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The Saudi Experience in Fludarabine-Based Conditioning Regimens in Patients with Fanconi Anemia Undergoing Stem Cell Transplantation: Excellent Outcome in Recipients of Matched Related Stem Cells but Not in Recipients of Unrelated Cord Blood Stem Cells

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Low-dose cyclophosphamide (CY) is now considered the backbone of many of the conditioning regimens used in patients with Fanconi anemia undergoing allogeneic stem cell transplantation (SCT). To reduce the risk of rejection and improve results, CY is usually used in combination with other agents/modalities, such as antithymocyte globulin (ATG), busulfan, radiation, and, more recently, fludarabine (Flu). In this study, we used a uniform Flu-based conditioning regimen (ie, CY, Flu, ATG) in 26 pediatric patients with Fanconi anemia undergoing SCT. The median patient age at the time of SCT was 7.8 years, and the stem cell source was an HLA-matched related donor in 19 patients and partially HLA-matched unrelated cord blood in 7 patients. The CY, Flu, ATG regimen was well tolerated overall, with a remarkably low incidence of graft-versus-host disease and hemorrhagic cystitis. All 19 patients in the matched related donor group engrafted and were alive and transfusion-independent at a median follow-up time of 19 months, compared with only 2 of 7 patients in the unrelated cord blood group. We conclude that the combination of CY, Flu, and ATG in the doses used in this study is well tolerated, and that the proclaimed positive effect of adding Flu to the conditioning regimens of patients with Fanconi anemia undergoing SCT is most pronounced in recipients of HLA-matched related transplants. Its value in unrelated cord blood transplantation probably depends on other factors, such as the degree of HLA matching and the cell dose.

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INTRODUCTION

Fanconi anemia (FA) is highly prevalent in the Kingdom of Saudi Arabia, due mainly to a high rate of consanguinity and interrelated marriages. As a result, more than 120 allogeneic stem cell transplantations (SCTs) have been performed in Saudi patients with FA over the last 30 years at King Faisal Specialist Hospital and Research Center, located in the capital city of Riyadh [1-4]. The optimal conditioning regimen for patients with FA is a matter of debate, but low-dose cyclophosphamide (CY) has been accepted as the backbone of many regimens used in these patients. To optimize results, CY has been traditionally used in combination with other agents, such as busulfan, antithymocyte globulin (ATG), and low-dose radiation [1-9]. Fludarabine (Flu) has emerged over the last 2 decades as a potent immunosuppressive agent and is being increasingly used in conditioning regimens for patients with FA and others [10-17]. In this prospective study, we report our experience in a single center using a uniform Flu-based conditioning regimen in 26 patients with FA undergoing SCT.

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PATIENTS AND METHODS

This prospective study was approved by the Research Advisory Council and the Ethics Committee at King Faisal Specialist Hospital and Research Center. Informed consent was obtained for all participants.

Patients

Between October 2007 and August 2010, 26 patients with bone marrow failure due to FA were referred to the Pediatric SCT Section at King Faisal Specialist Hospital and Research Center for allogeneic SCT. After referral, all patients had undergone chromosomal breakage studies with mitomycin-C and/or diepoxybutane to confirm the diagnosis of FA. All patients underwent morphological and cytogenetic examination of the bone marrow before SCT, and all demonstrated some degree of bone marrow aplasia with no myelodysplasia or leukemia. Cytogenetic studies were normal in 20 patients, and 1 patient had monosomy 7.

The study group comprised 11 females and 15 males, with a median age at the time of SCT of 7.8 years (range, 1.4-12.9 years). Nineteen patients received stem cells from an HLA-matched related donor (group A), and 7 patients received partially HLA-matched unrelated cord blood (group B). Engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count of $>500 \times 10^6$/L and was further confirmed by donor–recipient chimerism studies at least once during the first 3 months post-SCT, then at 6 months and 1 year post-SCT using a short tandem repeat method on peripheral blood (granulocytes and lymphocytes). A total of 16 short tandem repeat loci were analyzed.

Conditioning Regimen

All patients were conditioned with CY 5 mg/kg i.v. on days −5, −4, −3, and –2; Flu 30 mg/m^2/dose i.v. on days −6, −5, −4, −3, and −2; and rabbit ATG (Fresenius) 5 mg/kg i.v. on days −5, −4, −3, and −2. Mesna was given to all patients during administration of the conditioning regimen to prevent hemorrhagic cystitis.

GVHD Prophylaxis

GVHD prophylaxis was with cyclosporine at standard doses. In addition, all patients undergoing SCT before February 2009 (a total of 14 patients; 9 in group A and 5 in group B) received Fresenius ATG 2.5 mg/kg i.v. on days +1, +3, +6, and +11; the post-SCT ATG was later removed from the study in view of the noted low incidence of GVHD. Cyclosporine was tapered and discontinued by 6 months post-SCT unless the patient developed GVHD. The patients in group B also received methylprednisolone 1 mg/kg i.v. from day +5 to day +20, which was tapered over 2 weeks if no GVDH developed.

Donors

The 19 patients in group A received a transplant from a related donor (16 from fully HLA-matched siblings, 2 from fully HLA-matched fathers, and 1 from a single antigen HLA-mismatched sibling on the A locus). All related donors had documented negative chromosomal breakage study results. Harvested bone marrows were not manipulated. The median CD34$^+$ cell count was 6.1×10^6/kg of recipient body weight (range, 1.6-24.6 $\times 10^6$/kg), and the median dose of total nucleated cells (TNCs) was 3.5×10^8/kg of recipient body weight (range, 0.9-69.3 $\times 10^8$/kg). The 7 patients in group B received partially HLA-mismatched single unrelated cord blood units; 5 received single-antigen–mismatched units, and 2 received 2-antigen–mismatched units. In these patients, the median CD34$^+$ cell count was 3.2×10^5/kg (range, 0.3-6.5 $\times 10^5$/kg), and the median total TNC dose was 8×10^7/kg (range, 3.6-17.3 $\times 10^7$/kg).

Supportive Care

All patients were treated in high-efficiency particulate air–filtered rooms and were isolated until engraftment. All patients received i.v. immunoglobulin every 2 weeks at a dose of 500 mg/kg from day −4 up to day +90, as well as acyclovir 45 mg/kg/day from day −3 to day +28. All patients also received fluconazole therapy from day 0 until engraftment. No prophylactic ganciclovir was given, and cytomegalovirus (CMV) status was monitored by weekly polymerase chain reaction analysis; preemptive therapy was started in patients with positive results. All blood products were leukocyte-filtered and irradiated. All 7 patients in group B and 16 of the 19 patients in group A received granulocyte colony-stimulating factor (GCSF) post-SCT.

RESULTS

Engraftment

All 19 patients in group A engrafted. The median time to engraftment was 13 days (range, 11-26 days). The 3 patients who did not receive GCSF also engrafted promptly, at 16, 12, and 16 days post-SCT. The median time to achieve red blood cells transfusion independence was 15 days (range, 9-46 days), and the median time to a self-sustained platelet count of 20×10^9/L was 19 days (range, 14-47 days). On last follow-up, 18 patients had 100% donor cells in the myeloid line, and 1 patient had 80% donor cells; in the lymphoid line, donor cell chimerism ranged between 56% and 100% (median, 100%).