Hematol Oncol Stem Cell Ther (2017) xxx, xxx–xxx

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/hemonc

ORIGINAL RESEARCH REPORT

Therapeutic drug monitoring-guided dosing of busulfan differs from weight-based dosing in hematopoietic stem cell transplant patients

Bushra Salman [a], Mohammed Al-Za'abi [a], Mohammed Al-Huneini [b], David Dennison [b], Abdulhakeem Al-Rawas [c], Salam Al-Kindi [b], Khalil Al-Farsi [b], Melanie Tauro [b], Murtadha Al-Khabori [b,*]

[a] *Pharmacy Department, Sultan Qaboos University Hospital, Muscat, Oman*
[b] *Department of Hematology, Sultan Qaboos University Hospital, Muscat, Oman*
[c] *Department of Child Health, Sultan Qaboos University Hospital, Muscat, Oman*

Received 27 June 2016; accepted 14 March 2017

KEYWORDS
Busulfan;
Pharmacokinetics;
Drug monitoring;
Hematopoietic stem cell transplantation

Abstract
Busulfan (Bu)-based preparative regimens in hematopoietic stem cell transplantation are commonly used. Previous studies have shown that Bu at a fixed dose of 3.2 mg/kg/day (FBD) given intravenously decreases variability in drug pharmacokinetics and this decreases the dependency on therapeutic drug monitoring (TDM) of Bu. We compared the Bu dose given using TDM with the FBD of 3.2 mg/kg/day. Seventy-three patients with acute leukemia, myelodysplasia, chronic myeloid leukemia, thalassemia major, and sickle cell disease were included. The mean age at transplant was 15 years (range 2—55 years) with 57% adults. Indication for transplantation was leukemia/myelodysplastic syndrome in 46% of the patients, while the remaining 54% were transplanted for inherited blood disorders. We found that the median FBD was lower than the median TDM dose by 39 mg/day with a statistically significant difference ($p < 0.001$) even after adjusting for the weight (median total FBD of 349 mg, median TDM dose of 494 mg, $p < 0.0001$). Age and underlying condition (malignant vs. nonmalignant) were the main factors affecting Bu clearance ($p < 0.001$ and $p < 0.07$, respectively). TDM remains an important tool for the appropriate dosing of Bu in preparative regimens of hematopoietic stem cell transplantation, especially in populations with genetic admixture.

* Corresponding author at: Hematology and BMT, Sultan Qaboos University Hospital, PO Box 35, PC 123, Muscat, Oman.
E-mail address: mkkhabori@gmail.com (M. Al-Khabori).

http://dx.doi.org/10.1016/j.hemonc.2017.03.003
1658-3876/

Please cite this article in press as: Salman B et al., Therapeutic drug monitoring-guided dosing of busulfan differs from weight-based dosing in hematopoietic stem cell transplant patients ..., *Hematol Oncol Stem Cell Ther* (2017), http://dx.doi.org/10.1016/j.hemonc.2017.03.003

Background

Busulfan (Bu) is a bifunctional DNA alkylating agent of the alkyl sulfonate type [1]. It is one of the most frequently used chemotherapeutic agents in preparative chemotherapy combination regimens in patients undergoing hematopoietic stem cell transplantation (HSCT) for various malignant and nonmalignant diseases. Bu pharmacokinetic (PK) profile is best described as a single-compartment model [2]. Absorption is rapid with maximum concentration (Cmax) achieved at around 1 h with a highly variable oral bioavailability of approximately 70–90%. Bu is predominantly metabolized in the liver and excreted in the urine mainly as its metabolites, with very minimal amount (<2%) of the parent compound recovered. The terminal half-life of Bu was found to be 2–3 h [2].

Several investigators demonstrated a relation between Bu exposure and clinical outcome [2]. It was found that Bu has a narrow therapeutic window. Studies have shown that myeloablative doses of Bu are one of the factors that may contribute to enhanced toxicity in HSCT, such as the development of acute graft-versus-host disease and veno-occlusive disease (VOD) of the liver, whereas underexposure to Bu may be one of the predictors of graft rejection or relapse [2]. Therapeutic drug monitoring (TDM) strategy was developed for Bu to allow patients to reach and maintain Bu concentration within the therapeutic window. TDM for Bu using steady state concentration (Css) and area under the curve (AUC) was found to correlate with the incidence of graft failure, transplant-related mortality, and relapse of the primary disease [1]. For example, the incidence of graft rejection was reduced with a target Css > 600 ng/mL or AUC > 900 μM/min. Similarly, the incidence of VOD and severe toxicities increases when Bu Css exceeds a threshold value of 1025 ng/mL (AUC > 1500 μM/min) [1,2].

Recent studies of Bu drug exposure and clinical outcomes have suggested that Bu dose targeting can be eliminated as the fixed-dose intravenous (IV) Bu (FBD) regimens are as safe and effective as targeted doses based on AUC or Css, and at least 80% of the patients achieved the therapeutic window, close to the threshold values [3]. This needs to be proven for populations with genetic admixture and to include patients with benign and malignant indications for transplant.

Therefore, the primary objective of this study was to estimate the difference in the total Bu dose between TDM-based and the calculated weight-based Bu dosing methods. Secondary objectives included assessment of the impact of patients' age and diagnosis on the difference in the total Bu actual TDM dose versus FBD.

Patients and methods

Patients and study design

This was a retrospective study of patients who received IV Bu as part of their preparative regimen prior to HSCT at Sultan Qaboos University Hospital (Muscat, Oman) from 2003 to 2014.

We included male and female patients, from all age groups, undergoing identical sibling or matched (8/8) related donor allogeneic stem cell transplant who received IV TDM-based Bu for any of the following conditions: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), beta-thalassemia major (β-TM), and sickle cell disease (SCD). Patients with missing outcome and PK data were excluded. Patients 13 years and older were taken care of by an adult hematologist and were analyzed under the adult group for the purpose of this study.

Conditioning regimens

For patients transplanted in 2003–2004, the preparative regimen consisted of targeted IV Bu given from Day −9 to Day −6 and IV cyclophosphamide (Cy) 50 mg/kg from Day −5 to Day −2. One patient received IV Bu with melphalan and antithymocyte globulin (ATG). The preparative regimen was changed in September 2004, when fludarabine (Flu) replaced Cy. Patients with acute ALL, AML or MDS, aged < 50 years old, received myeloablative conditioning which consisted of TDM-based IV Bu and Flu 40 mg/m^2 from Day −6 to Day −3, inclusive. Bu was administered as a single daily dose (SDD). The same regimen was also used in patients with β-TM with the addition of ATG-F (Fresenius) 10 mg/kg from Day −4 to Day −1. Patients older than 50 years of age with AML or MDS received a reduced-intensity conditioning (RIC) regimen that consisted of SDD, TDM-based IV Bu for 2 days (Day −6 and Day −5), IV Flu 30 mg/m^2 (Day −10 to Day −5), and ATG-F 10 mg/kg (Day −4 to Day −1). Patients with SCD received the same RIC with the 6-hourly Bu regimen. The target Css for RIC and myeloablative conditioning were 800 ng/mL and 900 ng/mL, respectively.

Dose and administration of Bu

Patients received a test dose of 0.5 mg/kg 48 h prior to conditioning. Dose 1 was adjusted if needed linearly to reach the target Css according to the Css achieved after the test dose. Similarly, dose adjustments were made possible for Dose 5, Dose 9, and Dose 13. When using the SDD regimen, adjustments were only possible for Dose 3 given the time needed to get the results of Bu PK. The total TDM-based dosing was calculated by adding the actual doses given to the patients, which were retrieved from the chemotherapy request forms sent to the pharmacy for the preparation of IV Bu doses. Bu was administered IV via a central venous catheter as a 2-h infusion for multiple daily doses (MDD) or 3-h infusion for SDD.

We calculated the FBD using 0.8 mg/kg administered every 6 h for MDD or 3.2 mg/kg for SDD. The total dose was the sum of calculated doses according to the number of days as per protocol used. This dose was not actually administered to the patient and comparison was done based on theoretical measures. All doses were calculated according to actual body weight.

Bu blood concentration measurement and PK analysis

Heparinised blood samples (2 mL) were drawn in conjugation with the administration of the test dose and Dose 1,

Please cite this article in press as: Salman B et al., Therapeutic drug monitoring-guided dosing of busulfan differs from weight-based dosing in hematopoietic stem cell transplant patients ..., *Hematol Oncol Stem Cell Ther* (2017), http://dx.doi.org/10.1016/j.hemonc.2017.03.003