Biology of Blood and Marrow Transplantation 12:868-875 (2006)

1083-8791/06/1208-0001$32.00/0
doi:10.1016/j.bbmt.2006.05.006

A Study of a Reduced-Intensity Conditioning Regimen Followed by Allogeneic Stem Cell Transplantation for Patients with Hematologic Malignancies Using Campath-1H as Part of a Graft-versus-Host Disease Strategy

Tsiporah Shore, John Harpel, Michael W. Schuster, Gail J. Roboz, John P. Leonard, Morton Coleman, Eric J. Feldman, Richard T. Silver

Weill Medical College of Cornell University–New York Presbyterian Hospital, New York, New York

Correspondence and reprint requests: Tsiporah Shore, MD, FRCPC, FACP, New York Presbyterian Hospital-Cornell, 520 E 70th Street, Suite ST 341, New York, NY, 10021 (e-mail: tbs2001@med.cornell.edu).

Received February 10, 2006; accepted May 16, 2006

ABSTRACT

Nonmyeloablative transplantation (NMT) is intended to be less toxic than traditional allografts, but such regimens as fludarabine/melphalan still pose a significant risk of graft-versus-host disease (GVHD). We used Campath-1H in an attempt to reduce the risk of GVHD in NMT. Patients with hematologic malignancies suitable for allogeneic transplantation underwent transplantation using a regimen of fludarabine 30 mg/m^2 on days −5 to −2 (total, 120 mg/m^2), total body irradiation of 200 cGy on day −1, and Campath-1H 20 mg/day on days −7 to −3 (total dose, 100 mg). After loss of graft in 5 of the first 6 patients, the protocol was amended by decreasing the Campath-1H dose to 20 mg on days −4 and −3 and 10 mg on day −2 (total dose, 50 mg) for all subsequent patients. GVHD prophylaxis consisted of only cyclosporine, due to the immunosuppressive effect of Campath-1H. Patients received prophylactic acyclovir, fluconazole, and a quinolone. Other requirements included creatinine clearance ≥ 25 mL/min, diffusing capacity ≥ 45% of predicted, and cardiac ejection fraction ≥ 40%. Twenty-five patients with hematologic malignancies entered the study. The median age was 40 years (range, 26-71 years). Median time to engraftment (defined as a neutrophil count of 500 mm^3 and a platelet count of 20,000 mm^3 without platelet support on at least 2 days) was 19 days (range, 9-32 days). All patients who were treated after the amendment engrafted with 90%-100% donor cells by day 100 except for 2 early deaths. Acute GVHD developed in 40% of the patients. Patients who underwent related transplants developed GVHD after donor lymphocyte infusions for poor engraftment or relapse whereas those undergoing unrelated transplants developed GVHD de novo. Two patients (8%) developed chronic GVHD, and 48% had cytomegalovirus reactivation, which was easily managed medically. Nonrelapse mortality within the first 12 months was 12%; 32% of the patients survived at a median of 269 days. We conclude that Campath-1H, fludarabine, and melphalan is a reasonable preparative regimen for reduced-intensity transplantation with a low nonrelapse mortality, but that issues of GVHD remain problematic, due to either the use of donor lymphocyte infusions or the use of volunteer unrelated donors.

KEY WORDS

Reduced intensity transplantation • Campath • Hematological malignancies • Graft-vs-host disease

INTRODUCTION

Bone marrow transplantation was originally developed to allow replacement of diseased marrow by new stem cells after ablative chemotherapy with or without radiation therapy. In the last decade, it has become apparent that immunologic effects of transplanted cells, graft-versus-host disease (GVHD), and graft-versus-tumor effect play a large role in the eradication of malignancy in transplant recipients [1,2]. This has been evident because patients undergoing allogeneic transplantation have a lower recurrence rate that those

undergoing syngeneic transplantation; moreover, those patients who develop GVHD experience a lower relapse rate [3-5]. This effect has been most apparent in transplantation for chronic myeloid leukemia (CML), although it has also been noted for acute myeloid leukemia, multiple myeloma, and lymphoma. Furthermore, the use of donor lymphocyte infusions has been shown to achieve remission in patients who have relapsed posttransplantation, especially those with molecular relapse of CML [6,7].

Nonmyeloablative transplantation (NMT), which uses a less intense preparative regimen but is significantly immunosuppressive to allow donor engraftment, has permitted older patients and those with comorbid conditions to undergo transplantation for hematologic malignancies. Engraftment and GVHD have remained a major problem in NMT, often leading to other complications, including infection and multiorgan failure. Thus, appropriate GVHD prophylaxis is key in an attempt to balance the benefits and risks of these transplantations.

Traditional approaches to prevent GVHD have included immunosuppressive combinations of cyclosporine and methotrexate, cyclosporine alone, and tacrolimus and mycophenolate mofetil. A novel approach is to use Campath-1H (alemtuzumab) for the prevention of GVHD. Campath-1H is a humanized antibody against the CD52 antigen that is highly expressed on human lymphocytes and monocytes. This antigen is also expressed on dendritic cells [8]. These cells present recipient (host) antigens to donor cells, resulting in the induction of GVHD by the donor cells. Campath-1H is lympholytic and depletes the lymphocytes that cause GVHD. It also destroys the recipient antigen-presenting cells (dendritic cells), providing an additional mechanism for preventing GVHD. Campath-1H can be added to a cyclosporine and/or methotrexate regimen given posttransplantation.

The present protocol was designed to test the feasibility of a nonmyeloablative regimen with adequate immunosuppression to allow engraftment and prevent GVHD but permit a graft-versus-tumor effect. We report a prospective study of nonmyeloablative allogeneic transplantation for hematologic malignancies using Campath-1H as an in vivo agent of prophylaxis of GVHD followed by fludarabine and then by 200 cGy of total body irradiation (TBI).

METHODS

Patients and Donors

The Institutional Review Board of Weill Medical College of Cornell University approved this study. Written informed consent was obtained from all patients. Patients with hematologic malignancies suitable for therapy with allogeneic transplantation were eligible. Patients with acute leukemia required $< 10\%$ blasts in the marrow at the time of transplantation. An HLA-compatible donor, related or unrelated, allowing only 1 antigen mismatch was required. Molecular techniques were used for HLA-A, -B, -C, -DRB1, and -DQB1 loci (high-resolution) for HLA typing for patients and unrelated donors. For related donors, HLA typing was done by serologic techniques for HLA-A, -B, and -C and by high-resolution molecular techniques for HLA-DRB1 and -DQB1. Confirmatory testing was done for all patients and donors before the final donor selection. Donors were referred from the National Marrow Donor Program or other registries and were accepted for this protocol only if peripheral blood progenitor cells would be available. Patients had to be age 18 years or older; have a life expectancy of at least 12 weeks; have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; and had to be ineligible or unwilling to undergo a myeloablative standard allogeneic transplantation. Requirements also included a measured or calculated creatinine clearance of at least 25 mL/min, no active or uncontrolled infection or medical condition, no evidence of impaired hepatic function (defined as a bilirubin level > 1.5 times the upper limit of normal or an alanine aminotransferase or aspartate aminotransferase level > 5 times normal), satisfactory pulmonary function (with a diffusing capacity of the lung for carbon dioxide of at least 45% of predicted), and reasonable cardiac function (with an ejection fraction of at least 40% of predicted).

Preparative Regimen

The conditioning pretransplantation regimen consisted of fludarabine 30 mg/m^2 on days -5 to -2 (total, 120 mg/m^2), TBI 200 cGy on day -1, and Campath-1H 20 mg/day on days -7 to -3 (total, 100 mg). After loss of graft occurred in 5 of the first 6 patients who underwent this regimen, the protocol was amended to decrease the Campath-1H dose to 20 mg on days -3 and -4 and 10 mg on day -2 (total, 50 mg) for all subsequent patients. Dosing of all drugs was based on actual body weight. TBI (200 cGy) was administered using a linear accelerator without lung shielding on day -1. Allogeneic donor hematopoietic stem cells were infused on day 0 using standard donor infusion techniques. Completion of infusion of the stem cells was defined as day 0 for the purpose of engraftment and other posttransplantation events.

GVHD Prophylaxis and Therapy

In addition to the Campath-1H, cyclosporine A (Sandimmune; Novartis Pharmaceuticals) was started on day -1 at a dose of 3 mg/kg/day IV given in 2 divided doses. Oral cyclosporine was given as soon as it could be tolerated. Levels were monitored weekly to