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Hepatic sinusoidal obstruction syndrome after allogeneic hematopoietic stem cell transplantation in adult patients with idiopathic aplastic anemia

Hawk Kim[a,1], Kyoo-Hyung Lee[b,1], Sang Kyun Sohn[c,1], Chul Won Jung[d,1], Young Don Joo[e,1], Sung Hyun Kim[f,1], Byung Soo Kim[g,1], Jung Hye Choi[h,1], Jae-Yong Kwak[i,1], Min Kyoung Kim[j,1], Sung Hwa Bae[k,1], Ho-Jin Shin[l,1], Jong Ho Won[m,1], Sukjoong Oh[n,1], Won Sik Lee[o,1], Jae-Hoo Park[a,1], Sung-Soo Yoon[p,*,1]

[a] Divison of Hematology and Hematological Malignancies, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea
[b] Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[c] Department of Hemato/Oncology, Kyungpook National University Hospital, Kyungpook National University, Daegu, Republic of Korea
[d] Department of Hemato/Oncology, Samsung Medical Center, School of Medicine, Sungkyunkwan University, Seoul, Republic of Korea
[e] Department of Hemato-Oncology, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea
[f] Department of Hemato-Oncology, Dong-A University Medical Center, Dong-A University, Busan, Republic of Korea
[g] Department of Hematology/Oncology, Korea University Hospital Seoul Hospital, Korea University, Seoul, Republic of Korea
[h] Department of Hematology/Oncology, Hanyang University Hospital, Hanyang University, Seoul, Republic of Korea
[i] Department of Internal Medicine, Chonbuk National University Hospital, Chonbuk National University, Jeonju, Republic of Korea
[j] Department of Hematology/Oncology, Yeungnam University Medical Center, Yeungnam University, Daegu, Republic of Korea
[k] Division of Hematology/Oncology, Daegu Catholic University Hospital, Daegu Catholic University School of Medicine, Daegu, Republic of Korea
[l] Department of Hematology and Oncology, Pusan National University Hospital, Pusan National University, Busan, Republic of Korea
[m] Department of Hematology/Oncology, Soon Chun Hyang University Hospital, Soon Chun Hyang University, Seoul, Republic of Korea
[n] Department of Hematology/Oncology, Kangbuk Samsung Hospital, School of Medicine, Sungkyunkwan University, Seoul, Republic of Korea
[o] Department of Hematology/Oncology, Busan Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea
[p] Department of Internal Medicine, Seoul National University Hospital, Seoul National University, Seoul, Republic of Korea

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ABSTRACT

We retrospectively investigated the incidence, risk factors, and outcomes of SOS (sinusoidal obstruction syndrome; previously veno-occlusive disease [VOD]) after allogeneic hematopoietic stem cell transplantation (alloHSCT) in aplastic anemia. Two hundred and sixty patients were included in the analysis. SOS developed in 7.3% (n = 19/260) of patients. Classical Cy (200 mg/m^2)-ATG was the most common conditioning regimen (84.2%) in the SOS group. The SOS mortality rate was 4/19 (21.1%). Univariate analyses revealed that Cy 200 mg/m^2 conditioning (p = 0.035), classical Cy-ATG conditioning (p = 0.007), and horse ATG conditioning (p < 0.001) were significant risk factors for developing SOS. Multivariate analysis revealed that only horse ATG conditioning was a poor prognostic factor (HR = 3.484; 95% CI 1.226–9.904; p = 0.002). Rabbit ATG (HR 12.719; 95% CI 2.332–69.373; p = 0.003) and weight gain > 10% (HR 35.655; 95% CI 2.208–575.805; p = 0.012) were risk factors in the overall SOS group. Both rabbit ATG conditioning and weight gain of more than 10% were associated with poor overall survival with a median of 1.2 months (5Y survival rate, any risk factor vs. none: 74.6% vs. 0.0%; p < 0.001; Fig. 2) in the SOS group.

In conclusion, SOS is a relatively rare (7.3%) but highly fatal (21.1%) acute complication of alloHSCT in AA, and the horse ATG conditioning regimen was a significant risk factor for developing SOS.

1. Introduction

Hepatic sinusoidal obstruction syndrome (SOS; previously known as veno-occlusive disease [VOD]) is a rare complication after allogeneic hematopoietic stem cell transplantation (alloHSCT). The diagnosis of SOS is generally based on clinical features such as hyperbilirubinemia, tender hepatomegaly, and weight gain. In a large study of patients undergoing alloHSCT, the reported incidence

* Corresponding author at: Department of Internal Medicine, Seoul National University Hospital. Seoul National University 101 Daehang-ro, Jongno-gu, Seoul, 110-744, Republic of Korea. Tel.: +82 2 2072 3079; fax: +82 2 762 9662.
E-mail address: ssysmc@snu.ac.kr (S.-S. Yoon).
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of SOS was as high as 53% and the case fatality rate was 47% [1–3]. However, the reported incidence and fatality rates of SOS show high variability, ranging from 0% to 70% [4–6]. Recent reports indicate that the incidence and mortality are decreasing. This decline might be caused by the low incidence of SOS among reduced-intensity conditioning and the reduction among those receiving myeloablative alloHSCT from unrelated donors [7,8]. These data not only come from patients with many different diseases, mainly hematologic malignancies, but also from patients with many different conditioning regimens.

There have been only a few reports of SOS in AA (aplastic anemia), involving very small numbers of patients. In our previous report of SOS incidence after alloHSCT for AA, 7 of 17 patients who received cyclophosphamide at 200 mg/kg developed SOS (5 mild, 2 moderate) with maximum bilirubin levels of 4.2–21 mg/dL. The maximum weight gain ranged from 3.5 to 29% [9]. Retrospective data obtained after alloHSCT for a few patients with Fanconi anemia or hepatitis-associated AA revealed a similar incidence of veno-occlusive disease (5.9–16.7%) in the cyclophosphamide (Cy)-antithymocyte globulin (ATG) arm [10,11].

Many transplantation-related risk factors for SOS have been suggested, such as a high-dose conditioning regimen, busulfan for conditioning, total body irradiation (TBI), graft from unrelated donors or related HLA mismatched transplants, and methotrexate as part of graft versus host disease (GvHD) prophylaxis [1,12–14]. Usually, there is no need for a high-dose or busulfan-containing conditioning regimen for AA patients, which implies that the risk factors for SOS will be different in AA patients. Here we present a retrospective analysis of the incidence, clinical characteristics, and risk factors of SOS after alloHSCT in AA patients.

2. Patients and methods

2.1. Patient eligibility

Patients were included if transfusion dependent/severe/very severe acquired aplastic anemia (AA) was diagnosed; if patients were >15 years of age at the time of the alloHSCT treatment; and if patients had undergone alloHSCT from an HLA-matched related donor (MRD) or alternative donor (AD), regardless of immunosuppressive therapy (IST) history. Exclusion criteria were the presence of congenital aplasia, including Fanconi anemia, Diamond–Blackfan syndrome, congenital dyskeratosis, or hypoplastic myelodysplastic syndrome.

2.2. Data collection

The original protocol was approved by the Korean Society of Blood and Marrow Transplantation (KSBMT) Clinical Study Committee (approval no. KSBMT07-02) for retrospective comparison between MRD and AD, and by the Cooperative Study Group A for Hematology (C-006A study) phase III prospective trial [15]. These two study populations were combined for this analysis. Data were also collected from patients with pure red cell aplasia and paroxysmal nocturnal hemoglobinuria in the KSBMT07-02 study and from patients with hypoplastic myelodysplastic syndrome in the COSAH (C-006A) study, but such patients were not included in this final analysis. The detailed SOS-related data were collected separately from additional queries for each patient who had developed SOS.

2.3. Evaluation criteria

The principal concern of the study was to define the actual incidence of SOS after alloHSCT in adult patients with AA. We also aimed to define which factors influenced the development and final outcome of SOS. SOS was diagnosed using McDonald's guidelines and modified Seattle criteria [1,4]. At least two of the following three criteria should be present to fit the diagnosis of SOS within 30 days after transplantation: weight gain > 5% from baseline body weight; hepatomegaly with right upper quadrant pain; and hyperbilirubinemia (serum bilirubin > 2 mg/dL). No other explanation for these signs and symptoms were present at the time of diagnosis. The first day on which the clinical criteria were satisfied was defined as day 0 of SOS. Doppler sonogram or other imaging modalities were not required for the diagnosis of SOS in this study. Patients who met the criteria for SOS, but who were not treated and whose illness was self-limiting, were classified as having mild SOS. Those whose SOS resolved but who received treatment, such as diuretics for fluid retention or narcotic analgesics for painful hepatomegaly, were classified as having moderate SOS. Patients who died of SOS or whose SOS had not resolved by 100 days post-transplant were considered to have severe SOS. All patients who had developed SOS were defined as the SOS group and the others as the no-SOS group.

Performance status was graded by ECOG performance scoring. Relapse was defined as the reacquisition of transfusion dependence or fulfillment of severe/very severe criteria after successful engraftment. Other evaluation criteria were the same as in our previous study [15].

2.4. Statistical analyses

All analyses were performed on an intention-to-treat basis. The patients were divided into two groups: a no-SOS group who did not develop hepatic SOS and an SOS group who did develop SOS. The Chi-square test was used to compare categorical variables and Student's *t*-test was used to compare continuous variables between any two groups. The start point for the determination of time-dependent parameters was the first day of stem cell infusion. Time to SOS was defined from the first day of stem cell infusion to the day on which SOS was diagnosed. Overall survival was measured from the time of stem cell infusion to the date of death, or the last date on which the patient was known to be alive (this constituted censoring). Survival curves were computed according to the Kaplan–Meier method, and differences in survival were compared by the log-rank test. Death directly due to SOS was defined as an event in SOS-specific survival and SOS-specific mortality. A Cox's proportional hazard model was used to determine the effects on survival of various prognostic factors, including age, donor/recipient gender matching, number of cells transfused, use of irradiated blood products, time from diagnosis to alloHSCT, stem cell source, dose of irradiation, HLA matching, method of immune suppression used to prevent GvHD, IST history, and type of ATG. All variables were dichotomized and converted into categorical classes. The variables included in the multivariate analysis were the patients' ages, and all prognostic factors with p-values <0.05 in the univariate analyses. Differences were assessed using a two-sided test at the $p = 0.05$ level of significance.

3. Results

3.1. Patients

Data from 260 adult patients who received alloHSCT for acquired severe aplastic anemia (sAA) between 1985 and 2010 were collected from 15 Korean institutions. The median age was 31.2 (range 14.1–63.6) years; 134 (51.5%) were male; 68.1% of patients had matched-related donors, 82.7% had HLA full-matched donors, and 17.7% had female to male donor–recipient sex-matched donors. Three patients aged less than 15 years (14.1, 14.5, and 14.9 years) were included in the final analysis. The drugs used for the conditioning regimens were cyclophosphamide in 97.7%, ATG in 84.3%, and fludarabine in 33.8%. TBI was incorporated in the conditioning regimen of 9.2% of patients. Table 1 shows the detailed patient characteristics.

3.2. Clinical features of SOS

SOS was found in 19/260 (7.3%) of patients. In the SOS group (Table 2), all patients received ATG as the conditioning regimen. Classical Cy (200 mg/kg)-ATG was the most common conditioning regimen (84.2%). The median number of days to SOS was 4 (range, 1–15) days. None of the patients received the TBI conditioning regimen and all of the patients received the Cy conditioning regimen. Sixteen patients (84.2%) received preventive medication for SOS and heparin was the drug used in the majority of them (78.9%). Among the diagnostic criteria for SOS, weight gain was observed in 17 (89.5%), hepatomegaly in 15 (78.9%), and hyperbilirubinemia in 18 (94.7%) patients. The average total bilirubin was 6.65 (range 1.8–26.9) mg/dL. The severity of SOS was mild in 10 (52.6%), moderate in 5 (26.3%), and severe in 4 (21.1%) patients. Treatments for SOS were supportive care (68.4%), ursodeoxycholic acid (15.8%), and corticosteroids (10.5%). Ascites was found in two of the four severe SOS patients. Ultrasound findings in these four severe SOS patients were various: inhomogeneously enhanced liver parenchyma and early opacification of the portal vein in the arterial phase; minimal dilatation of the intrahepatic bile duct; and slightly increased periportal echogenicity. There was no histological confirmation and no autopsies were performed.