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Comparison of toxicity following different conditioning regimens (busulfan/melphalan and carboplatin/etoposide/melphalan) for advanced stage neuroblastoma: Experience of two transplant centers

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Abstract: The outcome for advanced neuroblastoma has improved with combined modality therapy: induction chemotherapy, surgery, and consolidation with high-dose chemotherapy/autologous HSCT, followed by local radiation, cisretinoic acid, and recently antibody therapy. In the United States, the most common conditioning regimen is CEM, while in Europe/Middle East, Bu/Mel has been widely used; it remains unclear which regimen has the best outcome. Assess renal, hepatic, and infectious toxicity through Day+100 in 2 different regimens. Retrospective comparison between CEM-DFCHCC Boston and Bu/Mel- CCHE-57357. Thirty-five patients, median age 4, in Boston (2007–2011) and 38 patients, median age 3, in Cairo (2009–2011). Renal toxicity; creatinine was significantly higher in CEM than Bu/Mel: 57% (median day+90) vs. 29% (median>day+100), p = 0.004. One CEM patient died from renal dialysis at day+19. Hepatic toxicity was significantly higher in CEM than Bu/Mel: 80% (median day+26) vs. 58% (median day+60), p = 0.04. In infectious complications with CEM 14%, bacteremia (n = 4) and fungemia (n = 1), 3 had culture-negative sepsis requiring vasopressors. With Bu/Mel 18%, bacteremia (n = 7), none required pressors, p = 0.4. Bu/Mel was associated with less acute hepatic and renal toxicity and thus may be preferable for preserving organ functions.

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Key words: neuroblastoma – autologous hematopoietic stem cell transplantation (HSCT) – carboplatin – etoposide – melphalan (CEM) – busulfan/melphalan (Bu/Mel) – renal toxicity

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Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BCH, Boston Children's Hospital; Bu/Mel, busulfan/melphalan; CCHE, Children's Cancer Hospital Egypt; CEM, carboplatin/etoposide/melphalan; COG, Children's Oncology Group; DFCHCC, Dana Farber Children's Hospital Cancer Center; DFCI, Dana-Farber Cancer Institute; EFS, event free survival; GFR, glomerular filtration rate; HSCT, hematopoietic stem cell transplantation; IRB, institutional review board; NHL, non-Hodgkin's lymphoma; PBSCT, peripheral blood stem cell transplantation; PO, per oral; SOS, sinusoidal obstruction syndrome; TBI, total body irradiation; TB, total bilirubin; TDM, therapeutic drug monitoring; TEPA/CPM, thiotepa/cyclophosphamide; ULN, upper limit normal; VOD, veno-occlusive disease; XRT, radiation therapy.

Neuroblastoma is the second most common solid malignancy of childhood (1). These tumors are heterogeneous in their morphologic, biological, and genetic characteristics and demonstrate correspondingly diverse clinical behavior (2). The management of patients with neuroblastoma is based on prognostic factors derived from studies correlating clinic-biological variables with outcome (3). Some infants have 4S disease that spontaneously regresses and differentiates. Children with non-metastatic disease can often be cured with chemotherapy, surgery, and /or radiation therapy (4). However, 40% of patients

present with advanced stage neuroblastoma and this group remains a significant clinical challenge (5). These patients receive intensive multimodality therapy including chemotherapy, surgery, and radiation therapy for local control and a consolidation phase of high-dose chemotherapy with autologous HSCT rescue (6). Despite this approach of high intensity and long duration, many children still experience recurrent disease. Although further therapy can prolong life, most still succumb to progressive disease (7).

Based on the results of a randomized trial, autologous HSCT is considered an essential component of care for advanced stage neuroblastoma (6); however, the most effective preparative regimen prior to autologous HSCT has not been definitively ascertained. In the United States, initial studies used a TBI-based regimen (6). However, due to concerns regarding the long-term effects of radiation in this young population in the current era, trials have employed a platinum-based regimen; CEM (8). In Europe and the Middle East, Bu/Mel has been the standard approach (9). Although recent data from Europe suggested a survival benefit with busulfan conditioning, there is a scarcity of comparative data regarding efficacy or toxicity (10).

The treatment of advanced stage neuroblastoma continues to evolve. Most notably, the addition of antibody therapy following HSCT has been found to significantly improve outcome (11). Thus, autologous HSCT is currently only one component of an intensive approach of long duration with planned therapy lasting many months. In addition, if relapse occurs after transplant, patients can have prolonged survival using other intense approaches such as MIBG therapy (12).

There are currently insufficient data regarding which conditioning regimen for autologous HSCT is most effective in terms of disease control and, extrapolating from other diseases treated with autologous HSCT such as NHL, it may be difficult to demonstrate a meaningful difference in terms or relapse. However, if differences in toxicity can be demonstrated, that would be of import given the subsequent planned and unplanned therapy these patients receive. Thus, one of the goals of high-dose chemotherapy should be to minimize end organ toxicity so that the patients are able to receive these subsequent interventions. In this study, we evaluated the acute renal, hepatic, and infectious complications associated with autologous HSCT for advanced stage neuroblastoma performed at CCHE where the preparative regimen was Bu/Mel and BCH where CEM was used. Evaluating differences in toxicity that occur in two comparable transplant centers using different preparative regimens can help inform the choice of conditioning for future studies.

Patients and methods

Study population

This retrospective study includes all consecutive high-risk neuroblastoma pediatric patients aged 0–18 yr who underwent PBSCT at CCHE-57357, Cairo Egypt from 2009 to 2011 and at DFCI/BCH, Boston USA from 2006 to 2011. IRB approval was obtained at both institutions, and data were stored in a password-protected database.

There were 38 patients transplanted in Cairo with median age of 3 (range 1–7 yr) and 35 patients in Boston with median age of 4 (range 0.6–12 yr). The myeloablative conditioning regimen used in Cairo was Bu/Mel: busulfan 5 mg/kg/day PO divided in four doses (or 4 mg/kg/day PO if >four yr old) on days −9, −8, −7, and −6 and melphalan −70 mg/m^2/day IV over 20 min on days −3 and −2. TDM was not available at our center, and busulfan levels were not obtained.

The myeloablative conditioning regimen used in Boston was carboplatin / etoposide / melphalan (CEM): carboplatin 425 mg/m^2/dose on day −7, −6, −5, and −4 with the initial dose of carboplatin adjusted according to the pre-transplant GFR, etoposide 338 mg/m^2/dose on day −7, −6, −5, and −4, and melphalan 70 mg/m^2/dose on day −7, −6, and −5. Seven patients underwent planned tandem transplants, receiving TEPA/CPM: thiotepa 300 mg/m^2/dose (or if < 12 kg, 10 mg/kg/dose) once daily on day −7, −6, and −5 and cyclophosphamide 1500 mg/m^2/dose (or if < 12 kg, 50 mg/kg/dose) daily on day −5, −4, −3, and −2. Four to six wk following stem cell infusion, a second transplant using the above CEM regimen was started. Local XRT was given beginning at day +42 after HSCT in both institutions.

Methods

The patients were followed for 100 days after bone marrow transplantation for renal, hepatic, and infectious complications using electronic medical records review. Toxicities affecting other organ systems or occurring after day 100 post-transplant were not assessed. We collected baseline values within three weeks prior to the initiation of conditioning. To assess renal toxicity, the following was collected: baseline serum creatinine, maximum level of creatinine within first 100 days post-transplant, and need for renal dialysis. Renal toxicity was defined according to Common Terminology Criteria for Adverse Events (CTCAE v. 4.03) as grades 1–5. To assess hepatic toxicity, the following was collected: maximum levels of liver function tests (ALT, AST, TB), and the presence of SOS previously known as VOD. Hepatic toxicity was defined as maximum ALT > 60 (2× ULN), maximum AST > 80 (2× ULN), and maximum TB >2 mg/dL occurring within first 100 days post-transplant. Infectious complications captured included positive blood cultures and need for vasopressor therapy.

Statistical consideration

Univariate analyses were conducted with χ^2 or Fisher's exact tests for categorical variables and the Kruskal–Wallis test for continuous variables. All clinical and demographic

data were merged and analyzed with the use of STATA software (STATA Corp, College Station, TX, USA).

Overall, time to toxicity was defined as the time between treatment initiation and toxicity (renal, hepatic, and infection). Median time to develop toxicity was estimated using the Kaplan–Meier product-limit method, and significant differences between toxicity-related treatments were determined using the log-rank test.

Results

A total of 73 children with high-risk neuroblastoma are included in this analysis: 38 children from Cairo who received Bu/Mel and 35 children from Boston who received CEM. The induction therapy in both groups is the same, and it was not associated with significant toxicity in any patients. Table 1 presents the clinical features of patients in both institutions. There was no significant difference between populations in term of gender, age at diagnosis and stage. There was no difference in the 2 groups in the percent of patients in complete remission (CR) prior to transplant, the cell dose provided for all patients, or time to engraftment. Both groups received radiation therapy at day +45. During conditioning, all patients received antifungal prophylaxis with fluconazole and antiviral prophylaxis with acyclovir if at risk for HSV reactivation. Performance status as measured by the Lansky was between 80% and 100% and not significantly different between the 2 cohorts.

The incidence of renal toxicity as measured by maximum serum creatinine was significantly higher in those receiving CEM than Bu/Mel: 57% vs. 29%, respectively (p = 0.004), as shown in Table 2. Nephrotoxic antibiotics were given to all patients in both groups according to the clinical situation, and there was no significant difference regarding the doses and duration between groups. According to Common Terminology Criteria for Adverse Events (CTCAE v. 4.03), the number of patients with Grade 1 nephrotoxicity in CEM vs. Bu/Mel group was 9/35 (26%) and 9/38 (24%), respectively. Grade 2 toxicity, creatinine 2.0–3.0 × above baseline, was 6/35 (17%) and 2/38 (5%), in the CEM and Bu/Mel groups, respectively. Grade 3 toxicity, creatinine >3 × baseline or >4.0 mg/dL with hospitalization in CEM vs. Bu/Mel groups, was 4/35 (11%) and 0/38 (0%), respectively. No patient in either group experienced Grade 4 toxicity, and one CEM patient required renal dialysis and subsequently died from complications of renal failure, so he experienced Grade 5 nephrotoxicity. No Bu/Mel patients required dialysis. Overall, 50% of CEM patients experienced renal dysfunction by day 90 (Fig. 1a).

The incidence of hepatic toxicity as measured by any elevation above normal in the value of the liver function tests was significantly higher in CEM than Bu/Mel patients; 80% vs. 58%, respectively (p = 0.04) (Table 2). ALT elevation was the most significant difference in the groups (p = 0.004). The median time to develop hepatic toxicity was 60 vs. 26 days for Bu/Mel and CEM patients (p = 0.05) (Fig. 1b). According to Seat-

Table 1. Patient characteristics of Children's Cancer Hospital Egypt and Boston Children's Hospital

	Boston Children's Hospital CEM		Children's Cancer Hospital Egypt Bu/Mel		
Characteristics	n = 35	(%)	n = 38	(%)	p
Age (yr)					
Median age (range)	4 (1–12)		3 (1–7)		0.4
Sex					
Females	21	60	22	57.9	0.5
Males	14	40	16	42.1	
Stage					
III	6	17.1	7	18.4	0.5
IV	29	82.9	31	81.6	
Response					
VGPR	30	85.7	24	63.2	0.6
CR	5	14.3	14	36.8	

VGPR, very good partial response; CR, complete remission.

Table 2. Results of renal, hepatic, and infection toxicity in Children's Cancer Hospital Egypt and Boston Children's Hospital

	Boston Children's Hospital CEM		Children's Cancer Hospital Egypt Bu/Mel		
Characteristics	n = 35	(%)	n = 38	(%)	p
Renal toxicity					
No	15	42.9	27	71.1	0.004
Yes	20	57.1	11	28.9	
ALT toxicity					
No	8	22.9	21	55.3	0.004
Yes	27	77.1	17	44.7	
AST toxicity					
No	9	25.7	18	47.4	0.05
Yes	26	74.3	20	52.6	
Bilirubin toxicity					
No	21	75	36	94.7	0.06
Yes	7	25	2	5.3	
SOS					
No	33	94.3	38	100	0.2
Yes	2	5.7	0	0	
Hepatic toxicity (all types)					
No	7	20	16	42.9	0.04
Yes	28	80	22	57.9	
Infection					
No	30	85.7	31	81.6	0.4
Yes	5	14.3	7	18.4	

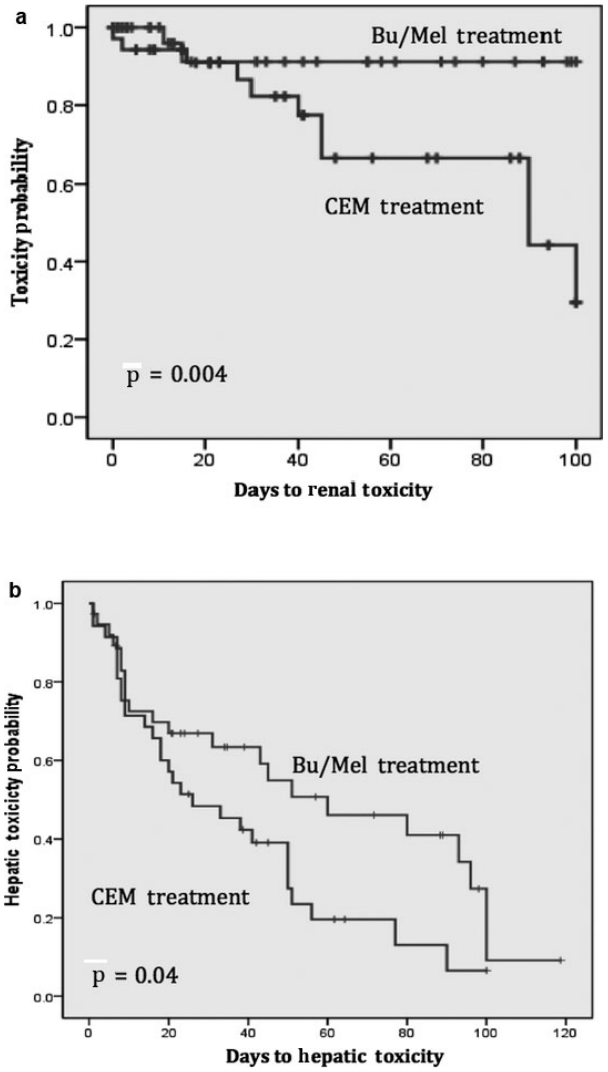

Fig. 1. (a) Renal toxicity in both conditioning regimens. (b) Hepatic toxicity in both conditioning regimens.

tle criteria (McDonald's criteria) for SOS (13), SOS was observed in 2/35 cases in CEM group, one case at day+20 and the other case at day+29 (neither in patients receiving tandem transplants) and both patients recovered completely. The incidence of SOS was not significantly different between patient populations (p = 0.2). SOS was treated supportively in both institutions using transfusions, careful fluid management, and avoidance of nephrotoxins. In addition, the one patient who developed severe SOS according to the Seattle criteria was treated with defibrotide, a DNA derivative with antithrombotic activity, on a research protocol.

Bacteremia, fungemia, and culture-negative sepsis occurred with similar frequency in both groups of patients (Table 2). Seven Egyptian children (18%) had blood-positive cultures for bacteria, and none required vasopressor support. In Boston, five children (14%) had positive blood cultures for bacteria (n = 4) and fungus (n = 1). Three patients had culture-negative sepsis requiring vasopressor support. There were no infectious deaths in either cohort.

We found no impact of baseline clinical and demographic characteristics on the prediction of treatment-related toxicity (Table 1). All evaluated toxicities were reversible except for the patient with acute renal failure. One-yr survival for Cairo and Boston patients was similar, 76% and 74%, respectively. There was one transplant-related death from renal failure in the CEM group. The remainder of deaths were due to progressive disease.

Discussion

High-dose chemotherapy with autologous rescue is an essential component of treatment for advanced stage neuroblastoma. However, the most effective conditioning regimen has not been definitively demonstrated. In the earliest trials, total body irradiation was used (6), but more recent trials have avoided radiation due to concerns regarding late effects and the development of secondary malignancies (14). In the United States, CEM has been the backbone of COG trials and is the most common regimen used for patients on or off research protocols. In Europe and the Middle East, Bu/Mel has been the standard approach. There have been no published comparative trials examining the impact of pre-HSCT conditioning regimen on outcome (10). A recent abstract reporting on the results of a European randomized trial showed superior disease-free survival for the Bu/Mel cohort (three yr EFS 48 vs. 33%), but this has not yet been replicated in other settings. Further complicating the interpretation of historical data, a recent COG study demonstrated the favorable impact of antibody therapy following CEM-based HSCT, and immunotherapy is now almost always administered following HSCT (15).

Given the difficulty in determining which preparative regimen offers the best disease control in the current era of therapy, understanding the comparative toxicities of the approaches becomes of heightened interest. The HSCT programs in Cairo (CCHE) and Boston (BCH) have been collaborating for the past five yr with shared educational and academic initiatives and similar practices in terms of supportive care and data collection. However, neuroblastoma patients undergoing autologous HSCT have

received different institution-specific conditioning: Bu/Mel in Cairo and CEM in Boston. In this retrospective study, we compared toxicities by center to delineate the impact of conditioning regimens. We focused on acute (first 100 days post-HSCT) renal, hepatic, and infectious toxicities as these complications could affect the administration and toxicity of subsequent planned therapy (XRT, cisRA, and antibody therapy) ultimately impacting outcome.

We found that the incidence of renal toxicity as measured by maximum serum creatinine was significantly higher with CEM (57 vs. 29%). 50% of patients receiving CEM had developed renal dysfunction by day 90 including one patient who required hemodialysis and ultimately succumbed to complications arising from renal failure. This occurred in the setting of pre-SCT assessment of renal function by GFR for all patients and dose adjustment of carboplatin based on the pre-HSCT results. In addition, the incidence of hepatic toxicity as measured by elevation in hepatic enzymes and bilirubin was significantly higher (80 vs. 58%) and the toxicity occurred earlier (median day 26 vs. 60). Infectious complications as defined by positive blood culture or need for vasopressor support were not different between the groups.

Our retrospective analysis cannot address the etiology of the increased liver and renal toxicity with CEM. However, carboplatin is known to cause to renal injury (16) and the increase in creatinine is likely related to cumulative platinum exposure in the setting of other potential renal insults associated with HSCT – nephrotoxic antibiotics, intravascular depletion or sepsis. In addition, high-dose carboplatin can result in an acute hepatitis predominantly marked by an increase in liver enzymes as seen in our CEM cohort. This does not herald SOS and, in fact, the incidence of SOS was similar in both groups, and there were no SOS-associated fatalities. However, during HSCT, patients are at risk for additional liver toxicity from many sources including infection, drugs, and parenteral nutrition, and the impact of this early insult on overall hepatic health is not known. Oral busulfan has variable bioavailability especially in children, which can impact both efficacy and toxicity. Therapeutic drug monitoring and busulfan levels were not available at CCHE.

In summary, we have compared the incidence of acute renal, hepatic, and infectious toxicities associated with the two common approaches to conditioning prior to autologous HSCT for advanced stage neuroblastoma. We report more renal and hepatic toxicity in patients receiving CEM vs. Bu/Mel. Following transplant, these children receive planned therapy including local radiation, cis-retinoic acid, and immunotherapy in an attempt to improve disease control. Despite this, there is still a high rate of relapse and consequent use of salvage chemotherapy regimens. Thus, it is essential to minimize toxicity during HSCT to maximize the likelihood of being able to deliver these subsequent planned and unplanned interventions. Our data suggest that Bu/Mel may be associated with fewer acute renal and hepatic insults. Thus, even if disease control is equivalent, a busulfan-based regimen may be the preferred approach. The limitations of this study are its restriction to two institutions and the possibility that other supportive care practices instead of the conditioning approach may have contributed to the differences in toxicity. In addition, some of the CEM patients received tandem transplants thus being exposed to conditioning agents prior to CEM. However, all had no active infections and normal liver and kidney function prior to beginning therapy with CEM per protocol requirement. We also did not capture longer term organ dysfunction. Further multi-institutional studies will be necessary to definitively determine the best conditioning regimen for these patients.

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Authors' contributions

Yasser Elborai participated in concept/design, data analysis/interpretation, drafting article, statistics, and data collection. Hanafy Hafez, Emad A Moussa, and Mahmoud Hammad were involved in concept/design and data collection. Hany Hussein was involved in approval of the article. Leslie Lehmann and Alaa Elhaddad participated in concept/design, data analysis/interpretation, statistics, critical revision of the article, and approval of the article.

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