original report

Acute Complications After High-Dose Chemotherapy and Stem-Cell Rescue in Pediatric Patients With High-Risk Neuroblastoma Treated in Countries With Different Resources

abstract

Purpose High-dose chemotherapy with autologous stem-cell rescue (SCR) is a key component of high-risk neuroblastoma (HRNB) therapy. Carboplatin, etoposide, and melphalan (CEM) or busulfan and melphalan (Bu/Mel) are the most evaluated, effective high-dose chemotherapy for HRNB on the basis of results from major cooperative group studies. Toxicity profiles vary between these regimens, and practice variation exists regarding the preferred high-dose therapy (HDT). We sought to evaluate the safety of HDT and autologous SCR for HRNB in a resource-limited country (Egypt) compared with the resource-rich United States.

Patients and Methods We performed a retrospective comparative review of single CEM-based HDT/SCR outcomes through day 100 for HRNB at the Fred Hutchinson Cancer Research Center (FH) in the United States (2005 to 2015) versus Bu/Mel-based HDT at El-Sheikh Zayed Specialized Hospital (SZ) in Egypt (2009 to 2015).

Results Forty-four patients at FH and 77 patients at SZ were reviewed. Pretransplant hepatic comorbidities were significantly higher at SZ (29 of 77 *v* nine of 44; $P = .05$), with 19 of 77 patients at SZ having hepatitis infection. Engraftment was delayed after SZ-Bu/Mel therapy compared with FH-CEM therapy for neutrophils (median 12 days *v* 10 days, respectively; $P < .001$) and platelets (median 20 days *v* 18 days, respectively; $P < .001$). Sinusoidal obstruction syndrome occurred later, after SZ-Bu/Mel therapy (median 19 days *v* 7 days; $P = .033$), and four of eight cases were fatal (six of eight patients had underlying hepatitis infection), whereas three of three cases after FH-CEM therapy were moderately severe. Resource utilization associated with the number of days with fever, antibiotic use, and the number of transfusions administered was significantly higher after FH-CEM therapy than after SZ-Bu/Mel therapy.

Conclusion Use of autologous stem-cell transplantation is feasible in the context of a resource-limited country.

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INTRODUCTION

Neuroblastoma (NB) is the most common extra cranial solid tumor in children younger than age 14 years, representing 7% of all childhood cancer diagnoses in the United States (US) between 1999 and 2013,[1] 7.6% of childhood cancer diagnoses in Europe from 1998 to 2007,[2] and 8% of childhood cancer diagnoses in Egypt between 2002 and 2010.[3] High-risk NB (HRNB) represents nearly half of all newly diagnosed patients with NB.[4] HRNB requires intensive multimodality treatment, and gradual improvements in overall survival have been achieved through the adoption of more intensive therapy and novel immunotherapeutic strategies.[5] Several randomized clinical trials demonstrated that high-dose chemotherapy (HDC) with stem-cell rescue (SCR) improved event-free survival (EFS) of patients with HRNB relative to observation,[6] low-dose chemotherapy,[7] or dose-intensive chemotherapy.[8] There is no international consensus on the best HDC regimen for consolidation treatment of HRNB. Total-body irradiation has been

removed from HDC-SCR on the basis of data from the Children's Oncology Group COG A3973 study, which demonstrated similar 5-year EFS after HDC-SCR with carboplatin, etoposide, and melphalan (CEM), followed by delayed primary site–involved field radiotherapy compared with EFS after the CCG 3891 regimen of total-body irradiation and lower-dose CEM.[9] A retrospective analysis by the European Group for Blood and Marrow Transplantation of 2,741 patients with HRNB who received HDC-SCR in Europe from 1984 to 2006 demonstrated that busulfan and melphalan (Bu/Mel) therapy resulted in a significantly improved 5-year overall survival rate of 48% in first remission compared with other reported regimens.[10] Hartman et al[11] retrospectively reviewed 218 patients who underwent transplantation at Gustave Rousey Institute from 1980 through 1996 and demonstrated similarly that Bu/Mel was associated with better progression-free survival than other regimens. These data prompted a randomized controlled trial that was conducted by the NB group of the International Society of Pediatric Oncology (the HRNBL1/SIOPEN trial) that demonstrated superior survival for children with responsive HRNB who received Bu/Mel compared with CEM (3-year EFS: 49% *v* 33%; $P < .001$) and with less acute toxicity.[12] As a result, Bu/Mel is the preferred consolidation chemotherapy regimen in Europe and some areas in the Middle East. Although Bu/Mel has been studied in pilot trials performed in North America, it has not been adopted as the standard North American consolidation regimen as a result of the discrepancy in outcomes for CEM noted in the HRNBL1/SIOPEN trial compared with those in the COG A3973 trial[9] and the results of the recently completed randomized trial ANBL0532 that demonstrated a superior outcome after tandem transplantation consolidation compared with single transplantation.[13]

The purpose of our study was to compare acute complications, regimen-related toxicities, and 100-day survival between two regimens of HDC-SCR for the treatment of HRNB administered in two different centers within two countries with different economic status and different pretransplantation health problems.

PATIENTS AND METHODS

We conducted a retrospective cohort study that compared patients with HRNB who were treated at either Fred Hutchinson Cancer Research Center (FH) in Seattle, WA, between 2005 and 2015 or El-Sheikh Zayed Specialized Hospital (SZ) in 6th of October, Egypt, between 2009 and 2015. SZ is the second largest hematopoietic cell transplantation (HCT) center in Egypt and performs the largest number of autologous transplantations in the country, with approximately 100 patients per year, of which 30 are pediatric patients who undergo autologous transplantation. FH is one of the largest bone marrow transplantation centers in the United States, with approximately 75 pediatric patients who undergo transplantation per year, approximately 10 of whom undergo autologous transplantation annually. Research was conducted after approval was obtained from the institutional review boards of both institutions. Eligible patients had HRNB classified by using the Children's Oncology Group risk classification incorporating the international staging system,[14] age, MYCN status, ploidy, and histology at diagnosis. Patients were included if they underwent a single HDC-SCR with Bu/Mel at SZ or with CEM at FH regardless of where they received induction therapy. Data for eligible individuals were collected from medical records and transplantation databases at each institution from the time of transplant admission until 100 days after stem-cell infusion (D+100). The following data were collected: demographics, disease status at the time of transplantation, pretransplant morbidity, HCT comorbidity index (HCT-CI),[15] post-transplantation acute complications according to the Common Toxicity Criteria of Adverse Events (version 4.03),[16] and D+100 mortality.

HD Chemotherapy

At SZ, all patients received myeloablative conditioning with oral busulfan 5 mg/kg/d, divided into four oral doses—or 4 mg/kg/d if younger than age 10 years—on each of days –7, –6, –5, and –4, and intravenous melphalan 70 mg/m^2/d on days –3 and –2. Therapeutic drug monitoring was not available, and busulfan levels were therefore not obtained. Anticonvulsant prophylaxis with phenytoin 6 mg/kg/d was administered on days –7 through –2. At FH, all patients received myeloablative conditioning with carboplatin 425 mg/m^2 per dose—14.2 mg/kg for patients < 12 kg—on days –7, –6, –5, and –4 (dose modified according to pretransplant glomerular

filtration rate and the Calvert formula)[9]; etoposide 338 mg/m^2 per dose—11.3 mg/kg for patients < 12 kg—on days –7, –6, –5, and –4; and melphalan 70 mg/m^2 per dose—2.3 mg/kg for patients < 12 kg—on days –7, –6, and –5.

Supportive Care

Eligible patients at both institutions received granulocyte colony-stimulating factor (G-CSF)–mobilized peripheral blood stem cells with an infused cell dose of ≥ 2 × 10^6 CD34-positive cells per kilogram. At SZ, G-CSF 5 μg/kg/d was administered from day +6 post-transplantation until neutrophils > 1,000/mm^3 for 3 consecutive days. At FH, G-CSF 5 μg/kg/d was administered starting 24 hours after transplantation until neutrophils > 2,000/mm^3 for 3 consecutive days. At both centers, patients received transfusions with packed RBCs for hematocrit < 20% and platelet transfusion for a platelet count < 10,000/μL or in the presence of bleeding. Prophylactic ursodeoxycholic acid was used in both cohorts. Policies for the use of prophylactic antibiotics, antivirals, and antifungal were the same.

Evaluation of Acute Toxicities

Toxicities were graded according to the Common Toxicity Criteria of Adverse Events (version 4.03).[16] Sinusoidal obstruction syndrome (SOS) was defined according to modified Seattle[17] or Baltimore criteria.[18] Time to engraftment was defined as the first of 3 consecutive days of absolute neutrophil count > 500/μL and the first of 3 consecutive days of platelets ≥ 20,000/μL, at least 7 days from the last platelet transfusion. Transfusion support was quantified as the number of packed RBC and platelet transfusions received. Blood stream infection was defined as the isolation of bacteria not normally known to colonize the skin from at least one blood culture. Blood stream infections for bacteria that typically colonize the skin—coagulase-negative *Staphylococcus*, *Propionibacterium*, and *Streptococcus* viridians group—were defined as two consecutive positive blood cultures within 72 h, or one positive peripheral blood culture and one positive culture from an indwelling catheter within 72 h. All blood cultures were obtained in response to an infectious indication, usually fever.

Statistical Analysis

Quantitative data were expressed as medians, means, minimum, and maximum, and were compared by using Mann-Whitney *U* test. Qualitative data were expressed as numbers and percentages, and were compared by using χ^2 test or Fischer's exact test when appropriate. A significance level of .05 was used in all statistical tests.

RESULTS

Patient Characteristics

Among the 50 and 95 patients at FH and SZ, respectively, who were identified as having received HDC-SCR for upfront HRNB therapy during the study period, 44 individuals at FH received CEM and 77 patients at SZ received Bu/Mel and were eligible for review. Patients were excluded if they were conditioned with regimens other than CEM (n = 5), Bu/Mel (n = 0), and tandem transplantation (n = 1), or if records were unavailable (n = 12). Age at transplantation was significantly higher in the SZ-Bu/Mel group compared with the FH-CEM group (P = .002). Characteristics of patients at each center are listed in Table 1.

Pretransplant Comorbidity

HCT-CI scores were obtained for all patients and categorized into three groups: the first group with an HCT-CI score of 0, the second group with an HCT-CI score of 1 to 2, and the third group with and HCT-CI score of ≥ 3 (Table 1). There was no statistically significant difference in the distribution of HCT-CI scores between centers. We additionally categorized patients into HCT-CI scores 0 and ≥ 1 and observed no statistically significant difference in the proportion of patients with score ≥ 1 between the FH-CEM cohort (31.8%) and the SZ-Bu/Mel cohort (37.7%). Pretransplant hepatic comorbidity was significantly higher in the SZ-Bu/Mel cohort than in the FH-CEM cohort (88% *v* 47.4%, respectively; P = .05). In addition, pretransplant hepatitis was present only in the SZ-Bu/Mel cohort.

Acute Complications of HDC-SCR

Median length for hospital stay in the FH-CEM cohort was 32 days, which was not significantly different compared with 36 days in the SZ-Bu/Mel

Table 1. Patient Characteristics

Characteristic	FH-CEM	SZ-Bu/Mel	*P*
Frequency, No.	44	77	
Sex			.89
Male	24 (54.5)	43 (55.8)	
Female	20 (45.5)	34 (44.2)	
Median age (range), years	3 (6 months to 27 years)	4.5 (1 year to 12 years)	.002
Median No. of CD34 cells\kg (range)	10.3 (2.5-57.4)	3.9 (2-34)	< .001
Pretransplant morbidity			
Types of pretransplant morbidity			
Hepatic	9 (20.5)	29 (37.7)	.05
Mild	8	24	.12
Moderate/Severe	1	5	.42
Pretransplant infection	1 (2.3)	2 (2.6)	.912
Hepatitis B virus	0	7 (9)	.047
Hepatitis C virus	0	12 (15.6)	.004
Coinfection (Hepatitis B+C)	0	4 (5.2)	.295
HCT-CI score			.638
1st group (HCT-CI score = 0)	30 (68.2)	48 (62.3)	
2nd group (HCT-CI score = 1-2)	10 (22.7)	22 (28.6)	
3rd group (HCT-CI score ≥ 3)	4 (9.1)	7 (9.1)	
100-day transplant-related mortality	0	4 (5.2)	.295
Median length of hospital stay (range), days	32 (22-60)	36 (24-70)	.07

NOTE. Data are presented as No. (%) unless otherwise noted.
Abbreviations: Bu/Mel, busulfan and melphalan; CEM, carboplatin, etoposide, and melphalan; FH, Fred Hutchinson Cancer Research Center; HCT-CI, hematopoietic cell transplantation comorbidity index; SZ, El-Sheikh Zayed Specialized Hospital.

cohort ($P = .07$). Details of acute complications are listed in Table 2.

Hematologic Toxicities

Median number of infused CD34-positive stem cells was significantly higher in the FH-CEM cohort compared with the SZ-Bu/Mel cohort ($P \leq .001$). Median time for neutrophil engraftment was 12 days (range, nine to 48 days) for the SZ-Bu/Mel cohort and longer than the 10 days (range, eight to 39 days) observed for the FH-CEM cohort ($P < .001$; Fig 1). Median time to platelet engraftment was 20 days (range, 12 to 78 days) in the SZ-Bu/Mel cohort compared with 18 days (range, 10 to 50 days) in the FH-CEM cohort ($P < .001$). We used 3.9 CD34/kg as a cutoff value to compare the median time to neutrophil and platelet engraftments in both cohorts. We found that median times for neutrophil and platelet engraftments were significantly lower in patients who received an infused stem-cell dose of $\geq 3.9 \times 10^6$/kg compared with those who received a stem-cell dose of $< 3.9 \times 10^6$/kg in FH-CEM and SZ-Bu/Mel cohorts, respectively (FH-CEM: $P = .05$ and .033, respectively; SZ-Bu/Mel: $P = .03$ and .045, respectively). Median number of RBC transfusions in the FH-CEM cohort was three (range, zero to 10 transfusions) compared with two (range, zero to 16 transfusions) in the SZ-Bu/Mel cohort ($P = .033$). Median number of platelet transfusions was also significantly higher in the FH-CEM cohort compared with the SZ-Bu/Mel cohort at six transfusions (range, one to 22 transfusions) versus one transfusion (range, zero to 17 transfusions), respectively ($P \leq .001$).

Hepatic Toxicity

There were no statistically significant differences in hepatic dysfunction—elevated liver enzymes—and hyperbilirubinemia between both cohorts (Table 2). Three patients (6.8%) were diagnosed with SOS in the FH-CEM cohort, whereas eight patients (10.4%) were diagnosed with SOS in the SZ-Bu/Mel cohort. Median time to the onset to SOS was 19 days after SZ-Bu/Mel conditioning compared with 7 days after

Table 2. Acute Complications of High-Dose Chemotherapy With Stem-Cell Rescue

Acute Complication	FH-CEM	SZ-Bu/Mel	*P*
Hepatic toxicity			
ALT abnormalities	37 (84.1%)	69 (89.6%)	.375
CTCAE grading			
Grade 1 (> ULN to 3.0 × ULN)	21 (56.8%)	30 (43.5%)	
Grade 2 (> 3.0-5.0 × ULN)	7 (18.9%)	14 (20.3%)	.401
Grade 3 (> 5.0-20.0 × ULN)	9 (24.3%)	23 (33.3%)	
Grade 4 (> 20.0 × ULN)	0	2 (2.9%)	
AST abnormalities	41 (93.2%)	73 (94.8%)	.48
CTCAE grading			
Grade 1 (> ULN to 3.0 × ULN)	21 (51.2%)	30 (41.1%)	
Grade 2 (> 3.0-5.0 × ULN)	11 (26.8%)	15 (20.5%)	.264
Grade 3 (> 5.0-20.0 × ULN)	9 (22%)	25 (34.2%)	
Grade 4 (> 20.0 × ULN)	0	3 (4.1%)	
Bilirubin total abnormalities	7 (15.9%)	16 (20.8%)	.731
CTCAE grading			
Grade 1 (> ULN to 1.5 × ULN)	2 (28.6%)	6 (37.5%)	.581
Grade 2 (> 1.5-3.0 × ULN)	4 (57.1%)	3 (18.8%)	
Grade 3 (> 3.0-10.0 × ULN)	1 (14.3%)	3 (18.8%)	
Grade 4 (> 10.0 × ULN)	0	4 (25%)	
Nephrotoxicity (> 2× baseline creatinine or requiring dialysis)	8 (18.2%)	5 (6.5%)	.047
Febrile neutropenia	39 (88.6%)	71 (92.2%)	.8
CTCAE grading			
Grade3*	35 (89.7%)	65 (91.5%)	.771
Grade4†	4 (10.3%)	6 (8.5%)	
Blood stream infection	10 (22.7%)	16 (20.8%)	.802
Single episode	9 (90%)	14 (87.5%)	.76
Multiple episodes	1 (10%)	2 (12.5%)	.91
Single-agent bacteremia	5 (50%)	13 (81.3%)	.596
Multiple-agent bacteremia	5 (50%)	3 (18.7%)	.138
Causative organism			
Gram-positive organisms	11 (68.8%)	11 (55%)	.142
Gram-negative organisms	5 (31.2%)	9 (45%)	.957
Type of organism			
Coagulase-negative staphylococci	7 (43.7%)	6 (30%)	.223
Staphylococcus aureus	0	3 (15%)	.553
Enterobacteriaceae	5 (31.2%)	7 (35%)	.756
Enterococcus faecalis	3 (18.8%)	2 (10%)	.352
Leuconostoc species	1 (6.3%)	0	.364
Pseudomonas	0	2 (10%)	.553
Fungaemia	2 (4.5%)	0	.13
No. of days with fever	7 (0-21)	5 (0-22)	.041
No. of days with antibiotics	14 (0-29)	11 (0-40)	.004

Abbreviations: Bu/Mel, busulfan and melphalan; CEM, carboplatin, etoposide, and melphalan; CTCAE, Common Toxicity Criteria of Adverse Events; FH; Fred Hutchinson Cancer Research Center; SZ, El-Sheikh Zayed Specialized Hospital; ULN, upper limit of normal.

*Grade 3 febrile neutropenia: absolute neutrophil count < 1,000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour.

†Grade 4 febrile neutropenia: life-threatening consequences—urgent intervention indicated.

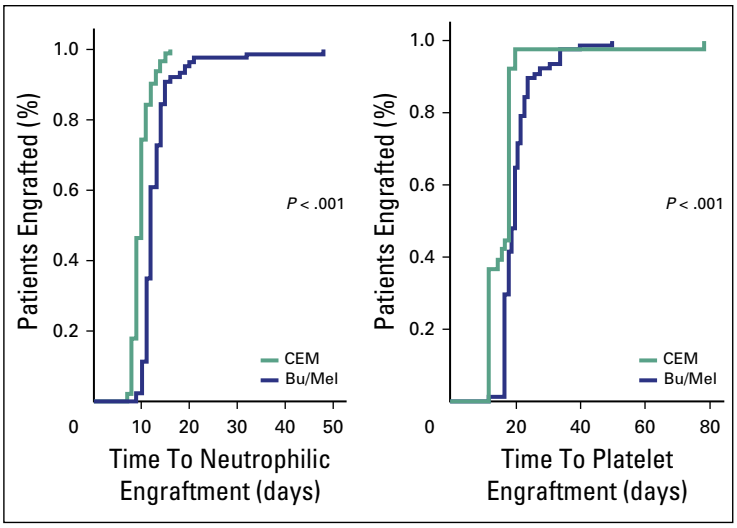

Fig 1. Time to neutrophil and platelet engraftment. FH-CEM, carboplatin, etoposide, and melphalan at Fred Hutchinson Cancer Research Center; SZ-Bu/Mel, busulfan and melphalan at El-Sheikh Zayed Specialized Hospital.

FH-CEM conditioning ($P = .033$; Fig 2). Details of the diagnostic criteria for SOS, underlying hepatitis infection, complications, and outcome are listed in Table 3. Using χ^2 test, hepatitis infection was significantly related to the development of SOS ($P < .001$). All SOS cases from the FH-CEM cohort were of moderate severity, whereas in the SZ-Bu/Mel cohort, four cases (50%) were severe and four cases (50%) were moderately severe. Underlying liver infection was present in all four of the severe cases and in one-half of the cases of moderate severity in the SZ-Bu/Mel cohort

Nephrotoxicity

There were more patients with nephrotoxicity in the FH-CEM cohort than in the SZ-Bu/MEL cohort ($P = .047$), although two patients in the SZ-Bu/Mel group required dialysis as a result of hepatorenal syndrome as a complication of severe SOS.

Infectious Complications

Febrile neutropenia occurred commonly and was observed in 39 patients (88.6%) from the FH-CEM cohort and in 71 patients (92.2%) from the SZ-Bu/Mel cohort. The number of days with fever and days receiving antibiotics were significantly higher for the FH-CEM cohort compared with the SZ-Bu/Mel cohort (Table 2).

100-Day Transplant-Related mortality

Four patients who underwent transplantation after SZ-Bu/Mel died before day 100 (Fig 3). All had severe SOS, developed respiratory failure, and required mechanical ventilation. Two patients developed hepatorenal syndrome and required dialysis. There was no transplantation-related mortality in the FH-CEM cohort.

DISCUSSION

HDC-SCR plays a major role in the treatment strategy for HRNB, although there currently is no consensus about what comprises the best conditioning regimen. We explored the acute complications, regimen-related toxicities, and 100-day survival in two cohorts of patients with HRNB who were conditioned with either CEM or Bu/Mel. One cohort received HDC-SCR at a bone marrow transplantation (BMT) center located in Egypt, a developing lower middle-income country where the BMT program started in 1989,[19] whereas the other cohort received HDC-SCR in the United States, a high-income country where the BMT program started in the early 1950s, with significantly larger numbers of transplantations having been performed.[20] Egyptian patients with HRNB have been receiving the same Bu/Mel conditioning regimen used in Europe. Meanwhile, patients with HRNB in the United States, for the most part, have received CEM.

The prevailing public health problems in Egypt and the United States are different. Hepatitis is a major public health problem in Egypt, with intermediate endemicity for hepatitis B (2% to 5% hepatitis B surface antigen prevalence) and high endemicity for hepatitis C (17.5%).[21-23] In this analysis, there were no significant differences in HCT-CI scores between FH-CEM and SZ-Bu/Mel cohorts; however, pretransplant hepatic comorbidities were significantly higher in the SZ-Bu/Mel cohort compared with the FH-CEM cohort. Of importance, there was a high incidence of hepatitis B and C infections in the SZ-Bu/Mel cohort—5.2% of patients were coinfected with both hepatitis B and C virus.

SOS developed in fewer patients in the FH-CEM cohort than in the SZ-Bu/Mel cohort. Ladenstein et al[12] reported similar findings in the HRNBL1/SIOPEN trial. As Bu depletes intracellular glutathione and alters melphalan metabolism, glutathione-depleted cells are predisposed to the hepatotoxic metabolites of high-dose Mel[24,25] SOS developed earlier in the FH-CEM cohort compared with the SZ-Bu/Mel. Different studies

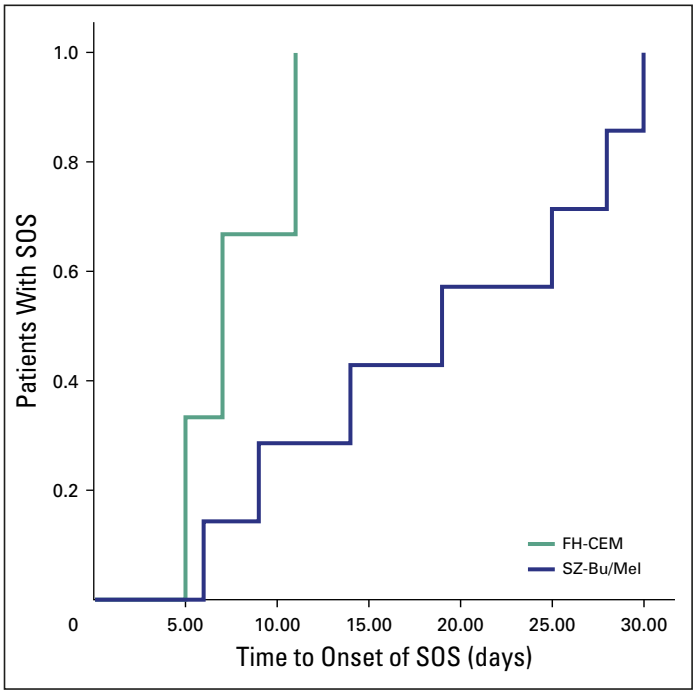

Fig 2. Time to onset of sinusoidal obstruction syndrome (SOS). FH-CEM, carboplatin, etoposide, and melphalan at Fred Hutchinson Cancer Research Center; SZ-Bu/Mel, busulfan and melphalan at El-Sheikh Zayed Specialized Hospital.

that compared Bu/Mel and CEM reported similar results.[12,26-28] Although the frequency of SOS was higher in other studies by Proust-Houdemont et al[29] and the HRNBL1/SIOPEN trial[12] compared with SZ-Bu/Mel, severe SOS developed more frequently in the SZ-Bu/Mel group. The higher frequency of infectious hepatitis in the SZ-Bu/Mel group might be a contributing factor in the development of severe SOS. Several studies have demonstrated that pretransplant hepatitis infection increased the severity of SOS in recipients of stem-cell transplantation.[30-32] Potential differences in the method of Bu administration between different centers might also be relevant to the frequency of occurrence of severe SOS. In the SZ-Bu/Mel cohort, oral Bu was used without therapeutic drug monitoring, whereas oral Bu with therapeutic drug monitoring was used until 2006 in Proust-Houdemont et al and until 2007 in the HRNBL1/SIOPEN trial, when intravenous Bu was used. Oral bioavailability of Bu is unpredictable, with marked interpatient variability in the plasma concentration, especially in children.[33] Veal et al[34] compared the pharmacokinetics of oral and intravenous Bu in patients with HRNB who were treated in the HRNBL1/SIOPEN trial. They reported that oral Bu was significantly related to the development of grade 3 and 4 hepatic toxicity and SOS. This is likely a result of the effect of the first-pass metabolism that leads to higher Bu concentrations in liver-enhancing hepatic toxicity.

The practice and supportive care of HDC-SCR differ between Egypt and the United States, which may be responsible, in part, for the difference in the pattern of acute toxicity of HDC-SCR between the two centers. The earlier use of G-CSF in the FH-CEM cohort—starting 24 hours after infusion compared with 6 days after stem-cell infusion in the SZ-Bu/Mel cohort—might explain, in part, the longer median time for neutrophil engraftment in SZ-Bu/Mel patients compared with FH-CEM patients. Longer median time can also be explained by differences in the infused cell dose. Median infused cell dose in the FH-CEM cohort was significantly higher than that in the SZ-Bu/Mel cohort ($P < .001$). We found that the median times for neutrophil and platelet engraftments were significantly lower in patients who received an infused stem-cell dose of $\geq 3.9 \times 10^6$ cells/kg compared with those who received a stem-cell dose of $< 3.9 \times 10^6$ cells/kg in FH-CEM and SZ-Bu/Mel cohorts. This finding was similar to that reported by Morgenstern et al.[35] Desai et al[26] compared the time to neutrophil and platelet engraftment between Bu/Mel and CEM for the treatment of patients with HRNB who received the same dose of infused CD34-positive cells per kilogram and found no significant difference in the time to neutrophil and platelet engraftments between both cohorts.

Nephrotoxicity was significantly more frequent after conditioning with FH-CEM compared with SZ-Bu/Mel. Several studies have reported similar results.[12-29] This is likely correlated with the use of high-dose carboplatin. Carboplatin is a platinum derivative that is less toxic than cisplatin but still associated with a decrease in the glomerular filtration rate and hypomagnesaemia.[36] There were two patients after SZ-Bu/Mel conditioning who required renal dialysis as a result of hepato-renal syndrome secondary to severe SOS.

Despite the differences in economic status between Egypt and the United States, we found no significant difference in the frequency of blood stream infections between the two cohorts. This may suggest that the overall quality of supportive care provided to these vulnerable, high-risk patients in a lower middle-income country was equivalent to that in a high-income country.

Table 3. Characteristics of Patients With Sinusoidal Obstruction Syndrome

No.	Time (bil by mg/dl)	Ultrasonography	Maximum ALT/AST	Maximum BIL-T	Hepatomegaly	Creatinine	PICU	Complication	Mortality	Hepatitis
FH-CEM										
1	+5	Normal	247/201	2.4	Yes	Normal	No	No	No	No
2	+7	Reversal of flow, moderate ascites	136/212	Normal	No	1 (2× baseline)	No	No	No	No
3	+11	Normal	159/411	2.4	Yes	Normal	Yes	Pulmonary edema	No	No
SZ-Bu/Mel										
1	+30	Moderate ascites	950/1,250	20	Yes	5 (6× baseline)	Yes	ARF on dialysis, pulmonary edema on MV	Yes	C
2	+19	Normal	5,179/8,647	33	Yes	3 (4× baseline)	Yes	ARF on dialysis, pulmonary edema on MV	Yes	C
3	+28	Tense ascites	459/247	18	Yes	Normal	Yes	ARF on MV and inotropes	Yes	B/C
4	+25	Normal	740/1,100	7	Yes	Normal	Yes	Pulmonary edema on MV and inotropes, DIC	Yes	B
5	+19	Reversal of flow, moderate ascites	225/200	3	Yes	Normal	Yes	DIC	No	B/C
6	+14	Reversal of flow, moderate ascites	300/270	5	Yes	Normal	No	DIC	No	No
7	+9	Mild ascites	192/250	4	Yes	Normal	No	No	No	B
8	+16	Moderate ascites	296/330	5	Yes	Normal	No	No	No	No

Abbreviations: ARF, acute renal failure; B, hepatitis B virus; B/C, hepatitis B and C virus; BIL-T, bilirubin total; Bu/Mel, busulfan and melphalan; C, hepatitis C virus; CEM, carboplatin, etoposide, and melphalan; DIC, disseminated intravascular coagulation; FH, Fred Hutchinson Cancer Research Center; MV, mechanical ventilation; PICU, pediatric intensive care unit; SZ, El-Sheikh Zayed Specialized Hospital.

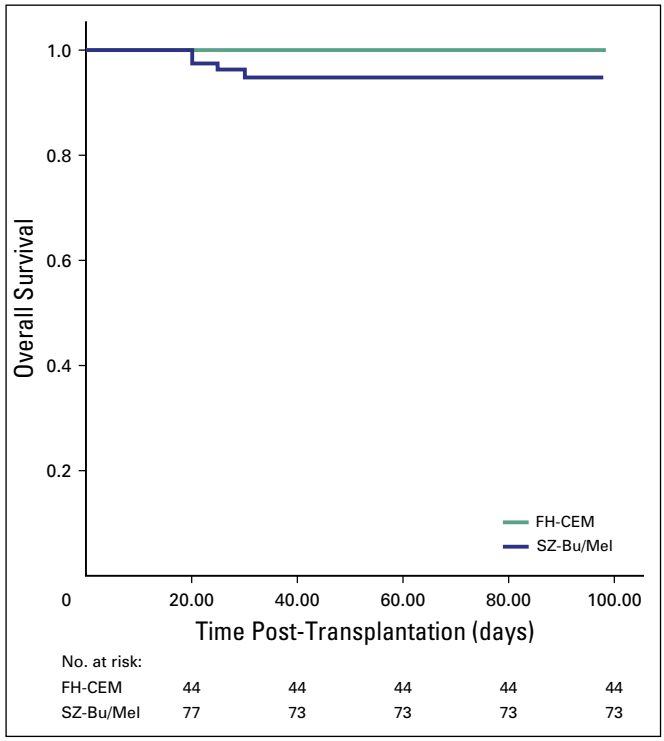

Fig 3. Kaplan-Meier curve of overall survival at 100 days between carboplatin, etoposide, and melphalan at Fred Hutchinson Cancer Research Center (FH-CEM) and busulfan and melphalan at El-Sheikh Zayed Specialized Hospital (SZ-Bu/Mel).

There was a trend toward a higher, but insignificant, percentage of Gram-negative organisms in the SZ-Bu/Mel cohort compared with the FH-CEM cohort. This is in agreement with other reports that have noted the re-emergence of infections with Gram-negative organisms in Egypt.[37]

Overall, resource utilization was greater in the FH-CEM cohort than in the SZ-Bu/Mel cohort, as evidenced by a significantly higher number of days with fever, antibiotic use, and number of packed RBC and platelet transfusions administered. Thus, SZ-Bu/Mel is more suitable to be used as HDC-SCR for the treatment of HRNB in lower middle-income Egypt.

Our study is limited by its retrospective design that included two different centers with different practice guidelines and resources; however, these data demonstrate that, compared with a well-established program, such as that in the United States, the utilization of a highly technical intensive therapy, such as BMT, can be safely undertaken in a developing country. It also demonstrates the unique challenges that exist for a country with endemic hepatitis that lead to significantly higher risks of potentially fatal hepatic toxicity.

In conclusion, use of HDC-SCR is feasible in the context of a resource-limited country. Bu/Mel is preferred in Egypt because of fewer infections, lower resource utilization, and less nephrotoxicity, although its contribution to hepatic complications is still a major concern and requires consideration of earlier supportive and/or prophylactic interventions.

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