THERAPEUTIC DRUG MONITORING OF INTRAVENOUS BUSULFAN IN PAEDIATRIC PATIENTS

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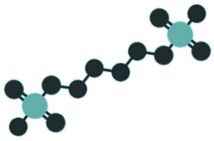
Background and importance

Busulfan is a chemotherapeutic drug commonly used in preparative regimens for hematopoietic stem-cell transplantation in adults and children or a variety of malignant and non-malignant diseases. Its efficacy and safety could be affected by its narrow therapeutic margin and its great pharmacokinetic variability.



Aim and objectives

Quantifying the adjustments magnitude of busulfan dose made in our cohort of patients in the last ten years.

Materials and methods

Retrospective observational study in bone marrow transplantation center.

Paediatric patients

Treated with intravenous busulfan between 2010 and 2020

Different types of variables were recorded

- **Demographic:** age, sex, weight, baseline disease
- **Treatment:** type of conditioning protocol, dose by weight
- **Drug monitoring:** need for dose modification, number of adjustments, percentage of variation between received dose and theoretical dose
- **Efficacy:** incidence of implant failure
- **Safety:** incidence of sinusoidal obstruction syndrome

Pharmacokinetic studies

- **Method:** non-linear regression with ID3 software
- **Area under the curve target:** 55000-95000 ng/ml·h (depending on exposure target: reduced intensity or myeloablative conditioning).

Results

We included **45 patients** with **median age 3 years old** (range: 4 month to 16 years). In 43 cases transplantations were **allogeneic** and two of them were autologous. Baseline diseases in the allogeneic group were **23 malignant and 20 non-malignant haematological diseases** while in the autologous group were two neuroblastomas.
Conditioning regimens were: **38/45 myeloablative** and **7/45 non-myeloablative**.
Busulfan initial doses ranged from **3.2 to 5.1 mg/kg/day** (related to adjusted body weight), according to the protocol and the weight band. All patients received seizures prophylaxis with phenytoin.

	MYELOABLATIVE (N=39)	NON-MYELOABLATIVE (N=6)	GLOBAL (N=45)
Patients with dose variation	33	6	39
Dose reductions	21	3	24
Median (IQR)	-7.5% (-15.1 to -4.2%)	-6.8% (-10.6 to -3.8%)	-7.1% (-15.0 to -4.0%)
Dose Increases	12	3	15
Median (IQR)	11.4% (9.1 to 17.5%)	10.7% (9.3 to 11.7%)	11.4% (8.9 to 14.8%)

Eight patients presented implant failure (seven with secondary failure). Five of them had received myeloablative conditioning.
Four patients presented sinusoidal obstruction syndrome, all of them had received myeloablative conditioning.

Conclusion and relevance

This data shows that therapeutic drug monitoring of busulfan is an essential tool that helps improving **its efficacy and safety**. We have observed a **high variability in the direction and magnitude of dose adjustments made** to optimize the exposure.