Eltrombopag Enhances Recovery from Cytopenias Due to Poor Graft Function after Hematopoietic Cell Transplantation

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Abstract

Introduction: Poor graft function (PrGF) is a serious complication of allogeneic hematopoietic cell transplantation (allo-HCT), and current therapies are only partially effective. Eight published reports on the effect of eltrombopag on PrGF showed encouraging results. This study aimed to assess the safety and efficacy of eltrombopag for the treatment of PrGF after allo-HCT.

Methods: A retrospective study was conducted on 23 patients with PrGF following allo-HCT at the King Hussein Cancer Center (KHCC), Amman, Jordan between January 2013 and December 2023. The patient-, disease-, and transplant-related characteristics were obtained from the KHCC-BMT database.

Results: The median age was 47 years (range, 26-68 years), and 13 patients were female. Fourteen patients received reduced-intensity conditioning, and 14 donors were human-leukocyte antigen (HLA) -identical siblings. Median hemoglobin (Hb) concentration pre-eltrombopag administration was 8.5 g/dL (range: 6-14.2 g/dL), granulocytes 7.1×10^9/L (range: $1.6\text{-}85 \times 10^9$/L), and platelets 18×10^9/L (range: $6\text{-}50 \times 10^9$/L). Thirteen patients had platelets $< 20 \times 10^9$/L, and 15 had reduced megakaryocytes. The median CD34-positive cell dose was 6.10×10^6/kg (range: $2.75\text{-}9.78 \times 10^6$/kg). Eltrombopag was initiated at a median of 105 day (d) post-transplant (range: 29-800 d). The median weekly dose was 488 mg (range: 350-700 mg), and the median treatment duration was 75 d (range: 5-446 d). In total, 65% of patients (n=15) responded at a median of 30 d (range, 7-122 d). Twelve responders were alive at a median follow-up of 30 months (range: 7.0-122 months) with normal blood counts. The 2-year overall rate was 48% (95% confidence intervals, 27-70%), and seven non-responders died because of relapse. No major adverse events were reported.

Conclusion: Eltrombopag improved peripheral blood counts in patients with PrGF following allo-HCT. Thus, response to eltrombopag was predictable and has a significant effect on survival.

Introduction

Poor graft function (PrGF) is a serious complication of allogeneic hematopoietic cell transplantation (allo-HCT), and current PrGF therapies are only partially effective. PrGF diagnosis is based on the presence of two or more of the following criteria: hemoglobin (Hb) concentration < 100 g/L, neutrophil count $< 1.0 \times 10^9$/L, or platelet count $< 30 \times 10^9$/L, occurring ≥ 30 d post-transplant[1]. Additional criteria include the need for red blood cell (RBC) and platelet transfusions, decreased bone marrow cellularity, complete donor chimerism, and absence of graft-*versus*-host disease (GvHD) or relapse.

PrGF is distinct from graft failure, which is due to retained recipient immune cells, and manifests as a loss of donor chimerism or late platelet recovery failure. PrGF incidence varies widely, with reports ranging from 5% to 27%, and its clinical course can range from spontaneous recovery to death due to cytopenia-related complications[1-3].

Treatment options for PrGF include RBC and platelet transfusions, intravenous immunoglobulin, hematopoietic growth factors (e.g., granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF)), donor blood or bone marrow infusions, mesenchymal cell infusions, or a second transplant from the same or a different donor[4-8]. However, these treatments are often partially effective. Eltrombopag, an oral thrombopoietin receptor agonist, has shown efficacy in the treatment of severe aplastic anemia, idiopathic thrombocytopenic purpura, thrombocytopenia associated with hepatitis C, myelodysplastic syndrome, and acute myeloid leukemia[9-15]. Eltrombopag has also been reported to improve PrGF-induced cytopenia[16-24]. This study aimed to enhance our understanding of eltrombopag use in the treatment of PrGF post-allo-HCT.

Materials and Methods

This retrospective, single-center study evaluated the safety and efficacy of eltrombopag in patients with PrGF post-allo-HCT. After obtaining approval from the Institutional Review Board of the King Hussein Cancer Center (18 KHCC 146) and exemption of consent, data were collected from electronic medical records. Patient-, disease-, and transplant-related variables are presented in **Table 1**. Complete response was defined as the normalization of blood counts, and partial response as transfusion independence[25]. Statistical analyses were performed using IBM SPSS Statistics for Windows version 26, SPSS Inc. Here, we report 82 patients with PrGF, 23 of whom received eltrombopag from a single center in Jordan[25].

Continuous variables are presented as medians and ranges, and categorical variables are presented as frequencies (percentages). To compare groups, we used the chi-square or Fisher's exact test for categorical variables, and the Mann-Whitney U test for continuous variables. P values < 0.05 are considered statistically significant.

Results

Between January 2013 and December 2023, we documented that 82 of 1,000 consecutive allotransplant recipients (8.2%) who developed PrGF. Thirty-five pa-

tients received a second transplant, all for aplastic anemia or B-thalassemia, and 23 for eltrombopag therapy, all of which were female. The median patient age was 47 years (range: 26-68 years). Fourteen patients received reduced-intensity preparative conditioning and nine received conventional myeloablative conditioning. Fourteen donors were HLA-identical siblings and nine were HLA-mismatched related relatives. The median Hb concentration pre-eltrombopag administration was 8.5 g/dL (range: 6-14.2 g/dL), granulocyte count was $7.1 \times 10^9/L$ (range: $1.6-85 \times 10^9/L$), and platelet count was $18 \times 10^9/L$ (range: $6-50 \times 10^9/L$). Thirteen patients had platelet counts $< 20 \times 10^9/L$. Pre-eltrombopag administration, bone marrow aspirations and biopsies were normocellular with trilineage hematopoiesis in six patients and hypocellular with trilineage hypoplasia in 17 patients, and 15 patients had decreased or absent megakaryocytes. Chimerism was complete ($> 95\%$ donor cells) in all patients pre-eltrombopag treatment. The median CD34-positive cell dose was $6.10 \times 10^6/kg$ (range: $2.75-9.78 \times 10^6/kg$). The median interval between transplantation and eltrombopag initiation was 105 d (range: 29-800 d). The median weekly dose of eltrombopag was 488 mg (range, 350-700 mg), and the median treatment duration was 75 d (range, 5-446 d). Thetransition of hemoglobin, platelet, and granulocyte levels are shown in **Figure 1 (A, B, C)**.

Eltrombopag was initiated at a dose of 50 mg/day and increased in 25 mg increments every 2 weeks if no response was achieved. Fifteen allotransplant recipients (65%) responded to the treatment. The median interval to response was 30 d (range: 7-122 d). Eltrombopag was gradually tapered off after achieving a stable platelet count of 25 mg every 1-2 weeks. One patient lost response after eltrombopag discontinuation because of primary disease relapse and dense marrow fibrosis. Adequate bone marrow megakaryocytes were predictive of response ($p=0.019$). There was no statistically significant difference in the objective response between patients with primary and secondary graft failure ($p=0.074$).

At 2 years, graft function was better preserved in the responders than in the non-responders (67% vs 12.5%; $p=0.0001$). The median follow-up period for responders was 30 months (range, 7-122 months). Twelve of the 15 responders survived with normal blood cell concentrations. The 2-year survival rate was 48% (range: 27%-70%) (**Figure 2**), which was significantly improved in responders compared to that in non-responders (67.0% vs 12.5%; $p=0.0001$; **Figure 3**). Three responding patients and seven non-responders died (none owing to relapse). The causes of death, GvHD (n=3), infection (n=3), and pulmonary hemorrhage (n=2). One patient re-

Table 1. Patients, disease, transplant characteristics

Number	Age	Sex	Disease	Conditioning	GvHD prevention	Graft source	CD34 × 10E+6/ kg	D-R ABO Mismatch	Prior therapy	Dose/ w (mg)	Best response	Disease status	Pa- tient status
1	60	M	MDS	FLU /TBI	CSA/MMF	PBSC	4.4	No	SDP, IVIG, G-CSF	350	No remission	Complete remission	Dead
2	34	M	AA	CY/ATG	CSA/MTX	PBSC	2.8	No	SDP, IVIG, G-CSF	350	Complete remission	Complete remission	Alive
3	47	M	MDS	BU/CY/ATG	TAC/MMF	PBSC	6.0	No	SDP, IVIG, G-CSF	700	No remission	Complete remission	Alive
4	48	F	AML	FLU/CY/TBI	CSA/MMF/ PTCY	PBSC	4.2	No	SDP, IVIG, G-CSF	700	No remission	Complete remission	Dead
5	43	F	HL	FLU/BU	CSA/MMF	PBSC	4.8	Yes	SDP, IVIG	525	Complete remission	Complete remission	Dead
6	8	M	AA	FLU/CY/ TBI/ATG	TAC/MMF/ PTCY	BM	9.2	Yes	SDP, IVIG, G-CSF, CD34 boost	700	No remission	Complete remission	Alive
7	47	F	AML	FLU/CY/TBI	CSA/MMF/ PTCY	PBSC	6.6	No	SDP, G-CSF	350	No remission	Complete remission	Dead
8	49	F	ALL	BU/CY/TBI	TAC/MMF/ PTCY	BM	4.3	Yes	SDP	700	Complete remission	Complete remission	Alive
9	28	M	HL	FLU/CY/TBI	CSA/MMF	PBSC	6.2	No	SDP	350	Complete remission	No remission	Dead
10	45	F	AML	BU/CY	CSA/MTX	PBSC	6.5	Yes	SDP, IVIG, G-CSF	450	Complete remission	Complete remission	Alive
11	61	F	MF	T/BU/FLU	TAC/MTX	PBSC	8.9	Yes	SDP, IVIG, G-CSF	525	Complete remission	Complete remission	Alive
12	26	M	DC	FLU/CY/ TBI/ATG	TAC/MMF	BM	4.6	Yes	SDP, IVIG	350	Complete remission	Complete remission	Alive
13	26	F	FA/ MDS	FLU/CY/ TBI/ATG	TAC/MMF	BM	2.6	No	SDP, IVIG	625	Complete remission	Complete remission	Alive
14	37	M	HL	FLU/CY/TBI	CSA/MMF/ PTCY	PBSC	9.5	No	IVIG	700	No remission	Complete remission	Alive
15	39	F	FA/ MDS	FLU/CY/ TBI/ATG	CSA/MMF/ PTCY	PBSC	7.7	No	SDP	625	Complete remission	Complete remission	Alive
16	45	M	ATCL	FLU/CY/TBI	TAC/MMF	PBSC	18.2	No	SDP, IVIG, Rituximab	700	Complete remission	Complete remission	Alive
17	67	F	MF	FLU/TBI	TAC/MMF	PBSC	5.4	No	SDP, IVIG	350	No remission	Complete remission	Dead
18	36	F	PNH	FLU/BU4	TAC/MTX/ ATG	PBSC	9.8	No	SDP, IVIG	525	No remission	No remission	Dead
19	68	F	MDS	T/BU/FLU	TAC/MMF	PBSC	8.0	No	SDP, IVIG	525	No remission	Complete remission	Dead
20	63	F	AML	FLU/CY/TBI	TAC/MMF/ PTCY	PBSC	8.6	No	SDP, IVIG	525	Complete remission	Complete remission	Alive
21	44	M	MF	T/BU/FLU/ ATG	CSA/MTX	PBSC	5.3	Yes	SDP, IVIG	700	Complete remission	Complete remission	Alive
22	51	M	MF	T/BU/FLU/ ATG	TAC/MTX	PBSC	4.0	No	SDP, Erythropoeitic	700	No remission	No remission	Alive
23	63	M	MDS	FLU/CY/TBI	TAC/MMF/ PTCY	PBSC	8.6	No	SDP, IVIG, Erythropoeitic	700	No remission	No remission	Dead

MDS, myelodysplastic syndrome; AA, aplastic anemia; HL, Hodgkin's lymphoma; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; FA, Fanconi anemia; ATCL, acute T-cell leukemia/lymphoma; MF, myelofibrosis; PNH, paroxysmal nocturnal hemoglobinuria; FLU, fludarabine; BU, busulfan; ATG, antithymoglobulin; TBI, total body irradiation; DC, dyskeratosis congenital; CY, cyclophosphamide; PTCY, posttransplant cyclophosphamide; T, thiotepa; CSA, cyclosporine A; MMF, mycophenolate mofetil; TAC, tacrolimus; PBSC, peripheral blood stem cells; BM, bone marrow; SDP, single donor platelets; IVIG, intravenous immunoglobulin; G-CSF, granulocyte colony-stimulating factor; GvHD, graft versus host disease

sponded, but died due to disease progression. No major adverse events were reported.

Conclusion

Twenty-three patients with PrGF following allo-HCT in whom prior therapies failed responded to eltrombopag treatment, as it improved their peripheral blood
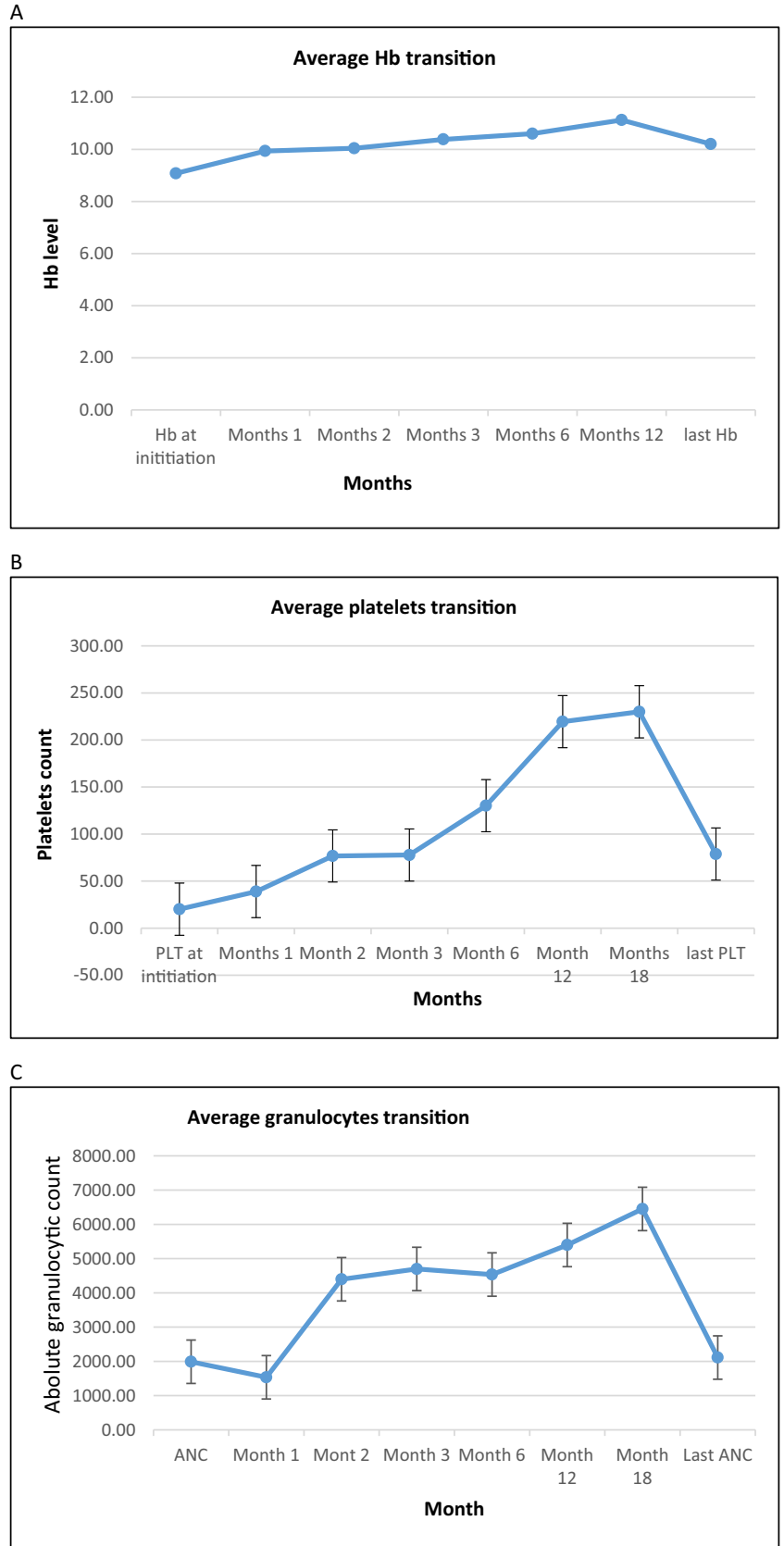
A

B

C

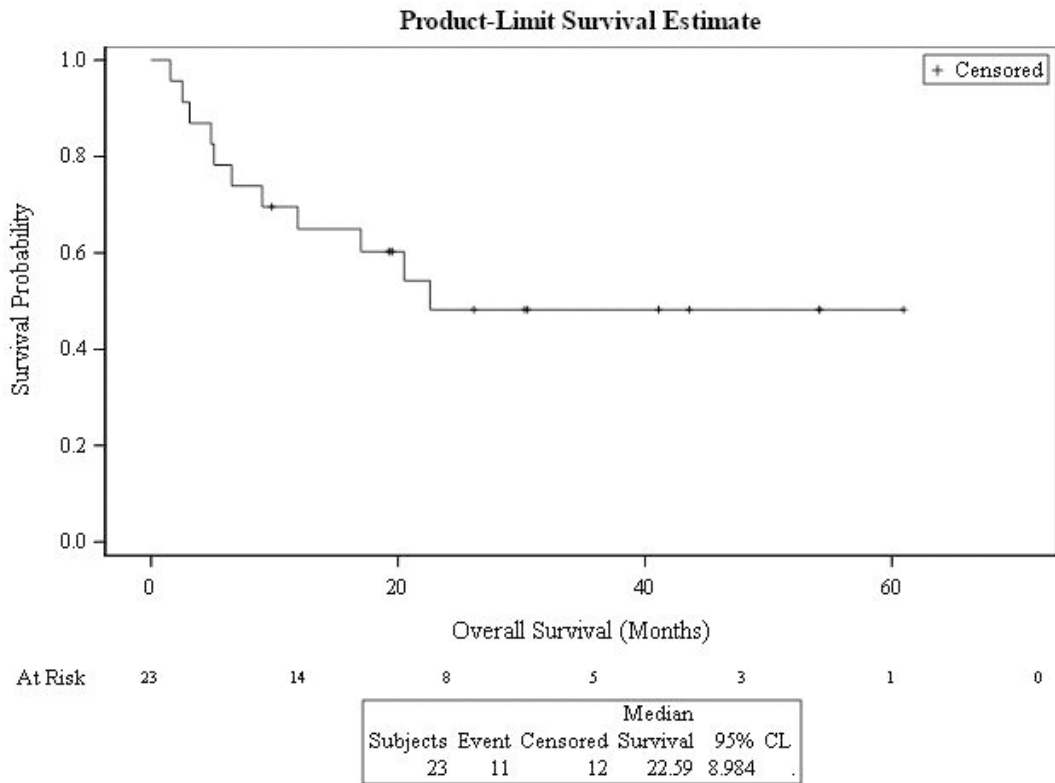**Figure 1.   The transition of complete blood count; (A) Hemoglobin, (B) Platelet, and (C) Granulocyte**

Product-Limit Survival Estimate

	Subjects	Event	Censored	Median Survival	95% CL	
	23	11	12	22.59	8.984	.

Figure 2. Overall survival for the whole cohort (n=23)

Kaplan-Meier Plot

Log Rank p = 0.0001

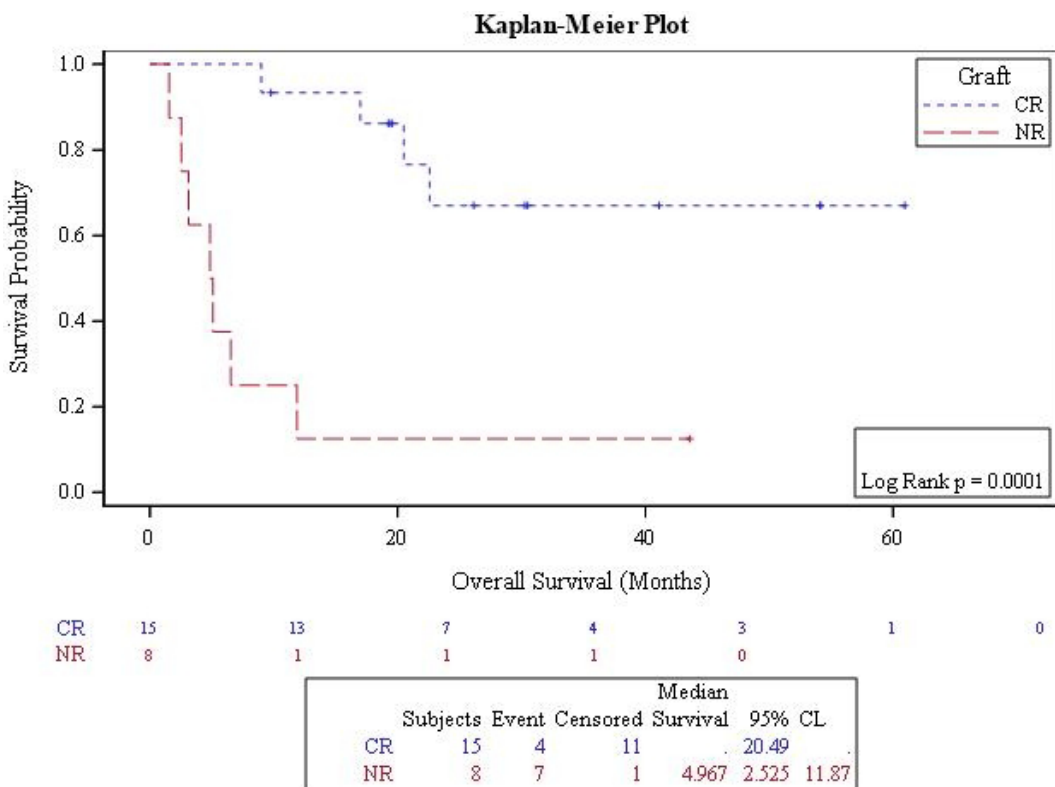|	Subjects	Event	Censored	Median Survival	95% CL	
CR	15	4	11	.	20.49	.
NR	8	7	1	4.967	2.525	11.87

Figure 3. Overall survival according to response (complete remission versus no remission)

cell concentration. Thus, patient response to eltrombopag treatment is predictable, and eltrombopag has significant impact on patient survival outcomes.

Discussion

Our study reports the use of eltrombopag to resolve PrGF in patients post-allo-HCT. Fifteen patients (65%) achieved an objective response and became transfusion independent after a median treatment duration of 75 d. Twelve patients were alive with normal blood cell concentrations, and the 2-year survival rate was 48% (range, 27%-70%). Therefore, eltrombopag administration is safe, with no reported adverse events at the highest daily dose of 100 mg.

The efficacy of thrombopoietic agonists in severe aplastic anemia, in which the bone marrow is hypocellular, led to their use in the management of post-allo-HCT cytopenias[26]. Giammarco et al. reported the largest cohort of patients with PrGF-induced post-transplant cytopenia (n=48) who were treated with eltrombopag (50-150 mg) for a median of 120 d. They reported an overall response rate of 75% (n=36), with complete normalization of blood counts in 24 patients (50%). This multicenter study included prolonged idiopathic thrombocytopenia as a criterion for PrGF[27]. In our cohort, eltrombopag was used to treat PrGF-induced post-transplant cytopenia (uni-, bi-, or tri-lineage cytopenia). We observed an increase in platelet, hemoglobin, and granulocyte counts. Most of our cohort was on supportive G-CSF, and a few were on erythropoietin agonists.

Kırcalı et al. documented 39 patients with post-transplant cytopenia (8 with isolated thrombocytopenia, 19 with bi-lineage cytopenia, and 12 with pancytopenia), including nine patients after autologous bone marrow transplants. In their cohort, 84.6% (n=33) of patients responded to eltrombopag after a median of 82 d. Furthermore, they observed a trend toward improved 1-year overall survival rates for responders (75% vs 66.7%; *p*=0.3), with no major safety concerns. This is consistent with our results, which showed that survival at 2 years was significantly better in responders than in non-responders (67.0% vs 12.5%; *p*=0.0001). Additionally, 61.5% of patients in their study discontinued eltrombopag successfully after a median of 82 d, which is comparable to that in our cohort (65%) at a median of 75 d.

This study has many limitations, including its retrospective single-center design and small sample size. Moreover, the variable definitions of PrGF across different studies made comparing results challenging. Larger real-world data, registry reports, and randomized studies are warranted to draw stronger conclusions.

Acknowledgments

Author Contributions

KH contributed to the conception, design of the study, and interpretation of results, wrote the first draft and final manuscript. MA, IM, RA, WD, and RA did the data acquisition. MM, HA, and MS, designed the study. AT analyzed results. All authors approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the website.

Data Sharing Statement

All data generated or analyzed during this study are included in this article.

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