Positive selection of CD34+ peripheral blood progenitor cells in patients with low-grade lymphoid malignancies and bone marrow involvement*


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Abbreviations: CLL, Chronic Lymphocytic Leukemia; Cy, Cyclophosphamide; PBSC, Peripheral Blood Progenitor Cell; PCR, Polymerase Chain Reaction; TBI, Total Body Irradiation; VP16, Etoposide.

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Abstract

Abstract. Purpose. 16 patients with low-grade lymphoid malignancies and bone marrow involvement were transplanted with selected CD34 positive Peripheral Blood Progenitor Cell (PBSC) prepared from autologous aphereses. Patient and methods. All but one patients were mobilized with a combination of chemotherapy (including high-dose cyclophosphamide and VP16 or Adriamycin, aracytin with cisplatyl) and recombinant human Granulocyte Colony-Stimulating Factor (rhG-CSF).

Results. A median of 3 (range, 1 to 9) aphereses yielded 15.35 x 10^6 CD34+ cells/kg (range, 4.45 to 70.88). A median of 5.01 x 10^6 adsorbed CD34+ cells/kg (range 2.01 to 24.13) was obtained after selection (median purity: 86%; range, 59-99%). The CD34 PBSC were infused one day after either one of two conditioning regimens: 11 patients received the association of cyclophosphamide (120 mg/kg) and TBI (8Gy), and 5 patients received the BEAM regimen. No recombinant hematopoietic growth factor was used after cell reinfusion. Median days to 0.5 x 10^9/l neutrophils and 50 x 10^9/l platelets were 13 (range, 9 to 18) and 16 (range, 11 to 35), respectively. The median number of red blood cell (RBC) unit transfusions was 4 (range, 0 to 10). The median number of platelet transfusions was 3.5 (range, 0 to 8). No individual received backup PBSC, nor required platelet transfusion beyond 3 months post-transplant. Conclusion. This study confirms the feasability of using blood CD34 cells to support hematopoietic recovery after myelo-suppressive or myelo-ablative regimens, in patients with low-grade NHL.

Advanced stage low grade non Hodgkin’s lymphomas remain an incurable disease with current conventional therapy. Although they are sensitive to a variety of chemotherapeutic agents, a continuous pattern of relapse is seen, and the quality and duration of subsequent responses progressively decreases [11, 30].

The use of high-dose therapy with autologous bone marrow or peripheral-blood stem-cell transplantation has increased for the treatment of malignancies (hematological and solid tumors) [18], and has been shown to be
curative for some patients with relapsed or refractory intermediate-grade and high-grade non-Hodgkin's lymphoma \cite{1, 28, 33}.

Recently published studies suggest that prolonged relapse-free survival can be achieved with high-dose therapy and autologous hematopoietic rescue for low-grade lymphoma (mostly follicular lymphoma), despite the fact that patients usually have bone marrow involvement \cite{4, 9}. However, gene marking studies suggest that tumor cells present in the graft are associated with relapse in patients with neuroblastoma, acute leukemia or chronic myeloid leukemia \cite{5, 12, 29}. Effective purging (in vitro treatment of grafts before reinfusion) could reduce or abolish the risk of infusing tumor cells. Several techniques are proposed to reduce tumor cell contamination in hematopoietic grafts, such as chemicals or monoclonal antibodies. In patients with advanced follicular non-Hodgkin's lymphoma treated with high-dose chemoradiotherapy and anti-B-cell monoclonal antibody purged autologous bone marrow transplantation, the disease-free survival was better in patients who have a negative polymerase chain reaction (PCR) for bcl-2/IgH rearrangement in purged marrows \cite{14}. Positive selection of CD34+ hematopoietic progenitor cells is a reasonable alternative for purging, because lymphoma cells do not express the CD34 membrane antigen. Two recent studies demonstrate the feasibility of using CD34+ cells from blood stem cells or bone marrow as a support of high-dose therapy in treatment of low-grade non-Hodgkin's lymphoma \cite{17, 27}, in addition to studies in patients with other types of malignancies \cite{3, 8, 20, 22, 23, 26, 31, 32}.

We here report our experience in 16 patients with a variety of low-grade lymphoid malignancies, all with bone marrow infiltration, who where transplanted with blood CD34+ cells selected with either one of two medical devices (CEPRATE-Cellpro: 4 patients or ISOLEX-Baxter: 12 patients).

**Patients and methods**

**Patient selection**

Sixteen subjects, 37 to 56 years old (median, 47), with NHL (15 patients) or Chronic Lymphoid Leukemia (CLL) (1 patient) were consecutively enrolled from June 1995 through November 1996. Diagnosis and classification of NHL, initial staging and status at time of transplant are described in Table 1. Ten patients had follicular lymphoma, 2 had lymphocytic NHL, 1 had mantle cell NHL, 1 had Sezary NHL, 1 small cleaved cell NHL and 1 B CLL. At diagnosis, all patients were stage IV, with detectable bone marrow infiltration. Inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and evidence of adequate hepatic, renal, and cardiac functions. Negative human immunodeficiency virus antibody testing was required before transplantation. The upper age limit for transplantation was 60 years.