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A Phase 1 Trial of Eltrombopag in Patients Undergoing Stem Cell Transplantation after Total Body Irradiation

Jane L. Liesveld [1], Gordon L. Phillips II [1], Michael Becker [1], Louis S. Constine [2,3], Jonathan Friedberg [1], Jeffrey R. Andolina [3], Laurie A. Milner [4], Jessica DeBolt [2], Therese Smudzin [2], Ollivier Hyrien [5], Connie L. Erickson-Miller [6], Brendan M. Johnson [6], Katie-Louise Dawson [6], Yuhchyau Chen [2,*]

[1] *Department of Medicine, Hematology/Oncology Division, University of Rochester Medical Center, Rochester, New York*
[2] *Department of Radiation Oncology, University of Rochester Medical Center, Rochester, New York*
[3] *Department of Pediatrics, University of Rochester Medical Center, Rochester, New York*
[4] *Department of Pathology, University of Rochester Medical Center, Rochester, New York*
[5] *Department of Biostatistics and Computational Biology, University of Rochester Medical Center, Rochester, New York*
[6] *GlaxoSmithKline, King of Prussia, Pennsylvania*

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A B S T R A C T

Stem cell transplantation can be associated with significant periods of thrombocytopenia, necessitating platelet transfusions and contributing to the risk of bleeding. Thrombopoietin receptor agonists have been shown to enhance platelet counts in other clinical settings, and so a phase 1 clinical trial was conducted to assess the safety, pharmacokinetics, and maximum tolerated dose of once-daily eltrombopag in patients undergoing stem cell transplantation with conditioning regimens containing total body irradiation ≥400 cGy. Eltrombopag was examined at dosage levels of 75, 150, 225, and 300 mg given orally once daily for 27 days, starting at 24 to 48 hours post-transplantation. Pharmacokinetic sampling was performed over a 24-hour period after the first dose of eltrombopag, as well as during the second week of treatment (steady-state). Nineteen patients were enrolled, 15 of whom completed protocol treatments. Three patients completed each dose level up to 225 mg, and 6 completed treatment at the highest dose of 300 mg. Four patients were replaced because drug compliance was <75% of planned doses. No dose-limiting toxicities were observed in this heterogeneous post-transplantation patient population. Common adverse events were related to standard stem cell transplantation. One episode of pulmonary embolus occurred 9 days after discontinuation of eltrombopag, and the only other thromboembolic episode was a grade 2 catheter-related clot. We conclude that up to 27 days of once-daily dosing of eltrombopag after stem cell transplantation is well tolerated.

INTRODUCTION

Patients undergoing stem cell transplantation experience significant thrombocytopenia, often related to effects of the preparative regimen, which usually consists of high-dose chemotherapy or a combination of chemotherapy and total body irradiation (TBI). This period of thrombocytopenia increases the risk for bleeding and necessitates platelet transfusions [1].

Many patients do not respond well to platelet transfusions, even though storage and processing methods have improved significantly in recent years. The short survival of platelets in vivo also contributes to a frequent requirement for significant transfusion support before platelet engraftment, criteria for which have been defined by the Center for International Bone Marrow Transplantation Research (CIBMTR) [2].

In a retrospective analysis of our center's platelet transfusion use and time to platelet engraftment, we found that a mean of 5.3 (median, 3) platelet transfusions were required during the first 30 days post-transplantation (range, 0 to 57 days), and that the median time to platelet engraftment was 17 days for recipients of an autologous stem cell transplant and 19 days for recipients of an unrelated donor transplant [3].

The development of thrombopoietic agents for treating thrombocytopenia has evolved significantly in recent years. Recombinant human thrombopoietin (TPO) and its pegylated derivatives once held promise as clinically useful agents [4,5]. However, these agents were associated with episodes of persistent thrombocytopenia owing to the development of autoantibodies that neutralized endogenous TPO [6,7]. Other agents considered for the clinical treatment of thrombocytopenia included interleukins, such as IL-3, IL-6, and IL-11 [8].

Second-generation TPO agonists with unique pharmacologic properties have been developed and Food and Drug Administration–approved since 2008 [9]. Eltrombopag, a nonpeptide TPO receptor agonist, is approved as an oral agent for the treatment of chronic idiopathic thrombocytopenia purpura (ITP), as well as thrombocytopenia associated with chronic hepatitis C [10-13]. Drug-related adverse events (AEs) in patients with ITP, such as headache, nasopharyngitis, nausea, and fatigue, are of low-grade severity [11,12]. Eltrombopag has been examined for thrombopoietic effects in other settings, including phase II studies in patients with solid tumors receiving carboplatin/paclitaxel [14], in patients with myelodysplastic syndrome and acute myelogenous leukemia (AML) [15], and in patients with severe aplastic anemia [16].

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* Correspondence and reprint requests: Yuhchyau Chen, MD, PhD, Department of Radiation Oncology, University of Rochester, James P. Wilmot Cancer Center, 601 Elmwood Ave, Box 647, Rochester, NY 14642.
E-mail address: yuhchyau_chen@urmc.rochester.edu (Y. Chen).

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Given that a means to accelerate platelet recovery would be desirable in the post-transplantation period, there is rationale for examining TPO mimetics in this setting. There is also an interest in mitigating the radiation damage to bone marrow in the event of nuclear terror events [17]. Thus, we focused this phase I dose escalation study on patients receiving TBI as part of conditioning for stem cell transplantation, to examine the safety of eltrombopag in the post-transplantation setting.

METHODS

Study Design

This phase I open-label dose-escalation clinical trial, approved by the Research Subjects Review Board of the University of Rochester, was conducted to evaluate the safety and pharmacokinetics of eltrombopag administered at 4 different dose levels: 75, 150, 225, and 300 mg given once daily for 27 days starting at 24 to 48 hours after stem cell infusion. This dose range was selected based on doses previously found to be effective in treating chronic ITP, [11,12] which was the only approved indication at the time the protocol for this study was planned [10].

The daily maximum allowed dose in the ITP population is 75 mg. Ongoing clinical trials of eltrombopag in patients with myeloid malignancies had administered doses as high as 300 mg. In stem cell transplant recipients who underwent TBI, it was anticipated that higher doses of eltrombopag might be required in states with decreased megakaryocyte mass from radiation injury to bone marrow with or without bone marrow toxicity from preconditioning chemotherapy. Thus, our clinical study design tested a dosage range of 75 to 300 mg/day.

The study drug was started at 24 hours in most cases, but in some cases was delayed up to 48 hours to accommodate pharmacokinetic studies. A course of 27 days was chosen because in a retrospective study of time to platelet engraftment, >95% of comparable transplant recipients had engrafted by this time [3]. A complete blood count with differential and serum creatinine and serum liver enzyme levels were obtained pre-TBI, post-TBI, and either twice weekly or weekly thereafter until platelet engraftment. Blood samples were collected for serum TPO measurements pre-TBI, post-TBI, and before stem cell infusion, and then at weeks 1 and 4 after stem cell infusion. The primary objectives of the study were to establish safety and to define a maximum tolerated dose (MTD).

Inclusion/Exclusion Criteria

Eligibility requirements included age ≥18 years and Karnofsky performance status ≥70% in patients undergoing standard of care stem cell transplantation for any disease with a conditioning regimen containing planned administration of ≥400 cGy TBI. Graft source could be from an autologous, related sibling, or unrelated donor. Because the goal of the study was safety determination in the setting of TBI and stem cell rescue, it was decided to include both autologous and allogeneic transplant recipients, given that they both experience significant periods of thrombocytopenia and many overlapping toxicities. Cord blood graft recipients were not included. Patients with active infection, those with renal or hepatic dysfunction, and those at risk for thromboembolism based on known genetic thrombophilias or history of thromboembolic disease in the previous 6 months were excluded. Granulocyte colony-stimulating factor could be administered post-transplantation in accordance with usual clinical practice.

Dose Escalation

Dose escalation was based on a standard 3 + 3 design. A group of 3 patients were enrolled at a given dose level; if none of these patients experienced dose-limiting toxicity (DLT), then the dose could be escalated. If 1 of the 3 patients experienced DLT, then 3 more patients would be enrolled at the same dose level. If no additional patients experienced a DLT, then dose escalation could occur, but if 2 or more of the 6 patients experienced a DLT, then that dose would be the MTD. Dose deescalation to 50 mg/day or 25 mg/day was provided for in the event that the 75-mg/day dose proved too toxic; however, this deescalation was not required, because of the successful dose escalation through the 4 dosing levels.

For patients who achieved a platelet count of 200,000 to 400,000/μL during the 27 days of eltrombopag administration, a dose reduction of 25 mg per day was instituted. If the platelet count rose to >400,000/μL, then eltrombopag was discontinued until the platelet count fell to ≤150,000/μL. Dose adjustments for Asian patients were specified because of known higher exposures [18], but no patients of Asian origin were accrued to the present study.

At the completion of each dose level, a review of all AEs and serious adverse events (SAEs) was conducted before any patient was enrolled at the next dose level. This study was conducted under the purview of the Data Safety Monitoring Committee of the University of Rochester. Six patients were planned in the last cohort for additional safety evaluation. Patients who were unable to take at least 75% of the planned doses were replaced to allow adequate evaluation of safety.

Determination of AEs and DLT

All AEs and SAEs were recorded and assessed for association with the study drug. AEs were graded based on Common Terminology Criteria for Adverse Events version 3.0. An AE was defined as any untoward medical occurrence in a patient temporally associated with the use of eltrombopag whether or not considered related to its use.

An SAE was defined in accordance with standard criteria as an event that resulted in death, was life-threatening, required hospitalization or prolongation of hospitalization, resulted in disability or incapacity, or resulted in a congenital anomaly or birth defect. DLT was defined by protocol as a grade 3 or higher AE determined to be probably or definitely related to the study drug. The MTD was defined as the highest dose (300 mg) if no DLT was observed, or the highest dose at which less than one-third of the patients experienced toxicities not expected in the standard TBI/stem cell transplantation setting.

Pharmacokinetics

Pharmacokinetic samples were obtained before and at 1, 2, 4, 6, 8 and 24 hours after the first dose of eltrombopag, as well as during the second week of treatment (ie, pharmacokinetic steady-state). Plasma samples were analyzed for eltrombopag by GlaxoSmithKline using a validated analytical method [19]. Plasma pharmacokinetic parameters were determined using standard noncompartmental methods, and dose proportionality (ie, how plasma exposure increases in proportion to increases in dose administered) was assessed by a power model using log-log transformed data (Phoenix WinNonlin 6.0; Pharsight, Mountain View, CA).

Platelet Engraftment

Platelet engraftment was as defined by the CIBMTR as the first of 3 consecutive days of a platelet count ≥20,000/μL without platelet transfusions for 7 days and/or the first day of a platelet count ≥100,000/μL without platelet transfusions for 7 days [2]. Guidelines for transfusion support stipulated a 10,000/μL threshold for platelets in the absence of bleeding and a hemoglobin concentration of 8.0 g/dL for RBC transfusion in the absence of other symptoms. The time to platelet engraftment and the number of platelet transfusions required by day 30 and day 100 post-transplantation were recorded for all enrolled patients.

Serum Thrombopoietin Levels

Serum was collected at indicated times for the analysis of TPO levels by ELISA (R&D Systems, Minneapolis, MN). Assays were performed in accordance with the manufacturer's instructions, with a lower limit of detection of 7.4 pg/mL.

Statistical Methods

Implementation of the 3 + 3 dose escalation design resulted in enrollment of 16 evaluable patients. The median time to engraftment was computed using a Kaplan-Meier estimate of the time to engraftment. Serum TPO levels were compared across time points using a 2-way mixed ANOVA model as well as random intercepts to describe the between-subject variation. TPO levels were log-transformed to correct for skewness, and 1 was added to each value because of the presence of 0s (undetectable levels).

RESULTS

Patient Demographics

The study was open over a 2-year period. Thirty-six patients were offered the study, and 15 declined participation. Of the 21 patients who consented to participate, 19 were enrolled and 2 were screen failures (1 because of active infection and 1 because of delayed administration of conditioning). Table 1 presents demographic data for the 19 enrolled study patients. One patient self-identified as Hispanic, 1 patient self-identified as African-American, and 17 patients self-identified as Caucasian.

Table 1 also presents information on underlying diseases for which transplantation was performed, conditioning regimens, TBI doses, donor types, and graft types. Seven patients received 1200 cGy TBI, all of whom underwent conditioning