Hematopoietic Stem Cell Transplantation in Children and Young Adults with Secondary Myelodysplastic Syndrome and Acute Myelogenous Leukemia after Aplastic Anemia

Ayami Yoshimi [1,*], Brigitte Strahm [1], Irith Baumann [2], Ingrid Furlan [3], Stephan Schwarz [4], Andrea Teigler-Schlegel [5], Joachim-Ulrich Walther [6], Brigitte Schlegelberger [7], Gudrun Göhring [7], Peter Nöllke [1], Monika Führer [6], Charlotte M. Niemeyer [1]

[1] *Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, University of Freiburg, Freiburg, Germany*
[2] *Department of Pathology, Boeblingen Hospital, Clinical Centre South West, Boeblingen, Germany*
[3] *Department of Pediatrics and Adolescent Medicine, University Hospital Ulm, Ulm, Germany*
[4] *Department of Pathology, University Medical Center Erlangen, Erlangen, Germany*
[5] *Department of General Pediatrics, Hematology and Oncology, Children's University Hospital, Giessen, Germany*
[6] *Dr von Haunersches Kinderspital, Children Hospital of the Ludwig-Maximilians-University of Munich, Munich, Germany*
[7] *Institute of Cell and Molecular Pathology, Hannover Medical School, Hannover, Germany*

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A B S T R A C T

Secondary myelodysplastic syndrome and acute myelogenous leukemia (sMDS/sAML) are the most serious secondary events occurring after immunosuppressive therapy in patients with aplastic anemia. Here we evaluate the outcome of hematopoietic stem cell transplantation (HSCT) in 17 children and young adults with sMDS/sAML after childhood aplastic anemia. The median interval between the diagnosis of aplastic anemia and the development of sMDS/sAML was 2.9 years (range, 1.2 to 13.0 years). At a median age of 13.1 years (range, 4.4 to 26.7 years), patients underwent HSCT with bone marrow (n = 6) or peripheral blood stem cell (n = 11) grafts from HLA-matched sibling donors (n = 2), mismatched family donors (n = 2), or unrelated donors (n = 13). Monosomy 7 was detected in 13 patients. The preparative regimen consisted of busulfan, cyclophosphamide, and melphalan in 11 patients and other agents in 6 patients. All patients achieved neutrophil engraftment. The cumulative incidence of grade II-IV acute graft-versus-host disease (GVHD) was 47%, and that of chronic GVHD was 70%. Relapse occurred in 1 patient. The major cause of death was transplant-related complication (n = 9). Overall survival and event-free survival at 5 years after HSCT were both 41%. In summary, this study indicates that HSCT is a curative therapy for some patients with sMDS/sAML after aplastic anemia. Future efforts should focus on reducing transplantation-related mortality.
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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) from a HLA-matched sibling donor is the currently recommended first-line treatment in young patients with aplastic anemia [1], associated with an overall survival (OS) rate of >90% in children [2,3]. This approach is limited by the unavailability of such donors for the majority of patients, however. For patients without a matched sibling donor, immunesuppressive therapy (IST) comprising antithymocyte globulin (ATG) and cyclosporine A (CSA) has been the standard therapy, restoring hematopoiesis in approximately two-thirds of patients [2-6]. Currently, long-term survival after IST is approximately 80% to 90% in children [2,3,7,8]. Nevertheless, IST remains a suboptimal option; blood counts often remain subnormal, and approximately one-third of treatment responders experience relapse at a later time point. Moreover, a small number of patients develop serious complications, such as secondary myelodysplastic syndrome/acute myelogenous leukemia (sMDS/sAML) or paroxysmal nocturnal hemoglobinuria [5,6,8].

Previous studies have shown that sMDS/sAML develops in 2% to 26% of patients with aplastic anemia after IST and is associated with a very poor prognosis [5,8-15]. HSCT is currently the only curative approach for such patients, but to our knowledge, efficacy has not yet been systematically evaluated. Here we report on the outcomes of HSCT in 17 children and young adults with sMDS/sAML after aplastic anemia in childhood.

METHODS

Study Cohort

This retrospective study included 17 German children and young adults (13 males and 4 females) who had undergone HSCT for sMDS/sAML after IST for aplastic anemia in childhood. Among 287 children (age <18 years) who underwent IST in the German Speaking Society of Pediatric Oncology and Hematology (GPOH) SAA-94 study (November 1993 to September 2011) [3], 14 developed sMDS/sAML. In the European Working Group of Myelodysplastic Syndrome in Childhood (EWOG-MDS) studies (EWOG-MDS 98, January 1997 to December 2006; EWOG-MDS 2006, January 2007 to September 2011; ClinicalTrial.gov identifier: NCT00662090), an additional 5 German children with sMDS/sAML after aplastic anemia were identified. Of these 19 patients, 17 had undergone HSCT and were included in this study. Study approvals were obtained from the Institutional Review Boards of each participating institution. Written informed consent was provided by each patient's parents in accordance with the Declaration of Helsinki.

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* Correspondence and reprint requests: Ayami Yoshimi, Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, University of Freiburg, Mathildenstrasse 1, 79106 Freiburg, Germany.
E-mail address: ayami.yoshimi@uniklinik-freiburg.de (A. Yoshimi).
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Table 1
Patient Characteristics

ID	Age at Diagnosis of AA, yr	Sex	AA Etiology	IST	Duration of G-CSF, mo	Overall Response to IST and Relapse	Interval from AA to MDS/AML, yr	Karyotype at Diagnosis of MDS/AML	Highest FAB Subtype before HSCT	Pre-HSCT Complications
1	8.6	M	Idiopathic	ATG/CSA	3	PR	3.0	Monosomy 7	AML	Disseminated candidiasis
2	14.5	M	Idiopathic	ATG/CSA	15	NR	1.5	Monosomy 7	RA	
3	8.9	F	Idiopathic	ATG/CSA	24	PR	2.2	Monosomy 7	RAEB	
4	8.4	F	Idiopathic	ATG/CSA	30	NR	2.6	Monosomy 7	AML	Sepsis
5	9.8	M	Idiopathic	ATG/CSA	0	PR, relapse	2.3	Monosomy 7	RA	
6	3.2	M	Hepatitis*	ATG/CSA	26	NR	3.3	Monosomy 7	AML	Invasive aspergillosis
7	6.7	M	Idiopathic	ATG/CSA	8	PR	2.6	Monosomy 7	RA	
8	13.0	F	Idiopathic	ATG/CSA	5	PR	2.9	Monosomy 7	RA	
9	11.1	M	Idiopathic	ATG/CSA	1	PR	4.0	Monosomy 7	RA	
10	10.1	M	Idiopathic	ATG/CSA	4	PR, relapse	11.1	Monosomy 7	RAEB	
11	3.9	F	Idiopathic	ATG/CSA	24	NR	1.6	Monosomy 7†	RA	
12	2.8	M	Idiopathic	ATG/CSA	1	NR	1.2	Monosomy 7	RAEB	Gastrointestinal bleeding
13	14.5	M	Idiopathic	ATG/CSA	3	CR, relapse	10.9	Monosomy 7	CMML (17% BM blasts)	
14	12.6	M	Idiopathic	CSA	19	CR	6.2	del (7)(q22)	AML	PNH
15	13.2	M	Idiopathic	ATG	0	PR	13.0	Normal	CMML (13% BM blasts)	
16	8.8	M	Hepatitis	ATG/CSA	12	CR	4.2	Normal	RAEB	
17	12.5	M	Idiopathic	ATG/CSA	6	PR	8.6	Normal	AML	Multiple abscess, pulmonary aspergillosis

AA indicates aplastic anemia; G-CSF, granulocyte colony-stimulating factor; CR, complete response; PR, partial response; NR, nonresponse; AML, acute myelogenous leukemia; RA, refractory anemia; CMML, chronic myelomonocytic leukemia; RAEB, RA with excess blasts; PNH, paroxysmal nocturnal hemoglobinuria.
* This patient underwent liver transplantation.
† This patient had constitutional mosaic trisomy 21. Monosomy 7 was detected only in the subpopulation of hematopoietic cells with trisomy 21.

Diagnosis of Aplastic Anemia and Immunosuppressive Therapy

Aplastic anemia was diagnosed as pancytopenia, hypoplastic bone marrow (BM) without dysplasia, as described previously [3]. The diagnosis was confirmed by a central review of the BM biopsy specimens by reference pathologists in 13 patients. The karyotype was normal in 10 patients, and metaphase analysis data were not available for 7 patients. In the latter patients, negative results of fluorescent in situ hybridization for monosomy 7 and trisomy 8 were available for 5 patients. The median age at diagnosis was 8.9 years (range, 2.8 to 14.5 years) (Table 1). Fanconi anemia and other inherited BM failure syndromes had been excluded in all patients. One patient had a constitutional trisomy 21 mosaic with no clinical signs of Down syndrome (patient 11).

Fifteen patients received an IST regimen with horse ATG (15 mg/kg/day × 8 days; Lymphoglobulin; Genzyme, Cambridge, MA) and CSA described by the GPOH-SAA-94 study as reported previously (Table 1) [3]. Two patients diagnosed with aplastic anemia before 1994 received horse ATG (n = 1) or CSA (n = 1) only. Complete and partial response to IST was evaluated as reported previously [3]. Nonresponse was considered when the criteria for partial response were not fulfilled. Relapse of aplastic anemia was defined by conversion to nonresponse from partial or complete response.

Diagnosis of Secondary MDS/AML

Herein, sMDS/sAML after IST was diagnosed if 1 of the following criteria was met: (1) ≥5% blasts in BM, (2) evolution of an abnormal karyotype and myelodysplasia, or (3) hypercellular BM in the presence of pancytopenia and myelodysplasia. Morphology was subdivided using the French-American-British (FAB) classification [16]. The highest FAB classification before HSCT for each patient is shown in Table 1. Monosomy 7 was the most common cytogenetic aberration. The median interval between the diagnosis of aplastic anemia and the development of sMDS/sAML was 2.9 years (range, 1.2 to 13.0 years).

Pre-HSCT Condition and Treatment

Thirteen patients were receiving CSA therapy when they were diagnosed with sMDS/sAML. Three patients developed invasive fungal infections, and 3 patients had severe bacterial infections before undergoing HSCT (Table 1). Pre-HSCT therapy was performed at the discretion of the treating physician. Patient 1 achieved remission from sAML after 1 course of chemotherapy, but developed disseminated candidiasis. Patient 17, with sAML, did not achieve remission after 2 courses of chemotherapy and developed multiple abscesses and fungal pneumonia. Patient 13, with the morphology of chronic myelomonocytic leukemia and 17% blasts in BM, received 7 courses of azacytidine therapy, which resulted in the reduction of blasts in the BM (<5%) and improvement of blood counts before HSCT.

Transplantation Procedure

Transplantation procedures, including stem cell sources, donors, preparative regimens, and graft-versus-host disease (GVHD) prophylaxis are summarized in Table 2. Donors and recipients were tested for HLA compatibility by serologic typing to identify HLA-A, -B, and -C (class I) and by high-resolution molecular typing to detect HLA-DRB1 (class II) specificities in 12 patients and by high-resolution molecular typing for both class I and II in 5 patients. Three patients who received a transplant from an unrelated donor had an HLA mismatch: patient 3 (HLA-B) and patients 9 and 13 (HLA-C).

Eleven patients received a preparative regimen consisting of busulfan (oral 16 mg/kg/day for 4 days in 9 patients, i.v. in 2 patients), cyclophosphamide (60 mg/kg/day for 2 days), and melphalan (140 mg/m^2 in a single dose), a schedule recommended by the EWOG-MDS study for patients with high-risk MDS (Table 2) [17]. Two patients were given a regimen with thiotepa (8 mg/kg/day for 1 day), treosulfan (14 g/m^2/day for 3 days), and fludarabine (40 mg/m^2/day for 4 days), as currently recommend by the EWOG-MDS for patients age ≥12 years with high-risk MDS to reduce transplantation-related toxicity in older children. The remaining 4 patients received conditioning regimens according to each medical center policy (Table 2).

The median dose of infused nucleated cells was 2.4×10^8 ($1.5\text{-}4.0 \times 10^8$)/kg of recipient body weight for BM (n = 6). The median dose of infused CD34$^+$ cells for peripheral blood stem cells was 5.4×10^6/kg (range, $2.1\text{-}10.3 \times 10^6$/kg) of recipient body weight in 9 patients; this information was not available for 2 patients.

Definitions and Statistics

Acute and chronic GVHD were diagnosed and graded according to previously reported criteria [18-20]. Neutrophil engraftment was defined as the first of 3 consecutive days with a neutrophil count $>0.5 \times 10^9$/L, and platelet engraftment was defined as the first of 3 consecutive days with an unsupported platelet count $>20 \times 10^9$/L. The Kaplan-Meier method was used to estimate survival rates, and a 2-sided log-rank test was used to test the equality of survivorship functions in different subgroups [21]. Death, relapse, and graft failure were classified as qualifying events for event-free survival (EFS). Statistical analysis of data was performed using SPSS for Windows version 20.0 (IBM, Armonk, NY) and NCSS 2004 (Number Cruncher Statistical Systems, Kaysville, UT).

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