A Phase II Trial of Fludarabine/Melphalan 100 Conditioning Therapy Followed by Allogeneic Hematopoietic Cell Transplantation for Patients With Lymphoma

Jung-Hee Lee, Je-Hwan Lee, Dae-Young Kim, Miee Seol, Young-Shin Lee, Young-Ah Kang, Mijin Jeon, Kyoo-Hyung Lee

Abstract

In our phase II trial, we investigated a conditioning regimen of fludarabine and melphalan 100 mg/m^2 for allogeneic hematopoietic cell transplantation for lymphoma. The 5-year overall survival rate was 40.4%, and the nonrelapse mortality rate was 21.6%. Patients with severe chronic graft-versus-host disease (GVHD) had greater overall survival than those with no, mild, or moderate chronic GVHD. Conditioning therapy with a lower dose of melphalan, combined with fludarabine, appears to be promising for allogeneic transplantation for lymphoma.

Background: Conditioning therapy with fludarabine and melphalan 140 mg/m^2 has been widely used before allogeneic hematopoietic cell transplantation (HCT) for lymphoma. A lower dose of melphalan might result in lower mortality and morbidity without compromising engraftment. **Patients and Methods:** In our phase II trial, we investigated a conditioning regimen of fludarabine (30 mg/m^2/day for 5 days on days −6 to −2) and melphalan (100 mg/m^2 on day −2). Antithymocyte globulin was added to fludarabine and melphalan for unrelated or mismatched familial donor HCT. The present study included 26 patients with lymphoma (B-cell in 10, T-cell in 11, and natural killer/T-cell lymphoma in 2). **Results:** An objective tumor response after HCT was observed in 18 patients (75.0%; complete in 14 and partial in 4). Acute and chronic graft-versus-host disease (GVHD) occurred in 23.1% and 55.0% of the assessable patients, respectively. The 5-year overall survival, nonrelapse mortality, progression-free survival, and event-free survival rate was 40.4%, 21.6%, 39.2%, and 30.8%, respectively. Donor lymphocyte infusions were given to 3 patients who had developed a relapse or progression after HCT, and 2 of whom had a showed partial response. Patients with severe chronic GVHD had greater overall survival than those with no, mild, or moderate chronic GVHD. **Conclusion:** Conditioning therapy with a lower dose of melphalan, combined with fludarabine, appears to be promising in allogeneic HCT for lymphoma. The Clinicaltrials.gov identification number for the present study is NCT00772811.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 11, 655-63 © 2015 Elsevier Inc. All rights reserved.
Keywords: Allogeneic, HCT, Lymphoma, Melphalan, Non-myeloablative

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a well-established, potentially curative treatment for patients with lymphoid malignancies. However, myeloablative HCT has been limited to young patients owing to the increased risk of treatment-related mortality (TRM) and graft-versus-host disease (GVHD) that occurs with increasing age.[1,2] Patients with lymphoma or multiple myeloma (MM) undergoing allogeneic HCT, although young, are heavily pretreated and do not tolerate myeloablative conditioning well. Many patients with lymphoid malignancies are not suitable for myeloablative allogeneic HCT. The introduction of a reduced-intensity conditioning (RIC) regimen extends the use of allogeneic HCT to these heavily pretreated patients and those with comorbidities.[3-5] High-dose melphalan has been reported to achieve a durable

Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Submitted: Apr 11, 2015; Revised: Jul 29, 2015; Accepted: Aug 24, 2015; Epub: Sep 03, 2015

Address for correspondence: Je-Hwan Lee, MD, Department of Hematology, Asan Medical Center, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea
E-mail contact: dr.jehwan.lee@gmail.com

2152-2650/$ - see frontmatter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clml.2015.08.087

remission in patients with acute leukemia and other hematologic malignancies, with little extramedullary toxicity.[6,7] Also, purine analogs have been shown to inhibit the repair of DNA after alkylator-induced damage.[8] Because of the synergistic antitumor effect of melphalan and purine analogs, conditioning with fludarabine and melphalan (Flu/Mel) has been one of the most commonly used RIC regimens for patients with hematologic malignancies.[9] Although many studies have used a melphalan dose of 140 mg/m^2,[10] no consensus has been reached regarding the optimal dose of melphalan in the Flu/Mel combination for RIC. It is, therefore, reasonable to assume that less-intense conditioning regimens, as long as they allow engraftment, will result in improved TRM. Thus, efforts have been made to find a lower dose of melphalan that is effective without compromising engraftment or disease control. In a study reporting the results of melphalan 100 mg/m^2 only as a conditioning regimen in 16 poor-risk myeloma patients with relapse after autologous HCT, 15 patients experienced myeloid engraftment, and the 1-year TRM was 19%.[11]

In the present report, we describe the results of a prospective clinical trial evaluating a less-intense conditioning regimen of fludarabine plus melphalan 100 mg/m^2 (Flu/Mel 100) in allogeneic HCT for lymphoma.

Patients and Methods

Patient Population

Patients with lymphoid malignancies, including non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), MM, and hemophagocytic lymphohistiocytosis, were included in the study protocol. However, those with lymphoma (NHL or HL) only were analyzed for the present analysis. All enrolled patients (aged 15-65 years) had an human leukocyte antigen (HLA)-identical or 1-locus mismatched sibling or unrelated or a mismatched (haploidentical) familial donor, Karnofsky performance scores of $\geq$ 50, adequate cardiac, pulmonary, hepatic, and renal function, and no significant infection or uncontrolled bleeding. Patients were excluded if they had any history of malignancy within the previous 5 years (except for curatively treated cervical carcinoma in situ or basal cell carcinoma of the skin) or if they had severe coexistent disease. Pregnant and lactating women were also excluded.

Chemosensitivity was determined according to the response to the previous chemotherapy regimen, which had been given $\leq$ 6 months before HCT. When a partial response or better response had occurred, the patients were designated as "chemosensitive."

The institutional review board of the Asan Medical Center approved the present study, and all patients provided informed consent in accordance with the Declaration of Helsinki before registration. The present study was registered at www.Clinicaltrials.gov (NCT00772811).

Conditioning Therapy and Transplantation Procedure

Conditioning therapy before infusion of allogeneic hematopoietic cells included fludarabine 30 mg/m^2/day for 5 consecutive days (days −6 to −2) and melphalan 100 mg/m^2 on day −2. Fludarabine and melphalan were intravenously infused over 30 minutes in 100 mL of 5% dextrose water. Melphalan was administered after completion of the fludarabine infusion. With unrelated or mismatched familial donors, rabbit antithymocyte globulin (Thymoglobulin; Sang-Stat Medical Corp, Lyon, France), 3 mg/kg, was given intravenously in 500 mL of normal saline on days −4, −3, and −2. Instead of rabbit antithymocyte globulin, 1 patient received horse antithymocyte globulin (Lymphoglobulin; Sang-Stat), 7.5 mg/kg/day on days −4 to −2, and 2 received 20 mg of alemtuzumab (MabCampath; Schering, Berlin, Germany) on day −7, because rabbit antithymocyte globulin was unavailable in Korea at that time.

Ciprofloxacin and acyclovir were administered for gut decontamination and viral prophylaxis, respectively. All cellular blood products were leukocyte depleted and irradiated before transfusion. Immunoglobulin (500 mg/kg) was administered intravenously on day −7 and then on days 30, 60, and 90 for matched sibling donor HCT or every other week until day 120 and monthly until day 180 for unrelated or mismatched familial donor HCT. Prophylactic therapy for GVHD consisted of cyclosporine plus methotrexate (MTX). Cyclosporine (1.5 mg/kg) was given intravenously every 12 hours starting on day −1 and then orally once oral intake became feasible. Intravenous MTX was administered at a dose of 15 mg/m^2 on day 1 and then at a dose of 10 mg/m^2 on days 3, 6, and 11. The dose of MTX on day 11 was omitted for patients undergoing matched sibling donor HCT. Hematopoietic cell grafts were infused on day 0 (for bone marrow) or days 0 and 1 (for granulocyte colony-stimulating factor [G-CSF] mobilized peripheral mononuclear cells) without T-cell depletion. All patients received intravenous G-CSF (450 μg, once daily), beginning on day 5 and until the peripheral blood absolute neutrophil counts were > 3000/μL.

Patient Monitoring

All patients were monitored for engraftment and post-transplant adverse events, including GVHD, hepatic sinusoidal obstruction syndrome (SOS), and infections. Hematologic and coagulation tests were measured as follows: complete blood counts, including reticulocyte counts daily; chemistry panels, including electrolytes and magnesium twice a week; and prothrombin time and activated partial thromboplastin time weekly.

The first day with an absolute neutrophil count of $\geq$ 500/μL for 3 consecutive days was recorded for bone marrow engraftment. The first day of unsupported platelet counts $\geq$ of 20,000/μL for 7 consecutive days was also recorded. Hematopoietic chimerism was evaluated in peripheral blood samples from the donor and recipient using polymerase chain reaction of short tandem repeats or amelogenin loci.[12] After transplantation, recipient peripheral blood samples for chimerism analysis were drawn monthly for the first 3 months, followed by every 3 months for an additional 1 to 2 years or until death. Complete donor chimerism was defined as the presence of only donor-type hematopoietic cells after allogeneic HCT. Mixed chimerism was defined as the coexistence of both recipient and donor hematopoietic cells after allogeneic HCT. Immune reconstitution was evaluated by analysis of the T-cell subsets, natural killer (NK) cells, and IgG, IgM, IgA, and IgE. These tests were repeated on days 30, 60, 90, 180, and 365.

For evaluation of the tumor response, appropriate radiologic and pathologic studies were performed after the patient had achieved stable engraftment and then at regular intervals. The tumor response was assessed in each patient using the appropriate criteria.[13]

Acute and chronic GVHD were diagnosed according to the clinical symptoms, laboratory test results, and, whenever possible, the histopathologic findings of the skin, oral mucosa, and