Review Article

Donor lymphocyte infusion

An adaptive cellular immunotherapy for treatment of hematological malignancies

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ABSTRACT

The application of immunotherapy in the treatment of hematological malignancies is relatively new. Donor lymphocyte infusion (DLI) is a form of adaptive cellular therapy where the transfer of cells from immunocompetent donor to patient with cancer who relapsed after bone marrow transplantation results in destruction of the malignant cells. Hereby, we review the concepts, mechanisms, and results of the application of DLI in treatment of some hematological malignancies.

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Since its clinical introduction over 40 years ago, allogeneic bone marrow transplantation (BMT) has allowed escalation of the intensity of chemotherapy for cancer patients with disease resistance to conventional chemotherapy or those in relapse. Barnes et al[1] in 1956 and Mathe et al[2] in 1965 suggested that marrow graft might destroy the remaining leukemia cells after allogeneic BMT. Sullivan et al[3] analyzed the data of patients with acute leukemia who had allogeneic BMT in Seattle between 1970-1986. They showed that the incidence of recurrent leukemia was 28% in recipients who developed acute or chronic graft versus host disease (GVHD), and 52% in patients who never had GVHD. Several additional clinical observations provided indirect evidence in support of graft versus leukemia (GVL) effect in recipients of syngeneic BMT and in recipients of T-cell depleted BMT. Horowitz et al[4] supported an anti-leukemia effect independent of GVHD that is altered by T-cell depletion which provided evidence for a role of the immune system in controlling human cancers. The first published reports for direct evidence of GVL effect in humans originate from Kolb and his colleagues[5] when they demonstrated that the combination of interferon and buffy coat cells obtained by leukopheresis induced cytogenetic remission in 3 patients with relapsed chronic myeloid leukemia (CML) after allogeneic BMT. Although a variety of immune mechanisms play important roles in GVHD and GVL, data derived from both animal models and clinical experience suggested that both effects are primarily mediated by donor T-cells.[6] The complex immune machinery responsible for activation and clonal expansion of major histocompatibility complex (MHC) restricted effectors T-cells and non-MHC restricted effectors, natural killer cells (NK-cells), should be intact.[7] However, in fully MHC-matched donor, minor histocompatibility complex (mHC) differences expressed on the surface of tumor cells is presumably the main pathway of tumor lyses with donor lymphocyte infusion (DLI).[8] While variety of cells are infused the

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most prevalent cells are lymphocyte. Administration of both CD4+ and CD8+ T-cells can mediate GVL. However, some reports had indicated that depletion of CD8+ T-cells appears to be associated with reduction in GVHD without significant reduction in GVL effect.[9,10] Although the exact role of NK-cells as cytotoxic effectors in DLI needs more studies, BMT studies in mice indicated that the use of activated NK-cells after allogeneic BMT can prevent GVHD by the released immunosuppressive cytokines but at the same time may provide GVL effect.[11] Switch from mixed T-cell chimerism to all donor T-cells post DLI, had been demonstrated which suggests that effector cells may not be leukemia-specific, but rather allo-specific. Blazar et al[12] demonstrated in murine study the important role of CD28/B7 interaction in augmentation of GVL effect in DLI without adversely increasing GVHD. The role of cytokines in mediating effects in DLI is under investigation. Murine studies showed that IL-12 inhibits GVHD through interferon-gamma, and Fas-apoptosis mediated mechanisms, but preserves and activate the allogeneic immunocompetent donor lymphocytes.[13,14] The experience of infusion of IL-2 with DLI is limited. Some reports suggested that IL-2 appears to increase response rate to DLI in refractory or partial responders.[15,16] Observed differences in response to DLI in different leukemia had been attributed to inadequate antigen presentation to effector cells, defective co-stimulatory molecules, secretion of inhibitory cytokines or inappropriate expression of the Fas antigen.[17,18] In most of the clinical trials of DLI, peripheral blood lymphocytes are obtained by lymphopheresis from the same HLA-matched donor. Donor lymphocyte infusion was given initially as a single bulky dose. However, it was shown that the incidence of GVHD decreased if the DLI is given as an escalating dose regimen.[19] Number of studies had evaluated the dose of DLI at different levels starting from 1x 10^5/kg to 5x10^8/kg CD3+ T-cells. These studies had demonstrated that the incidence of GVHD was correlated with the dose of DLI, and higher cell doses were associated with faster response.[20] The chimerism status of T-cells at time of relapse is an important determinant of response to DLI, with the best result obtained when the percentage of T-cells from donor origin at time of DLI >40%.[21] Graft versus host disease (acute or chronic) represents the major toxicity of DLI and occurs in approximately 60-70% of DLI recipients with approximate overall mortality rate of 10%. Pancytopenia occurs in approximately 10% as a result of graft versus host activity of DLI on recipient hemopoiesis. Mackinnon et al[20] demonstrated that limiting the total number of allogeneic T-cells infused could reduce the incidence of GVHD. Giralt et al,[22] have suggested that manipulation of the DLI by depletion of CD8+ T-cells or clonal expansion of selective allogeneic T-cell induce anti leukemic effect but also effectively reduce the incidence of GVHD associated with DLI.

Donor lymphocyte infusion in relapsed chronic myeloid leukemia post allogeneic bone marrow transplantation. Clinical experience from patients with CML in chronic phase who received BMT from identical twin or T-cell depleted matched donor, in which an effective GVL effect was not present, showed increase in relapse rate. Kolb et al[23] and Collins et al,[24] in 2 large multi center studies have confirmed the successful application of DLI for the treatment of relapsed CML in chronic phase after allogeneic BMT with DLI. The use of different sensitive methods, allowed the detection of minimal residual disease (MRD) by qualitative and when positive, quantitative reverse transcripts polymerase chain reaction (Rt-PCR) or fluorescence in site hybridization (FISH). Several studies showed that PCR is a good predictor of early relapse. Radich et al[25] showed a total of 90 CML patients post allogeneic BMT for CML, that the estimated relapse rate with positive bcr-abl was carried out at 6 and 12 months post transplant was 62% compared with 3% for negative bcr-abl. Implementation of DLI for post BMT CML patients in molecular or cytogenetic relapse has been shown to be more effective than in advanced relapse (hematogenical relapse) and is less likely to induce marrow aplasia.[26]

The MD Anderson Cancer Center had evaluated a number of innovative programs to enhance GVL and separate the beneficial GVL effect from GVHD. Following high dose chemotherapy the leukemic mass is markedly reduced but usually not eliminated completely. In the absence of GVL effect the number of leukemic cells will increase with time. Adoptive immunotherapy either coming from the unmodified graft cells or by using interferon or lymphocyte infusion can control or prevent development of overt leukemia. The best result of DLI is seen in patients with CML with approximately 60-80% of patients achieving a complete hematological remission. The majority of these patients show cytogenetic and molecular remission. There seems to be a relationship between the stage of CML and the response to DLI. Collins et al[24] had reported less frequent complete remission in relapse of accelerated phase CML or blast crisis, with more DLI associated GVHD and pancytopenia.[24] Falkenburg et al[27] and his colleague suggested that in vitro cultured leukemia reactive T-cells can be successfully applied to treat accelerated phase CML after allogeneic BMT. No correlation has been found between response and the donor type.

Donor lymphocyte infusion in other hematological malignancies. The success of DLI in treatment of relapsed CML post BMT, raised the possibility of the potential role of this treatment to treat relapses post allogeneic BMT for other hematologic malignancies. Although a number of reports suggested beneficial effect of DLI in acute leukemia,[28-33] it has become clear that DLI is far less effective in acute leukemia than in CML. One multicenter study and another single center

experience of large number of patients, reported low response rate in acute leukemia of both myeloid (15-29%) and lymphoid (0-18%) types. [23,34] Donor lymphocyte infusion has been tried in treatment of multiple myeloma (MM) relapsing after allogeneic BMT. Verdonck et al[35] reported 2 different series of myeloma patients where DLI was effective in high percentage of patients relapsing after BMT.[35,36] The major toxicity in these patients was the high rate of severe acute and chronic GVHD. Another limitation with DLI in MM patients, is high rate of extramedullary relapse. The same group suggested that DLI could be used as maintenance to control the relapse.[37] Few reports showed the beneficial effect of DLI in post BMT relapses of other hematologic malignancies including lymphoma, myelodysplastic syndrome and myelofibrosis.[24,38,39] Prophylactic DLI has been proposed for hematological malignancies with a high incidence of relapse post BMT.

In summary, the beneficial effect of DLI in treatment of relapsed CML patients is beyond doubt; however, it is far less effective in treatment of other hematological malignancies.

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Title: Bone marrow and histochemical features of malignant histiocytosis

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Abstract

Objectives: To study the hematological and histochemical features of malignant histiocytosis cases diagnosed at King Khalid University Hospital. **Methods:** This is a retrospective analysis of malignant histiocytosis cases diagnosed by bone marrow examinations at the Hematology Section, Department of Pathology, King Khalid University Hospital. The medical records were evaluated for clinical symptoms and signs at presentation and peripheral blood count. Bone marrow aspirates and biopsies were reviewed for morphological features. Immunohisto-chemical staining of bone marrow trephine biopsies was performed. **Results:** Over 11 years, from February 1984 to March 1995, 4 cases of malignant histiocytosis were diagnosed at King Khalid University Hospital (KKUH) in Riyadh. They were 2 males and 2 females. The age range was 25-56 years. The predominant symptoms at presentation were fever and fatigability. All patients had hepatomegaly and 3 had splenomegaly. One patient had localized lymphadenopathy and skin involvement. Three patients had pancytopenia while one patient had anemia, thrombocytopenia and leukocytosis. Immunohistochemical stains on 3 cases showed positivity with all antitrypsin and lysozyme. One cast showed CDS (T cell marker) positivity by flow cytometry. The clinical, hematological and immunohistochemical staining findings are described.