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Single Daily Busulfan Dosing for Infants with Nonmalignant Diseases Undergoing Reduced-Intensity Conditioning for Allogeneic Hematopoietic Progenitor Cell Transplantation

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A B S T R A C T

Busulfan (Bu) is widely used in conditioning regimens for infants undergoing allogeneic hematopoietic progenitor cell transplantation (HPCT), but the best approach to administer Bu in this population is still unknown. Here, we report a single-center experience of the use of a test dose to guide dose adjustment of intravenous (i.v.) Bu therapy in infants. Between 2004 and 2013, 33 infants younger than 1 year with nonmalignant conditions received allogeneic peripheral blood or cord blood HPCT after a reduced-intensity conditioning (RIC) regimen consisting of fludarabine, antithymocyte globulin, and 2 single daily doses of i.v. Bu. Pharmacokinetic results of a test dose of i.v. Bu (.8 mg/kg) were used to determine the dose of 2 single daily i.v. Bu regimen doses, adjusted to target an area under the curve (AUC) of 4000 μMol*minute per day in a first cohort (n = 12) and 5000 μMol*minute in a second cohort (n = 21). The mean Bu clearance in our infant patients was found to be 3.67 ± 1.03 mL/minute/kg, and the test dose clearance was highly predictive of the regimen dose clearance. The mean AUC achieved after the first single daily regimen dose was 3951 ± 1239 in the AUC 4000 cohort and 4884 ± 766 for the AUC 5000 cohort. No patient in either cohort developed hepatic sinusoidal obstructive syndrome or seizures attributable to Bu. Primary graft failure occurred in 4 patients and secondary graft failure occurred in 3, predominantly in the AUC 4000 cohort (6 of 7). Among the engrafted patients (n = 28), 16 achieved full donor chimerism and 9 patients attained stable mixed chimerism. Overall survival of patients at 6 years after transplantation was 59.5% for the AUC 4000 cohort and 85.4% for the AUC 5000 cohort, with primary graft failure in the first cohort being a major contributor to morbidity. Logistic regression analysis showed that the risk of graft failure increased significantly if cord blood hematopoietic progenitor cells were used or if total Bu exposure was below 4000 μMol*minute per day for 2 days. The difference in clinical outcomes between the 2 cohorts supports the conclusion that targeting a higher Bu AUC of 5000 μMol*minute per day for 2 days improves donor engraftment in infants with nonmalignant conditions undergoing RIC HPCT without increasing toxicity. Measuring i.v. Bu pharmokinetics using a test dose allows timely adjustment of single daily regimen doses and optimization of total Bu exposure, resulting in an effective and safe regimen for these infants.

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INTRODUCTION

Busulfan (Bu; Otsuka Laboratories, Japan) is a critical component of many conditioning regimens used to prepare infant patients for hematopoietic progenitor cell transplantation (HPCT). The profound immunosuppressive effect of Bu allows for the avoidance of total body irradiation in young children, which can adversely affect growth and development [1,2]. A patient's total exposure to Bu is an important parameter that guides its use: a higher-than-optimal exposure predisposes the patient to the toxic effects of the drug, whereas a suboptimal exposure increases the risk of graft failure [3]. The effective Bu exposure in patients who receive the drug could be highly variable, particularly in young children [4]. Unpredictable pharmacokinetic (PK) values are commonly seen after oral Bu doses in children [5-7], as erratic intestinal absorption of oral Bu and

an age-dependent clearance of the drug contribute to a wide variability in effective Bu exposure [7,8]. The increasing use of an i.v. Bu formulation has partially addressed this variability problem. One exception is in infant recipients, as infants generally have a faster clearance of the drug, thereby invalidating dosing conclusions drawn from i.v. Bu PK data obtained in adults or older children [4]. The best clinical strategy to ensure optimal Bu exposure in infants receiving i.v. Bu is, hence, still unknown.

Most experience with the i.v. formulation of Bu has been with the traditional 4-times daily dosing (16 doses) regimens [8-10]. To optimize total Bu exposure in these regimens, PK data are usually obtained after the first regimen Bu dose and then used to adjust the remaining doses [6,7]. More recently, once daily and twice daily dosing schedules of i.v. Bu were found to be safe and effective alternatives in patients with hematological malignancies undergoing HPCT [11-14]. To ensure an optimal Bu exposure with the single daily dosing schedule, a small i.v. Bu test dose is given several days before the administration of the regimen doses. The collection and analysis of 4 or 5 blood samples after the test dose has been shown to provide reproducible PK values that allow timely adjustment of the regimen Bu doses [11]. This finding confirms previous sampling strategies for pharmacokinetically directed dosing with high-dose i.v. Bu in HPCT preparative regimens [15]. Several other studies in adult patients have similarly demonstrated that conditioning regiments using once or twice daily i.v. Bu, coupled with a dose-adjustment strategy, were relatively well tolerated and showed predictable Bu blood concentrations [9,11-13].

Our group has previously reported the feasibility of using a test dose followed by 2 single daily doses of i.v. Bu as part of a reduced-intensity conditioning (RIC) regimen for pediatric patients [4,14]. To develop and validate a clinical strategy to optimally administer i.v. Bu to infant transplantation patients, we undertook a clinical study to assess the PK of test and single daily regimen doses of i.v. Bu in infants with nonmalignant diseases. We hypothesized that using a test dose of i.v. Bu to obtain a PK profile for each patient before transplantation would enable more accurate targeting of total Bu exposure and result in better donor engraftment and decreased toxicity. There are no previously reported clinical studies examining the administration procedure, feasibility, and efficacy of single daily dose i.v. Bu for infants undergoing HPCT. This paper provides useful information that can guide HPCT conditioning using single-dose i.v. Bu in this unique patient population.

PATIENTS AND METHODS
Patient Enrollment

Patients in this study were infants less than 1 year of age with nonmalignant diseases, who participated in a RIC allogeneic HPCT protocol at the Ann & Robert H. Lurie Children's Hospital of Chicago (formerly Children's Memorial Hospital) between 2004 and 2013. These infants underwent allogeneic HPCT after receiving a single daily dose i.v. Bu conditioning regimen. All patients had disease diagnosis confirmed by histology, enzyme, or genetic testing before the start of treatment. Informed consent for participation on this protocol was given by their parents in compliance with the policies of the institutional review board.

Treatment Regimen

Patients were enrolled on an RIC HPCT protocol developed at this institution [14]. The RIC regimen included a single test dose (.8 mg/kg) of i.v. Bu given over 3 hours on day −10, fludarabine 30 mg/m²/day on days −10 to −5, 2 single daily doses of i.v. Bu on days −5 and −4 (as a 3-hour infusion), and rabbit antithymocyte globulin (ATG) 2 mg/kg/day on days −4 to −1. The single daily regimen doses of i.v. Bu were adjusted to target area under the curve (AUC) of 4000 μMol*minute per day in a first cohort of patients and

5000 μMol*minute per day in a second cohort (see below). For 4 patients who received cord blood in the second cohort, a dose of thiotepa (5 mg/kg) was administered on day −5.

Allogeneic hematopoietic progenitor cells (HPC) were infused on day 0. The choice of HPC source depended on donor availability. The acceptable HLA mismatches were ≤ 1 of 8 allele loci for peripheral blood HPC and ≤ 2 of 6 antigenic loci for cord blood HPC. All patients received prophylaxis against graft-versus-host disease (GVHD) using mycophenolate mofetil and cyclosporine A for 1 and 3 months after transplantation, respectively.

PK Studies of Bu Test and Regimen Doses

PK studies were performed after the Bu test dose to determine the regimen dose to be administered and repeated after the first single daily regimen dose to measure the total Bu exposure, evaluated as the plasma concentration-time AUC. Blood samples for the test dose studies were collected at hour 3, 3.5, 5, and 7 after the completion of drug infusion. Blood samples for the first regimen dose were collected at hour 3, 3.5, 5, 8, and 24, with the 24-hour sample drawn before the start of the second regimen dose. Blood samples were placed on wet ice and processed within 1 hour after collection. Plasma was separated by centrifugation at 2500 rpm for 10 minutes at 4°C. Plasma was split into 2 equal amounts in 2 separate cryovials and stored at −20°C until the complete set of blood samples for each dose was obtained. The samples were shipped to the Seattle Cancer Care Alliance Clinical Pharmacokinetics Laboratory for determination of Bu AUC and clearance [4].

Calculation of Bu AUC, Clearance, and Dose Adjustment

Bu PK parameters were calculated by fitting a biexponential equation with the RSTRIP program (MicroMath, Salt Lake City, UT) to the data [13]. AUC was calculated by trapezoidal approximation and extrapolation based on computer-generated parameters from time 0 to infinity. The clearance was calculated using the dose given divided by the weight times AUC. Based on these parameters of the test dose, the regimen dose was adjusted to target an optimal AUC (4000 or 5000 μMol*minute per day depending on the cohort) for single daily dose administration. The following formula was used in the dose adjustment: regimen dose to be given in mg = 4000 or 5000 μMol*minute × (test dose given in mg/rest dose AUC achieved in μMol*minute) [4].

Supportive Care

Lorazepan .05 mg/kg daily was administered for anticonvulsant prophylaxis 2 hours before starting i.v. Bu. Antiyeast prophylaxis (fluconazole, 3 to 5 mg/kg/day) was started with the conditioning therapy and continued until day +100. Anti-herpes prophylaxis (acyclovir, 250 mg/m²/dose) was administered twice each day beginning on day −5 and continued until day +100. Anti-Pneumocystis jirovecii prophylaxis, (pentamidine, 4 mg/kg i.v.) was administered on day −1 and every 30 days up to 6 months after transplantation or 3 months after the cessation of immunosuppressive therapy. Patients received i.v. immune globulin (400 mg/kg) every 3 weeks through day +100. After day +100, immune globulin was administered to maintain serum IgG levels > 400 mg/dL.

Donor Engraftment and Chimerism Analysis

Donor chimerism after HPCT was assessed by variable-number tandem repeat or short tandem repeat polymorphism analysis, using genomic DNA isolated from peripheral blood samples. Donor chimerism was evaluated weekly after initial engraftment until the chimerism reached stability and then followed at regular intervals as clinically indicated. Full donor chimerism was defined as donor contribution > 95% and mixed donor chimerism as donor contribution between 5% and 95%. Primary graft failure was defined as the absence of absolute neutrophil counts recovery > 500 cells per μL by day +28 and day +42 for peripheral blood and cord blood HPCT, respectively. Secondary graft failure was defined as a progressive loss in donor chimerism after initial engraftment, with a cumulative decline of ~20% or more on 3 consecutive studies. In patients with severe combined immunodeficiency, T cell−specific donor chimerism was be used in the definition.

Statistical Analysis

Statistical analyses were performed using software programs from the GraphPad Prism (San Diego, CA) and the R statistical packages. A t-test, paired t-test, Fisher exact test, or Pearson correlation test was used to compare data where appropriate. Survival curves were produced using the product limit method of Kaplan and Meier and the survfit program, and log-rank test was performed using survdiff program. In the analysis of event-free survival (EFS), major events are defined to include primary graft failure, secondary graft failure, and death.