Hematopoietic Stem Cell Transplantation in Children with Refractory Cytopenia of Childhood: Single-Center Experience Using High-Dose Cytarabine Containing Myeloablative and Aplastic Anemia Oriented Reduced-Intensity Conditioning Regimens

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A B S T R A C T

Refractory cytopenia of childhood (RCC) is the most common subtype of myelodysplastic syndrome in children, and the clinical course of RCC is heterogeneous. A certain proportion of RCC patients need allogeneic hematopoietic stem cell transplantation (HSCT); however, data on HSCT outcomes are not abundant, and the optimal intensity of a preparative conditioning regimen remains uncertain. In this study, we evaluated the outcomes of HSCT in 24 patients with RCC. Eleven patients received myeloablative conditioning (MAC) consisting of high-dose cytarabine, cyclophosphamide, and either total body irradiation (TBI) or busulfan. Nine patients (38%) received a reduced-intensity conditioning (RIC) regimen; of these, 7 received low-dose TBI and cyclophosphamide (200 mg/kg) with or without antithymocyte globulin or fludarabine, and 2 patients received low-dose TBI, fludarabine, and melphalan (140 mg/m^2). The remaining 4 patients had disease progression before HSCT and received the MAC regimen. With a median follow-up of 91 months (range, 6 to 263), the probability of overall survival at 5 years was 81.1% (95% CI, 57.0 to 92.5). The 5-year overall survival for the 15 patients who received MAC was 73.3% (95% CI, 43.6 to 89.1), and all 9 patients with RIC are alive without any events. Further study is needed to evaluate the efficacy of RIC for children with RCC with an expectation for reduction of late effects such as growth retardation and infertility.

INTRODUCTION

Refractory cytopenia of childhood (RCC) is the most common subtype of myelodysplastic syndrome (MDS) in children, characterized by persistent cytopenia with <5% blasts in the bone marrow (BM), <2% blasts in the peripheral blood, and dysplastic changes in 2 or 3 lineages or exceeding 10% in 1 single cell line [1-4]. Some patients with RCC without cytogenetic abnormalities may experience a long, stable clinical course of the disease. For patients without a transfusion requirement, severe neutropenia, or infections, careful observation (watch and wait) is the reasonable treatment strategy. In contrast, hematopoietic stem cell transplantation (HSCT) is the treatment of choice for patients with monosomy 7 or complex karyotypes because of the risk of progression to advanced MDS [3,4]. HSCT can also be recommended for patients with other karyotypes if a suitable donor is available [2,4]. Practically, some RCC patients need HSCT for the reason of transfusion dependency or severe neutropenia and/or infection irrespective of the presence of cytogenetic abnormalities.

Reported disease-free survival rates after HSCT in patients with MDS range between 30% and 75% in previous reports, most of which included patients with various subtypes of MDS, ranging from RCC to advanced MDS, juvenile myelomonocytic leukemia, and therapy-related MDS [5-10]. However, limited data are available on the outcome of HSCT focusing on patients with RCC [3,11]. Therefore, little is known regarding treatment-related factors associated with transplant outcome, such as the optimal intensity of conditioning regimen for patients with RCC. In 2007, Strahm et al. [11] reported that a reduced-intensity conditioning (RIC) regimen consisting of fludarabine (Flu), thiotepa, and antithymocyte globulin achieved favorable outcomes of HSCT in children with hypocellular refractory cytopenia without chromosomal abnormality. In this study, we report the outcomes of HSCT in 24 pediatric patients with RCC after conditioning regimens of myeloablative conditioning (MAC) with high-dose cytarabine, cyclophosphamide (CY), and total body irradiation (TBI) or busulfan (BU) and RIC with low-dose TBI and CY or melphalan (Mel).

METHODS

Patients

Twenty-four patients with RCC aged < 19 years at diagnosis received HSCT at the Department of Pediatrics, National Kyushu Cancer Center between April 1991 and May 2014. Fifteen patients were diagnosed with refractory anemia or refractory cytopenia with multilineage dysplasia based on the French-American-British classification or World Health Organization 1999 criteria [12,13]. All 24 patients were compatible with the classification of RCC according to the World Health Organization 2008 criteria [4,14].

BM biopsy to evaluate marrow cellularity was performed in 19 patients (79%). Patients who had received previous HSCT, those with inherited BM failure disorder, such as Fanconi anemia or dyskeratosis congenita, or those with treatment-related MDS were excluded. The most frequent reasons for recommendation of HSCT were transfusion dependency in 14 patients, followed by monosomy 7 in 4, and disease progression to advanced MDS in 3.

All patients or their parents provided written informed consent for HSCT. This retrospective study and patient data use was approved by the institutional review board of the National Kyushu Cancer Center. Patient characteristics are shown in Table 1.

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Table 1
Patient Characteristics

Number of patients	24
Median age at HSCT, yr (range)	10 (3-21)
Median time from diagnosis to HSCT, mo (range)	13.5 (3-95)
Sex	
Male	14
Female	10
Cytogenetics at diagnosis	
Normal	14
Monosomy 7	5
Trisomy 8	2
Structural complex	1
Other abnormalities	1
Unknown	1
Disease progression before HSCT	
Yes	4
No	20
Year of HSCT	
1991-2000	8
2001-2014	16
Donor	
MSD-BM	8
MUD-BM	12
UCB	4
Conditioning regimen	
BU/CA/CY	8
TBI/CA/CY	5
TBI/Others	2
RIC	9
GVHD prophylaxis	
CsA based	11
TaC based	13

MSD indicates matched sibling donor; MUD, matched unrelated donor; UCB, unrelated cord blood; CA, cytarabine; CsA, cyclosporine; Tac, tacrolimus.

The study included 14 male and 10 female patients, with a median age of 10 years (range, 3 to 21) at the time of HSCT. Before HSCT, 18 patients had neutropenia (absolute neutrophil count $< 1.0 \times 10^9$/L), and 12 patients had ANC $< .5 \times 10^9$/L. The number of transfusions for RBCs and/or platelets before HSCT was $>$ 10 times in 20 patients and $>$20 times in 17 patients. Four patients experienced disease progression to advanced MDS (refractory anemia with excess blast in 3 patients and acute myeloid leukemia in 1 patient) before HSCT at a median of 11 months (range, 3 to 17) from diagnosis. Cytogenetic analysis at diagnosis was available in 23 patients, including normal karyotype (n = 14), monosomy 7 with or without additional aberrations (n = 5), structurally complex karyotype (defined as more than 3 chromosomal aberrations in the presence of at least 1 structural aberration, n = 1), or other abnormalities such as trisomy 8 (n = 3). Sixteen patients received immunosuppressive therapy, including steroid therapy in 4 patients, cyclosporine A in 2 patients, and antithymocyte globulin in combination with cyclosporine A in 10 patients as the initial treatment for RCC. Two patients with disease progression received acute myeloid leukemia–oriented chemotherapy.

Transplantation Procedures

Until 2006, 11 patients received the MAC regimen consisting of high-dose cytarabine (12 g/m^2), CY (120 mg/kg), and either TBI ($\geq$12 Gy) or BU (Figure 1). Another 4 patients with disease progression before HSCT received the MAC regimen, which was determined at the treating physician's discretion. Since 2007, the RIC regimen has been applied to patients with RCC, and a total of 9 patients (38%) received RIC. Six patients with hypocellular marrow without monosomy 7 or a structural complex karyotype received low-dose TBI (3 Gy) and CY (200 mg/kg) with antithymocyte globulin or Flu. Two patients with normocellular marrow received low-dose TBI (3 or 4 Gy), Flu (125 mg/m^2), and Mel (140 mg/m^2). One patient with hypocellular marrow who underwent HSCT in 2004 received RIC with TBI (3 Gy) and CY (200 mg/kg), because he was initially diagnosed with aplastic anemia. Transplantation characteristics of these 9 patients who received the RIC regimen are shown in Table 2.

Cyclosporine A with or without short-term methotrexate was used as prophylaxis for acute graft-versus-host disease (GVHD) in 11 patients; tacrolimus was used with or without short-term methotrexate in 13 patients. Stem cell sources were BM for 20 patients and cord blood for 4 patients. Eight patients received BM transplantation from an HLA-matched sibling donor, 12 patients received BM transplantation from an HLA-matched unrelated donor, and 4 patients received unrelated cord blood stem cell transplantation.

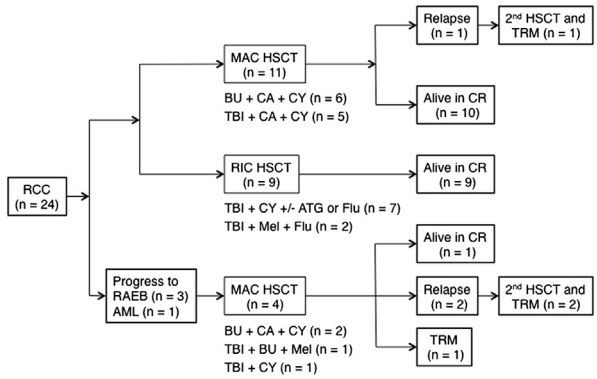

Figure 1. Outcomes of HSCT in 24 patients with RCC. After the first HSCT, treatment-related death was observed in 1 patient who had disease progression before HSCT. No patient who received RIC relapsed, and 1 of 11 patients who received MAC without disease progression relapsed after HSCT. One of 4 patients with disease progression before HSCT is alive in remission.

Definitions and Statistical Analysis

Engraftment was defined as the first day when the absolute neutrophil count reached .5 $\times$ 10^9/L for 3 consecutive days. Both the platelets and reticulocytes were considered to be recovered when they reached counts $>$20 $\times$ 10^9/L and $>$1%, respectively, without transfusion support. Graft failure was defined as a lack of engraftment irrespective of donor chimerism. A chimerism analysis was performed using BM samples when engraftment was observed. Fluorescence in situ hybridization with sex chromosomes for sex-mismatched HSCT and short tandem repeat PCR for sex-matched HSCT was carried out. Acute and chronic GVHD were diagnosed and classified according to previously reported criteria [15,16]. Overall survival (OS) was calculated as the time from HSCT to death or last follow-up. Probability of survival was estimated by the Kaplan-Meier method with the corresponding 95% confidence intervals (CI). Univariate analysis of OS was performed using the log-rank test. All statistical analyses were performed using SPSS version 19 (SPSS Co., Tokyo, Japan).

RESULTS

Engraftment, GVHD, and Complications

Twenty-three of 24 patients (96%) were engrafted on a median of day 17 (range, 11 to 49). Graft failure occurred in 1 patient who had disease progression to refractory anemia with excess blast before unrelated cord blood stem cell transplantation. Thereafter, he had autologous recovery and relapsed. Platelet and reticulocyte recovery was achieved on a median of day 27 (range, 17 to 75) in 21 assessable patients and day 25 (range, 17 to 41) in 22 assessable patients, respectively. The data on 16 patients were available for chimerism analysis, and all 16 patients showed complete donor chimerism when engraftment was observed. All 9 patients who received the RIC regimen engrafted with complete donor chimerism.

Acute GVHD of grades II to III occurred in 12 of 23 assessable patients including 8 of 14 patients (57%) with MAC and 4 of 9 (44%) with RIC. No grade IV acute GVHD occurred. Chronic GVHD occurred in 5 of 21 assessable patients. In 9 patients with RIC, only 1 (11%) developed mild chronic GVHD limited to skin, whereas 4 of 12 patients (33%) with MAC developed chronic GVHD, including 3 with the severe type. Within 100 days after HSCT, viral infections were the most frequent complication. In patients with MAC, 9 patients (60%) developed cytomegalovirus infection, including 8 patients with cytomegalovirus reactivation in the blood and 1 with interstitial pneumonia. In patients with RIC,