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Phase I/II Trial of Dose-Escalated Busulfan Delivered by Prolonged Continuous Infusion in Allogeneic Transplant Patients

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A B S T R A C T

Intensive chemotherapy or chemotherapy plus irradiation and allogeneic stem cell transplantation can be curative for patients with hematologic diseases. Reduced-intensity transplants can also achieve cure and result in less treatment-related mortality but higher relapse rates. Thus, optimizing the conditioning regimens used in allogeneic transplantation remains an important goal. We conducted a phase I/II trial to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of a continuous infusion of busulfan over 90 hours in conjunction with fludarabine followed by allogeneic related or unrelated donor transplant. Fifty-four patients with advanced hematologic malignancies were enrolled on this study. The MTD was identified as a 24-hour area under the curve (AUC) of approximately 7095 μM/min, which represents a 43% increase over the standard total daily AUC dose of 4800 μM/min given by intermittent schedules. DLTs at doses over 8000 μM/min were identified by a desquamative skin rash and mucositis. No dose-related increase in hepatic, pulmonary, or other organ toxicities were seen, whereas efficacy appeared to be improved at higher dose levels. Continuous-infusion busulfan with intermittent fludarabine provides an alternative treatment strategy that is generally well tolerated and permits an increase in total busulfan dose with encouraging efficacy. (NCI study no. NCT00448357.)

INTRODUCTION

The use of high-dose therapy with allogeneic stem cell transplantation has been shown to be curative in a number of hematologic diseases. Cure rates of 30% to 70% in different populations of patients can be identified, with failure being attributed either to relapse of the underlying disease or to treatment-related mortality [1,2]. In some cases the mortality and morbidity associated with treatment is a result of the conditioning regimen given before the infusion of donor stem cells, whereas in other situations it is a result of the immunologic dysregulation that results in graft rejection, infections, or graft-versus-host disease (GVHD) from infused donor immune cells. With improvement in therapeutic regimens before transplant and prevention of GVHD, better antibiotic and transfusion support, and high-resolution HLA typing, an increasing percentage of treatment failures are the result of relapse of underlying disease [3-5]. This shift toward higher disease relapse rates has also resulted from improvements in prognostic factors and identification of residual disease in patients with acute and chronic leukemia. Increasingly, patients who are in better risk categories are not taken to transplant, because they have a significant cure rate with standard therapy [6]. Relapse has also become an increasingly important source of treatment failure in the setting of patients undergoing therapy with either reduced-intensity or nonablative conditioning regimens, both of

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which rely significantly on the underlying graft-versus-tumor effect to maintain remission status post-transplant [7-9].

Although data suggest the importance of comorbidities, age, cytomegalovirus (CMV) status, disease risk, and quality of donor–recipient match in outcomes [10-12], other data suggest that conditioning regimen intensity is important in long-term control of the underlying malignancy [13-16]. In some diseases, such as acute lymphoblastic leukemia, there is general agreement that better disease control is provided by the use of total body radiation but that in most patients with myeloid disease, any increased benefits in disease control with total body radiation are offset by a higher likelihood of treatment-related morbidity and mortality [17,18]. Nevertheless, because of the high relapse rate in these advanced malignancies, there continues to be value in identifying more effective conditioning regimens to control the underlying disease.

Preclinical data by Teicher et al. [19] demonstrated that continuous exposure of malignant cells to alkylating agents in vitro provides a greater cell kill than comparable area under the curve (AUC) exposure delivered by intermittent schedules. Clinical data also show that this approach, as demonstrated by the prolonged infusion of anthracycline in the EPOCH and VAD regimens, may be associated with better outcomes and improved tumor control [20-22]. Based on this work, we postulated that administering busulfan as a prolonged infusion might permit a higher total AUC with reduced toxicity as a result of lower peak concentrations while still providing greater disease control. In the current report we describe the results of a phase I/II study report that assessed the maximum tolerated dose (MTD), toxicities, and clinical outcomes after the administration of busulfan via a prolonged infusion schedule in allogeneic transplant patients with advanced hematologic malignancies.

METHODS

Patients

Patients with advanced, refractory, or high-risk hematologic cancers who were deemed suitable for myeloablative conditioning and were between ages 20 and 55 years were eligible for enrollment. All patients provided appropriate informed consent according to University of North Carolina Institutional Review Board policies. Patients were stratified by disease risk according to American Society for Blood and Marrow Transplantation/Center for International Blood and Marrow Transplant Research (CIBMTR) criteria [23]. Comorbidity scores were assessed using the Sorror index [10], and severity of veno-occlusive disease (VOD) was assessed according to the Bearman criteria [24]. Patients with other malignancies that did not qualify for CIBMTR stratification required demonstration of high-risk features or advanced disease beyond complete response for which no other curative therapy was available. Acute and chronic GVHD scoring were as outlined by Glucksberg et al. [25] and Shulman et al. [26], respectively.

Busulfan Pharmacokinetic Analysis

A test dose of .8 mg/kg busulfan adjusted for ideal body weight was administered over 30 minutes followed by plasma levels at baseline, 30 minutes, and 1, 2, 4, and 6 hours after start of the infusion. Based on the AUC and steady state clearance values obtained with the test dose, targeted AUC dosing estimated to achieve the desired AUC dosing level per protocol was then undertaken [27-30]. Within 1 week of the test dose, patients were admitted for the therapeutic dose and subsequent transplant. Busulfan plasma concentrations were collected before the start of the 90-hour infusion and then at 30 minutes and 1, 2, 4, 6, 12, 18, 24, 36, 48, 60, 72, 84, 90.5, 92, and 96 hours after start of the infusion. A 90-hour infusion was chosen to reflect 15/16ths of a full 16-dose schedule, whereas the test dose represented 1/16th of the full 16-dose schedule. All whole blood samples were centrifuged at 1000 $\times g$ for 10 minutes at 4°C, and aliquots of plasma were collected and stored at −80°C until analysis. Busulfan concentrations were quantified at Emory University Hospital using high-pressure gas chromatography [30]. The lower limit of quantitation was .1 μmol/L, and the assay was linear between .1 and 20.0 μmol/L. AUC calculations were assessed for the test dose and on the first 6 hours of therapeutic infusion, and dosages were adjusted for hours 42 through 90 after return of the initial AUC values if they were more than 10% above or below the desired range.

Individual busulfan plasma concentrations were used to estimate the following pharmacokinetic (PK) parameters using a noncompartmental model on WinNonlin 4.0 (Pharsight Corp., Mountain View, CA): maximum plasma concentration, area under the concentration-time curve through the last measurable time point (AUC), terminal half-life, and whole blood clearance. The AUC was calculated using the log-linear trapezoid method. All AUC and clearance data were natural log-transformed and reported using descriptive statistics.

Statistical Considerations

In the phase I portion of the study, patients were dosed in cohorts according to the 5 target AUC levels. Additional patients were enrolled at dose level 1 (standard dose) during the phase I and II portions of the study if their insurance coverage did not allow enrollment onto a phase I study. The MTD was defined as the dose with the dose-limiting toxicity (DLT) rate of .25. A dose assignment strategy that allowed for delayed toxicity outcome was used [31]. Initial escalation was in cohorts of 3 patients until at least 1 patient developed a DLT. After the initial dose escalation, patients were assigned to the current dose cohort if estimated DLT rate at the current dose was between .15 and .35. The dose was increased or decreased if the estimated DLT rate at the current dose was below .15 or higher than .35.

The sample size for phase I was set at 35 patients. An additional 25 patients were enrolled to the estimated MTD. During the phase II portion of the trial, the rate of nonrelapse mortality at day 100 was monitored using the Pocock boundary to stop the trial if the rate was too high [32]. Similarly, the rate of irreversible grade 3 toxicity or grade 4 toxicity lasting more than 2 weeks was monitored. The acceptable rate for each was set to .2.

Treatment

In addition to busulfan, all patients also received daily fludarabine at a dose of 30 mg/m^2/day × 5 according to the schedule outlined in Figure 1. All patients received GVHD prophylaxis with tacrolimus starting on day −1 and targeted to maintain serum levels of 3 to 8 μg/dL. Patients received either alemtuzumab at a dose of 30 mg/day × 1 or 2 days depending on whether they were a matched related (1 day) or mismatched related or unrelated (2 days) donor–recipient pair. After the first 30 patients were enrolled, because of concerns over a high rate of viral infections, matched related patients received methotrexate (MTX) and tacrolimus alone and mismatched related or unrelated patients received tacrolimus, MTX + antithymocyte globulin (ATG). MTX was given at a dose of 5 mg/m^2 on days +1, +3, and +6 [33].

	K*	K →												
		F	F	F	F	F								
	B*	B →						T	PBSC					
Grp 1	~~A~~	A								M		M		M
Grp 2	~~A~~	A				ATG	AT G			M		M		M
	-15 to -10*	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6

Figure 1. Treatment schema for patients enrolled in our phase I/II study (UNC LCCC 0510). K indicates Keppra (1 g b.i.d. to start 24 hours before the test dose to continue through day −2 for seizure prophylaxis); F, fludarabine (30 mg/m^2/day × 5 days i.v. infusion over 30 minutes on days −7 through −3); B, busulfan (dose by continuous i.v. infusion over 90 hours on days −7 to −4. Patients receive a single dose of busulfan at .8 mg/kg over 2 hours between days −15 and −10 followed by the targeted 90-hour infusion on days −7 to −4 as described above); T, tacrolimus (target serum levels 3 to 8 ng/mL; suggested starting dose .03 mg/kg p.o. b.i.d from day −1 to day +120 and then taper by day +180); PBSC, peripheral blood stem cell; A, alemtuzumab (30 patients at a dose of 30 mg/day × 1 or 2 days depending on whether they were a matched related [1 day] or mismatched related or unrelated [2 days] donor–recipient pair); M, MTX (5 mg/m^2 on days +1, +3, and +6); ATG, rabbit ATG (.5 mg/kg on day −3 and 2.5 mg/kg on day −2 [group 2 only]).