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Bloodstream Infection after Stem Cell Transplantation in Children with Idiopathic Aplastic Anemia

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A B S T R A C T

Bloodstream infection (BSI) is the most common infectious complication of hematopoietic stem cell transplantation (HSCT) and can cause substantial morbidity and mortality. Identification of risk factors for BSI might be helpful in efforts to reduce transplantation-related death. This study analyzed the incidence of BSI and risk factors for BSI after HSCT in pediatric patients with aplastic anemia (AA). BSI occurred in 39 of the 351 patients with AA (11.1%). Onset of BSI occurred at a median of 8 days after HSCT (range, 0 to 92 days). The 5-year overall survival rate was lower in patients with BSI than in patients without BSI (63.32% ± 7.90% versus 93.35% ± 1.44%; $P < .0001$). Univariate analysis identified the following variables as associated with BSI: history of immunosuppressive therapy with antithymocyte globulin (ATG), transplantation from an unrelated donor, frequent blood transfusion before transplantation, major or major plus minor ABO type mismatch, graft-versus-host disease prophylaxis with tacrolimus and without cyclosporine, and long interval from diagnosis to transplantation. Among these factors, long interval from diagnosis to transplantation was the sole statistically significant risk factor for BSI on multivariate analysis. In patients who underwent HSCT from a related donor, age ≥14 years at transplantation was risk factor for BSI. In contrast, history of immunosuppressive therapy with ATG, frequent blood transfusion before HSCT, graft failure, and major or major plus minor ABO type mismatch were risk factors for BSI in patients who underwent HSCT from an unrelated donor. Because the overall 5-year survival rate without BSI was >90%, even in patients who were received a transplant from an unrelated donor, control of BSI is very important for successful HSCT in pediatric patients with AA.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is first-line therapy for severe aplastic anemia (AA). HSCT from an HLA-matched sibling donor is an established standard therapy for children with severe AA and is associated with high survival rates [1]. Outcomes of HSCT from an unrelated donor have gradually improved [2,3].

Bloodstream infection (BSI) is the most common infectious complication of HSCT and causes substantial morbidity and mortality [4,5]. Identification of risk factors for BSI may aid efforts to reduce transplantation-related deaths. We previously identified AA as a common risk factor for BSI in a retrospective multicenter study [6]. In the present study, we analyzed the incidence of BSI and risk factors for BSI after

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HSCT in pediatric patients with AA using the Transplant Registry Unified Management Program (TRUMP) system of the Japanese Society of Stem Cell Transplantation.

PATIENTS AND METHODS

Between 1980 and 2011, 1098 patients age ≤19 years who underwent HSCT for AA (excluding hereditary bone marrow failure, paroxysmal nocturnal hemoglobinemia, and secondary AA) were registered with the TRUMP system of the Japanese Society of Stem Cell Transplantation. Of these 1098 patients, 516 who underwent HSCT before 2000 were excluded from this analysis, owing to the drastic changes in infection control practices promulgated by the Japanese Society of Stem Cell Transplantation in 2000, including antibiotics and antifungal drugs and guidelines for infection management in the early post-transplantation period. Of the remaining 582 patients, 231 were excluded due to insufficient data; thus, our study group comprised 351 pediatric patients with AA who underwent HSCT, including 193 males and 158 females, with a median age of 11 years (range, 0 to 19 years).

Diagnosis and assessment of severity of disease were established according to published criteria [7]. Severity of AA at initial diagnosis was as follows: very severe, n = 84; severe, n = 137; nonsevere, n = 130. Severity of AA at HSCT was as follows: very severe, n = 122; severe, n = 166; nonsevere, n = 63. The median interval from diagnosis to transplantation was 337 days (range, 9 to 5261 days). Two hundred and seventy-eight patients had received some specific treatment for AA before transplantation, including steroids (n = 171), antithymocyte globulin (ATG; n = 210), cyclosporine (CsA; n = 244), and granulocyte colony-stimulating factor (n = 141). Stem cell source was bone marrow in 315 patients, peripheral blood in 12 patients, bone marrow plus peripheral blood in 1 patient, and cord blood in 23 patients. One hundred seventy-three patients had a related donor, 1 patient had a syngeneic donor, and 177 patients had an unrelated donor.

The conditioning regimen included ATG for 240 patients, cyclophosphamide for 317, fludarabine for 244, melphalan for 39, total body irradiation for 145, thoracoabdominal irradiation for 49, and total lymphoid irradiation for 70 patients. Graft-versus-host disease (GVHD) prophylaxis, defined as planed administration of immunosuppressive drugs before evidence of acute GVHD, included steroids in 17 patients, CsA in 160, tacrolimus in 191, and methotrexate in 319.

Twenty-four patients underwent a second HSCT, 3 patients underwent a third HSCT, and 1 patient underwent a fourth HSCT. Twenty-one patients had a bacterial or fungal infection at the time of transplantation. In patients with multiple HSCTs, each transplantation was analyzed separately.

BSI was defined as isolation of 1 or more recognized bacterial or fungal pathogens from 1 or more blood cultures and at least 1 of the following signs and symptoms within 24 hours of collection of a positive blood culture: fever (>38°C), chills or rigors, or hypotension. We classified ABO compatibility as minor (eg, from an type O donor to a type A, B, or AB recipient), major (eg, from a type A, AB, or B donor to an type O recipient), and major and minor (eg, type A donor to type B recipient). We defined an HLA match donor as a 6/6 HLA-A, -B, and -DR antigen match between recipient and donor, using low-resolution typing. The median duration of follow-up was 39 months. Data collected as of October 2012 were analyzed.

In univariate analysis, the chi square test and Fisher's exact test were used to assess risk factors for BSI. Multivariate stepwise regression was performed to explore the independent effects of variables that demonstrated a significant influence in univariate analysis ($P < .10$). Overall survival was analyzed using the Kaplan-Meier method, with differences compared using the log-rank test. Statistical analyses were performed using SPSS 11.0 for Windows release 11.0.1J (SPSS Japan, Tokyo, Japan).

RESULTS

Assessment of BSI in All 351 Patients Who Underwent HSCT

BSI occurred in 39 of the 351 patients with AA (11.1%). Onset of BSI occurred at a median of 8 days after transplantation (range, 0 to 92 days). The bacteria that were isolated are summarized in Table 1. *Staphylococcus* spp were detected in 11 patients, and *Streptococcus* spp were detected in 7 patients. Gram-positive cocci were detected in 20 patients (51.3%); gram-positive bacilli, in 5 patients (12.8%); gram-negative bacilli, in 11 patients (28.2%); and *Candida* spp, in 3 patients (7.7%). The 5-year overall survival rate was lower in patients with BSI compared with patients without BSI (65.32% ± 7.90% versus 93.35% ± 1.44%; $P < .0001$) (Figure 1). The cause of death was directly associated with BSI in 5 of the 13 patients with BSI who died.

Table 1
Organisms Isolated from Blood Cultures of Patients with AA Who Underwent HSCT

Organism	n
Staphylococcus	11
Staphylococcus epidermidis	8
Staphylococcus haemoliticus	1
Coagulase-negative staphylococci	1
Staphylococcus sp	1
Streptococcus	7
Streptococcus mitis	4
Streptococcus viridans	1
α-streptococci	1
Streptococcus sp	1
Micrococcus	1
Enterococcus	1
Bacillus	4
Gram-positive rods	1
Escherichia coli	1
Enterobacter cloacae	2
Acinetobacter	1
Pseudomonas aeruginosa	4
Stenotrophomonas maltophilia	3
Candida	3

We performed univariate and multivariate analyses to identify risk factors for BSI in the patients with AA (Table 2). Variables associated with BSI on univariate analysis included (1) history of immunosuppressive therapy with ATG, (2) transplantation from an unrelated donor, (3) frequent blood transfusions before HSCT, (4) major or major plus minor ABO mismatch, (5) tacrolimus as acute GVHD prophylaxis with use of CsA, and (6) extended interval from diagnosis of AA to HSCT. Infectious complications at the time of HSCT were not associated with BSI after transplantation. Multivariate analysis identified extended interval from diagnosis to HSCT (>300 days) as the sole statistically significant risk factor for BSI (Table 3).

Assessment of BSI in 158 Patients Who Underwent First HSCT from a Related Donor

BSI occurred in 11 of 158 patients with AA who underwent first HSCT from a related donor (7.0%). The 5-year overall survival rate was lower in patients with complicated BSI compared with patients without BSI (81.82% ±

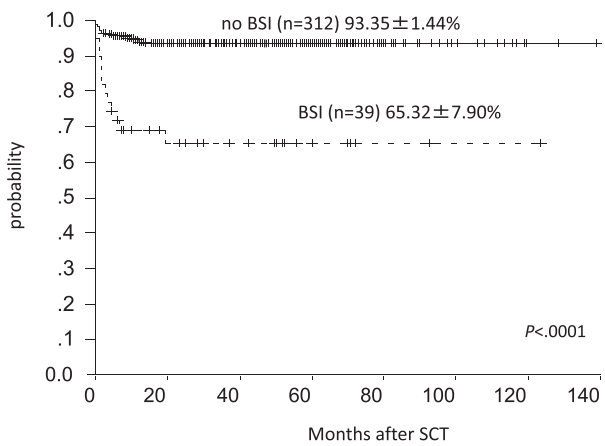

Figure 1. Kaplan-Meier estimate of overall survival for patients with BSI (n = 40; 63.68% ± 7.87%) and patients without BSI (n = 311; 93.65% ± 1.41%); $P < .0001$.