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Reduced Risk of Sinusoidal Obstruction Syndrome of the Liver after Busulfan-Cyclophosphamide Conditioning Prior to Allogeneic Hematopoietic Stem Cell Transplantation

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The aim of this study is to evaluate the incidence of sinusoidal obstruction syndrome (SOS) of the liver and the clinical outcome after hematopoietic stem cell transplantation (HSCT) based on several modifications in our protocols. We retrospectively investigated 372 patients undergoing myeloablative conditioning with oral busulfan (Bu) and cyclophosphamide before allogeneic HSCT during 1990–2015. Patients' supportive care was changed in order to reduce the regimen-related toxicities. Norethisterone use was terminated in 1998, therapeutic drug monitoring of Bu was initiated in 2000, and the use of liver supportive drugs, such as ursodeoxycholic acid and N-acetyl-L-cysteine, were started in 2002 and 2009, respectively. In total, 26 patients (7.0%) developed SOS at a median of 19 days after transplantation. Of these 26 patients, 20 died at a median of 119 days after HSCT and 102 days after the diagnosis of SOS. The incidence of SOS decreased over time in accordance with the improvements in supportive care. The highest incidence of SOS was during 1995–1999 (16.2%) compared with 2.3% during 2010–2015. Overall survival for patients with SOS was 62%, 46%, and 27% at 100 days, 1 year, and 5 years after HSCT, respectively, compared with 92%, 77%, and 66% for those who did not develop SOS ($P < 0.001$). In conclusion, the incidence of SOS and related deaths were significantly decreased over the last years. Our institution pursues massive preventative and personalized measures for SOS. This strategy may also be applicable in other conditioning protocols in order to reduce the incidence of SOS and, hence, improve the clinical outcome.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Sinusoidal obstruction syndrome (SOS) is one of the most common complications after busulfan-cyclophosphamide conditioning. Several modifications have been applied in the clinic protocols in order to reduce the incidence of SOS and improve the clinical outcome after hematopoietic stem cell transplantation.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What is the incidence of SOS since 1990 until 2015? After several modifications in our hospital protocols, how much improvement has happened?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The incidence of SOS-related deaths have significantly decreased over time in accordance with the improvements

in supportive care. The highest incidence of SOS was during 1995–1999 of 16.2% compared with 2.3% during 2010–2015. Our institution pursues massive preventative and personalized measures for SOS.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ All changes in our treatment strategies in addition to personalized patients' treatment have made SOS a very rare event at our center in recent years. These strategies may also be applicable in other conditioning protocols to reduce the incidence of SOS and, hence, improve the clinical outcome.

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INTRODUCTION

Sinusoidal obstruction syndrome (SOS; previously called veno-occlusive disease) is one of the most common and serious complications after myeloablative conditioning (MAC) for allogeneic hematopoietic stem cell transplantation (HSCT).¹ SOS is a clinical syndrome consisting of jaundice, ascites, and/or unexplained weight gain, as well as hepatomegaly and/or right upper quadrant abdominal pain.² Histologically, SOS is characterized by hepatic venular occlusion, sinusoidal fibrosis, phlebosclerosis, and zone 3 hepatocyte necrosis.³ The mean SOS incidence after HSCT is 20–30% with a mortality rate up to 67%.⁴

It was previously reported that the incidence ranges from 5 to 60%,^{2,5,6} however, recent reports showed that SOS incidence has decreased to 10–15% post-allogeneic HSCT with MAC and < 5% after allogeneic HSCT conditioned with reduced intensity conditioning (RIC) regimen and autologous HSCT.^{4,5,7}

Several studies have shown that busulfan (Bu)-based conditioning before HSCT is one of the most important risk factors for SOS development.^{2,9,10} Bu is a cytostatic drug that consumes up to 60% of hepatic glutathione (GSH), an important intracellular antioxidant.¹¹ In addition to the endothelial cell damage due to the toxicity of conditioning regimen, GSH exhaustion may contribute to SOS development.^{12,13}

Bu has a narrow therapeutic range with high interindividual drug kinetics, particularly in infants and children. Low exposure to Bu has been correlated with increased incidence of graft rejection and relapse.¹⁴ Conversely, high levels were associated with poor overall outcome and fatal toxicity, particularly SOS.¹⁵ Thus, individualization of the Bu therapy may be necessary. The target range for Bu area under the concentration-time curve (AUC) when administered twice per day is 9,000 and 12,000 ng hour/mL, whereas the AUC ranges between 3,600 and 5,400 ng hour/mL when Bu is given four times per day.^{8,16}

However, several other risk factors have been reported to be associated with the development of SOS. These risk factors were subdivided to: (i) transplant-related factors, including unrelated donor, human leukocyte antigen (HLA)-mismatched donor, non T-cell-depleted transplant, high-dose total body irradiation (TBI)-based regimen, and second HSCT; (ii) patient and disease-related factors, including older age, Karnofsky score below 90%, metabolic syndrome, female receiving norethisterone, advanced disease (beyond second complete remission, CR2, or relapse/refractory), thalassemia and genetic factors (glutathione S-transferase mu 1 polymorphism, C282Y allele, and others); (iii) hepatic-related factors, including transaminases > 2.5 upper limit of normal (ULN), serum bilirubin > 1.5 ULN, cirrhosis, active viral hepatitis, abdominal or hepatic irradiation, previous use of gemtuzumab ozogamicin or inotuzumab, hepatotoxic drugs, and iron overload.¹⁷

To reduce the incidence of SOS and to improve the clinical outcome after HSCT, several modifications have been applied to our protocols, such as individualized therapeutic

drug monitoring (TDM) of Bu, the use of RIC conditioning in patients with organ comorbidity, discontinued norethisterone treatment to prevent menstruation in women, and both N-acetyl-L-cysteine (NAC) and ursodeoxycholic acid (UDCA) were added as standard supportive care to prevent hepatic toxicity after HSCT.

METHODS

Patients

The incidence of SOS was retrospectively studied in 372 consecutive patients with HSCT receiving full dose myeloablative conditioning with Bu and cyclophosphamide (Cy) between 1990 and 2015 at the Karolinska University Hospital, Stockholm, Sweden. All patients and donors were typed using polymerase chain reaction-sequence-specific primer high-resolution typing for both HLA class I and II alleles. Patient characteristics are displayed in **Table 1**.

The study was approved by the regional ethical review board in Stockholm (DNR 425/97) and all procedures were in accordance with the Helsinki Declaration. The written informed consent was obtained from each patient (or their guardians for minor patients).

Conditioning regimen and graft-vs.-host disease prophylaxis

All patients received MAC consisting of Bu (4 mg/kg/day for 4 days) followed by Cy (60 mg/kg/day for 2 days in malignancies and 8 g/m² in nonmalignant disorders).¹⁸ Antithymocyte globulin (ATG) was given to all patients with an unrelated donor and all patients with a nonmalignant disorder as part of the conditioning with the last dose on the day before transplantation.¹⁹ Most patients received thymoglobulin ($n = 196$) at a total dose of 4–10 mg/kg, whereas a few patients received ATG-Fresenius (25–30 mg/kg; $n = 10$), muromonab-CD3 (OKT-3; 25 mg; $n = 5$) or alemtuzumab (30–90 mg; $n = 6$).

Prophylaxis against graft-vs.-host disease (GVHD) consisted of cyclosporine A (CsA) alone ($n = 4$) or in combination with methotrexate ($n = 332$), prednisolone ($n = 19$), or mycophenolate mofetil ($n = 5$). GVHD prophylaxis with sirolimus and tacrolimus was given to 12 patients.²⁰ During the first month, blood CsA levels were kept at 100 or 200 ng/mL when a sibling donor or unrelated donor was used, respectively.²¹ Patients with nonmalignant diseases were also kept at the higher CsA level of 200 ng/mL. In the absence of GVHD, patients with malignant diseases discontinued CsA after tapering at 34 months in HLA-identical transplants, and at 6 months in unrelated donor transplants, whereas it was discontinued after 12–24 months in patients with nonmalignant disorders.²²

Stem cell source

The graft source was bone marrow (BM) in 157 patients, peripheral blood stem cells (PBSCs) in 195 patients, and cord blood (CB) in 20 patients. Before aphaeresis to obtain PBSC, stem cells were mobilized with subcutaneous granulocyte-colony stimulating factor (G-CSF) daily for 4–6 days.

Table 1 Patient characteristics

	All patients	No SOS	SOS	P value
N	372	346	26	
Sex (male/female)	220/152	207/139	13/13	0.40
Age	34 (<1–61)	34 (<1–61)	29 (<1–57)	0.35
Children (< 18 years)	114 (31%)	105 (30%)	9 (35%)	0.65
Diagnosis				0.77
AML/ALL	196/14	186/11	10/3	
Chronic leukemia	58	54	4	
MDS	43	40	3	
Other malignancy	6	4	2	
Nonmalignant	55	51	4	
Disease phase (early/late)	235/136	223/122	12/14	0.09
Donor				0.03
MRD	164 (44%)	148 (43%)	16 (62%)	
MUD	166 (45%)	160 (46%)	6 (23%)	
Mismatched	42 (11%)	38 (11%)	4 (15%)	
Donor age	31 (0–66)	31 (0–66)	29 (0–58)	0.19
Female to male	82 (22%)	74 (21%)	8 (31%)	0.39
Stem cell source				
BM/PBSC/CB	157/195/20	140/189/17	17/6/3	0.06
TNC dose ($\times 10^6$ /kg)	6.5 (0.03–80.0)	6.7 (0.03–80)	2.7 (0.2–16.8)	0.001
CD34 ⁺ cell dose ($\times 10^6$ /kg)	6.5 (0.01–46.0)	6.6 (0.01–46)	3.8 (0.2–22.1)	0.02
GVHD prophylaxis				
CsA + MTX	329	307	22	0.82
CsA + prednisolone	19	16	3	0.28
Other	24	23	1	0.80
ATG	219 (59%)	208 (60%)	11 (42%)	0.12

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, anti-thymocyte globulin; BM, bone-marrow; CB, cord blood; CsA, cyclosporine; Early, >CR1/CP1 or nonmalignant disorder; Female to male, female donor to male recipient; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome; MRD, matched related donor; MTX, methotrexate; MUD, human leukocyte antigen-A, HLA-B, and HLA-DR matched unrelated donor; PBSC, peripheral blood stem cells; TNC dose, total nucleated cell dose.

SOS

According to our hospital protocols; the diagnosis of hepatic SOS was based on the following clinical criteria: bilirubin > 34 μ mol/L within 1 month after HSCT and 2 of the following: painful hepatomegaly, ascites, or > 5% weight gain.²

Supportive care

Supportive care has been described in detail previously.²³ The use of norethisterone to women was stopped in 1998,¹⁰ TDM of Bu was initiated in 2000,²⁴ a minimal time interval of 24 hours between Bu and Cy treatment was also introduced in the year 2000,²⁵ the use of UDCA²⁶ for prevention of hepatic complications started in 2002, and, finally, the prophylactic administration of NAC during Bu conditioning was introduced in 2009.²⁷

Statistics

Overall survival was calculated using the Kaplan–Meier method and compared with the log rank test. Survival time was calculated from the day of transplantation until death or last follow-up. The incidence of SOS was obtained using an estimator of cumulative incidence curves. A competing event was death within 30 days after HSCT without SOS. Univariate and multivariate predictive analyses for SOS were performed with logistic regression, as SOS is an early

event occurring within 30 days after HSCT. Factors with a *P* value < 0.10 in the univariate analysis were included in the backward elimination multivariate analysis. Factors analyzed were patient, donor age, sex, diagnosis, donor type, GVHD prophylaxis, disease phase, year of HSCT, previous allo/auto HSCT, total nucleated and CD34⁺ cell dose, ABO blood group match, ATG, sex match, and stem-cell source. Analyses were performed using the freely available EZR software, and Statistica 13 software.

RESULTS

In total, 26 patients (7.0%) developed SOS at a median of 19 days (6–30) after transplantation (**Figure 1a**). Of these 26 patients, 20 died at a median of 119 days (12–3,107) after HSCT and 102 days (1–3,097) after the diagnosis of SOS. Among those 20 patients, only 8 patients died because of SOS itself, whereas the other causes of death for the rest of the patients were: relapse (*n* = 7), infection (*n* = 2), chronic GVHD (*n* = 1), and other causes (*n* = 2). The incidence of SOS decreased over time in accordance with the improvements in supportive care. The incidence of SOS during 1990–1995 was 14.7%, whereas the highest incidence of SOS was during 1995–1999 (16.2%) compared with 5.1% (2000–2004), 3.7% (2005–2009), and 2.3% during 2010–2015 (**Figure 1b**).

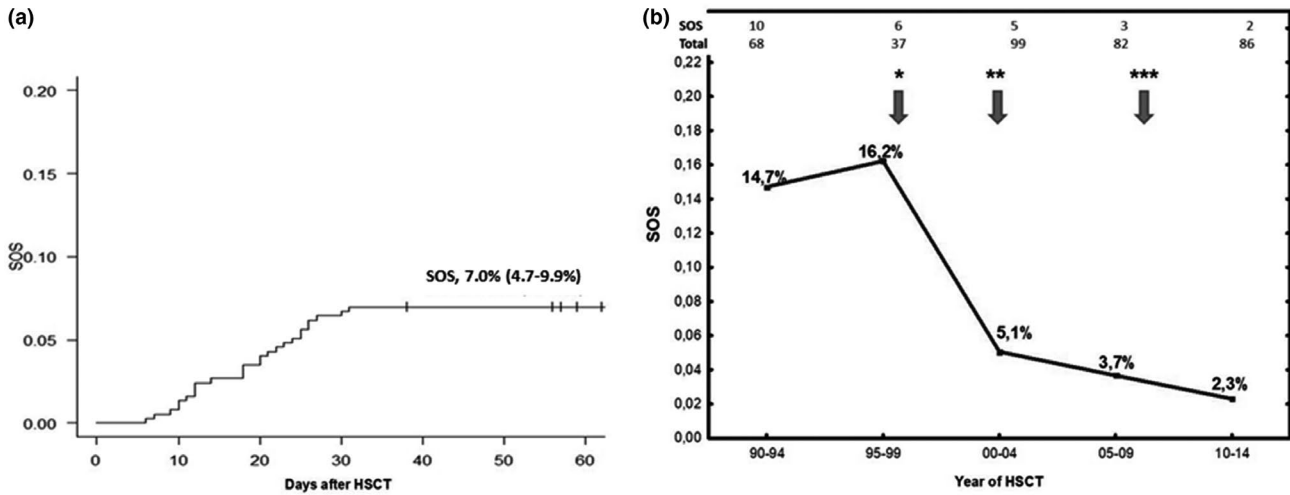


Figure 1 Incidence of SOS after hematopoietic stem cell transplantation (HSCT) in patients receiving busulfan-based myeloablative conditioning. (a) cumulative incidence of sinusoidal obstruction syndrome (SOS; 95% confidence interval). (b) Incidence of SOS depending on year of HSCT. *Stop of norethisterone therapy + individualized dosing guided by busulfan (Bu) blood concentration. **Introduction of ursodiol. ***Introduction of N-acetyl-L-cysteine during Bu.

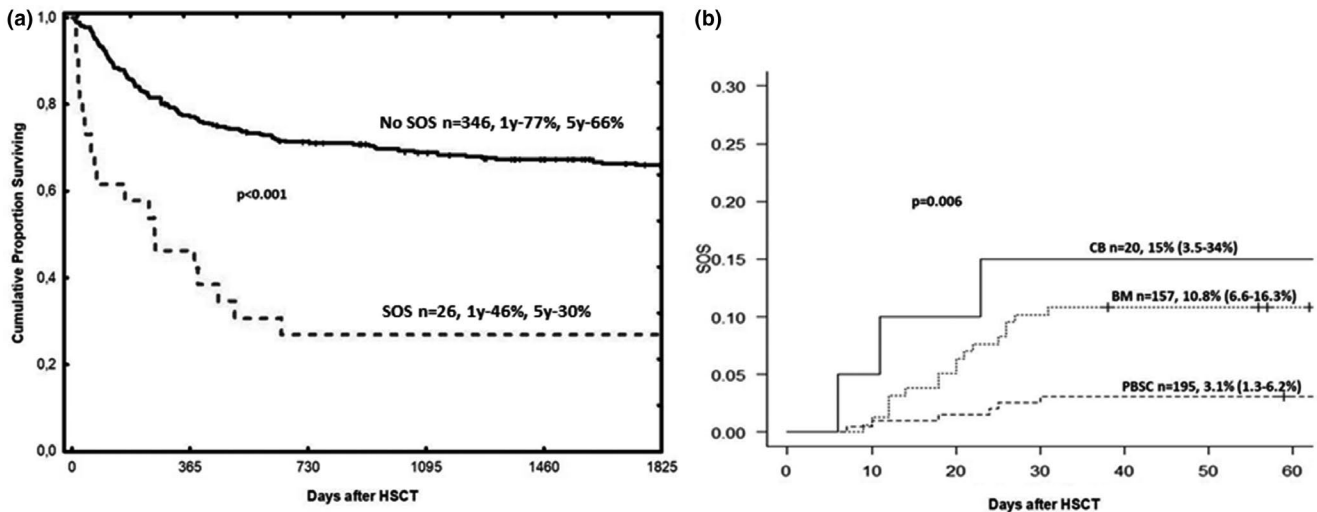


Figure 2 Survival and effect of the stem cell source after hematopoietic stem cell transplantation (HSCT) in patients receiving busulfan (Bu)-based myeloablative conditioning. (a) Overall survival in patients with and without sinusoidal obstruction syndrome (SOS). (b) Incidence of SOS depending on stem cell source (95% confidence interval). BM, bone marrow; CB, cord blood; PBSC, peripheral blood stem cells.

OS for patients with SOS was 62%, 46%, and 27% at 100 days, 1 and 5 years after HSCT, respectively (**Figure 2a**). For patients who did not develop SOS, the corresponding survival was 92%, 77%, and 66% ($P < 0.001$ vs. SOS). Patients received PBSC had an SOS incidence of 3.1% (6/195), compared with 10.8% (17/157) and 15.0% (3/20) in patients given BM and CB, respectively ($P = 0.006$; **Figure 2b**). A few patients with acute lymphoblastic leukemia (ALL; $n = 14$) received Bu-Cy, mainly before the year 1995. The incidence of SOS among those patients was high at 21.4%.

In multivariate analysis (corrected for year of transplant), late phase disease (second complete remission/chronic phase or more advanced phase) was associated to SOS (odds ratio 2.39; 95% confidence interval 1.04–5.45; $P = 0.038$). Moreover; patients with a mismatched donor and

developed SOS had significant lower survival rates ($P < 0.05$) compared with matched related donor and matched unrelated donor, although no significant difference was observed in patients' survival between matched related donor and matched unrelated donor ($P = 0.28$) (**Figure 3a**). Late-phase disease in patients with SOS (second complete remission/chronic phase or more advanced phase) was significantly associated with lower survival rates ($P < 0.001$) compared with early phase disease (**Figure 3b**). Finally, male patients with immunized female donors and developed SOS had significantly lower survival rates ($P < 0.001$) compared with female patients with male donors or others (**Figure 3c**).

Because of the clear decrease in SOS incidence after 1999, a separate multivariate analysis was performed including only patients who underwent a transplantation after 1999 ($n = 267$).

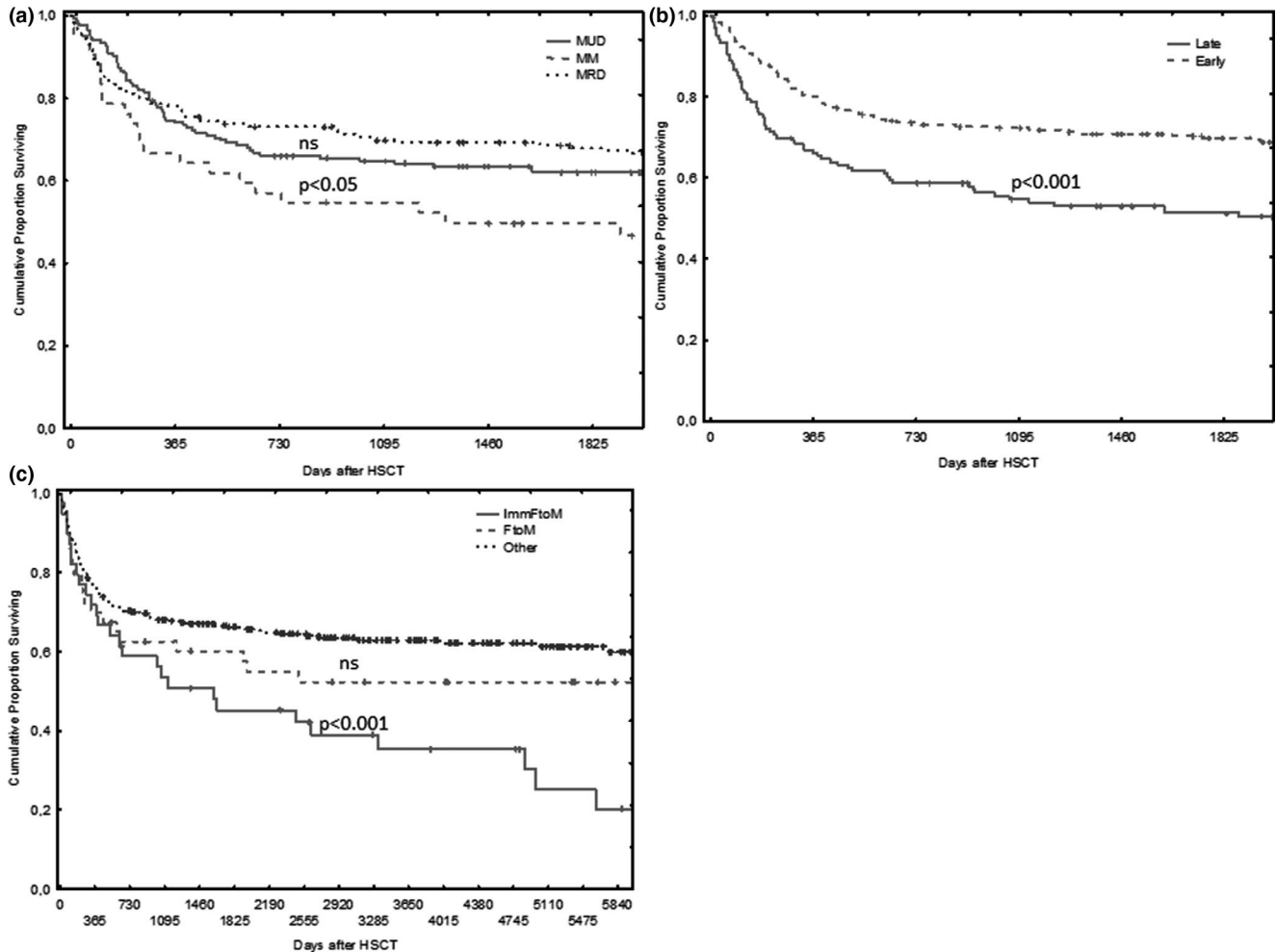


Figure 3 Overall survival in patients with sinusoidal obstruction syndrome after hematopoietic stem cell transplantation (HSCT) in patients receiving busulfan-based myeloablative conditioning. (a) Human leukocyte antigen (HLA)-A, HLA-B, and HLA-DR matched unrelated donor (MUD) compared with mismatched (MM) donors and matched related donor (MRD). (b) Late disease phases (> CR1/CP1) compared with early disease phase. (c) Male patients with immunized female donors compared female patients with male donors or others. ImmFtoM, immunized female donor to male recipient; FtoM, female donor to male recipient; ns, not significant.

This analysis revealed that donor age (by decades, odds ratio 0.42; 95% confidence interval 0.25–0.73; $P = 0.002$) had a significant effect on the incidence of SOS ($n = 10$).

Factors included in these analyses were patients' sex and age, diagnosis, donor type, GVHD prophylaxis, disease phase, total nucleated cell (TNC) dose, CD34+ cell-dose, donor age, female-to-male, G-CSF, and stem cell source (Table 1).

During the period 2010–2015, 418 patients received other conditioning protocols than Bu-Cy and only 5 patients (1.2%) developed SOS. Among the 80 patients who received other MAC conditioning (mainly TBI), the incidence of SOS was 2.5% (2/80), whereas 338 patients received RIC and the incidence of SOS was 0.9% (3/338).

DISCUSSION

HSCT is a curative treatment for several malignant and nonmalignant diseases. However, life-threatening toxicities and adverse effects can negatively affect clinical outcome. The conditioning used prior to HSCT, mainly Bu-based

conditioning, is one of the most common causes of these toxicities and several strategies have been introduced to improve clinical outcome. Several serious complications, such as elevated liver enzymes, SOS, hemorrhagic cystitis, interstitial pneumonia, and mucositis have been correlated to high-dose Bu.^{1,2,18,28,29}

In our center, we have developed several strategies over more than 20 years to reduce the incidence of the serious adverse effects, mainly SOS, improving both the clinical outcome and the patients' quality of life. Among patients receiving conventional Bu-based myeloablative conditioning prior to HSCT, the incidence of SOS decreased dramatically during 1995–2015. In the last 3 years, only five patients were diagnosed with SOS (1.8%) among all transplants ($n = 280$). Based on our investigations, the decrease of SOS incidence is the result of an effective and stepwise prevention based on continuously increased knowledge of factors associated with SOS over time.

SOS was defined by McDonald *et al.* as the onset of two of the following occurring before day 30 post-HSCT:

(i) jaundice (bilirubin > 27 $\mu\text{mol/L}$), (ii) tender hepatomegaly, and (iii) ascites or weight gain. Although Jones *et al.* narrowed the definition to the following: onset before day 21 post-HSCT of hyperbilirubinemia (bilirubin > 34 $\mu\text{mol/L}$) as well as two of the following: (i) hepatomegaly, (ii) ascites, and (iii) weight gain.^{2,31} However, the European Society for Blood and Marrow Transplantation (EBMT) has published in 2016 revised criteria for SOS diagnosis in adults based on the onset of SOS: (i) classic SOS onset within 21 days post-HSCT (bilirubin \geq 34 $\mu\text{mol/L}$ and two of the following criteria must be present: painful hepatomegaly, weight gain \geq 5% and ascites), (ii) late onset \geq 21 days post-HSCT (classical veno-occlusive disease/SOS beyond day 21 or histologically proven SOS or two or more of the following criteria must be present: bilirubin \geq 34 $\mu\text{mol/L}$, painful hepatomegaly, weight gain > 5%, ascites and hemodynamic or/and ultrasound evidence of SOS).¹⁷ New EBMT criteria for severity grading of a suspected SOS in adults was reported in the same publication.¹⁷ Similarly, revised criteria for pediatric patients were recently published by EBMT as well.³²

We have previously reported that norethisterone, Bu, and an HLA mismatched donor increased the incidence of SOS.¹⁰ In 1998, the use of norethisterone as menopausal hormone therapy was stopped when we had the highest incidence of SOS (16.2%). This was followed by a major modification in our conditioning strategy as the daily individualized Bu TDM and dose adjustment was introduced in 2000²⁴ that resulted in a dramatic decrease in the incidence of SOS to be 5.1% (2000–2004). This change was made in response to reports that Bu has a wide interindividual and intra-individual variation in its kinetics.³³ Bu is also known to have a narrow therapeutic window and its adverse effects are delayed.^{34,35} Copelan *et al.*³⁶ have reported a significant positive correlation between high Bu AUC and SOS. In agreement with our findings, the incidence of SOS decreased from 24.1% to 3.4% in patients when dose individualization was introduced.³⁷

In the same year (2000), we introduced a minimal time interval of 24 hour between Bu and Cy treatment, which has also contributed to reduced SOS incidence.²⁵ Cy is a prodrug that is converted to its active metabolite, 4-hydroxycyclophosphamide (4-OH-Cy) through cytochrome P450. As mentioned earlier; Bu consumes up to 60% of hepatic GSH¹¹ that is a valuable enzyme in the Cy metabolic pathway.^{38,39} Moreover, several cytochrome P450 enzymes are involved in Bu metabolism.⁴⁰ It was also reported that altering the order of administration from Bu-Cy to Cy-Bu yields the same engraftment outcome but reduces the toxicity of the conditioning regimen in patients.^{41,42} The accumulation of the cytotoxic 4-OH-Cy due to GSH consumption by Bu can increase the incidence of SOS.²⁵

To prevent hepatic complications, UDCA was introduced in 2002²⁶ that further decreased the incidence of SOS (3.7%; 2005–2009). In agreement with our findings, UDCA was reported to be effective for SOS prophylaxis in patients undergoing HSCT in a systematic review of controlled clinical trials.⁴³ This step was followed by the prophylactic administration of NAC during Bu conditioning in 2009.²⁷ Bu is a hepatotoxic drug that consumes up to 60% of the

hepatic GSH *in vivo*,¹¹ whereas NAC is a GSH precursor that increases the cellular content of GSH. NAC is also used in the treatment of hepatotoxicity caused by acetaminophen as well as for the treatment of SOS. It was previously reported that NAC did not interfere with the myeloablative effect or kinetics of Bu²⁷ and normalized the liver enzymes in three patients who developed SOS after HSCT.⁴⁴ In our current hospital protocol, all patients receive prophylactic NAC treatment upon start of Bu conditioning twice daily at a dose of 100 mg/kg regardless of their liver status. We recently reported that NAC is a potential prophylactic treatment for hepatotoxicity during Bu conditioning and does not alter the clinical outcome.⁴⁵ In patients treated with NAC, liver enzymes were significantly decreased after Bu conditioning compared with their start values, moreover; liver enzymes were normalized in those patients who had significantly high start values.⁴⁵ However, further prospective controlled studies are warranted to confirm the role of UDCA and NAC in reducing the incidence of SOS.

In patients who underwent transplantation between 2010 and 2015 who received other conditioning protocols than Bu-based MAC, SOS incidence was only 1.2% (5/418). Most of these patients received RIC conditioning. RIC was introduced to older patients and those with higher comorbidity index with an SOS incidence of only 0.9% (3/338). Among patients receiving MAC, mainly TBI-based (4 \times 3 Gy), the incidence of SOS was 2.5% (2/80). During the same period, 2.3% of the patients who received Bu-based MAC have developed SOS, which confirms that SOS preventive measures could be applied to other conditioning regimens as well.

To investigate additional factors that can affect the incidence of SOS, further analyses were performed. In the multivariate analysis, patients with late-phase disease (beyond CR1/CP1) were associated with higher SOS incidence. These patients received more cytostatic treatment prior to HSCT and may, therefore, be more vulnerable due to pre-existing liver damage prior to the start of HSCT conditioning. The univariate analysis revealed that patients receiving PBSC had lower SOS incidence than those with BM or CB grafts. The same findings were reported previously in autologous HSCT by Fisher *et al.*⁴⁶ PBSCs are associated to an increased alloreactivity of the graft; moreover, the endothelial damage subsequent to alloreactivity is known to be a risk factor for the occurrence of SOS. The lower SOS incidence in patients who received PBSC can be due to the higher cell dose because a high TNC was also significantly associated to less SOS in the univariate analysis. However, analyzing the effect of TNC on SOS incidence in BM and PBSC separately showed no statistical correlation.

Moreover, BM contains low numbers of mesenchymal stem cells (MSCs; < 1 MSC/10,000 nucleated cells).⁴⁷ Although higher numbers of MSC (> 1%) have strong immunosuppressive and anti-inflammatory effects, low numbers of MSCs may be immunostimulatory. Such an immunostimulatory effect by low numbers of MSCs in BM, but absent in PBSC grafts could induce SOS. Interestingly, patients with PBSC had less SOS than recipients of BM. Another explanation could be that the G-CSF treatment of the donor

before PBSC aphaeresis may result in reduced donor T-cell alloreactivity.⁴⁸

Bu-based conditioning in patients with ALL has ceased due to the poor outcome and increased relapse incidence compared with TBI.^{18,49} Fourteen patients with ALL receiving Bu-based conditioning were included in this study. Most of these patients ($n = 12$) underwent transplantation before 1995. Patients with ALL who received Bu-Cy conditioning had a high incidence of SOS (21.4%) confirming that patients with ALL have a high risk for toxicity using Bu-Cy conditioning.

Finally, results obtained from patients who underwent transplantation after 1999 showed that increasing donor age correlated to lower SOS incidence. As SOS is partly an immune-mediated disease, higher donor age is associated with slower engraftment and immune reconstitution, which may indicate a less immune-reactive immune system in older donors.⁵⁰

In conclusion, all previous changes in our strategies (including appropriate conditioning regimen selection, such as RIC for older patients, personalized dose adjustment, and early prophylactic management for hepatotoxicity) in addition to personalized patients' treatment (according to their general condition, age, and diagnosis) have made SOS a very rare event at our center in recent years. These results clearly show that it is possible to reduce the incidence of SOS by aggressive prevention targeting known risk factors. Even though many centers today have replaced the Bu-Cy conditioning with the less toxic fludarabine and Bu 16 mg/kg conditioning, these strategies may also be applicable in other conditioning protocols to reduce the incidence of SOS.

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Conflict of Interest. The authors declared no competing interests for this work.

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