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Retrospective Study

Impact of Intravenous Busulfan Pharmacokinetics on Safety in Pediatric Patients who have undergone Hematopoietic Stem Cell Transplant

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Abstract

Introduction: Busulfan (Bu)-based regimens are crucial for myeloablative conditioning in pediatric allogeneic stem cell transplantation. Despite its efficacy, Intravenous Bu has a narrow therapeutic index and variable pharmacodynamics especially in children, heightening the risk of adverse events. This study explores Bu dosing and related organ toxicities in pediatric patients at a tertiary center in Saudi Arabia.

Methodology: This retrospective study at King Fahad Specialist Hospital in Dammam (KFSH-D), Saudi Arabia, included pediatric patients (≤16 years) treated with intravenous Bu before bone marrow transplantation from 2010 to 2022. Pharmacokinetic dose adjustments were based on AUC targets of 900-1350 µMol-min. Descriptive measures included mean, Standard Deviation (SD), median, minimum-maximum values, counts, and percentages. Statistical analyses used Kruskal-Wallis, Chi-square, and Fisher's exact tests. Ethical approval was obtained from KFSH-D.

Results: We identified 44 pediatric patients who underwent Bu prior to HSCT. Mean age was 4.95 ± 2.49 years, with a female majority (56.8%). Primary diseases included Beta Thalassemia (34.09%), Neuroblastoma (29.55%) among others. There was no significant difference in the cohort's demographic and clinical features of the cohort. Nonetheless, higher infections were found in the Low-AUC group (66.7%) compared to the Target-AUC (40.0%) and Higher-AUC groups (0.0%) (p = 0.015).

Conclusion: This study emphasizes the need for therapeutic drug monitoring and individualized Bu dosing in pediatric HSCT to minimize toxicity and improve outcomes. Larger multicenter studies are recommended to refine dosing strategies and enhance the safety and efficacy of Bu-based regimens.

More Information

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Keywords: Busulfan; Pediatrics; Adverse events; AUC; Toxicity; HSCT; Drug monitoring

Introduction

Busulfan (Bu)-based regimens are a cornerstone of myeloablative conditioning in allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for infants and young children, particularly to avoid total body irradiation, such as growth impairment, endocrine dysfunction, and secondary malignancies [1]. This drug is utilized in various conditioning regimens: it serves as myeloablative conditioning when combined with Cyclophosphamide (Cy) and Anti-thymocyte globulin (ATG), Thiotepa-fludarabine (TBF), or melphalan or thiotepa alone. These regimens are integral in achieving durable engraftment and improving survival outcomes in pediatric patients with hematological malignancies and non-malignant disorders requiring HSCT [2].

Bu has a narrow therapeutic index and exhibits variable pharmacodynamics across different populations, leading to differences in toxicity and outcomes among patients [3-5]. The maximum tolerated dose of Bu is limited by its potential to cause liver damage, with the most serious hepatic complication being Sinusoidal Obstructive Syndrome (SOS) [6,7]. To mitigate

the drug's toxicity, intravenous administration of Bu has been preferred since the 2000s, as oral administration has been associated with a higher incidence of SOS and unpredictable metabolic variability [8-10].

Nonetheless, intravenous Bu (IVBu) pharmacokinetics have been described mainly in adults. Thus, results and dosing regimens cannot be extrapolated to pediatric patients due to variability in their drug-metabolizing enzymes. This variability in Bu pharmacokinetics is attributed to its metabolism by hepatic enzymes such as Glutathione-S-Transferase and cytochrome P450, which are significantly influenced by the pharmacogenetic diversity of patients [11-17].

Additionally, Therapeutic Drug Monitoring (TDM) of Bu-pharmacokinetics (Bu-PK) is recommended, allowing for individualized dosing based on the calculated area-under-the-curve (AUC), thus significantly reducing adverse events and non-relapse mortality [5]. Studies show variability in the target AUC for Bu, generally ranging between 900 to 1350 µmol/l*min for myeloablative purposes, an exposure that has been associated with reliable engraftment and no increase in organ toxicity. Several studies have suggested that Bu toxicity and a higher incidence of graft failure may be due to plasma drug concentration and/or improper dosing in children [18].

Saudi Arabia presents a unique context for studying Bu use in pediatric HSCT due to its genetic diversity, high prevalence of consanguinity, and increasing incidence of inherited hematological disorders requiring HSCT [19-23]. Hence, understanding Bu's pharmacokinetics in this population is critical for developing effective and safe dosing protocols tailored to the region's specific demographic and genetic profile.

This retrospective study will examine the association between Bu dosing and secondary organ toxicities among pediatric patients in a tertiary center in Saudi Arabia. By addressing the pharmacogenetic variability and challenges of TDM in this population, we aim to contribute to optimizing conditioning regimens and improving outcomes in pediatric HSCT.

Methods

Study population

This is a single-center retrospective study conducted at King Fahad Specialist Hospital in Dammam, Saudi Arabia. The study included all pediatric patients who received IVBu prior to bone marrow transplantation between January 1, 2010, and August 1, 2022.

Inclusion and exclusion criteria

The inclusion criteria for this study were pediatric patients aged 16 years or younger who were treated with IVBu prior to bone marrow transplantation at King Fahad Specialist Hospital in Dammam between 2010 and 2022, with complete data available. The exclusion criteria were patients older than 16 years, those who did not receive IVBU, missed data, and non-BMT patients.

Pharmacokinetics

In this study, a conventional BuCy regimen using IVBu instead of oral Bu was tested. IVBu was administered every 6 hours for 16 doses with a targeted Area Under the Curve (AUC) of 900–1,350 µMol-min. Pharmacokinetic data were obtained at the initial dose allowing for a single dose adjustment based on the AUC of this dose to achieve a target Bu-AUC of 900–1,350 µmol/l*min, with ranges below and above the target defined as Lower-AUC and Higher-AUC, respectively.

The initial dose was calculated based on patient weight according to the protocol: patients weighing less than 9 kg received 1.0 mg/kg, those weighing between 9 kg and less than 16 kg received 1.2 mg/kg, patients weighing between 16 kg and less than 23 kg received 1.1 mg/kg, those weighing between 23 kg and 34 kg received 0.95 mg/kg, and patients weighing more than 34 kg received 0.8 mg/kg.

The pharmacokinetics of the first dose of IVBu were determined immediately after the termination of the intravenous infusion of Bu to calculate a single dosage adjustment and at 1 hour, 2 hours, and 4 hours after termination of the infusion to confirm steady-state pharmacokinetics.

Statistical analysis

Descriptive measures included mean, Standard Deviation (SD), median, and minimum-maximum values for quantitative variables, while counts and percentages were presented for categorical variables. Differences between quantitative variables among AUC-Level groups were determined using ANOVA. Data normality was tested using the Shapiro-Wilk test. When normality was violated, the Kruskal-Wallis test was used instead. The Chi-square test, or Fisher's exact test when more than 20% of cells had counts less than five, was used to assess the relationship between categorical variables. A two-sided p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 26.

Ethical approval

Our study is a retrospective study conducted at King Fahad Specialist Hospital, Dammam from Jan 2010 – Aug 2022. This tertiary care hospital is located in the Eastern Province of Saudi Arabia and provides services in the following specialties: Oncology, Neurosciences, Organ Transplant, Cardiac Services Programs, and Genetic Sciences. Revision of the medical records for all the selected cases was done after obtaining approval from the Institutional Review Board (IRB Number: HAEM0331).

Results

Demographic and clinical

A total of 44 patients received Bu prior to HSCT at King Fahad Specialist Hospital-Dammam. The mean ± SD (Range) age of the patients was 4.95 ± 2.49 (1-7) years, with a female predisposition of 25 patients (56.8%). Along with Bu, the patients received additional treatments, including Melphalan in 14 (31.8%) patients, Thiotepa in 1 (2.3%) patient, Fludarabine (Flu) and Thiotepa in 11 (25.0%) patients, and Cyclophosphamide (Cy) and Anti-Thymocyte Globulin (ATG) in 18 (40.9%) patients. The primary diseases diagnosed in these patients included Beta Thalassemia in 15 (34.09%) patients, Sickle Cell Disease in 2 (4.55%) patients, B-Cell Acute Lymphoblastic Leukemia (ALL) in 3 (6.82%) patients, T-Cell ALL in 1 (2.27%) patient, Acute Myeloid Leukemia (AML) in 8 (18.18%) patients, Neuroblastoma in 13 (29.55%) patients, and Medulloblastoma in 2 (4.55%) patients. There was no significant difference in the demographic and clinical features of the cohort (Table 1).

Pharmacokinetics

Regarding pharmacokinetics, the median Bu-AUC was 958 µmol/l*min (range 420.94–1900.0). The target range was reached in 20 (45.5%) patients, 18 (40.9%) were in the low-AUC group and 6 (13.6%) were in high-AUC group. The dosing of Bu was changed in 32 (72.7%) patients, 24 (54.5%) patients received an increased dose and 8 (18.2%) received a decreased dose; 12 (27.3%) patients did not have their initial dose modified. The median AUC measured at 0, 1, 2, and 4 hours was 917, 701, 500, and 271, respectively.

Outcome and toxicity

Between days -8 and 30, the total number of adverse events (AEs) was 51 in 41 (93.2%) patients, with 23 (45.1%) AEs in the Low-AUC group, 24 (47.1%) AEs in the Target-AUC group, and 4 (7.8%) AEs in the High-AUC group. Three (6.82%) patients were stable in total, with 1 (33.3%) in the Target-AUC group and 2 (66.7%) in the High-AUC group.

Between days 31 and 100, the total number of adverse events was 28 in 28 (63.6%) patients, with 13 (46.4%) AEs in the Low-AUC group, 12 (42.9%) AEs in the Target-AUC group, and 3 (10.7%) AEs in the High-AUC group. Eight patients were stable in total, with 2 (25.0%) in the Low-AUC group, 3 (37.5%) patients in the Target-AUC group, and 3 (37.5%) in the High-AUC group.

Between days 101 and 2 years, the total number of adverse events was 24 in 24 (54.5%), with 10 (41.7%) AEs in the Low-AUC group, 11 (45.8%) AEs in the Target-AUC group, and 3 (12.5%) AEs in the High-AUC group. Five (11.4%) patients in total passed away, with 2 (40.0%) of them in the Low-AUC group, and 3 (60.0%) of them in the Target-AUC group. Seven (15.9%) patients were stable in total, with 2 (28.6%) in the Low-AUC group, 4 (57.1%) in the Target-AUC group, and 1 (14.3%) in the High-AUC group.

There was no significant difference in the proportion of patients with AEs between the groups except for higher rates of infections in the Low-AUC group compared to the Target-AUC and High-AUC groups (66.7% *vs.* 40.0% *vs.* 0.0%, respectively; $p = .015$) (Table 2).

Table 1: Demographic and clinical characteristics stratified by AUC.

Demographic and Clinical Data	All Patients $N = 44$	AUC Group			p - value
		Lower-AUC ($N = 18$)	In Range-AUC ($N = 20$)	Higher AUC ($N = 6$)	
	N (%)	N (%)	N (%)	N (%)	
Age	44	18	20	6	
Mean ± SD	4.95 ± 2.49	5.17 ± 2.55	5.2 ± 2.262	3.5 ± 2.95	.353
95% CI	4.20-5.71	3.9-6.43	4.14-6.26	0.40-6.6	
Median	7.0	7.0	7.0	2.5	
Minimum-Maximum	1-7	1-7	1-7	1-7	
Gender	44	18	20	6	.146
Male	19 (43.2)	5 (27.8)	12 (60.0)	2 (33.3)	
Female	25 (56.8)	13 (72.2)	8 (40.0)	4 (66.7)	
Other Medications	44	18	20	6	.063
Melphalan	14 (31.8)	6 (33.3)	5 (25.0)	3 (50.0)	
Thiotepa	1 (2.3)	0 (0.0)	0 (0.0)	1 (16.7)	
TBF	11 (25.0)	3 (16.7)	8 (40.0)	0 (0.0)	
Cy & ATG	18 (40.9)	9 (50.0)	7 (35.0)	2 (33.3)	
Primary Disease	44	18	20	6	.7
Beta Thalassemia	15 (34.09)	7 (38.89)	6 (30.0)	2 (33.3)	
Sickle Cell Disease	2 (4.55)	2 (11.11)	0 (0.0)	0 (0.0)	
B-Cell ALL	3 (6.82)	1 (5.56)	2 (10.0)	0 (0.0)	
T-Cell ALL	1 (2.27)	0 (0.0)	1 (5.0)	0 (0.0)	
AML	8 (18.18)	2 (11.11)	6 (30.0)	0 (0.0)	
Neuroblastoma	13 (29.55)	5 (27.78)	5 (25.0)	3 (50.0)	
Medulloblastoma	2 (4.55)	1 (5.56)	0 (0.0)	1 (16.7)	

AUC: Area Under Curve; ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; ATG: Anti-thymocyte Globulin; Cy: Cyclophosphamide; SD: Standard Deviation; TBF: Thiotepa-fludarabine

Table 2: Outcomes and Adverse Event stratified by AUC.

Outcome and AE Data	All Patients N = 44	AUC Group		
		Lower-AUC (N = 18)	In Range-AUC (N = 20)	Higher AUC (N = 6)
	N (%)	N (%)	N (%)	N (%)
Day 8 until 30	44	18	20	6
GVHD	1 (1.85)	3 (16.67)	2 (10.0)	0 (0.0)
Infection	20 (37.04)	4 (22.22)	6 (30.0)	0 (0.0)
Mucositis	25 (46.3)	0 (0)	1 (5.0)	3 (50.0)
SOS	4 (7.41)	1 (5.56)	1 (5.0)	1 (16.7)
Haemorrhagic Cystitis	1 (1.85)	0 (0)	1 (5.0)	0 (0.0)
Stable	3 (5.56)	2 (11.11)	1 (5.0)	2 (33.3)
Day 31 until 100	44	18	20	6
GVHD	5 (13.9)	3 (20.0)	2 (13.3)	0 (0.0)
Infection	15 (41.7)	6 (40.0)	6 (40)	3 (50.0)
Nephrotoxicity	2 (5.56)	1 (6.67)	1 (6.67)	0 (0.0)
Hepatotoxicity	1 (2.78)	0 (0)	1 (6.67)	0 (0.0)
SOS	3 (8.33)	2 (13.3)	1 (6.67)	0 (0.0)
RAS	1 (2.78)	1 (6.67)	0 (0)	0 (0.0)
PTLD	1 (2.78)	0 (0)	1 (6.67)	0 (0.0)
Stable	8 (22.2)	2 (13.3)	3 (20.0)	3 (50.0)
Day 101 until 2 years	44	18	20	6
GVHD	7 (22.6)	3 (25.0)	4 (26.7)	0 (0.0)
Infection	9 (29.0)	4 (33.3)	2 (13.3)	3 (75.0)
Nephrotoxicity	1 (3.23)	0 (0)	1 (6.7)	0 (0.0)
Hepatotoxicity	1 (3.23)	1 (8.3)	0 (0)	0 (0.0)
RAS	1 (3.23)	0 (0)	1 (6.7)	0 (0.0)
Death	5 (16.1)	2 (16.7)	3 (20.0)	0 (0.0)
Stable	7 (22.6)	2 (16.7)	4 (26.7)	1 (25.0)

AE: Adverse Event; AUC: Area Under Curve; GVHD: Graft-versus-host disease; PTLD: Post-transplant Lymphoproliferative Disorder; RAS: Restrictive Allograft Syndrome; SOS: Sinusoidal Obstruction Syndrome

Discussion

In the present study, Bu pharmacokinetics were investigated in children receiving intravenous Bu as part of a myeloablative regimen prior to HSCT. Given the common use of Bu in pediatric patients and the known differences in Bu metabolism among children, it was important to test for safety and efficacy and to characterize the PK profile of IVBu in children.

In our study, the comparison groups were similar in disease and patient characteristics. The comparability of the groups enabled us to analyze the impact of conditioning intensity on transplantation outcomes with minimal interference by possible confounding demographic and disease-related variables.

Pharmacokinetics and dosing adjustments

The study revealed a wide range of Bu-AUC values, highlighting the necessity for individualized dosing strategies. Approximately 45.5% of patients achieved the target AUC range, while 40.9% fell into the low AUC group, and 13.6% were in the high AUC group. The significant proportion of patients requiring dose adjustments (72.7%) after initial PK assessment aligns with previous studies suggesting that initial weight-based dosing without subsequent TDM often leads to suboptimal drug exposure. Therapeutic dose adjustments in Bu dosing based on early PK measurements likely contributed to achieving more accurate target exposures and optimizing therapeutic outcomes reducing the risk of adverse events and enhancing transplantation success rates [24-26].

The incidence of AEs was substantial, with a total of 51 AEs occurring in 41 patients (93.2%) within the first 30 days post-transplantation. The distribution of AEs across different AUC groups did not show a significant overall difference, except for infection rates, which were significantly higher in the low-AUC group (66.7%) compared to the target-AUC (40.0%) and high-AUC (0.0%) groups (p = .015).

This is inconsistent with previous studies that have shown an association between lower Bu exposure and higher rates of graft failure and relapse but not infections. The higher infection rate among patients with low-AUC ranges remains unclear, but it could be attributed to the higher proportion of other medications such as Cy and ATG in the low-AUC group. ATG has been associated with higher rates of infections; nonetheless, when combined with Bu, Cy has demonstrated comparable levels of toxicity to melphalan in a head-to-head study. Thus, maintaining optimal Bu levels in conjunction with the dosing and choice of other medications might be a worthwhile approach to investigate to prevent infections [27-32].

The study did not report significant differences in the proportions of stable patients between the groups. However, there was a trend towards better stability in the target-

AUC and high-AUC groups compared to the low-AUC group between the initiation of transplant and 2 years. These results emphasize the role of adequate Bu exposure to ensure successful engraftment without adverse events.

Limitations

The retrospective nature of the study is a notable limitation, potentially introducing selection bias and limiting the ability to establish causal relationships. Additionally, the single-center design may affect the generalizability of the results. The relatively small sample size further limits the statistical power to detect differences between groups. Potential confounding variables, such as concurrent medications and comorbidities, may have influenced the observed outcomes. For example, the higher infection rates in the low-AUC group might be partially explained by the concurrent use of ATG, which is known to increase infection risks. Despite these limitations, the study provides valuable insights into the importance of Bu-PK monitoring in pediatric HSCT patients.

Conclusion

In conclusion, our study highlights the importance of therapeutic drug monitoring and individualized dosing of Bu in pediatric patients undergoing HSCT. Low-AUC levels correlated with higher infection rates and suboptimal stability, while target and high-AUC groups demonstrated better engraftment outcomes and fewer infections. Achieving target Bu-AUC while monitoring other medications is essential to minimize toxicity, and to improve overall outcomes. Further prospective, multicenter studies with larger cohorts are warranted to validate these findings and to refine dosing strategies to enhance the safety and efficacy of Bu-based conditioning regimens in pediatric HSCT.

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