Serum ferritin as risk factor for sinusoidal obstruction syndrome of the liver in patients undergoing hematopoietic stem cell transplantation

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Hepatic sinusoidal obstruction syndrome (SOS) is a serious complication in hematopoietic stem cell transplant (HSCT) recipients. To determine the impact of pretransplantation hyperferritinemia on the risk of SOS after HSC transplantation, we retrospectively studied 427 HSCT recipients (179 autologous and 248 allogeneic). Serum ferritin levels were measured before transplantation. Patients with and without a diagnosis of SOS were compared regarding demographics; underlying disease; transplant characteristics; receipt of imatinib, busulfan, total body irradiation, gemtuzumab, vancomycin, acyclovir, or methotrexate; and baseline serum ferritin. Univariate and multivariate (stepwise logistic regression) analyses were performed. SOS was diagnosed in 88 patients (21%) at a median of 10 days (range, 2-29 days) after transplantation. By multivariate analysis, allogeneic HSC transplantation (odds ratio [OR] = 8.25; 95% confidence interval [95% CI], 3.31-20.57), receipt of imatinib (OR = 2.60; 95% CI, 1.16-5.84), receipt of busulfan (OR = 2.18; 95% CI, 1.25-3.80), and ferritin serum level higher than 1000 ng/dL (OR = 1.78; 95% CI, 1.02-3.08) were risk factors for SOS. A ferritin serum level higher than 1000 ng/dL in the pretransplantation period is an independent risk factor for SOS. The results suggest the need for prospective studies addressing the use of iron chelation in the pretransplantation period. (Blood. 2009;114: 1270-1275)

Introduction

Sinusoidal obstruction syndrome (SOS), previously referred to as veno-occlusive disease, is one of the most common life-threatening complications of hematopoietic stem cell (HSC) transplantation. It is characterized by the presence of at least 2 of the following features: hyperbilirubinemia, painful hepatomegaly, and weight gain. In patients undergoing allogeneic HSC transplantation, SOS is the third cause of transplant-related death, with a reported mortality rate of up to 50%.[1-3] The frequency of SOS varies greatly, from 1% to 2% among pediatric HSC transplant (HSCT) recipients, to more than 50% in adult HSCT recipients with hematologic malignancies.[1,2] Cytoreductive therapy is presumably the primary cause of SOS, but other factors may also play a role. Pretransplantation liver disease; viral hepatitis; cytomegalovirus (CMV) seropositivity; intensity of the conditioning regimen; receipt of busulfan, gemtuzumab, estrogen-progestin, methotrexate, everolimus, acyclovir, amphotericin, or vancomycin; and mismatched or unrelated allogeneic HSC transplantations have also been associated with an increase in the risk of SOS.[3-9]

Recent studies have reported an association between pretransplantation iron overload and several outcomes in HSCT recipients, including an increased risk of infection[10] and transplant-related mortality.[11] In addition, 2 studies suggested that iron overload may be a risk factor for SOS.[11,12]

We sought to determine the risk factors for SOS in a cohort of autologous and allogeneic HSCT recipients. We were particularly interested in examining the role of pretransplantation serum ferritin as a risk factor for SOS.

Methods

This is a retrospective cohort study conducted at Instituto Nacional de Câncer. Between January 2002 and March 2007, 429 HSCT recipients were included in the study. The study protocol was approved by the local ethics committee at the Instituto Nacional de Câncer. Data were retrospectively collected from the medical files and stored in a Microsoft Excel spreadsheet (Seattle, WA). All HSCT recipients were considered eligible if they were alive at day +3 after transplantation and had a ferritin serum level measured before transplantation.

The diagnosis of SOS was based on clinical criteria originally proposed by McDonald et al.[13] Two of the following criteria had to be present within 20 days after transplantation, and not explained by other reasons: hyperbilirubinemia (bilirubin $>$ 34.2 μM [2.0 mg/dL]), painful hepatomegaly, and unexplained weight gain ($>$ 2% from baseline). Patients with a diagnosis of hepatic graft-versus-host disease (GVHD) were not considered to have SOS even if all diagnostic criteria for SOS were fulfilled. SOS severity was classified as mild if resolved before day +100 without treatment; moderate if resolved before day +100, but requiring specific treatment; and severe if not resolved before day +100. Two of the authors (S.C.M. and M.C.) prospectively followed all patients, and one author (S.C.M.) reviewed all medical charts to determine who developed SOS and to classify its severity.

Hepatic dysfunction was defined as any elevation in serum transaminases, hypoalbuminemia ($<$ 35 g/L [3.5 g/dL]), or histologic evidence of hepatic fibrosis or cirrhosis, documented before the administration of the conditioning regimen. Serum levels of ferritin were obtained before the start of the conditioning regimen, and were measured using the IMMULITE 2000 immunoassay system (Siemens Healthcare Diagnostics). Ferritin serum levels were measured prospectively in all patients. Status of the underlying disease was defined as early (nonmalignant diseases, acute

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leukemia in first complete remission, or chronic myeloid leukemia in first chronic phase) or advancer (other diseases). Fanconi anemia (5 patients), Krabbe disease and Wiskott-Aldrich syndrome (2 patients each) and Chédiak-Higashi syndrome, severe combined immunodeficiency syndrome, and Kostmann syndrome (1 patient each) were not classified.

For the evaluation of risk factors for SOS, patients with and without SOS were compared regarding age, sex, underlying disease, type (malignant vs nonmalignant) and status (early vs advanced) of the underlying disease, type of HSC transplantation (allogeneic vs autologous/syngeneic), relatedness of donor (sibling vs unrelated), human leukocyte antigen (HLA) match (matched vs mismatched), history of hepatitis, cytomegalovirus (CMV) serology of the recipient, previous HSC transplantation, receipt of imatinib before HSC transplantation, receipt of gemtuzumab, vancomycin, or acyclovir until 7 days before the start of the conditioning regimen, receipt of busulfan or total body irradiation in the conditioning regimen, intensity of the conditioning regimen (myeloablative vs nonmyeloablative), stem cell source (bone marrow vs peripheral blood vs cord blood), receipt of methotrexate in the prophylaxis of graft-versus-host disease (GVHD), and the presence of hepatic dysfunction.

For univariate analyses, chi-square and Fisher exact tests were used to analyze the association between SOS and the categoric variables. The comparison of continuous variables was performed with the Mann-Whitney test. Variables with P value less than .05 by univariate analysis were entered in a forward stepwise logistic regression analysis. To make sure that potential interactions between variables could negatively influence the results of the multivariate analysis, because some variables could be related, we tested the potential interaction between these variables (such as underlying disease and type of HSC transplantation or acute leukemia and receipt of busulfan in the conditioning regimen). If there was an interaction, the interaction term was entered in the multivariate model. Survival curves were constructed using the Kaplan-Meier method and compared by the log-rank test. The selection of the best cutoff point for ferritin as a risk factor for the diagnosis of SOS was done by constructing receiver operating characteristic (ROC) curves, with estimation of sensitivity, specificity, and area under the curve. All analyses were performed using SPSS 13.0 for Windows (SPSS). P values less than .05 were considered statistically significant.

Results

The characteristics of the 427 patients and transplants are summarized in Table 1. Two patients from the original cohort of 429 patients were excluded from the analysis: 1 died before day +3 due to sepsis, and the other had a diagnosis of SOS made on day +174, and was retrospectively considered a misdiagnosis.

The most frequent conditioning regimens used were CBV (cyclophosphamide 7200 mg/m^2, carmustine [BCNU] 450 mg/m^2, etoposide 2400 mg/m^2), given to 119 patients; Bu-Cy (busulfan 16 mg/kg by mouth, cyclophosphamide 120 mg/kg), given to 110 patients; and MEL200 (melphalan 200 mg/m^2), given to 51 patients. Among the 246 allogeneic HSCT recipients, 218 (89%) received cyclosporine and methotrexate as graft-versus-host disease (GVHD) prophylaxis. Methotrexate was given at a dose of 10 mg/m^2 on day +1, and 5 mg/m^2 on days +3 and +6 for nonmyeloablative allogeneic HSC transplantation, and 15 mg/m^2 on day +1, 10 mg/m^2 on days +3 and +6 for myeloablative allogeneic HSC transplantation. Patients with aplastic anemia and recipients of unrelated donor transplants received and an additional dose of 10 mg/m^2 on day +11.

The overall incidence of SOS was 21% (88 of 427). The median time of the diagnosis of SOS was 10 days from day zero of transplantation (range, 2-29 days). The severity of SOS was graded as mild in 35%, moderate in 50%, and severe in 15% of cases. Liver biopsy was not performed in any patient. Histopathology confirmed the diagnosis of SOS in the 3 patients who died and an autopsy was performed. The death rate among the 88 patients with SOS was 65%. The overall survival at day +60 after transplantation was significantly lower in patients with SOS compared with patients who did not develop SOS (73% vs 93%, $P < .001$, log-rank test). The 60-day and 5-year cumulative incidence of treatment-related mortality were 10% and 27%, respectively.

Table 1. Characteristics of the 427 patients

	No.
Male:female	255:172
Median age, y (range)	31 (0-66)
Underlying disease, no. (%)	
Lymphoma, multiple myeloma	196 (46)
Acute leukemia, myelodysplasia, PNH	136 (32)
Myeloproliferative disease	56 (13)
Other	39 (9)
Advanced underlying disease,* no. (%)	315/415 (76)
Type of HSC transplantation, no. (%)	
Autologous/syngeneic	181 (42)
Allogeneic, myeloablative	208 (49)
Allogeneic, nonmyeloablative	38 (9)
Type of donor and HLA status, no. (%)	
HLA-compatible sibling	187/246 (76)
HLA-compatible unrelated	28/246 (11)
HLA-mismatched unrelated	33/246 (13)
Conditioning regimen, no. (%)	
Busulfan based	119 (28)
TBI based	85 (20)
Other	223 (52)
Stem cell source, no. (%)	
Peripheral blood	225 (53)
Bone marrow	168 (39)
Cord blood	34 (8)

PNH indicates paroxysmal nocturnal hemoglobinuria; HSC, hematopoietic stem cell; HLA, human leukocyte antigen; and TBI, total body irradiation.

*Not applicable to hereditary disorders such as Fanconi anemia and Wiskott-Aldrich syndrome.

Table 2 shows the univariate analysis of risk factors for SOS. Patients with SOS were more likely to have chronic myeloid leukemia or acute leukemia as underlying disease, and less likely to have lymphoma or multiple myeloma. In addition, there was a strong association between SOS and allogeneic HSC transplantation (odds ratio [OR] = 14.60; 95% confidence interval [95% CI], 6.20-34.30), bone marrow as the source of stem cells (OR = 4.58; 95% CI, 2.69-7.83), receipt of imatinib (OR = 4.77; 95% CI, 2.21-10.30), and receipt of busulfan (OR = 3.99; 95% CI, 2.44-6.53). In the analysis of potential interaction between variables, the following variables presented interaction: a diagnosis of lymphoma and autologous HSC transplantation, a diagnosis of chronic myeloid leukemia and allogeneic HSC transplantation, a diagnosis of acute leukemia and receipt of busulfan in the conditioning regimen, and receipt of imatinib and a diagnosis of chronic myeloid leukemia.

A total of 305 patients (71%) had serum levels of ferritin above the normal range, with a median value of 622 ng/mL (range, 5.81-7785 ng/mL). The median ferritin was higher in patients who developed SOS (917.5 vs 531, $P = .002$). In the assessment of risk factors for SOS, ferritin was analyzed as a categoric variable with different cutoff points. Although different cutoff values were significantly associated with the development of SOS, a value of 1000 ng/mL showed the best sensitivity (48%) and specificity (71%), according to the ROC curve analysis (Table 3). Patients

Table 2. Risk factors for sinusoidal obstruction syndrome by univariate analysis

	SOS			
	Yes n=88	No n=339	*P*	Odds ratio (95% CI)
Male:female	49:39	206:133	.38	0.81 (0.50-1.30)
Median age, y (range)	34.5 (6-33)	30 (0-66)	.62	NA
Underlying disease, no. (%)				
Lymphoma	7 (8)	135 (40)	< .001	0.13 (0.06-0.30)
Acute leukemia/MDS	41 (46)	88 (26)	< .001	2.49 (1.49-4.15)
Chronic myeloid leukemia	26 (29)	29 (8)	< .001	4.48 (2.37-8.48)
Multiple myeloma	1 (1)	52 (15)	< .001	0.06 (0.02-0.43)
Neoplastic disease, no. (%)	79 (90)	316 (93)	.27	0.64 (0.28-1.43)
Advanced underlying disease, no. (%)	53 (60)	262 (77)	.001	0.44 (0.27-0.73)
Allogeneic HSC transplantation, no. (%)	82 (93)	164 (48)	< .001	14.60 (6.20-34.30)
Unrelated donor allogeneic HSC transplantation, no. (%)	15/82 (18)	46/164 (28)	.15	1.31 (0.69-2.47)
Matched-related donor allogeneic HSC transplantation, no. (%)	79/82 (96)	136/164 (83)	.003	5.42 (1.60-18.40)
History of hepatitis, no. (%)	4 (4)	3 (1)	.04	5.33 (1.17-24.30)
CMV-positive recipient, no. (%)	78 (89)	298 (88)	.85	1.07 (0.51-2.24)
Previous HSC transplantation, no. (%)	5 (6)	35 (10)	.18	0.52 (0.20-1.38)
Receipt of imatinib, no. (%)	15 (17)	14 (4)	< .001	4.77 (2.21-10.30)
Receipt of gemtuzumab, no. (%)	1 (1)	0	.21	NA
Receipt of vancomycin or acyclovir, no. (%)	2 (2)	7 (2)	.999	1.10 (0.22-5.40)
Busulfan-based conditioning regimen, no. (%)	46 (52)	73 (21)	< .001	3.99 (2.44-6.53)
TBI-based conditioning regimen, no. (%)	23 (26)	62 (18)	.10	1.58 (0.91-2.74)
Myeloablative HSC transplantation, no. (%)	81 (92)	308 (91)	.73	1.16 (0.49-2.74)
Bone marrow as the source of stem cells, no. (%)	60 (68)	108 (32)	< .001	4.58 (2.69-7.83)
Methotrexate in the prophylaxis for GVHD, no. (%)	76/82 (93)	142/164 (86)	.13	1.96 (0.76-5.05)
Hepatic dysfunction, no. (%)	26 (29)	94 (28)	.73	1.09 (0.65-1.83)

SOS indicates sinusoidal obstruction syndrome; 95% CI, 95% confidence interval; NA, not applicable; MDS, myelodysplasia; HSC, hematopoietic stem cell; CMV, cytomegalovirus; TBI, total body irradiation; GVHD, graft-versus-host disease; and TPN, total parenteral nutrition.

with ferritin level higher than 1000 ng/mL were more likely to develop SOS, with an OR of 2.49 (95% CI, 1.54-4.02). High ferritin levels (> 1000 ng/mL) were also strongly associated with lower 5-year overall survival (42% vs 73% for patients with ferritin ≤ 1000 ng/mL, $P < .001$, log-rank test).

As shown in Table 4, by multivariate analysis, the following variables were associated with SOS: allogeneic HSC transplantation (OR = 8.25; 95% CI, 3.31-20.57; $P < .001$), receipt of imatinib before HSC transplantation (OR = 2.60; 95% CI, 1.16-5.84; $P = .02$), receipt of busulfan in the conditioning regimen (OR = 2.18; 95% CI, 1.25-3.80; $P = .006$), and serum ferritin level higher than 1000 ng/mL (OR = 1.78; 95% CI, 1.02-3.08; $P = .04$).

Because most of the cases of SOS occurred in allogeneic HSCT recipients (82 of the 88 cases), we ran an analysis of risk factors in these patients. Multivariate predictors of SOS were receipt of imatinib before HSC transplantation (OR = 2.16; 95% CI, 1.22-3.82; $P = .01$), receipt of busulfan in the conditioning regimen (OR = 2.22; 95% CI, 1.26-3.89; $P = .005$), and serum ferritin level higher than 1000 ng/mL (OR = 2.16; 95% CI, 1.22-3.82; $P = .008$).

Discussion

Our results show that high ferritin serum level is an independent pretransplantation risk factor for SOS. Other risk factors identified were allogeneic HSC transplantation, and receipt of imatinib before transplantation and busulfan in the conditioning regimen.

Studies evaluating the impact of iron overload before HSC transplantation on different outcomes have been increasingly reported. Miceli et al observed that iron overload, assessed by bone marrow biopsy, was an independent risk factor for severe infection among patients with multiple myeloma receiving autologous HSCT conditioned with melphalan 200 mg/m^2.[10] In another study, high serum ferritin level was associated with a higher incidence of

Table 3. Univariate analysis of different cutoff values of serum ferritin and the risk for sinusoidal obstruction syndrome

	SOS, no. (%)				ROC curve analysis	
Ferritin serum level, ng/mL	Yes n=88	No n=339	*P*	Odds ratio (95% CI)	AUC	*P**
623 (median)	54 (61)	159 (47)	.02	1.80 (1.08-2.99)	0.572	.04
1000	43 (49)	94 (28)	< .001	2.49 (1.50-4.14)	0.606	.002
1500	30 (34)	56 (16)	< .001	2.61 (1.49-4.57)	0.588	.01
2000	21 (24)	41 (12)	.005	2.28 (1.21-4.27)	0.559	.09
3000	11 (12)	14 (4)	.003	3.32 (1.34-8.13)	0.542	.23
4000	7 (8)	7 (2)	.01	4.10 (1.25-13.44)	0.529	.39

SOS indicates sinusoidal obstruction syndrome; 95% CI, 95% confidence interval; ROC, receiver operating characteristic; and AUC, area under the curve.
*Probability that the area is different from .5.

Table 4. Factors associated with sinusoidal obstruction syndrome by multivariate analysis

Variable	Odds ratio	95% CI	*P*
Allogeneic HSC transplantation	8.25	3.31-20.57	< .001
Receipt of imatinib before HSC transplantation	2.60	1.16-5.84	.02
Receipt of busulfan in the conditioning regimen	2.18	1.25-3.80	.006
Serum ferritin level higher than 1000 ng/mL	1.78	1.02-3.08	.04

95% CI indicates 95% confidence interval; and HSC, hematopoietic stem cell.

relapse and relapse-associated mortality among 315 patients with lymphoma who received autologous HSCT.[14] Kataoka et al reported that high pretransplantation serum ferritin was associated with higher 5-year mortality among allogeneic HSCT recipients. The increase in death was attributed to organ failure (cardiac, renal, hepatic, and multiorgan) and infection.[15] An association between high pretransplantation ferritin serum levels and higher mortality was also reported in a study of 190 allogeneic HSCT recipients. In this study, patients with iron overload were more likely to die by day +100, both from GVHD and bloodstream infections.[16] In another study with a larger number of HSCT recipients, an elevated pretransplantation serum ferritin level was associated with lower overall and disease-free survival, especially in patients with acute leukemia and myelodysplasia.[17] We also observed an association between iron overload and higher 5-year mortality. It is not clear if iron overload per se contributes to the poor survival or if it is merely a surrogate marker of poor prognosis. Other studies are needed to explore these possibilities.

The association between high iron stores and SOS was reported by Morado et al in a study in 180 autologous HSCT recipients (mostly breast cancer and lymphoma). Diagnostic criteria for SOS were similar to ours. The incidence of SOS was 12.2%. By multivariate analysis, serum ferritin level more than 300 ng/dL remained significant as a risk factor for SOS.[12] A trend toward an association between high ferritin serum levels and the occurrence of SOS was reported in another study.[17]

In the present study, we confirm the association between high ferritin serum levels before transplantation and the occurrence of SOS, in a large cohort of both autologous and allogeneic HSCT recipients. Our patient's population was representative of a typical HSC transplantation center, and the period of study was relatively recent (between 2002 and 2007).

An association between iron overload and liver injury has been reported in different clinical scenarios. For example, in a study of 76 survivors of allogeneic HSC transplantation for at least 1 year, 88% had high ferritin serum levels. Impaired liver function was commonly observed among these patients, and improved with iron chelation.[18] Iron-induced hepatotoxicity is multifactorial, and involves oxidative stress and modulation of gene expression of Kupffer cells.[19] Cellular injury is induced by iron-generated oxyradicals and peroxidation of lipid membranes.[20] However, the mechanism by which iron overload is associated with SOS remains poorly understood.

In our study, other risk factors for SOS were allogeneic HSC transplantation, and the exposure to busulfan and imatinib. The association between allogeneic HSC transplantation and SOS was reported in other studies.[21,22] Oral busulfan in association with cyclophosphamide in the conditioning regimen is associated with liver toxicity and SOS.[22-24] By contrast, regimens containing busulfan in combination with other drugs, such as melphalan and thiotepa, seem not to be associated with liver toxicity.[24-26] In the present study, the overwhelming majority of patients received oral busulfan followed by cyclophosphamide as the conditioning regimen.

Busulfan is eliminated through glutathione conjugation, and therefore its metabolism consumes glutathione. The depletion of glutathione in the liver seems to play a major role in the pathogenesis of SOS, because many drugs that potentially cause injury to the endothelium (an early and key event in the development of SOS) are metabolized through the glutathione pathway.[27]

Pharmacogenetic profiles seem also to play a role in chemotherapy-induced liver injury and SOS. In a study in 84 adult allogeneic HSCT recipients who received busulfan and cyclophosphamide as part of the conditioning regimen, genetic polymorphisms of the methylene-tetrahydrofolate reductase (MTHFR) were evaluated by a polymerase chain reaction (PCR) technique. Multivariate analysis identified one polymorphism (MTHFR-1298A>C) as an independent predictor of hyperbilirubinemia and SOS.[28]

We observed that the use of imatinib before transplantation was associated with an increased risk of SOS. To our knowledge this is the first report of this association. Imatinib mesylate is the first tyrosine kinase inhibitor introduced in clinical practice. It is effective in the treatment of chronic myeloid leukemia, Philadelphia-positive acute lymphoid leukemia, and gastrointestinal stromal cell tumors. Imatinib is metabolized in the liver, using cytochrome P-450 (CYP) 3A4 enzyme.[29] CYP3A4 inducers, such as phenitoin, reduce serum concentration of imatinib, whereas CYP3A4 inhibitors (such as ketoconazole and some food products) increase significantly imatinib serum levels. Grades III-IV hepatic toxicity include elevations in transaminases in 1% to 3%, and hyperbilirubinemia in 0.4% to 3.5%.[29] In addition, reports of liver toxicity of imatinib have been published.[30-35] Liver toxicity usually occurs after more than 3 months of treatment, and drug interruption reverses the toxicity in the large majority of cases. The mechanisms of liver toxicity are unknown. Histology shows a hepatocellular pattern of injury, with mild cholestasis.[36] It is possible that liver toxicity of imatinib may predispose to toxic damage from the conditioning regimen and the subsequent development of SOS. However, further studies are needed, because the relationship between imatinib use and SOS was based on a small group of patients.

We used serum ferritin as a measure of iron stores. Other measures to assess iron stores include x-ray fluorescence of iron, magnetic resonance imaging, computed tomography, biomagnetic susceptometry,[37] and iron staining in biopsy sections of the bone marrow and the liver.[38,39] Serum ferritin may be increased in conditions other than iron overload, including chronic inflammation and infection.[40] Nevertheless, serum ferritin is considered a valuable method for hepatic iron evaluation.[41] Furthermore, values higher than 1000 ng/mL (the cutoff value that we used) are rarely reported in these conditions. Therefore, we think that our pretransplantation estimation of iron overload is reliable. Even if we consider the potential limitations of serum ferritin in the estimation of iron stores, a pretransplantation value higher than 1000 ng/mL (irrespective of iron stores) is still a valid risk factor for SOS.

Our study is limited by its retrospective nature. Therefore, other potentially important variables, such as duration of imatinib therapy before transplantation and exposure to other drugs that may increase liver toxicity, were not evaluated. Another limitation of

retrospective studies, the absence of important data, was not a problem in our study, because no patient was excluded due to missing data.

The results of the present study and of other recent reports argue in favor of the development of future studies to investigate the usefulness of prophylactic and therapeutic measures aimed at reducing the negative effects of iron overload on the outcome of HSCT recipients. Pretransplantation iron chelation in patients with ferritin levels higher than 1000 ng/mL would be a reasonable measure to be explored. Another strategy to reduce the incidence of SOS would be to change the way busulfan is administered. The use of intravenous (instead of oral) busulfan may decrease the risk of SOS by avoiding a hepatic first-pass extraction effect that results in high concentration of busulfan in the portal-hepatic venous system.[42] Finally, clinicians should be aware of the potential of chronic use of imatinib before transplantation to increase the risk of SOS. However, as mentioned, further studies are needed to confirm our findings.

In summary, our study identified high ferritin serum level, allogeneic HSC transplantation, and receipt of imatinib pretransplantation and busulfan in the conditioning regimen as independent risk factors for SOS.

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Authorship

Contribution: S.C.M. designed and performed the research, analyzed the data, and wrote the paper; A.M. designed the research and reviewed the paper; A.M.d.A. analyzed the data and wrote the paper; M.C. collected and reviewed the data; L.F.B. reviewed the paper; and M.N. analyzed the data and wrote the paper.

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