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Eltrombopag for Treatment of Thrombocytopenia after Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Persistent thrombocytopenia is a common complication after allogeneic hematopoietic cell transplantation (HCT). Eltrombopag is an oral thrombopoietin receptor agonist whose efficacy against persistent thrombocytopenia after allogeneic HCT has not been well characterized. This retrospective study evaluated the safety and efficacy of eltrombopag in 12 consecutive patients with persistent thrombocytopenia after allogeneic HCT. Eltrombopag was started at 12.5 mg once daily and the dose was increased by 12.5 mg daily every week until platelet counts exceeded 50,000/μL. Five patients had prolonged isolated thrombocytopenia (PIT) and 7 patients had secondary failure of platelet recovery (SFPR). The cumulative incidence rate of successful platelet recovery to ≥50,000/μL without transfusion support was 60% in PIT patients and 71% in SFPR patients. No patients discontinued the drug because of adverse events or intolerability. Notably, the rate of platelet recovery was higher (100% versus 58%; $P = .0017$) and recovery was faster (median, 33 days versus 137 days; $P = .0078$) in patients with normal numbers of bone marrow megakaryocytes before starting eltrombopag than in those with decreased numbers of megakaryocytes. Eltrombopag is a promising treatment for both PIT and SFPR after allogeneic HCT. The number of megakaryocytes in bone marrow before eltrombopag treatment may predict the response to eltrombopag.

INTRODUCTION

Thrombocytopenia after allogeneic hematopoietic cell transplantation (HCT) is a common complication [1] with several possible causes, including the following: (1) impaired platelet production, which is associated with poor graft function, viral infection, and adverse effects of medication; (2) increased platelet destruction, which is associated with infection and immune-mediated processes; or (3) a combination of these mechanisms [2,3]. Thrombocytopenia is often severe and requires treatment to prevent life-threatening bleeding. Corticosteroids and rituximab have been used to treat immune-mediated thrombocytopenia, but these drugs may increase the risk of infection [4]. Furthermore, no standard treatment has been available for thrombocytopenia caused by poor graft function. Thus, a mainstay of treatment for thrombocytopenia after allogeneic HCT is platelet transfusion, but transfusion is associated with several adverse effects, including infusion allergy, acute lung injury, cardiac failure due to volume overload, and viral transmission [5]. Besides, prolonged transfusion requires significant hospital resources and costs and decreases patients' quality of life. Thus, it is important to identify a new strategy to treat thrombocytopenia after allogeneic HCT.

Romiplostim and eltrombopag are currently available thrombopoietin receptor (TPO-R) agonists that stimulate platelet production. Romiplostim is administered subcutaneously and activates human TPO-R, despite the absence of sequence homology with human thrombopoietin [6]. Eltrombopag is administered orally and is a nonpeptide agonist that binds to a transmembrane site on TPO-R [7]. Their safety and efficacy have been reported for idiopathic thrombocytopenia purpura [8] and for thrombocytopenia in other conditions [9-12]. Several studies have reported the efficacy of romiplostim for the treatment of thrombocytopenia after allogeneic HCT [13-19], but data on eltrombopag

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treatment after allogeneic HCT are lacking. We report our experiences with 12 consecutive patients treated with eltrombopag for severe thrombocytopenia after allogeneic HCT at our center.

PATIENTS AND METHODS

Patients

A total of 319 allogeneic HCT were performed at the National Cancer Center Hospital from November 2011 to October 2015. This retrospective study cohort included 12 consecutive patients who received treatment with eltrombopag for persistent thrombocytopenia after allogeneic HCT during this period. Eltrombopag was used for patients who developed prolonged isolated thrombocytopenia (PIT) or secondary failure of platelet recovery (SFPR). *PIT* was defined as dependence on platelet transfusion for 90 days or longer after HCT [20]. *SFPR* was defined as a decline of platelet counts to $\leq$ 20,000/μL lasting at least 7 consecutive days or requiring platelet transfusions within 7 days after achieving primary platelet recovery [21]. The *onset day* of SFPR was defined as the first of the 7 consecutive days of thrombocytopenia with platelet counts $\leq$ 20,000/μL. This retrospective study was approved by the institutional review board of the National Cancer Center Hospital.

Endpoint

The primary endpoint was platelet recovery to $\geq$ 50,000/μL for 7 consecutive days without transfusion support after starting eltrombopag treatment. Secondary endpoints included independence from platelet transfusion, rate of patients who tapered off eltrombopag without recurrence of thrombocytopenia after successful platelet recovery, adverse events associated with eltrombopag treatment, and platelet recovery according to onset type of thrombocytopenia and according to the number of bone marrow megakaryocytes before starting eltrombopag treatment. Adverse events were graded using the National Cancer Institute Common Toxicity Criteria version 4.0. Clot sections stained with hematoxylin and eosin were used for assessment of numbers of bone marrow megakaryocytes. We defined 8 to 12 megakaryocytes per mm^2 as normal numbers.

Eltrombopag Treatment

Eltrombopag was started at 12.5 mg once daily and the dose was increased up to 50 mg daily by 12.5 mg every week until platelet counts exceeded 50,000/μL. When the platelet count exceeded 50,000/μL without platelet transfusion for 7 consecutive days, the dose was tapered by 12.5 mg weekly. Platelet transfusion was performed according to the institutional guidelines. Clinically stable, afebrile outpatients receive transfusions at platelet counts $\leq$ 10,000/μL. Inpatients and unstable outpatients receive transfusions at platelet counts $\leq$ 20,000/μL. Transfusions at higher platelet levels may be considered for some patients who plan an invasive procedure, are on anticoagulant medications, or have clinical bleeding.

Statistical Analysis

The cumulative incidence of successful platelet recovery was calculated, treating relapse and death before successful platelet recovery as competing risks, and groups were compared using Gray's test. Days from starting eltrombopag to platelets $\geq$ 50,000/μL without transfusion were compared between the groups using the Wilcoxon rank-sum test. P values $<$ .05 were considered statistically significant. Analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R version 2.13.0 (The R Foundation for Statistical Computing) [22].

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table 1. Indications for HCT were acute myeloid leukemia (AML, n = 7; 59%), myelodysplastic syndrome (MDS, n = 2; 17%), adult T cell lymphoma/leukemia (n = 1; 8%), lymphoblastic lymphoma (n = 1; 8%), and follicular lymphoma (n = 1; 8%). The median patient age was 53 years (range, 19 to 63 years). Three patients (25%) had HCT from a related donor and 9 (75%) had HCT from an unrelated donor. Seven patients (59%) had bone marrow transplantation, 4 (33%) had peripheral blood stem cell transplantation, and 1 (8%) had cord blood

Table 1
Patient Characteristics

Characteristic	Type of Thrombocytopenia		All (N = 12)
	PIT (n = 5)	SFPR (n = 7)	
Patient age at transplantation, median (range), yr	55 (19-62)	52 (31-63)	53 (19-63)
Patient gender			
Male	4 (80)	2 (29)	6 (50)
Female	1 (20)	5 (71)	6 (50)
Disease			
AML	4 (80)	3 (44)	7 (59)
MDS	1 (20)	1 (14)	2 (17)
Adult T cell lymphoma/leukemia	0 (0)	1 (14)	1 (8)
Lymphoblastic lymphoma	0 (0)	1 (14)	1 (8)
Follicular lymphoma	0 (0)	1 (14)	1 (8)
Donor			
Related	1 (20)	2 (29)	3 (25)
Unrelated	4 (80)	5 (71)	9 (75)
Stem cell source			
Bone marrow	4 (80)	3 (43)	7 (59)
Peripheral blood stem cells	1 (20)	3 (43)	4 (33)
Cord blood	0 (0)	1 (14)	1 (8)
HLA			
Match	2 (40)	3 (43)	5 (42)
Mismatch	3 (60)	4 (57)	7 (58)
Conditioning			
Myeloablative	1 (20)	4 (57)	5 (42)
Reduced-intensity	4 (80)	3 (43)	7 (58)
Prior grades II-IV acute GVHD	5 (100)	4 (57)	9 (75)
Platelet transfusion before starting eltrombopag			
No transfusion	0 (0)	1 (14)	1 (8)
Once per week	1 (20)	2 (29)	3 (25)
$\geq$ 2 per Week	4 (80)	4 (57)	8 (67)
Platelet count before starting eltrombopag, median (range),/μL	13,000 (9000-27,000)	14,000 (7000-23,000)	13,500 (7000-27,000)
No. bone marrow megakaryocytes before starting eltrombopag			
Decreased	5 (100)	3 (43)	8 (67)
Normal	0 (0)	4 (57)	4 (33)

Data presented are n (%), unless otherwise indicated.