Case Report

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Quick Response Code:

Website: www.ajts.org

DOI: 10.4103/ajts.ajts_211_23

Donor lymphocyte infusions: An experience from a tertiary care center of North India

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Abstract:

Donor lymphocyte infusions (DLIs) are often recommended products after allogeneic hematopoietic stem cell transplant to increase graft – versus – leukemia effect. More success rate of DLI has been reported in relapsed posttransplant chronic myeloid leukemia. Whatever the indication for DLI, mortality related to post-DLI infusion is 5%–20%, and more than one-third of patients will develop acute and/or chronic graft versus host disease (GVHD) after DLI. We report two cases where DLIs were used for residual disease after posttransplant. Both of DLI went uneventful. None of the patient's developed signs of GVHD postinfusion. Although both patients expired with different causes, none were related to DLI infusion. Information from published literature suggests that DLI should be administered early after relapse or as a prophylactic strategy in patients receiving T-cell-depleted grafts, and patients with aggressive diseases may benefit from disease reduction before DLI. However, further evidence is required to evaluate its efficacy, especially in relapsed or residual hematological malignancies.

Keywords:

Bone marrow transplantation, CD3 + cells, cellular therapy, donor lymphocyte infusion, minimal residual disease

Introduction

Allogeneic hematopoietic stem cell transplant (allo-HSCT) is recommended as an effective therapy in the treatment of nonmalignant and several malignant hematological diseases over the last decades.[1] Numbers of allo-HSCT are still increasing.[2] Two complications are more important in this scenario, first is toxicity due to transplant, leading to morbidity and mortality and other one is relapse of the underlying disease. Talking about the toxicity of allo-HSCT, the progression had slightly decreased,[2,3] but a 1-year mortality rate of around 10%–15% or higher in groups of poor performance status, advanced disease, alternative grafted donors, and associated comorbidities has still been reported. Relapse of the disease is more disturbing for both patient and physician as the majority of relapses occur in the 1st year of life.[2] The key to reducing relapse rate can be an infusion of donor T cells that can react against tumor cells, which is known as the graft versus leukemia effect (GVL). Evidence of GVL with specific therapy was finally provided by complete remission of chronic myeloid leukemia (CML) in relapse (post-transplant) after donor lymphocyte infusions (DLIs).[2] After allo-HSCT, DLI is an effective treatment for hematological malignancies that have relapsed or are persistent.[4] There is a paradigm shift in the bone marrow transplant field by DLI. The GVL effect produced by DLI is now well-known in cases of CML.[5] However, it has not been tried with so much success in other hematopoietic malignancies. The forward step to use

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Submitted: 17-10-2023
Revised: 11-02-2024
Accepted: 03-03-2024
Published: 21-06-2024

How to cite this article: Lamba DS, Tripathi PP, Hans R, Khadwal A, Sharma RR. Donor lymphocyte infusions: An experience from a tertiary care center of north India. Asian J Transfus Sci 2024;18:124-7.

donor T cells (adoptive immunotherapy) is increasing in the treatment of hematological malignancies, mostly post–allo-HSCT therapy. In this article we are discussing two cases where DLIs were used after post–allo-HSCT therapy for chronic lymphocytic leukemia (CLL) and mixed phenotype acute leukemia (MPAL) cases, as an experience from our center.

Case Reports

Case 1

A 40-year-old young female with a known case of CLL (high risk, deletion 19, deletion 11q, and deletion 13 positive–March 2016) with primary hypothyroidism and hepatitis B positive was in disease progression in the 1st year (2017) and on chemotherapy. The patient was continued on chemotherapy for the next 5 months and further planned for a hematopoietic stem cell transplant. The transplant was done successfully after conditioning with matched related donor (sex mismatched) and the patient was discharged after 1 month of transplant with graft versus host disease (GVHD) in October 2017. On day 60 of posttransplant, positron emission tomography (PET)–computed tomography scan was done which revealed the residual disease. The patient presented with complaints of palpable increasing lymph nodes including the right and left axillary region as well as in the cervical region. The patient also complained of a history of weight loss and pain in the abdomen. There was no history of night sweats, anorexia, fever, and GVHD. On general examination, the patient had palpable lymph nodes of different regions (supraclavicular, cervical, right axillary, and left axillary region) with different sizes (2 cm × 2 cm, 1.5 cm × 1.5 cm, 5 cm × 5 cm, and 5 cm × 5 cm), respectively. The rest of the systemic examination was normal. Fine-needle aspiration cytology (FNAC) of lymph nodes was done. On the basis of PET scan and FNAC report diagnosis of residual disease was made. Due to residual disease plan was made for DLI after variable number of tandem repeats testing. On day 90 posttransplant, DLI was done. The product was obtained from the same previous allo-HSCT donor. Donor lymphocytes were collected by Spectra Optia (Terumo BCT, Lakewood, CO, USA) based on the continuous flow principle by choosing the continuous mononuclear cell (CMNC) procedure option, through peripheral venous access by intravenous 16 G fistula needle [Colorogram of Optia Spectra for collection of donor lymphocyte product was used, with color matching at 0.5%–1% hematocrit, as depicted in Figure 1]. The procedure took a total of 240 min and 198 ml of total volume was collected. According to the patient's weight (34 kg), the total dose was calculated. The total leukocyte count in the bag was 146,000/uL with CD 3 + count was 16.4%. The total dose collected was 139.7 × 10^6 CD3 + cells/kg.

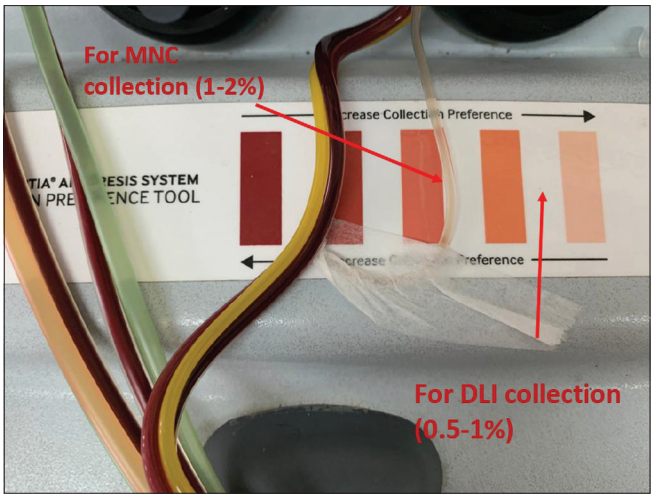

Figure 1: Colorogram of optia spectra for collection of donor lymphocytes

First bag (14.2 ml; 10 × 10^6 CD3 + cells/kg) of DLI was transfused to the patient on day 90 of posttransplant without any untoward adverse event. The remaining bags were cryopreserved and divided into 6 aliquots with the volume of each aliquot was 30 ml with 1 vial (1 mL) with each bag to check viability due to low weight of the patient. Again plan was made to look for any GVHD in subsequent days and to give second dose of DLI after 7 days of the first dose. Postinfusion patient was stable, and investigations, including bone marrow biopsy, Vitamin B12 levels and ferritin levels were sent. Five days postinfusion, the patient was stable but on the 6th day, the patient started deteriorating. She complained of three episodes of vomiting which was managed conservatively. Bone marrow biopsy reported as a residual disease with aggregates of lymphoid cells, and immunohistochemistry was still awaited. Due to still persistence of residual disease, the patient decided to take left against medical advice (LAMA). Further on follow-up, bone marrow biopsy was reported as a high-grade tumor (Anaplastic tumor). The patient expired after 20 days of post-DLI infusion.

Case 2

A 36-year-old young male came to our center in 2012 and presented with complaints of fever, rash, and dry cough for the past 1 year. On examination, he had eosinophilia and bone marrow examination revealed 23% blasts. Flow cytometry showed positivity for CD34, CD3, HLA–DR, anti-MPO, CD 38, TDT, and negative for CD 33, CD 117, CD 64, CD 14, and CD20. On the basis of examination, bone marrow and flow cytometry diagnosis of MPAL was made. Allogeneic peripheral blood stem cell transplant was done after 4½ years of diagnosis with HLA A mismatched, 9/10 HLA matched, ABO matched, sex-matched sibling donor, and with reduced intensity conditioning in December 2016. Engraftment took place after 18 days of transplant. Patient was doing

well for 2 years post transplant. Bone marrow revealed minimum residual disease (MRD) with increase in blast percentage after 2 years into posttransplant phase. Due to MRD, decision was taken further, to go for DLI. Donor lymphocytes were collected by Spectra Optia (Terumo BCT, Lakewood, CO, USA) based on the continuous flow principle by choosing CMNC mode through peripheral venous access by intravenous 16 G fistula needle. 220 ml of total volume was collected. According to the patient's weight (62 kg), the total dose was calculated. The total leukocyte count in the bag was 161,900/uL with CD 3 + count was 7.1%. The total dose collected was 40.7×10^6 CD3 + cells/kg. Out of 220 mL, first dose (3 mL) of DLI (with a count of 5.5×10^5 CD3 + cells/kg) was transfused to patient on day 31 of posttransplant without any unwanted adverse event with premedication with injection Avil and paracetamol. Again plan was made to look for any GVHD in subsequent days and to give second dose of DLI after 7 day of the first dose. No signs of GVHD occurred during post first dose of DLI but bone marrow showed increased blasts in March 2019, subsequently decision was taken, after explaining the prognosis to the patient in April 2019 for retransplant. Allogeneic peripheral blood stem cell transplant was done again with 6/10 HLA matched from daughter of the patient but the patient died of heart failure in July 2019.

Discussion

DLI is a new regimen for the patients with residual or relapsing disease for posttransplant hematological malignancies. DLI's first report was published by HJ Kolb in 1990. This report established the role of DLI in three patients with relapsed CML after allo-HSCT along with interferon-alpha obtaining a complete cytogenetic response.[2] Similar observations were obtained by other authors in CML patients.[6,7] Recent literature compared the utilization and toxicity of DLI with the use of tyrosine kinase inhibitor in relapsed CML patients and found that disease-free interval and decrease in relapse rate were much better after DLI.[8] The future trend may be T-cell-depleted stem cell graft followed by engraftment with DLI which is supported by the fact that the incidence of GVHD development is less after T-cell depletion.[9] Although most of the hematologically relapsed diseases have poor prognosis and options regarding treatment include chemotherapy, supportive care, re-transplant, and DLI from the original donor.[10] However, till now, there is no established standard approach to this clinical problem. We present two cases; both cases were different in diagnosis with different treatment protocols and DLI transfusion approaches. Most of the cases for which DLI therapy has been used in literature are different from our cases. Various studies have emphasized the role of DLI therapy in relapsed CLL with good clinical outcome.[11,12] However, in our experience, both the patients succumbed to the residual disease soon after the first dose of DLI and did not give us enough time to evaluate the effect of this treatment. This could be due to high tumor burden in residual or relapsed disease cases. Both the patients had received only the first dose of DLI which was unable to produce the GVL effect.

Although report by Ueda *et al*., mentioned that treatment with immunosuppressive regimen and DLI therapy can give promising results in terms of disease-free survival and lower relapse rate, especially in those treated without full hematologic relapse in patients with mixed malignancies.[13] Bachireddy and Wu explained the mechanism of action of donor lymphocytes in CML patients with predictive biological factors including low tumor burden in bone marrow and low number of CD3 + and CD8 + T cells in the peripheral blood. Their study suggested that there was an increased T-cell activation with an upregulation of programmed death 1 immune receptors after DLI.[2,14] The factors that had a notable impact on the outcome with DLI, were the extended duration between allo-HSCT and relapse (with a threshold of 1 year), the use of lower intensity/nonmyeloablative conditioning, age (with a threshold of 41 years), unfavorable cytogenetic profile, active acute GVHD, and the use of alternative donors (such as mismatched unrelated and cord blood).[2] Talking about toxicity, GVHD is the most frequent and expected complication with a median incidence of 40%.[2] This study contained only two cases with no significant results and that is not enough to determine the efficacy of DLI therapy. However, this is important in our setting to start using this treatment modality to treat various hematological malignancies with relapse. Critical factors for an effective DLI therapy that require further research are (1) level of tumor burden before initiation of DLI therapy; (2) tumor antigen-specific lymphocytes infusion; (3) using biological response modifiers to increase tumor immunogenicity; (4) controlled environment activity of the infused donor lymphocytes against normal host lymphocytes; (5) to increase expansion of clonal infused tumor-specific lymphocytes in the host; (6) to increase GVL effect; (7) to increase the role of the innate immune system (NK cells); and (8) to understand T-cell dose-response relationships which are not causing GVHD and inducing remission.

In conclusion, DLI can be an effective therapy but requires further clinical studies to evaluate its efficacy, especially in residual or relapsed hematological malignancies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in

the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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