infusion (DLI) in the treatment of Hodgkin Lymphoma.
Multiple Myeloma Version 5.2026	Donor lymphocyte infusion can be considered in patients with disease relapse after allogeneic HCT. Patients whose disease either does not respond to or relapses after allogeneic hematopoietic cell grafting may receive donor lymphocyte infusions to stimulate a beneficial graft-versus-myeloma effect or other myeloma therapies on or off clinical trial.
Myelodysplastic Syndromes Version 3.2026	Management of Higher-Risk Disease (IPSS-R Intermediate -, High-, Very-High-Risk Disease) and Transplant Candidate: • Relapse after allo-HCT or no response: Consider allo-HCT or donor lymphocyte infusion^{fff}

	^{fff}Consider second transplant or donor lymphocyte infusion immune-based therapy for appropriate patients who had prolonged remission after first transplant. In patients with disease relapse after prolonged remission following first transplant, second transplant or donor lymphocyte infusion immune-based therapy may be considered. In patients with disease relapse after allo-HCT or if there is no response. In patients with disease relapse after prolonged remission following the first transplant or with no response, a second transplant or donor lymphocyte infusion immune-based therapy may be considered.
Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions Version 1.2026	Does not include or indicate the use of donor lymphocyte infusion (DLI) in the treatment of Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions.
Myeloproliferative Neoplasms Version 1.2026 - Accelerated/Blast Phase Myeloproliferative Neoplasms - Essential Thrombocythemia - Myelofibrosis - Myeloproliferative Neoplasms - Polycythemia Vera	Does not include or indicate the use of donor lymphocyte infusion (DLI) in the treatment of Myeloproliferative Neoplasms.
Pediatric Acute Lymphoblastic Leukemia Version 1.2026	One of the early treatments for patients with advanced ALL included adoptive cell therapy to induce a graft-versus-leukemia effect through allogeneic HCT or donor lymphocyte infusions (DLI). However, this method resulted in a significant risk of graft-versus-host disease (GVHD). To circumvent this issue, current advances are focused on the use of the patient's own T cells to target the B-ALL cells. The generation of CAR T cells to treat B-ALL is a significant advancement in the field. The treatment of patients with CAR T has served as a bridge for transplant, enabling patients who were formerly unable to receive transplant due to poor remission status to achieve a CR and ultimately transplantation. It is also reported that patients who receive CAR T cells can maintain long-term remission without subsequent HCT.
Pediatric Aggressive Mature B-Cell Lymphoma Version 2.2025 - Burkitt Lymphoma and Diffuse Large-B Cell Lymphoma - Pediatric Aggressive Mature B-cell Lymphomas - Pediatric Post-Transplant Lymphoproliferative Disorders - Primary Mediastinal Large B-Cell Lymphomas	Does not include or indicate the use of donor lymphocyte infusion (DLI) in the treatment of Pediatric Aggressive Mature B-Cell Lymphomas.

Pediatric Hodgkin Lymphoma Version 2.2025 • Classic Hodgkin Lymphoma • Nodular Lymphocyte-Predominate Hodgkin Lymphoma • Pediatric Hodgkin Lymphoma	Does not include or indicate the use of donor lymphocyte infusion (DLI) in the treatment of Pediatric Aggressive Mature B-Cell Lymphomas.
Systematic Light Chain Amyloidosis Version 1.2026	Does not include or indicate the use of DLI in the treatment of Systemic Light Chain Amyloidosis
T-Cell Lymphomas Version 2.2026 • Adult T-cell Leukemia/Lymphoma • Breast Implant-Associated ALCL • Extranodal NKT-Cell Lymphomas • Hepatosplenic T-Cell Lymphoma • Indolent T-Cell Lymphoma • Indolent T-Cell Lymphomas and NK-Cell LPD of GI Tract • Peripheral T-Cell Lymphomas • T-Cell Large Granular Lymphocytic Leukemia • T-Cell Prolymphocytic Leukemia	The results of retrospective analysis showed that induction of GVL effect via donor lymphocyte infusion (DLI) may provide long-lasting remission in selected patients with relapsed adult T-cell leukemia/lymphoma (ATLL). However, prospective clinical trials are needed to confirm these findings.
Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 1.2026	Does not include or indicate the use of donor lymphocyte infusion (DLI) in the treatment of Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	38242	Allogeneic lymphocyte infusions

Codes	Number	Description
	38243	Hematopoietic progenitor cell (HCP); HPC Boost
HCPCS		
	None	
Type of Service	Hematology	
Place of Service	Outpatient	

POLICY HISTORY

Date	Action	Action
March 2026	Annual Review	Policy Renewed
March 2025	Annual Review	Policy Renewed
March 2024	Annual Review	Policy Renewed
March 2023	Annual Review	Policy Revised
November 2022	Annual Review	Policy Renewed
November 2021	Annual Review	Policy Renewed
November 2020		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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