Donor Lymphocyte Infusion

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Aetna considers donor lymphocyte infusion (DLI) medically necessary for persons who have a prior, medically necessary allogeneic bone marrow or peripheral stem cell transplantation.

II. Aetna considers the modification of donor lymphocytes (e.g., donor lymphocyte depletion, ex-vivo expansion, expanding antigen-specific T-cell lines, T-cell depletion, genetic modification) experimental and investigational because the clinical value of these approaches in the treatment of malignancies has not been established.

III. Aetna considers intrathecal donor lymphocyte infusion experimental and investigational because the effectiveness of this approach has not been established.

IV. Aetna considers donor lymphocyte infusion for the treatment of multiple myeloma experimental and investigational because the effectiveness of this approach has not been established.

See also CPB 0641 - Adoptive Immunotherapy and Cellular Therapy.
Background
High-dose chemotherapy (HDC) in combination with allogeneic bone marrow transplantation results in remission in significant numbers of patients with chronic myelogenous leukemia (CML), acute myeloid leukemia (AML) or acute lymphocytic leukemia (ALL). However, disease relapse is a major cause of treatment failure, and salvage treatment options for these patients are limited. Patients can either be treated with an additional course of conventional chemotherapy or a second round of HDC and repeat allogeneic transplantation. Conventional chemotherapy is unlikely to result in a complete durable remission, and the morbidity and mortality of a second allogeneic transplant is unacceptably high. Furthermore, patients with CML have been treated with interferon. While this treatment can be associated with normalization of peripheral blood counts, interferon fails to eradicate the malignant clone of cells.

Donor lymphocyte infusion (DLI), also known as donor leukocyte or buffy coat infusion, has been used in an attempt to stimulate a donor-versus-leukemia (GVL) reaction and thus eradicate the malignant clone of cells. Donor lymphocyte infusion entails the collection (from the original donor) of peripheral lymphocytes during an apheresis procedure; donors generally undergo 2 to 8 procedures. The lymphocytes are then simply infused into the patient either immediately or after frozen storage. Donor lymphocyte infusion differs from allogeneic bone marrow transplantation in that it is not preceded by chemotherapy and T cells are not depleted. Lymphocyte infusion with a defined T-cell dose can cause a profound GVL effect and is an effective form of salvage immunotherapy in allogeneic marrow transplanted recipients. The advantage in using DLI versus second allogeneic transplantation is the lower treatment-related morbidity and mortality.

The GVL effect is a well-described phenomenon, which is associated with the presence of graft versus-host disease (GVHD). For example, the likelihood of relapse post-allogeneic transplantation is lower in those patients who experience either acute or chronic GVHD. In addition, there is a higher rate of relapse in patients receiving a syngeneic (identical twin)
transplant compared to allogeneic transplant. However, the presence of GVL is not dependent on the presence of GVHD. For example, the rate of leukemic relapse is higher in patients receiving T-cell depleted allogeneic marrow, even after controlling for the degree of GVHD. This observation suggests that there may be a distinct subset of T cells responsible for GVL. Donor lymphocyte infusion attempts to harness the anti-leukemic properties of donor T cells.

In a recent review on adoptive allogeneic cellular therapy, Peggs and Mackinnon (2001) stated that DLI is effective in generating anti-tumor responses, especially for relapsed chronic-phase CML. Response rates and durability appear lower with myeloma, AML and myelodysplasia syndrome, and minimal with ALL. There is relatively little data on indolent lymphoid malignancies. This is in agreement with the observation of Slavin and associates (2001) who reported that pre-clinical and clinical studies have indicated that much more effective eradication of the host immunohematopoietic system cells can be attained by adoptive allogeneic cellular therapy with DLI following bone marrow transplantation. Thus, eradication of blood cancer cells, particularly in patients with CML and, less frequently, in patients with other hematological malignancies, can frequently be achieved despite the complete resistance of such tumor cells to maximally tolerated doses of chemo- and radio-therapy.

In a review on DLI for the treatment of hematologic malignancies in relapse following allogeneic blood or marrow transplantation, Luznik and Fuchs (2002) reported that DLI induces complete remissions in the majority of patients with CML in early-stage relapse and in less than 30% of patients with relapsed acute leukemia, myelodysplasia, and multiple myeloma. Remissions of chronic-phase CML induced by DLI are durable, but as many as half of patients with other diseases ultimately relapse.

Pre-planned DLI has also been used as part of transplant protocols in persons with hematologic malignant diseases who have not relapsed. Donor lymphocyte infusion is intended to facilitate establishment of full donor chimerism (complete donor stem cell grafting in the recipient’s bone marrow) and
potentiation of anti-tumor effect (graft versus-tumor reaction) (Cheong et al, 2002).

There is also ongoing research on the genetic modification of donor lymphocytes. Transplantation of suicide gene modified allogeneic T lymphocytes is an approach to prevent T-cell mediated GVHD while preserving the GVL effect of an allograft. However, existing techniques allow insufficient transduction of T lymphocytes. Further investigation is needed to develop more efficient gene transfer protocols and is possible value in the treatment of hematological malignancies.

Beitinjaneh et al (2012) stated that the role of DLI in mediating the graft versus-myeloma (GVM) effect after allogeneic hematopoietic stem cell transplant (allo-HCT) is not clearly defined. These investigators evaluated the safety and utility of DLI in patients with either persistent or recurrent multiple myeloma (MM) after allo-HCT. A total of 23 patients with MM received DLI after allo-HCT between July 1996 and June 2008 were included in this study. Eight patients received preemptive DLI for residual disease (RD) while 15 patients received DLI for the treatment of recurrent or progressive disease (PD). These researchers evaluated the response to DLI and the factors that may predict a response. Median DLI dose was $3.3 \times 10^{7}$ CD3 + cells (range of 0.5 to $14.8 \times 10^{7}$). Grade II to IV acute GVHD was seen in 5 patients (22 %). Median follow-up in surviving patients was 24 months. Five of 23 patients (22 %) achieved a complete or a very good partial response (2 CR, 3 VGPR), while 8 patients (34 %) had stable disease (SD) after the DLI. Patients who received DLI for RD had a higher response rate (greater than or equal to VGPR 50 % versus 7 %, p = 0.03), a longer overall survival (28.3 versus 7.6 months, p = 0.03) and a trend toward longer progression-free survival (11.9 versus 5.2 months, p = 0.1). In this largest single institution study, the authors concluded that the use of preemptive, non-manipulated DLI for RD after reduced-intensity conditioning allo-HCT is encouraging, and it was associated with a higher response rate and a longer overall survival when given preemptively. They stated that the role of DLI needs to be further explored in prospective clinical trials.
According to the 2009 edition of Thomas’ Hematopoietic Cell Transplantation, in patients with poor graft function following allogeneic transplantation, CD34+ selected cell boost following granulocyte-colony stimulating factor (G-CSF) mobilization was associated with a high likelihood of hematopoietic cell recovery and a low risk of GVHD. Patients did not receive conditioning prior to the CD34+ cell boost. It is unclear how long to wait before requesting a second donation of cells.

An UpToDate review on “Immunotherapy for the prevention and treatment of relapse following hematopoietic cell transplantation” (Negrin, 2014) states that “Various techniques have been used to manipulate the donor lymphocyte graft in an effort to increase the lymphocyte specificity to eradicate tumor while minimizing effects on the host. As yet, these techniques are considered experimental and require further study in humans before they can be widely applied”.

Intrathecal Donor Lymphocyte Infusion:

Yanagisawa et al (2016) reported on the case of an 8-year old boy with a bone marrow relapse of T cell acute lymphoblastic leukemia underwent stem-cell transplantation from a human leukocyte antigen (HLA)-haploidentical mother. Five months later, he relapsed with central nervous system (CNS) involvement. Systemic chemotherapy and repeated intrathecal chemotherapy induced consciousness disturbances and frequent arrhythmia, prompting discontinuation of the chemotherapy. He had already received an 18-Gy prophylactic cranial irradiation, an 8-Gy total body irradiation, and a 15-Gy local irradiation for pituitary gland involvement. Thus, these researchers performed 5 intrathecal DLIs (IDLIs) in escalating doses from $1 \times 10^4$ up to $1 \times 10^6$ cells/kg. All IDLIs were safe without infusion reactions or GVHD. After the 2nd and later IDLIs, donor mononuclear cells were continuously detected in cerebrospinal fluid; however, he did not achieve donor-dominant chimerism. The authors concluded that based on this case and 4 cases reported in the literature, the effectiveness of IDLI therapy is limited for CNS relapse of hematological malignancies. However, they suggested that IDLI remains a feasible and safe option, as no GVHD or other adverse
effects occurred, even in the HLA-haploidentical setting. These investigators noted that they will make further efforts to increase the efficacy.

**Multiple Myeloma:**

Oostvogels and colleagues (2017) stated that DLI can induce durable remissions in MM patients, but this occurs rather infrequently. As the graft versus-tumor (GvT) effect of DLI depends on the presence of host-dendritic cells (DCs), these researchers tested in a phase I/II clinical trial whether the effectiveness of DLI could be improved by simultaneous vaccination with host-DCs. They also analyzed the possibility of further improving the GvT effect by loading the DCs with peptides of mis-matched hematopoietic cell-specific minor histocompatibility antigens (mHags). A total of 15 MM patients not responding to a 1st DLI were included in this study; 11 patients could be treated with a 2nd equivalent dose DLI combined with DC vaccinations, generated from host monocytes (moDC). For 4 patients, the DC products did not meet the quality criteria. In 4 of the treated patients the DCs were loaded with host mHag peptides. Toxicity was limited and no acute GVHD occurred. Most patients developed objective anti-host T-cell responses and in 1 patient a distinct mHag-specific T-cell response accompanied a temporary clinical response. The authors concluded that these findings confirmed that DLI combined with host-DC vaccination, either unloaded or loaded with mHag peptides, is feasible, safe and capable of inducing host-specific T-cell responses. They stated that the limited clinical effects may be improved by developing more immunogenic DC products or by combining this therapy with immune potentiating modalities like checkpoint inhibitors.

National Comprehensive Cancer Network’s clinical practice guideline on “Multiple myeloma” (Version 3.2017) states that “Patients whose disease either does not respond to or relapse after allogeneic stem cell grafting may receive donor lymphocyte infusions to stimulate a beneficial graft versus-myeloma effect or other myeloma therapies on or off a clinical trial”. There is no explicit recommendation regarding the use of DLI.
Furthermore, an UpToDate review on “Treatment of relapsed or refractory multiple myeloma” (Rajkumar, 2017) does not mention DLI as a management tool.

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The above policy is based on the following references:


35. Negrin RS. Immunotherapy for the prevention and treatment of relapse following hematopoietic cell transplantation. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed May 2014.


43. Rajkumar SV. Treatment of relapsed or refractory multiple myeloma. UpToDate Inc., Waltham, MA. Last reviewed April 2017.
Amendment to
Aetna Clinical Policy Bulletin Number:
0638 Donor Lymphocyte Infusion

There are no amendments for Medicaid.