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Resource Utilization and Toxicities After Carboplatin/Etoposide/Melphalan and Busulfan/Melphalan for Autologous Stem Cell Rescue in High-Risk Neuroblastoma Using a National Administrative Database

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Abstract

Background—High-dose chemotherapy with autologous stem cell rescue (ASCR) is a key component of high-risk neuroblastoma therapy. Resources required to support patients treated with ASCR conditioning regimens [carboplatin/etoposide/melphalan (CEM) and busulfan/melphalan (BuMel)] have not been directly compared.

Procedure—An administrative database was used to analyze resource utilization and outcomes in a cohort of high-risk neuroblastoma patients. Patients were followed for 60 days from start of conditioning or until death. Length of hospitalization, length of intensive care unit (ICU) level of care, incidence of sepsis and sinusoidal obstruction syndrome (SOS), and duration of use of specific supportive care resources were analyzed.

Results—Six of 171 CEM patients and zero of 59 BuMel patients died during the study period ($P = 0.34$). Duration of hospitalization was longer following BuMel (median 35 vs. 31 days; $P = 0.01$); however, there was no difference in duration of ICU-level care. Antibiotic use was longer following CEM (median 19 vs. 15 days; $P = 0.01$), as was antihypertensive use (median 5 vs. 1.6

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days; $P = 0.0024$). Duration of opiate and nonnarcotic analgesic use was longer following CEM early in the study period. Resources consistent with a diagnosis of SOS were used in a higher proportion of BuMel patients. A higher proportion of BuMel treated patients required mechanical ventilation (17% vs. 6%; $P = 0.03$).

Conclusions—We used administrative billing data to compare resources associated with ASCR conditioning regimens. CEM patients required more extended use of analgesics, antibiotics, and antihypertensives, while duration of hospitalization was longer, and SOS and the use of mechanical ventilation were more frequent following BuMel. *Pediatr Blood Cancer* 2016;63:901–907.

Keywords

neuroblastoma; resource utilization; stem cell rescue

INTRODUCTION

While high-dose chemotherapy with autologous stem cell rescue (ASCR) is a key component of multimodality therapy for patients with high-risk neuroblastoma,[1] the optimal ASCR strategy is not yet defined. Currently, carboplatin/etoposide/melphalan (CEM) is the standard conditioning regimen used in North America for ASCR in patients with high-risk neuroblastoma, while in Europe busulfan/melphalan (BuMel) has become standard.[2] Results from a Children's Oncology Group study (ANBL12P1) in which BuMel has been included together with the other components of North American high-risk therapy will provide important safety data regarding this regimen. Clinical trials afford the opportunity to document adverse event (AE) rates using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) across different conditioning regimens. However, capture of AEs using CTCAE is laborious, and there is evidence to suggest that AE capture is limited on such trials.[3,4] Furthermore, these comparisons are only inclusive of patients enrolled on clinical trials and do not capture patients managed outside of a trial. A complementary approach is to compare resource utilization (RU) in the immediate post-ASCR period in an observational cohort inclusive of patients treated with either CEM or BuMel conditioning. Understanding the differences in resources utilized across conditioning regimens can further define toxicities associated with one regimen relative to the other. We used a previously assembled database-derived cohort of children with high-risk neuroblastoma [5] to evaluate variation in RU in patients undergoing CEM or BuMel ASCR. Data from a European cooperative group trial [2] indicate that severe toxicity in the first 100 days from ASCR was relatively rare, but severe toxicity was observed more frequently in patients treated with CEM ($P = 0.014$). Because BuMel has been associated with lower rates of severe toxicity, we hypothesized that the RU associated with delivery of BuMel would be lower than RU associated with delivery of CEM in children with high-risk neuroblastoma.

MATERIALS AND METHODS

Data Source

The Pediatric Health Information Systems (PHIS) database contains information regarding inpatient RU at free-standing children's hospitals across the United States. The database includes inpatient data from 43 not-for-profit tertiary care pediatric hospitals affiliated with the Children's Hospital Association (Overland Park, KS) and accounts for 85% of admissions to freestanding children's hospitals in the United States. Data include demographics, dates of service, discharge disposition, payor information, International Classification of Diseases, Ninth Revision (ICD-9) diagnosis and procedure codes, and billing data for medications, laboratory tests, imaging procedures, clinical services, and supplies. Patients are assigned a unique identifier and can be followed from one admission to another. Data quality is monitored via a joint effort among the Children's Hospital Association, Truven Health Analytics, and participating hospitals.

Study Cohort

Neuroblastoma-specific ICD-9 codes do not exist, and therefore a PHIS high-risk neuroblastoma cohort was previously assembled using an algorithm that was defined a priori and subsequently validated.[5] The initial cohort consisted of patients with an index neuroblastoma admission at a PHIS hospital between January 1, 1999 and February 23, 2011 (n = 952). The cohort was later expanded to include patients first admitted through June 30, 2013 (n = 1289). To capture patients receiving current-era therapy, only the subset of neuroblastoma patients who underwent single ASCR with CEM or BuMel preparative regimens between June 1, 2010 and June 30, 2013 was included in this analysis. This source population was identified using billing codes and patterns of administration of the chemotherapy drugs of interest (carboplatin, etoposide, melphalan, and busulfan). Patients treated with tandem ASCR regimens were excluded.

Study Design

Eligible patients who received CEM or BuMel were followed for the outcomes of interest for 60 days from the first day of the ASCR preparative regimens or until death, whichever came first. Sixty days was chosen as the duration of the follow-up period so that inpatient encounters likely related to ASCR would be analyzed, but admissions for anticipated subsequent inpatient therapy (i.e., immunotherapy with dinutuximab[6]) would be excluded. Data for the first 30 days from initiation of CEM or BuMel were also analyzed to permit a focus on early toxicities and RU.

Toxicity outcomes of interest during the study period included evidence of sepsis, sinusoidal obstruction syndrome (SOS), and death. Sepsis was defined by a subset of previously described ICD-9 diagnosis codes.[7] SOS is a clinical syndrome that is typically characterized by tender hepatomegaly, weight gain, and fluid retention with ascites. These symptoms are generally accompanied by elevated bilirubin and increased consumption of platelets.[8] The diagnosis is often supported with demonstration of slowing or reversal of portal venous flow via ultrasound. Children with SOS following ASCR are commonly treated with diuretics to reduce complications from ascites and tissue edema and frequently

require daily platelet transfusions. Because SOS is not associated with a specific ICD-9 diagnosis code, a RU-based definition of SOS was developed for this study. The presence of a CTC code for an abdominal ultrasound and ICD-9 codes for three consecutive daily platelet transfusions within 4 days of a billing code for a diuretic was designated as consistent with SOS. This RU-based definition of SOS had a sensitivity of 100%, a specificity of 96%, and a positive predictive value of 86% when validated via review of medical records of 65 consecutive patients treated with CEM or BuMel ASCR at The Children's Hospital of Philadelphia between 2004 and 2013.

Targeted RU outcomes (in days) included total length of hospitalization and length of intensive care unit (ICU) level of care. A previously described definition of ICU level care was used.[7] Additional targeted RU evaluated in this study included vasopressors, mechanical ventilation, oxygen, diuretics, antihypertensives, dialysis, antibiotics, nonnarcotic analgesics, opiates, diuretics, total parenteral nutrition, and antiemetics. For this study, rarely used resources were defined as those for which the median number of RU days was zero. The proportion of patients requiring targeted resources was also determined for each preparative regimen. Among those patients for whom such resources were used, median RU days were calculated.

Statistical Analyses

Demographics and toxicity outcomes of interest (evidence of sepsis, SOS, and mortality) were summarized by preparative regimen using descriptive statistics and compared using Fisher's exact test. Targeted RU outcomes (in days) for the two preparative regimens were compared using the Wilcoxon two-sample test. The proportions of patients in each group requiring targeted resources were summarized using descriptive statistics and compared using Fisher's exact test. The median number of days of utilization of resources in patients requiring these resources was compared in the two treatment groups using the Wilcoxon two-sample test.

RESULTS

Demographics

In total, 171 patients treated with CEM and 59 patients treated with BuMel were identified. Median age at time of ASCR was 3 years for both groups (ranges <1–14 years and 1–14 years for the CEM and BuMel groups, respectively; Table I). The majority of patients was male and white in both groups (Table I).

Targeted Toxicities: Sepsis, SOS, and Mortality

There was no significant difference in the percentage of patients who developed sepsis following administration of CEM compared with BuMel in the first 30 days (CEM 8.8% and BuMel 11.9%, $P = 0.45$), nor in the first 60 days (CEM 12.3% and BuMel 15.3%, $P = 0.65$). The composite RU data suggested that 13 of 59 (22%) patients in the BuMel group experienced SOS within 60 days after the start of regimen compared to 13 of 171 (7.6%) in the CEM group ($P = 0.0025$). There were three (1.8%) deaths in the CEM group and none in the BuMel group at 30 days ($P = 0.57$). There were six (3.5%) deaths among CEM patients

and no deaths among BuMel patients by day 60 ($P = 0.34$). In the CEM group, deaths occurred at 8, 10, 19, 35 (two patients), and 38 days from the start of the high-dose chemotherapy regimen.

Resource Utilization

Hospitalization and ICU level care—RU data for the first 30 and 60 days from the start of the ASCR preparative regimens are shown (Tables II and III). Over 30 days (Table II), the median number of inpatient hospital days associated with the two ASCR regimens was similar, as was the median number of ICU level of care days (Tables III and IV). However, by day 60, the median number of days in the hospital was greater for patients in the BuMel group by nearly a week ($P = 0.01$). The proportion of patients requiring hospitalization appeared to be higher in the BuMel group, particularly during the latter part of the study period (Fig. 1A), beginning day 28. At day 28, 60% treated with CEM and 68% of patients treated with BuMel were hospitalized ($P = 0.35$). By day 60, 8% of CEM patient and 19% of BuMel patients were inpatient ($P = 0.02$).

During the 60-day study period, 84% of CEM patients and 80% of BuMel patients had a single admission for ASCR. Approximately 14% of CEM patients and 20% of BuMel patients had two separate hospitalizations. Of those who received CEM, 2% had a total of three hospitalizations; none of the BuMel patients had more than two hospitalizations. The median number of inpatient days for the first hospitalization was 29 (range: 8–60) and 35 (range: 21–60) days for the CEM and BuMel groups, respectively, during the 60-day study period ($P = 0.04$).

Cardiorespiratory support—Vasopressor use did not differ in patients treated with CEM and BuMel, nor did use of oxygen (Tables II–IV). A higher proportion of patients treated with BuMel required mechanical ventilation compared with the proportion treated with CEM (Table IV, $P = 0.03$; Fig. 1B); however, the number of days of mechanical ventilation was low in both groups (Tables II and III).

Renal support—During the first 30 days from the start of ASCR conditioning, there was no difference in days of diuretic use in patients treated with the two preparative regimens (Table II); however, diuretics were more frequently used in the BuMel group during the first 60 days from the start of conditioning (Table III, $P = 0.04$; Table IV, $P = 0.0002$). A higher proportion of CEM patients required antihypertensive medications compared with BuMel patients (Table IV, $P = 0.005$). Antihypertensives were used for a longer period of time in the CEM group compared to the BuMel group (Table II, $P = 0.0001$; Table III, $P = 0.0024$). No difference in dialysis use was observed between the two groups (Tables II–IV).

Antibiotics—Antibiotics were administered longer in children in the CEM group compared with the BuMel group after both 30 and 60 days (Tables II–IV; Fig. 1C).

Pain management and nutrition support—During the first 30 days from the start of ASCR conditioning, the number of days of use of nonnarcotic analgesics and opiates was higher in the CEM group (Table II, Fig. 1D); however, by day 60 there was no significant difference in duration of use of either category of pain medication. There were no

differences in duration of use of parenteral nutrition or duration of antiemetic use in the two groups (Tables II–IV).

DISCUSSION

Using a high-risk neuroblastoma cohort created from a national pediatric database, we have compared RU associated with administration of the two ASCR preparative regimens most commonly used in Europe and North America. Our results suggest that the number of days in the hospital and the number of days of ICU level care were similar for patients treated with CEM and BuMel during the first 30 days from initiation of ASCR; however, over the entire study period, the duration of hospitalization was longer for patients in the BuMel group. In addition, targeted RU patterns differed by the treatment group.

CEM patients were more likely to receive nonnarcotic analgesics and opiates in the first 30 days from the start of conditioning. This is consistent with the increased mucosal toxicity associated with CEM as documented on the Children's Oncology Group A3973 trial [9] and with preliminary reports from the SIOPEN HR NBL-1 study comparing these two ASCR regimens.[3] Similarly, the increased utilization of antihypertensives and antibiotics may reflect the nephrotoxicity and febrile neutropenia associated with the CEM regimen.[9]

The number of patients in this cohort requiring mechanical ventilation was small; however, the proportion of patients requiring this type of support was higher in the BuMel group than in the CEM group. Mechanical ventilation was used more frequently in the latter part of the study period, particularly after day 30 (Fig. 1B). Myeloablative regimens, including busulfan-containing regimens, are associated with pulmonary toxicity,[10–13] and close monitoring for late pulmonary toxicity may be particularly important for patients receiving BuMel.

BuMel ASCR has been associated with a risk of SOS, a toxicity that can be difficult to assess because this constellation of findings is not associated with a discrete ICD-9 code and is not included in commonly used toxicity grading schemes such as the CTCAE. Historically, identification of SOS in patients on clinical trials has been challenging, and reported rates of SOS in patients undergoing BuMel transplantation have varied widely. [2,14–20] Analysis of RU made available through administrative databases may aid in the assessment of ASCR-related toxicities that are difficult to identify using other methods. We developed an operational definition of SOS using RU consistent with standard supportive care for this clinically defined syndrome (the presence of a CTC code for an abdominal ultrasound and ICD-9 codes for three consecutive daily platelet transfusions within 4 days of a billing code for a diuretic). Our results suggest that SOS occurred in a higher percentage of patients in the BuMel group compared with the CEM group. The incidence of SOS (22%) detected in the BuMel patients in the PHIS cohort is similar to that reported for patients treated with intravenous busulfan on the SIOPEN HR NBL-1 study for whom detailed pharmacokinetic data were available.[17] It is acknowledged that mild cases of SOS may not have been detected using this definition, and this resource-based definition of SOS requires additional evaluation in future studies. However, our findings suggest that it would be appropriate to have a high index of suspicion for SOS in children treated with BuMel, even

beyond the usual period in which they may be cared for by transplant specialists. Furthermore, it may be necessary to adjust the duration of clinical trial reporting periods to capture the evolution and resolution of this toxicity.

In our study, there were six deaths (3.5%) among those who received CEM and no deaths in the BuMel group during the 60-day study period. This is comparable to the 2% rate of death during consolidation on the Children's Oncology Group A3973 trial,[9] and to SIOPEN HR NBL-1 consolidation toxic death rates of 5% and 2% among patients receiving CEM and BuMel, respectively.[2]

Our results must be interpreted in the context of some limitations. First, the PHIS database is an inpatient database and outpatient resource use is not captured. We leveraged RU data as a proxy measure for toxicities after receipt of ASCR. While some of these resources (i.e., mechanical ventilation) may map well to a true toxicity, others may represent local center preferences (e.g., antibiotic exposures) rather than evidence of different outcomes. Center preferences influenced the selection of BuMel or CEM as the preparative regimen, as some centers moved more quickly than others to adopt BuMel during the time period evaluated. This center-level practice variation may track with center-level variations in supportive care; this will be studied in more detail in future analyses. Within-center factors, including patient-level factors such as organ function, may also have impacted preparative regimen selection, and in turn may have affected decision making regarding supportive care resources. Additionally, a constellation of RU was employed as a proxy measure for a single toxicity (i.e., SOS). Clinical practices, and therefore resources used to treat SOS, may vary among institutions. Thus, the approach used in this study requires validation in other contexts. Finally, numerous statistical tests were performed without correction for multiple testing. However, resources of interest for this study were defined a priori.

The relatively small sample size of the cohort and the low mortality rate in the two exposure groups limit our ability to compare posttransplant mortality among CEM and BuMel patients. In the 60-day post ASCR period, six (3.5%) CEM patients died while none of the BuMel patients died. Although not statistically significantly different, these data suggest that a true difference in mortality rates could exist but would require a larger sample size to detect. Additionally, as more CEM subjects died during the study period, their follow-up time was truncated. This could have contributed to an underestimation of total RU in this group. Alternatively, RU immediately preceding death may have been high, which could have increased the total RU in the CEM group due to the contribution of a small number of patients. Additionally, a subset of patients remained hospitalized 60 days after the start of BuMel conditioning; RU may therefore have been underestimated in the BuMel group. Finally, comparisons across the two exposure groups were unadjusted and did not account for differences in health status at the time of transplant. If there were an imbalance in overall health or organ function in patients receiving one type of conditioning versus the other, it could result in differences in outcomes that are not attributable to the conditioning regimen itself.

The current findings demonstrate that administrative data can be used to compare resources associated with the use of one ASCR conditioning regimen in comparison with another in

children with high-risk neuroblastoma. In this study, patients treated with CEM required more extended use of pain medications, antibiotics, and antihypertensives compared with patients treated with BuMel. SOS appeared to be more frequent in the BuMel group and total duration of hospitalization was longer following BuMel than it was following CEM. Data regarding the efficacy of CEM and BuMel in the overall context of differing institutional and cooperative group approaches to high-risk neuroblastoma therapy will ultimately determine selection of the optimal ASCR regimen; however, our results can provide key information that can be used by clinicians in counseling families approaching the ASCR portion of neuroblastoma therapy. Our findings will facilitate discussions regarding expected length of stay associated with each regimen, and will allow for more informed conversations regarding supportive care that may be required following BuMel or CEM. Evaluation of the clinical impact of other treatments and other transplant approaches, such as tandem ASCR, via study of RU is planned. As the complexity of high-risk neuroblastoma therapy continues to increase, a greater understanding of the supportive care required for patients could further aid in medical decision making.

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Fig. 1.

(**A**) The percent of patients in the CEM (solid line) and BuMel (dotted line) groups in the hospital during the 60-day study period. (**B**) The percent of patients in the CEM (solid line) and BuMel (dotted line) groups who required mechanical ventilation during the 60-day study period. (**C**) The percent of patients in the CEM (solid line) and BuMel (dotted line) groups who received antibiotics during the 60-day study period. (**D**) The percent of patients in the CEM (solid line) and BuMel (dotted line) groups who received opiates during the 60-day study period.

TABLE I

Demographics

	CEM (n = 171)	BuMel (n = 59)	P-value
Age at transplant years, median (range)	3.0 (0–14)	3.0 (0–14)	0.64
Gender			0.61
Male	105 (61.4%)	34 (57.6%)	
Female	66 (38.6%)	25 (42.4%)	
Race			0.70
White	107 (62.6%)	35 (59.3%)	
Black	19 (11.1%)	9 (15.3 %)	
Asian/Pacific Islander	13 (7.6%)	2 (3.4%)	
American Indian	3 (1.7%)	1 (1.7%)	
Other	29 (17.0%)	12 (20.3%)	

TABLE II

Resource Utilization: 30-Day Study Period

Resource	PHIS resource utilization days				P-value
	CEM (n = 171)		BuMel (n = 59)		
	Mean (Median)	Range	Mean (Median)	Range	
Hospitalization and ICU level care					
Hospital days	27.38 (29)	8–30	27.83 (30)	21–30	0.37
Intensive care days	1.32 (0)	0–24	0.42 (0)	0–24	0.72
Cardiorespiratory support					
Vasopressors	1.27 (0)	0–20	0.64 (0)	0–10	0.70
Mechanical ventilation	0.66 (0)	0–24	0.39 (0)	0–14	0.83
Oxygen	1.44 (0)	0–18	0.75 (0)	0–13	0.31
Renal support					
Diuretics	6.04 (4)	0–22	6.41 (5)	0–25	0.75
Antihypertensives	2.88 (0)	0–30	0.83 (0)	0–30	0.0001*
Dialysis	0.41 (0)	0–23	0.08 (0)	0–4	0.95
Infection surveillance and treatment					
Antibiotics	18.11 (18)	0–30	13.85 (14)	4–30	<0.0001*
Pain management and nutrition support					
Nonnarcotic analgesics	8.57 (8)	0–22	6.32 (6)	0–16	0.0052*
Opiates	13.77 (13)	0–30	9.90 (9)	3–20	<0.0001*
Total parenteral nutrition	12.17 (14)	0–26	10.63 (13)	0–29	0.18
Antiemetics	21.98 (23)	5–30	21.14 (21)	7–30	0.33

* Statistically significant ($P < 0.05$).

TABLE III

Resource Utilization: 60-Day Study Period

Resource	PHS resource utilization days				P-value
	CEM (n = 171)	BuMel (n = 59)			
	Mean (Median)	Range	Mean (Median)	Range	
Hospitalization and ICU level care					
Hospital days	32 (31)	8–60	38 (35)	21–60	0.01 *
Intensive care days	1.96 (0)	0–47	3.02 (0)	0–39	0.13
Cardiorespiratory support					
Vasopressors	1.52 (0)	0–31	2.15 (0)	0–32	0.84
Mechanical ventilation	1.12 (0)	0–48	2.59 (0)	0–39	0.02 *
Oxygen	1.61 (0)	0–18	2.17 (0)	0–21	0.71
Renal support					
Diuretics	7.05 (4)	0–51	11.85 (8)	0–48	0.04 *
Antihypertensives	4.97 (0)	0–58	1.63 (0)	0–43	0.0024 *
Dialysis	0.66 (0)	0–36	0.36 (0)	0–11	0.31
Infection surveillance and treatment					
Antibiotics	20 (19)	0–58	18 (15)	4–50	0.01 *
Pain management and nutrition support					
Nonnarcotic analgesics	9.35 (9.0)	0–32	7.92 (8.0)	0–28	0.07
Opiates	15.57 (14)	0–54	15.10 (10)	3–45	0.08
Total parenteral nutrition	13.88 (14)	0–54	14.58 (13)	0–51	0.92
Antiemetics	24.28 (24)	5–60	25.93 (22)	7–60	0.85

* Statistically significant ($P < 0.05$).

TABLE IV

Proportion of Patients Requiring Resources: 60-Day Study Period

	CEM (n = 171)	BuMel (n = 59)	P-value
ICU level care, n (%) ^a	23 (13)	13 (22)	0.15
Median intensive care days, days (range)	11 (1–47)	8 (1–39)	0.71
Cardiorespiratory support			
Vasopressors, n (%) ^a	54 (32)	19 (32)	1
Median days of vasopressor support, days (range)	2 (1–31)	2 (1–32)	0.58
Mechanical ventilation, n (%) ^a	11 (6)	10 (17)	0.03 *
Median days of mechanical ventilation, days (range)	12 (1–48)	9.5 (1–39)	0.65
Oxygen, n (%) ^a	49 (29)	18 (31)	0.87
Median days of oxygen support, days (range)	4 (1–18)	5 (1–21)	0.60
Renal support			
Diuretics, n (%)	135 (79)	44 (75)	0.47
Median days of diuretics, days (range)	6 (1–51)	12.5 (1–48)	0.0002 *
Antihypertensives, n (%) ^a	74 (43)	13 (22)	0.005 *
Median days of antihypertensive support, days (range)	5 (1–58)	2 (1–43)	0.19
Dialysis, n (%) ^a	6 (4)	6 (7)	0.28
Median days of dialysis, days (range)	18 (2–36)	4 (2–11)	0.23
Infection surveillance and treatment			
Antibiotics, n (%)	170 (99)	59 (100)	1.00
Median days of antibiotics, days (range)	19 (5–58)	15 (4–50)	0.009 *
Pain management and nutrition support			
Nonnarcotic analgesics, n (%)	165 (96)	55 (93)	0.28
Median days of nonnarcotic analgesics, days (range)	9 (1–32)	8 (1–28)	0.12
Opiates, n (%)	170 (99)	59 (100)	1.00
Median days of opiates, days (range)	14 (2–54)	10 (3–45)	0.07
Total parenteral nutrition, n (%)	122 (71)	40 (68)	0.62
Median days of total parenteral nutrition, days (range)	18 (1–54)	22 (3–51)	0.38
Antiemetics, n (%)	171 (100)	59 (100)	1.00
Median days of antiemetics, days (range)	24 (5–60)	22 (7–60)	0.85

^aRare resources.* Statistically significant ($P < 0.05$).