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Successful Engraftment with Fludarabine, Cyclophosphamide, and Thymoglobulin Conditioning Regimen in Unrelated Transplantation for Severe Aplastic Anemia: A Phase II Prospective Multicenter Study

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Antithymocyte globulin (ATG) has been used in severe aplastic anemia (SAA) as part of the conditioning regimen. Among the many kinds of ATG preparations, thymoglobulin had been found to be more effective for preventing graft-versus-host disease (GVHD) and the rejection of organ transplants. After the promising results of our preliminary study, we conducted a phase II prospective multicenter clinical trial using a fludarabine (Flu), cyclophosphamide (Cy), and thymoglobulin conditioning regimen to allow good engraftment in patients who underwent unrelated transplantation for SAA. Twenty-eight patients underwent bone marrow (N = 15) or mobilized peripheral blood (N = 13) transplantation from HLA-matched unrelated donors with Cy (50 mg/kg once daily intravenously (i.v.) on days −9, −8, −7, and −6), Flu (30 mg/m^2 once daily i.v. on days −5, −4, −3, and −2), and thymoglobulin (2.5 mg/kg once daily i.v. on days −3, −2, and −1). Donor-type hematologic recovery was achieved in all patients. The estimated survival rate (SR) was 67.9%, and all the events were treatment-related mortality (TRM), which included thrombotic microangiopathy (N = 2), pneumonia (N = 1), myocardiac infarction (N = 1), posttransplantation lymphoprolifarative disease (N = 3), and chronic GVHD-associated complications (N = 2). The SR of patients who received bone marrow (60.0%) was not different from that of patients who received mobilized peripheral blood (76.9%) ($P = .351$), but the SR of patients who received more than 15 units of red blood cells before transplantation (45.5%) was significantly lower than that of the other patients (82.4%) ($P = .048$). The Flu, Cy, and thymoglobulin conditioning regimen achieved promising results for successful engraftment, but the TRM was high. This study was registered at www.clinicaltrials.gov (NCT00737685), and now we are performing a new multicenter study (NCT00882323) to decrease the TRM by reducing the dose of Cy.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) with a matched related donor is a curative therapy for severe aplastic anemia (SAA), and cyclophosphamide (Cy)-based conditioning with or without antithymocyte globulin (ATG) is known to be optimal for HSCT with a matched related donor [1,2]. However, many patients have no appropriate related donor, and they need another treatment such as immunosuppressive therapy (IST) and/or stem cell transplantation (SCT) with an alternative donor. Transplantation with a matched unrelated donor (MUD) is associated with a high incidence of rejection, and the conditioning regimen for related donor transplantation is insufficient for HSCT with an MUD [3]. Two kinds of strategies have been developed to improve the engraftment by increasing the immunosuppressive activity of the conditioning regimen, but only 2 multicenter prospective studies have been conducted on this. One multicenter study in United State was conducted with adding total body irradiation (TBI) to Cy and ATG [4,5], and another was done by the European Group for Blood and Marrow Transplantation Severe Aplastic Anemia Working Party (EBMT-SAAWP) using the combination of fludarabine (Flu), Cy, and ATG [6].

These 2 studies included ATG, which has been commonly used for SAA as a part of the conditioning regimens. Among the many kinds of ATG, thymoglobulin (a rabbit-derived antithymocyte polyclonal antibody) is known to be more potent than the other available preparations, and it has been found to be more effective for preventing GVHD and the rejection of organ transplants [7-9]. Previously, we have reported the promising preliminary results of a Flu, Cy, and thymoglobulin conditioning regimen in matched unrelated transplantation for SAA [10]. After the promising results of our pilot study, the phase II prospective multicenter clinical trial was first conducted in Asia with a Flu, Cy, and thymoglobulin conditioning regimen to achieve good engraftment in unrelated transplantation for SAA.

PATIENTS AND METHODS

Patient and Donor Selection

From February 2006 to May 2008, 28 patients with SAA received HSCT from HLA matched unrelated donors at multicenter in Korea. Those patients, with the diagnosis of SAA, patients without prior HSCT, patients who had ECOG 0-2 performance status, patients who were free of significant functional deficits in major organs, and patients without any active viral infections or active fungal infection, were included in this study. Pregnant or nursing woman, patients with a malignant or nonmalignant illness that was uncontrolled or whose control had been jeopardized by complications of study therapy, patients with a psychiatric disorder that would preclude compliance, and patients with congenital AA including Fanconi anemia, were excluded. Transplantation performed at median 13 (3-210) months after the diagnosis of SAA. The clinical characteristics of patients are summarized in Table 1. The selection of donors was based on HLA serologic typing performed for class I antigens and HLA molecular typing for the DRB1 loci. HLA-A, -B, -C, and -DRB1 were confirmed by a high-resolution molecular method for all patients and donors. All patients received the designed conditioning regimen after obtaining informed consents from them or their guardians. This study was approved by the institutional review board of each center and registered at www.clinicaltrials.gov (NCT00737685).

Conditioning Regimen

The conditioning regimen was the same as that of the previous pilot study; the regimen was composed of Cy (50 mg/kg once daily intravenously [*i.v.*] on days −9, −8, −7, and −6), Flu (30 mg/m^2 once daily *i.v.* on days −5, −4, −3, and −2), and thymoglobulin (SangStat, Lyon, France and Genzyme, Cambridge, MA) (2.5 mg/kg once daily *i.v.* on days −3, −2, and −1) [10]. Patients received adequate hydration during the conditioning chemotherapy, and they also received mesna to prevent hemorrhagic cystitis. Unmanipulated bone marrow (BM) or mobilized peripheral blood (PB) harvest was infused on day 0 of the conditioning regimen.

Graft-versus-Host Disease (GVHD) Prophylaxis and Supportive Care

We allowed the use of each institution's protocol for GVHD prophylaxis. Patients received combination of cyclosporine (CsA) or tacrolimus (FK), and methotrexate (MTX), with or without posttransplant low-dose thymoglobulin (pATG: 1.25 mg/kg once daily *i.v.* on days 7, 9, and 11) (Table 2) [11,12]. Supportive care was done according to the guidelines for each institution.

Assess Engraftment and Toxicities

Myelogenous engraftment was defined as the first of 3 consecutive days with an absolute netrophil count (ANC) of 0.5 $\times$ 10^9/L, and platelet recovery was defined as the day the platelet count was 20 $\times$ 10^9/L without platelet transfusions. The BM was examined for morphology and cellularity at 1, 3, and 6 months, and 1 year after transplantation. Hematopoietic chimerism was evaluated by molecular analysis. Secondary graft failure was defined as engraftment followed by severe neutropenia (ANC $<$ 0.5 $\times$ 10^9/L) or the absence of donor cells in the BM or blood as demonstrated by