Original Study

Feasibility and Efficacy of High-Dose Chemotherapy and Autologous Hematopoietic Cell Transplantation for HIV-Associated Lymphoma: A Single-Institution Experience

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Abstract

This retrospective study reporting the efficacy and safety of autologous hematopoietic cell transplantation (HCT) in 20 patients with HIV-associated lymphomas found that autologous HCT is feasible, with progression-free survival and survival of 65% and 70%, respectively.

Background: HIV-associated lymphomas (HAL) remain an important cause of morbidity and mortality in HIV patients, especially in the setting of treatment-refractory disease. Hematopoietic cell transplantation (HCT) is considered a curative option for patients with refractory HAL. **Patients and Methods:** We report the efficacy of autologous HCT in 20 patients with HAL [non-Hodgkin lymphoma = 14 (70%), Hodgkin lymphoma = 6 (30%)]. At the time of transplantation, the median peripheral blood $CD4^+$ count was 226 cells/μL. HIV virus load was undetectable in 14 (70%) of 20 patients. **Results:** The median follow-up of surviving patients was 47 months (range, 20-119 months). The median time to neutrophil engraftment was 11 days. The median progression-free survival and median overall survival have not been reached. At 4 years after transplantation, progression-free survival and overall survival were 65% and 70%, respectively. Six patients died from disease relapse or progression (n = 5) and infection (n = 1). Nonrelapse mortality was 0 and 5% at 100 days and 4 years after transplantation, respectively. **Conclusion:** Autologous HCT is an effective therapy for refractory/relapsed HAL with manageable toxicity, similar to non-HIV patients.

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Introduction

HIV infection is associated with an increased incidence of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), collectively known as HIV-associated lymphomas (HAL).[1-3] The advent of highly active antiretroviral therapy (HAART) altered the natural history of HIV infection by greatly suppressing HIV viremia, allowing numerical recovery of $CD4^+$ T cells and reestablishment of a functional immune status.[4,5] HAART allowed the introduction of intensive therapies for the treatment of HAL with results comparable to those seen in HIV-negative patients.[6-8]

HAL frequently presents with poor risk features, including advanced stage disease, extranodal disease, associated B symptoms, and intermediate—high or high-risk International Prognostic Index, and many patients experience relapsed disease.[7] Autologous hematopoietic cell transplantation (auto-HCT) is the standard of care for patients with chemotherapy-sensitive relapsed or high-risk lymphoma.[9] However, until relatively recently, HIV infection was considered a contraindication for auto-HCT. Since 2000, several centers in Europe and the United States have published small retrospective series on the feasibility of auto-HCT for HAL.[10-14] Two small prospective multicenter studies of auto-HCT for HAL were published as well.[15,16] These studies confirmed the feasibility and safety of this approach in these patients. Yet there is still a paucity of data, and auto-HCT remains limited to relatively few transplant centers with expertise in these cases.

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Here we present our single-institution experience using auto-HCT for treatment of patients with HAL.

Patients and Methods

This is a retrospective registry analysis of patients ≥ 18 years of age with HIV-related lymphoma who received an auto-HCT at the Moffitt Cancer Center and who provided informed consent for collection of data from January 1, 2005, until December 31, 2011. This study was approved by the institutional review board of the University of South Florida and was conducted in accordance with the Declaration of Helsinki. Data were extracted from the Moffitt Blood and Marrow transplantation database (BRAIN) and were supplemented with manual chart review whenever needed.

Treatment

All patients received high-dose therapy consisting of BEAM (carmustine 300 mg/m^2 day −6, etoposide 100 mg/m^2 twice a day on days −5 to −2, cytarabine 100 mg/m^2 twice a day on days −5 to −2, and melphalan 140 mg/m^2 on day −1) as previously described.[17] Rituximab 375 mg/m^2 on days +1 and +8 was provided to 2 NHL patients according to physician preference. A peripheral blood stem-cell graft of at least 2 × 10^6 CD34$^+$ cells/kg was infused on day 0. Supportive care, infection prophylaxis, and growth factor support followed approved standards of practice at our institution. All patients had an evaluation with an infectious diseases specialist, and HIV therapy and/or infection prophylaxis were modified according to individual needs. All patients received HAART and were allowed (and required) to continue therapy during the peritransplantation process unless there were medical reasons (ie, inability to tolerate oral intake due to grade 3/4 mucositis) that required therapy to be withdrawn.

Study Objectives, Definition of End Points, and Statistical Methodology

The primary objective of the study was to describe the experience at Moffitt Cancer Center regarding the use of auto-HCT in HAL. Primary end points were overall survival (OS) and progression-free survival (PFS). OS was defined as the time from HCT until death from any cause. PFS was defined as the time from HCT until disease progression or death. Secondary end points were relapse incidence, nonrelapse mortality (NRM), rate of infectious complications, ability to collect CD34$^+$ cells, impact of HIV infection, and causes of death. NRM was defined as cumulative incidence of death without disease relapse or progression. Disease response followed the revised response criteria for malignant lymphoma.[18]

Disease-related variables included histologic diagnosis, number of lines of chemotherapy, months to HCT, and disease relapse or progression.

Transplant-related variables included CD34$^+$ cells collected, number of collection days, time to neutrophil engraftment (defined as the first of 3 consecutive assessments on different days with an absolute neutrophil count ≥ 500/μL), time to platelet engraftment (defined as the first of 3 consecutive assessments on different days with a platelet count ≥ 20,000/μL without a platelet transfusion in the prior 7 days), concomitant infections in the peritransplantation period (defined by proven microbiologic isolation or infectious syndrome), and NRM (as previously defined).

HIV-related variables included virus load and CD4 counts before transplantation and at days +100, +180, and +360 after transplantation.

The baseline patient characteristics were summarized using descriptive statistics including mean, median, standard deviation, and range for continuous measures, and proportions and frequencies for categorical measures. The Kaplan-Meier method was used to estimate PFS and OS. Survival curves were compared by the log-rank test. *P* values were 2 sided, and the significance level was set at 5%. The 95% confidence intervals (CIs) were provided for survival probabilities.

Results

Twenty patients with HAL [non-HL = 14 (70%), HL = 6 (30%)] and treatable HIV infection underwent high-dose therapy with BEAM with or without rituximab followed by peripheral blood auto-HCT during study period. In 2 NHL cases, rituximab was administered as part of the preparative regimen. Patient-, disease-, and transplant-related characteristics are summarized in Table 1.

Filgrastim-based hematopoietic stem-cell mobilization and collection were successful in all patients. Median number of collected cells was 2.6 × 10^6 CD34$^+$ cells/kg (range, 2.0-4.5 cells/kg), and median number of days of collection was 1 (range, 1-4).

Median age at transplantation was 48 years (range, 35-61 years). The median follow-up for surviving patients was 47 months (range, 20-119 months). At transplantation, median peripheral blood CD4$^+$ count was 226 cells/μL (range, 41-761 cells/μL). HIV virus load was undetectable in 14 of 20 patients, with < 4 logs for all subjects. The median time to neutrophil and platelet engraftment was 11 days (range, 10-13 days) and 14 days (range, 13-176 days), respectively. Seven patients were transplanted while in first complete remission (CR), and 13 patients were transplanted after experiencing lymphoma-relapsed disease. For patients transplanted beyond the first CR, first progression occurred within 2 years (from original lymphoma diagnosis) in 7 cases (53.8%).

Responses and Survival

Objective response rate at day +100 after autografting in 17 evaluable patients was 77%, including 11 (65%) of 17 with CR and 2 (12%) of 17 with partial response.

Median PFS and OS were not reached. At 4 years after transplantation, PFS and OS were 65% (95% CI, 44-86) and 70% (95% CI, 50-90), respectively (Figures 1 and 2).

We also compared PFS and OS on the basis of HAL histology (HL vs. NHL). The 4-year PFS for HL was 67% (95% CI, 29-100), and for NHL it was 64% (95% CI, 39-89) (P = .90, Log-rank). The 4-year OS for HL was 67% (95% CI, 29-100), and for NHL it was 71% (95% CI, 48-95) (P = .83, Log-rank).

Relapse or Progression

Cumulative incidence of relapse or progression at 4 years after transplantation was 30% (95% CI, 15-59).

Toxicities and NRM

Nonhematologic toxicities consisted of mucositis in 8 (grade 1 = 3, grade 2 = 5), and enteritis in 13 patients (grade 1 = 2, grade