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Autoimmune Hematological Diseases after Allogeneic Hematopoietic Stem Cell Transplantation in Children: An Italian Multicenter Experience

Maura Faraci [1,*], Marco Zecca [2], Marta Pillon [3], Attilio Rovelli [4], Maria Cristina Menconi [5], Mimmo Ripaldi [6], Franca Fagioli [7], Marco Rabusin [8], Ottavio Ziino [9], Edoardo Lanino [1], Franco Locatelli [10], Thomas Daikeler [11], Arcangelo Prete [12] on behalf of the Italian Association of Paediatric Haematology and Oncology

[1] *Haematopoietic Stem Cell Transplantation Unit, Haematology-Oncology Department, G. Gaslini Children's Research Institute, Genova, Italy*
[2] *Paediatric Haematology/Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[3] *Paediatric Oncology-Haematology Unit, University Hospital of Padova, Padova, Italy*
[4] *Paediatric Haematopoietic Stem Cell Transplantation Unit, MBBM Foundation, University of Milano-Bicocca, Monza, Italy*
[5] *Haematopoietic Stem Cell Transplantation Unit, Paediatric Clinic of University of Pisa, Pisa, Italy*
[6] *Haematopoietic Stem Cell Transplantation Unit, Haematology-Oncology Department, Pausilipon Hospital, Napoli, Italy*
[7] *Haematopoietic Stem Cell Transplantation Unit, Department of Paediatrics, Regina Margherita Children's Hospital, University of Turin, Turin, Italy*
[8] *Haematopoietic Stem Cell Transplantation Unit, Paediatric Clinic, Burlo Garofolo Research Institute, Trieste, Italy*
[9] *Paediatric Haematology Oncology, Ospedale dei Bambini "G. Di Cristina, Palermo", Palermo, Italy*
[10] *Department of Paediatric Haematology-Oncology, IRCCS Bambino Gesù Children's Hospital, Rome, University of Pavia, Pavia, Italy*
[11] *Department of Rheumatology, University Hospital Basel, Basel, Switzerland*
[12] *Paediatric Oncology and Haematology Unit Lalla Seràgnoli, Department of Paediatrics, University of Bologna Sant'Orsola-Malpighi Hospital, Bologna, Italy*

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A B S T R A C T

Autoimmune hematological diseases (AHDs) may occur after allogeneic hematopoietic stem cell transplantation (HSCT), but reports on these complications in large cohorts of pediatric patients are lacking. Between 1998 and 2011, 1574 consecutive children underwent allogeneic HSCT in 9 Italian centers. Thirty-three children (2.1%) developed AHDs: 15 autoimmune hemolytic anemia (45%), 10 immune thrombocytopenia (30%), 5 Evans' syndrome (15%), 2 pure red cell aplasia (6%), and 1 immune neutropenia (3%). The 10-year cumulative incidence of AHDs was 2.5% (95% confidence interval, 1.7 to 3.6). In a multivariate analysis, the use of alternative donor and nonmalignant disease was statistically associated with AHDs. Most patients with AHDs (64%) did not respond to steroids. Sustained complete remission was achieved in 87% of cases with the anti-CD20 monoclonal antibody (rituximab). Four patients (9%) (1 autoimmune hemolytic anemia, 1 Evans' syndrome, 2 immune thrombocytopenia) died at a median of 87 days after AHD diagnosis as a direct or indirect consequence of their disorder. Our data suggest that AHDs are a relatively rare complication occurring after HSCT that usually respond to treatment with rituximab.

INTRODUCTION

Autoimmune disorders, including autoimmune hematological diseases (AHDs), have been reported to occur more frequently than other autoimmune complications after both autologous and allogeneic hematopoietic stem cell transplantation (HSCT) [1-7]. AHDs may involve a single lineage of blood cells, such as autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), autoimmune neutropenia (AIN), or 2 and/or 3 lineages (such as Evans' syndrome in which AIHA is associated with ITP and/or AIN). The causes of AHDs after HSCT have been the object of several studies, but the association of these complications with graft-versus-host disease (GVHD), T cell depletion, HSCT from an unrelated donor, and the use of serotherapy, in particular alemtuzumab, suggest that immune dysregulation or incomplete immune reconstitution may be the pathogenetic mechanism leading to the development of these complications [1-5].

The management of post-transplantation AHDs is complex, and the response to immunosuppressive therapies is often either incomplete or transient. There are reports on the incidence of AIHA cases in pediatric HSCT recipients [3,7], and an analysis of autoimmune diseases occurring after cord blood transplantation has recently been published [6], but the description of post-transplantation AHDs in a large cohort of children is lacking. The aims of this Italian retrospective, observational, multicenter pediatric study are to report the cumulative incidence, to analyze the risk factors, and to describe the clinical features, treatment, and outcome of AHDs occurring in a series of children who underwent allogeneic HSCT.

METHODS

This study involved all consecutive allogeneic HSCT recipients reported to the Italian Association of Paediatric Haematology and Oncology (AIEOP)-HSCT Registry and treated between 1998 and December 2011 at any AIEOP

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* Correspondence and reprint requests: Maura Faraci, MD, Stem Cell Transplantation Unit, Department of Haematology/Oncology, G. Gaslini Children's Hospital, Largo G. Gaslini 5, 16147 Genova, Italy.
E-mail address: maurafaraci@ospedale-gaslini.ge.it (M. Faraci).

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center. Data regarding patients with a minimum follow-up of at least 6 months were collected and analyzed. The AIEOP centers that agreed to participate in the study were asked to identify patients affected by AHD and to answer a specific questionnaire, including queries addressing clinical features of AHDs, laboratory characteristics, therapies used, and outcome. Data concerning demographics, type of primary diagnosis, date and type of transplantation, conditioning regimen, type of stem cell source, and GVHD (maximum grade, duration, and treatment) were retrieved from the AIEOP-HSCT Registry for each study subject. HSCT was classified as (1) matched related donor, including patients who received geno-/phenotypically HLA identical or with a single locus mismatch, and (2) alternative donor, including patients who received HSCT from an unrelated volunteer or from an HLA partially matched/haploidentical related donor.

We analyzed the response to first- and second-line treatment and categorized it as (1) complete response (CR) in cases of normalization of the clinical signs and laboratory tests for AHD, (2) partial response when an improvement in clinical symptoms or laboratory analyses and/or steroid dependence was observed despite the presence of autoantibodies, or (3) nonresponse when the clinical signs/symptoms and laboratory findings were either unchanged or worsened despite therapy.

This retrospective study was approved by the AIEOP-HSCT board. The procedures we followed were in accordance with our institution's ethical standards and with the Helsinki Declaration. As per Italian guidelines, no other specific informed consent was required other than a general agreement to clinical and laboratory data collection for scientific purposes expressed at the time of transplantation.

Statistical Analysis

Patients' data were collected using patient-oriented forms, filled in by the physician in charge at each center and sent to the AIEOP Operations Office in Bologna where data were stored in an electronic database (AIEOP-HSCT Registry) for quality control and statistical analysis by Venus, a facilities-integrated software system running on an IBM mainframe at the Italian Inter-University Computing Centre (CINECA).

Quantitative variables were reported as median and range, whereas categorical variables were expressed as absolute number and percentage. The incidence of AHD was defined as the probability of having AHD at time *t*, death in remission or disease relapse considered the competing event [8]. AHD was calculated as a cumulative incidence curve to adjust the estimate for competing risks [9,10]. All results were expressed as 10-year cumulative incidences and 95% confidence intervals (CIs) [8].

The following variables were included in the univariate analysis of factors predicting the development of AHD: patient gender, median age at diagnosis, type of original disease (malignant versus nonmalignant), median age at HSCT, type of conditioning regimen (total body irradiation–based versus chemotherapy-based), type of stem cell source, type of GVHD prophylaxis, and acute and chronic GVHD occurrence. Logistic regression was used to perform the multivariate analysis, and the model included all variables with $P < .05$ in univariate analysis. The chi-square test was used to compare percentage differences. All *P* values were 2-sided, and $P < .05$ were considered statistically significant. $P > .1$ was reported as not significant (NS), whereas *P* between .05 and .1 were reported in detail.

Statistical analysis was performed using Number Cruncher Statistical System 2007 (Kaysville, UT) and R 2.5.0 software package (http://www.R-project.org) [11-13]. Data were analyzed as of December 15, 2012.

RESULTS

Nine of 20 AIEOP centers performing allogeneic HSCT (45%) agreed to participate in this study. Overall, they performed 41% (n = 1574) of the 3830 transplants reported to the AIEOP-HSCT Registry during the study period. These centers provided the data concerning the children who were eligible for this study, and among them a total of 33 AHDs (2.1%) were reported. The median follow-up after transplantation of AHD patients was 43.5 months (range, 6 to 163.6). AHD was diagnosed after a first transplant in 29 patients, whereas in 4 cases it occurred after a second HSCT performed for either relapse (n = 2) or graft failure (n = 2).

Cumulative Incidence

The cumulative incidence of AHDs was 1.53% (95% CI, 1.02 to 2.30) 1 year after HSCT; it was 2.05% (95% CI, 1.44 to 2.92) 2 years after HSCT, 2.13% (95% CI, 1.50 to 3.02) 3 and 5 years after transplantation, and 2.50% (95% CI, 1.74 to 3.57) 10 years after HSCT. The cumulative incidence was significantly different between groups of patients who received matched related (.74%) and alternative donor (3.62%) stem cells ($P < .001$) (Figure 1).

Risk Factors

The main characteristics of patients who did or did not develop AHDs are reported in Table 1. Univariate analysis (Table 1) showed no significant correlation between the development of AHD and patient gender, type of conditioning regimen (total body irradiation versus chemotherapy based), type of GVHD prophylaxis, or acute and chronic GVHD occurrence. On the contrary, the following factors were found to be significantly associated with an increased risk of AHD: younger age at HSCT (3.1 years [range, .7 to 18.9] for patients developing AHD versus 8.8 years [range, .3 to 22] for patients not developing these disorders; $P = .0005$), transplantation from an alternative donor ($P = .004$), primary

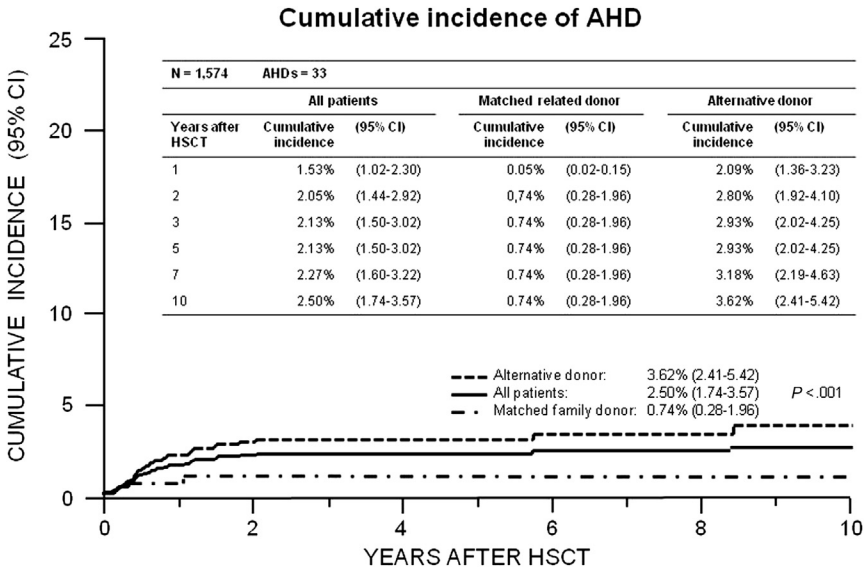

Figure 1. Cumulative incidence of AHDs.