THERAPEUTIC DRUG MONITORING OF ONCE-DAILY INTRAVENOUS BUSULFAN IN PEDIATRIC PATIENTS UNDERGOING STEM CELL TRANSPLANTATION IN A RESOURCE-LIMITED SETTING

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BACKGROUND

Busulfan is a cornerstone of myeloablative conditioning for pediatric hematopoietic stem cell transplantation (HSCT), but pharmacokinetic (PK) variability among children complicates its use. The conventional four-times-daily intravenous (IV) schedule is logistically demanding in resource-limited settings. A once-daily IV regimen offers a more practical alternative, provided PK-guided dosing with therapeutic drug monitoring (TDM) — targeting an area-under-the-curve (AUC) of 3200–4800 µmol·min/L — is used to preserve efficacy and safety.

OBJECTIVE

To characterize the pharmacokinetics of once-daily weight-based IV busulfan, evaluate TDM-guided dose adjustment, and describe early engraftment and transplant-related complications in children undergoing allogeneic HSCT at a resource-limited transplant center.

METHODS

- Prospective cohort of pediatric HSCT recipients; busulfan given Day −10 to Day −7 of conditioning
- Weight-based IV busulfan; blood sampled at 1, 2, and 3 h post-infusion for TDM
- Plasma busulfan measured via Roche Cobas c501 with the MyCare™ Oncology Assay Kit
- PK analysis with PK-Solver; statistics with SPSS v25 (Spearman correlation, linear regression, Wilcoxon signed-rank, Mann–Whitney U; Benjamini–Hochberg FDR correction)
- Conditioning: busulfan + fludarabine + cyclophosphamide ± ATG; target AUC 3200–4800 µmol·min/L; bone marrow was the stem-cell source for all patients

RESULTS

27 pediatric allogeneic HSCT recipients with busulfan PK data

PARTICIPANTS

Twenty-seven pediatric HSCT recipients with busulfan PK data were analyzed (median age 4.58 y; 59.3% male; 66.7% beta-thalassemia major). Repeat (4th-dose) AUC was available in 9 patients; the remaining 18 had first-dose AUC only. Early outcome data were evaluable in 21 of 27 patients (Figure 1).

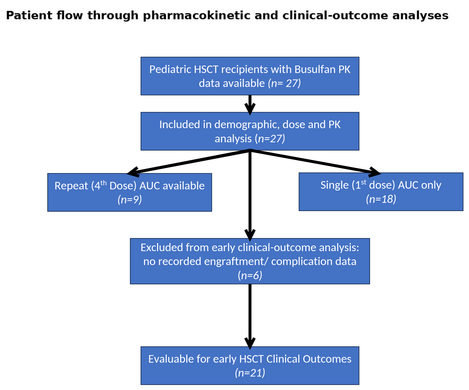

Figure 1. Patient flow through pharmacokinetic and clinical-outcome analyses.

Table 1. Baseline demographic and transplant characteristics (n = 27)

Age, years	4.58 (3.33–7.00)
Male sex, n (%)	16 (59.3%)
Weight, kg	16.0 (13.65–19.75)
Body surface area, m²	0.68 (0.61–0.77)
Beta-thalassemia major, n (%)	18 (66.7%)
Non-malignant disease, n (%)	22 (81.5%)
ABO mismatch, n (%)	14 (51.9%)
Stem-cell source: bone marrow, n (%)	27 (100%)
Conditioning: FLU/BU/CY/ATG, n (%)	16 (59.3%)

PHARMACOKINETICS

After the initial weight-based dose (median 72 mg), median peak concentration (Cmax) was 9.60 µmol/L, median first-dose AUC was 4375.0 µmol·min/L, median clearance was 0.0158 L/h/kg, and median elimination half-life was 431.4 minutes (Table 2).

Table 2. Busulfan pharmacokinetic and dose summary, median (IQR)

Initial busulfan dose, mg	72 (60–83)
Cmax, µmol/L	9.60 (8.75–11.60)
First-dose AUC, µmol·min/L	4375.0 (4048.6–5031.0)
Clearance, L/h/kg	0.0158 (0.0124–0.0179)
Elimination half-life, min	431.4 (389.7–467.3)
Adjusted busulfan dose, mg	68 (56.37–76.65)
Fourth-dose AUC (n = 9)	4751.7 (4611.2–5214.7)

Body size was the strongest correlate of clearance: both weight (ρ = 0.658, p < 0.001) and BSA (ρ = 0.666, p < 0.001) correlated positively with clearance, surviving FDR correction. In contrast, first-dose AUC — the principal exposure measure — was not significantly associated with age, weight, BSA, ferritin, bilirubin, or administered dose, consistent with effective weight-based dose individualization (Figure 2).

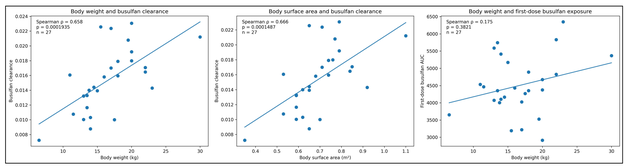

Figure 2. Body weight (A) and BSA (B) vs. clearance; body weight vs. first-dose AUC (C).

Taken together, clearance scaled with body size while systemic exposure stayed comparatively stable across the weight range — a pattern consistent with effective dose individualization rather than uncontrolled PK variability.

DOSE ADJUSTMENT & TDM

Following first-dose PK assessment, doses were individually adjusted from a median of 72 mg to 68 mg. Across the cohort this paired change was not statistically significant (Wilcoxon p = 0.125), indicating bidirectional, patient-specific adjustment rather than a uniform trend (Table 3).

Table 3. Paired therapeutic drug monitoring comparisons

Comparison	n	Before	After	p
Initial vs. adjusted dose, mg	27	72	68	0.125
First- vs. fourth-dose AUC	9	4826.9	4751.7	0.688

Among the 9 patients with repeat measurements, median exposure was similarly unchanged between first-dose (4826.9) and fourth-dose (4751.7) AUC (Wilcoxon p = 0.688) — consistent with TDM-guided adjustment successfully maintaining exposure within the therapeutic range (Figure 3).

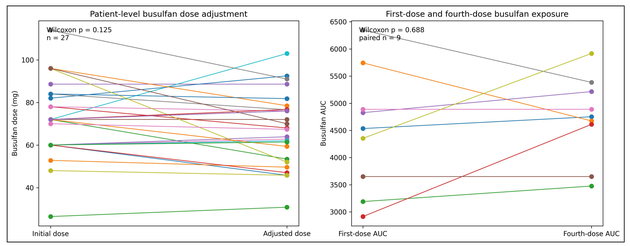

Figure 3. Patient-level dose adjustment (A) and paired first- vs. fourth-dose AUC (B).

Taken together, these paired comparisons show TDM-guided adjustment kept exposure within the intended range without a systematic drift in either direction, across both single and repeat-dose measurements.

ENGRAFTMENT & OUTCOMES

Among 21 patients with evaluable data, neutrophil engraftment occurred in 19 (90.5%) at a median of 14 days. Mucositis was the most common early complication (18/21, 85.7%), followed by nausea/vomiting (6/21, 28.6%). Veno-occlusive disease, primary graft failure, and mortality each occurred in 2/21 (9.5%), and acute GVHD in 1/21 (4.8%); no seizures or chronic GVHD were recorded (Figure 4).

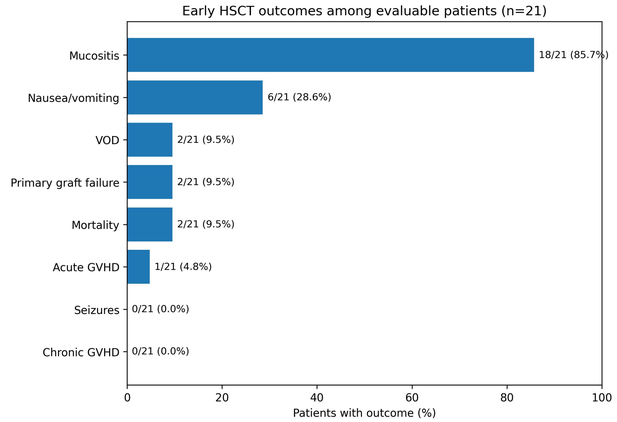

Figure 4. Frequency of early HSCT complications among 21 evaluable patients.

Time to engraftment was not significantly associated with first-dose AUC, clearance, Cmax, or dose. Patients with VOD had numerically higher first-dose AUC (6089.3 vs. 4430.7; p = 0.010), though this did not survive FDR correction (adjusted p = 0.171) and is reported as an exploratory, hypothesis-generating observation.

CONCLUSION

Once-daily IV busulfan with weight-based dosing and TDM-guided adjustment achieved target AUC levels in most pediatric HSCT recipients, with clearance scaling predictably with body size while systemic exposure remained stable. These findings support once-daily dosing as an effective, practical alternative to four-times-daily dosing in resource-limited settings.

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