REDUCED TRANSPLANT-RELATED MORTALITY BY BAYESIAN INDIVIDUALIZATION OF BUSULFAN DOSAGE IN CHILDREN

N. BLEYZAC [2,4], G. SOUILLET [3,4], P. MAGRON [2], A. JANOLY [2], P. MARTIN [2,3], Y. BERTRAND [3], C. GALAMBRUN [3], P. MAIRE [1,4], G. AULAGNER[2], and R. JELLIFFE[1,5]

[1]Laboratory of Applied Pharmacokinetics, USC School of Medicine, Los Angeles CA;
[2]Department of Pharmacy, Debrousse Hospital,29 Rue Sœur Bouvier, 69005 Lyon, France;
[3]Department of Pediatric Immuno-haematology and Bone Marrow Transplantation, Debrousse Hospital,;
[4] ADCAPT, A. Charial Hospital, 40 Avenue de la Table de Pierre, 69340 Francheville, France

[5].Corresponding author: USC School of Medicine, 2250 Alcazar St, Los Angeles CA 90033, USA.
Tel (323) 442-1300, fax (323) 442-1302, jelliffe@hsc.usc.edu

Topical areas:

Patient informatics
Decision support systems
Computer-aided systems
Software systems in medicine

REDUCED TRANSPLANT-RELATED MORTALITY BY BAYESIAN INDIVIDUALIZATION OF BUSULFAN DOSAGE IN CHILDREN

INTRODUCTION

Busulfan-based conditioning regimens have been proposed as an alternative to total body irradiation before bone marrow transplantation (BMT). Busulfan has a narrow therapeutic margin of safety, with major liver toxicity (veno-occlusive disease or VOD) limiting the success of BMT. As with alkylating agents in general, the therapeutic and toxic effects of busulfan have been related to area under the plasma concentration-time curve (AUC). The therapeutic range of plasma AUC has been shown to range from 4 to 6 $\mu g.h.ml^{-1}$. The wide inter-individual pharmacokinetic variability of busulfan makes it very difficult to reach a target value of AUC by using a standard dosing regimen of 1 mg/kg/6 hour, especially in children.

In order to control the pharmacokinetic variability and toxicity of busulfan, a specific monitoring protocol was instituted for our BMT pediatric patients. This consisted of a test dose and a daily Bayesian adaptive control of busulfan plasma levels. The purpose of this study was to examine the consequences of the busulfan dosage individualization upon the clinical outcome in these children.

PATIENTS AND METHODS:

Twenty nine patients (mean age $\pm$ SD = 6.9 $\pm$ 5.7 years) underwent allogeneic bone marrow transplantation after a busulfan-based conditioning regimen without irradiation. Nine had storage disease, two had thalassemia major, three had severe combined immunodeficiency or SCID, and the rest had hematological malignant diseases (ALL: n=2, AML: n=8, JMML: n=1, MDS: n=3).

Busulfan was given as an individualized dose every 6 hours over 4 days (16 doses total). Busulfan plasma concentrations were determined by reversed-phase liquid chromatography. Intra-day and inter-day coefficients of variation of the assay were less than 5%. The limit of detection was 25 ng/ml. Individual pharmacokinetic parameters (first order absorption rate constant: Ka, volume of distribution related to body weight: Vs, and elimination rate constant: Kel) were obtained from three blood samples drawn at 1, 2.5 and 5 hours following an oral test dose of busulfan (0.5 mg/kg) prior to the BMT preparative regimen, using the USC*PACK software. The patient values of Ka, Vs and Kel were used to develop the dosage regimen needed to reach the target AUC per 6 hour dosing interval between 4 and 6 $\mu g.h.ml^{-1}$

Busulfan pharmacokinetic parameter values were re-evaluated on each of the 4 days by using a minimal number of plasma concentration measurements and by AUC monitored, using the Bayesian modeling program included in the USC*PACK software and the pharmacokinetic parameter values determined at the time of the test dose. Busulfan dosage adjustment was performed before the third dose, each day.

The clinical benefit of busulfan dosage regimens individualization was evaluated after matching our 29 patients (Group A) with similar 29 control patients (Group B) which were transplanted earlier, and for whom the busulfan dosages regimen was that recommended by the usual SFGM or EBMT protocols. The incidence of toxicity (VOD, stomatitis, pulmonary complications), graft failure (defined as evidence of no donor cells), mixed chimerism and full engraftment (defined as 100% donor chimerism) were compared in the two groups. Overall Kaplan-Meier survival, and VOD free survival were also compared.

RESULTS:

Dosage regimens were decreased in 69.0%, increased in 27.6% and conserved in only 0.03% of patients with regards to conventional dosages. Values of mean AUC reached for a 6 hour interval were in the target range. The incidence of VOD (all grades) in the busulfan-individualized Group A was significantly lower (3.4%) than in the control Group B (24.1%) ($p< 0.05$). The incidence of stomatitis was not significantly different in the two groups, although severe stomatitis was less frequent in Group A. The rate of full engraftment at 3 months post-transplantation was significantly higher in Group A than in Group B. The incidence of mixed chimerism was similar in the 2 groups.

All patients in Group A engrafted, while a 12% graft failure rate was seen in Group B. The VOD free 90-day survival was 96.6 % in Group A, compared to 75.9 % for patients in Group B (Log-Rank test, $p= 0.026$). The probability of MVO was much lower ($p= 0.0218$) in patients with hematological malignant diseases in Group A (7.1%) than in Group B (42.9%). Overall survival was 82.8% in Group A versus 65.5% in Group B.

CONCLUSIONS:

This study shows that the clinical outcome of pediatric bone marrow recipients receiving a busulfan-containing BMT conditioning regimen can be improved by giving a busulfan dosage regimen individualized to each patient’s pharmacokinetic parameter values. Daily drug plasma monitoring appears essential to ensure that busulfan exposure is not too little or too much, due to intra-patient pharmacokinetic variability. This daily evaluation is facilitated by using population pharmacokinetic models and Bayesian algorithm of adaptive control of the dosage regimen, as only a few blood samples are needed.

Supported in part by NIH grants LM05401 and RR11526