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Calcineurin and mTOR Inhibitor–Free Post-Transplantation Cyclophosphamide and Bortezomib Combination for Graft-versus-Host Disease Prevention after Peripheral Blood Allogeneic Hematopoietic Stem Cell Transplantation: A Phase I/II Study

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A B S T R A C T

Graft-versus-host disease (GVHD) hampers the utility of allogeneic hematopoietic stem cell transplantation (AHSCT). The purpose of this study was to determine the feasibility, safety, and efficacy of a novel combination of post-transplantation cyclophosphamide (PTC) and bortezomib for the prevention of GVHD. Patients undergoing peripheral blood AHSCT for hematological malignancies after reduced-intensity conditioning with grafts from HLA-matched related or unrelated donors were enrolled in a phase I/II clinical trial. Patients received a fixed dose of PTC and an increasing dose of bortezomib in 3 cohorts, from .7 to 1 and then to 1.3 mg/m^2, administered 6 hours after graft infusion and 72 hours thereafter, during phase I. The study was then extended at the higher dose in phase II for a total of 28 patients. No graft failure and no unexpected grade ≥3 nonhematologic toxicities were encountered. The median times to neutrophil and platelet engraftment were 16 and 27 days, respectively. Day +100 treatment-related mortality was 3.6% (95% confidence interval [CI], .2% to 15.7%). The cumulative incidences of grades II to IV and grades III and IV acute GVHD were 35.9% (95% CI, 18.6% to 53.6%) and 11.7% (95% CI, 2.8% to 27.5%), respectively. The incidence of chronic GVHD was 27% (95% CI, 11.4% to 45.3%). Progression-free survival, overall survival, and GVHD and relapse-free survival rates were 50% (95% CI, 30.6% to 66.6%), 50.8% (95% CI, 30.1% to 68.2%), and 37.7% (95% CI, 20.1% to 55.3%), respectively. Immune reconstitution, measured by CD3, CD4, and CD8 recovery, was prompt. The combination of PTC and bortezomib for the prevention of GVHD is feasible, safe, and yields promising results. The combination warrants further examination in a multi-institutional trial.

INTRODUCTION

Exclusive and indiscriminate suppression of T cells employing different combinations of methotrexate or mycophenolate mofetil (MMF) and a calcineurin or mTOR inhibitor for the prevention of graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (AHSCT) is only partially efficacious [1,2]. Additionally, these agents delay immune reconstitution, impair the graft-versus-tumor effect, and possess unfavorable toxicity profiles [1,2]. Consequently, there is a pressing need to develop new strategies for preventing GVHD.

Post-transplantation cyclophosphamide (PTC) selectively depletes alloreactive T cells while sparing quiescent T cells [3,4]. First introduced by the Johns Hopkins University group to eliminate the need for ex vivo depletion of T cells in the setting of haploidentical AHSCT [5], PTC was shown to be effective for preventing chronic GVHD when used alone in matched related and unrelated donor AHSCT [6,7]. However, the incidence of acute GVHD continues to represent a challenge. A recent study revealed a higher incidence of acute GVHD and lower survival after reduced-intensity conditioning and peripheral blood AHSCT in patients receiving PTC

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compared with a matched control group receiving a conventional calcineurin inhibitor–based GVHD prophylaxis [8].

Dendritic cells (DCs) play a pivotal role in the early stages of development of GVHD [9]. Bortezomib, the first-in-class proteasome inhibitor, suppresses DC maturation and function and exhibits other immune-modulatory effects [10,11]. In murine and early human studies, bortezomib was demonstrated to prevent GVHD [12-15]. We performed a phase I/II study combining PTC and bortezomib after reduced-intensity conditioning and peripheral blood AHSCT. We previously reported the feasibility of this combination after enrolling the first 15 patients [16]. Herein, we report the results of the entire cohort.

PATIENTS AND METHODS

Study Design

The study was initiated as a phase I trial. The design was based on the hypothesis that the administration of PTC and bortezomib for the prevention of GVHD after peripheral blood AHSCT is feasible and safe. As previously described, the dose of bortezomib was escalated in a standard 3 + 3 design. *Dose-limiting toxicity* (DLT) was defined as grade ≥3 nonhematologic or grade ≥2 hepatic bilirubin toxicity related to study drug by Common Terminology Criteria for Adverse Events v4.0. Additionally, DLT included *graft failure*, defined as a lack of neutrophil engraftment by day +22 along with whole blood donor chimerism <50% by day +45. The study's secondary objectives were to measure the impact of treatment on neutrophil and platelet engraftment and determine the incidence of acute and chronic GVHD. Because no DLTs were experienced in any of the planned 3 cohorts, 6 additional patients were enrolled at the highest dose. The study was thereafter extended to phase II to expand upon the secondary objectives, primarily the incidence of grades III and IV acute GVHD. Thirteen additional patients were, therefore, enrolled.

Eligibility

The study was initiated at Roger Williams Medical Center in Providence, Rhode Island with a consenting period from April 2012 through November 2012 and subsequently continued and completed at Spectrum Health in Grand Rapids, Michigan with consents obtained between October 2013 and March 2016. Patients undergoing AHSCT for hematological malignancies were considered for this study. Patients were required to have, at minimum, an 8 of 8 allele HLA-matched related or unrelated donor to be screened for eligibility. Additional eligibility criteria were previously described in detail [16]. All recipient and donor testing were performed by institutional protocols, governed by the Food and Drug Administration, the National Marrow Donor Program, and the Foundation for Accreditation of Cellular Therapy standards. Institutional review board approval was obtained before enrollment and no study procedures were performed before obtaining informed consent. The study was registered with ClinicalTrials.gov, identifier: NCT01860170.

Conditioning Regimen and Supportive Care

Patients received a reduced-intensity conditioning regimen of fludarabine and busulfan. Fludarabine, 30 mg/m^2, was administered on days –7, –6, –5, –4, –3, and –2. Busulfan, .8 mg/kg, was administered every 6 hours on days –3 and –2 (total of 8 doses). Additionally, patients receiving unrelated donor grafts received rabbit antithymocyte globulin (rATG, Thymoglobulin; Genzyme, Cambridge, MA) per institutional standards. Per institutional practice, the dose of rATG was 2 mg/kg each day on days –4 through –1 (total 8 mg/kg) for the first 4 patients who received grafts from unrelated donors. The dose of rATG was 1, 1.5, and 2.5 mg/kg on days –4, –3, and –2, respectively (total 5 mg/kg) for the remaining recipients of grafts from unrelated donors. Patients received their AHSCT infusion on day 0. Six hours after the completion of graft infusion, patients received their first dose of bortezomib. A second dose was administered 72 hours afterwards (day +3). The bortezomib dose was escalated from .7 mg/m^2 to 1 mg/m^2 and to 1.3 mg/m^2 in cohorts 1, 2, and 3 respectively. Patients received forced hydration 4 hours before and for 24 hours after the administration of cyclophosphamide, 50 mg/kg, on days +3 and +4. Furosemide was administered to maintain fluid balance as indicated. Immunosuppressive agents, including steroids, were not permitted after graft infusion. All patients received filgrastim and supportive care per institutional protocols.

Patient Monitoring and Adverse Events

Patient monitoring was previously described [16]. Immune reconstitution monitoring for the last 21 patients enrolled included CD3$^+$, CD4$^+$, and CD8$^+$ cell quantification by flow cytometry on days +28, +100, +180, and +365. Adverse events and serious adverse events from the first dose of bortezomib through 30 days after the last dose of bortezomib were assessed and reported according to the International Conference on Harmonization Good Clinical Practice guidelines.

All cases of GVHD were independently reviewed and graded according to the modified Keystone criteria. Upper gastrointestinal GVHD was considered stage 1. Chronic GVHD grading was based on the 2014 National Institute of Health criteria. Additionally, all cases of acute GVHD were classified as possible, probable, or confirmed as described by Harris et al. [17].

RESULTS

Patient Characteristics

Patient characteristics are presented in Table 1. Twenty-eight patients in total were enrolled, 3 each in cohorts 1 and 2 and 22 in cohort 3. Seven patients were enrolled at Roger Williams Medical Center and the remaining 21 were enrolled at Spectrum Health. The median age was 58 years (range, 37 to 70). Sixteen males and 12 females were included. Twelve patients had acute myelogenous leukemia, 6 had myelodysplastic syndrome, 4 had chronic lymphocytic leukemia (CLL), 2 had diffuse large B cell lymphoma, and 1 each had acute lymphoblastic leukemia, follicular lymphoma, multiple myeloma, and primary myelofibrosis. At the time of transplantation, 10 patients were in first complete remission, 4 were in second complete remission, and the remaining had active disease. The patient with multiple myeloma had progressive disease after 2 autologous transplantations; both patients with diffuse large B cell lymphoma had received autologous transplants in the previous year but

Table 1
Patient Characteristics (n = 28)

Characteristics	Value
Age, median (range), yr	58 (37-70)
Gender	
Male	16
Female	12
PAM score	
<19	14
≥ 19	14
Donor source	
MRD	11
MUD	17
Disease	
AML	12
MDS	6
CLL	4
DLBCL	2
ALL	1
FL	1
MM	1
Myelofibrosis	1
Disease Risk Index	
Low	7
Intermediate	9
High or very high	12
Disease status	
CR1	10
CR2	4
Active disease	14
CMV status (donor/recipient)	
-/-	5
+/+	10
-/+	7
+/-	6

PAM indicates pretransplantation assessment of mortality; MRD, matched related donor; MUD, matched unrelated donor; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; DLBCL, diffuse large B cell lymphoma; ALL, acute lymphoblastic leukemia; FL, follicular lymphoma; MM, multiple myeloma; CR, complete remission.