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Effectiveness of Second-Line Treatment in Patients with Steroid-Refractory Immune Thrombocytopenic Purpura

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Abstract

Objective: To analyze and compare the data of ITP patients who received Eltrombopag and who underwent splenectomy and present outcome in these patients.

Methodology: Study was conducted retrospectively at tertiary care hospital in Rawalpindi, between 2019 and 2023. Inclusion criteria included patients who were steroid resistant, refractory or steroid dependent, and received Eltrombopag or underwent Splenectomy. WHO Bleeding Scale was used to asses bleeding score and response assessment was performed according to the American Society of Hematology's 2009 International Working Group Report.

Results: A total of 40 patients were included in the study, with a mean age of 24.8 years (Range 2-64) with male-to-female ratio of 1.5:1. The selected patients were divided into two groups: N=20 in the splenectomy group (Cohort 1) and N=20 in the Eltrombopag group (Cohort 2). All patients received oral steroids at 1 mg/kg dose as first line treatment. Both groups showed an overall response rate of 29 (72.5%), while 11(27.5%) had no response. Of those who responded, 17 (58.6%) belonged to Cohort 1 and 12 (41.4%) to Cohort 2. In Cohort 1, 15 patients (88.2%) achieved a complete response, and 2 (11.8%) had a partial response. In Cohort 2, complete response was seen in 10 patients (83.3%) and partial response in 2 (16.7%). There was a significant association of age with response. Major complications and OPSI was not seen in any patient. Among 40 patients only 4 (10%) relapsed post second line treatment.

Conclusion: Both splenectomy and Eltrombopag are effective as second line treatment options for steroids refractory ITP with fewer relapses and minimal side effects, however higher proportion of patients achieved complete response in the Splenectomy group compared to Eltrombopag group.

Keywords: Immune thrombocytopenia (ITP), Thrombopoietin receptor (TPO), overwhelming post splenectomy infection (OPSI).

Introduction

Primary immune thrombocytopenia (ITP) is a benign, acquired autoimmune disease characterized by decreased platelet count due to T cell-mediated platelet destruction or autoantibody formation against platelets or megakaryocytes. Clinically, ITP manifests with mucocutaneous (petechial, purpura).[1,2] It can rarely present with life-threatening organ bleeding in patients with a platelet count of < 30,000/µL.

The goal of management is to prevent fatal life-threatening bleeding. [1] Therapeutic agents aim to inhibit autoantibody production, modulate T-cells, and stimulate platelet production. First-line therapy includes corticosteroids alone or in combination with antimetabolites (azathioprine). Immunoglobulin (IVIg) and anti-D (Rho D) immune globulin in cases where a quick platelet increment is needed.[3] However, 40-80% of patients ultimately require second-line treatment due to steroid dependence, relapse, or refractory disease. Second-line therapies include TPO receptor agonists, anti-CD20 antibodies or splenectomy.[4]

As the spleen is the primary site of platelet destruction in the majority of cases, splenectomy remains an effective second-line treatment option for patients who are steroid-dependent or refractory. Splenectomy offers a one-time, irreversible intervention for ITP and is particularly useful for patients residing in remote rural areas with limited access to healthcare facilities and regular follow-up. However, it can be associated with significant morbidity, and despite adherence to post-splenectomy vaccination protocols, life-threatening sepsis remains a major concern.[1,5,6] Overwhelming post-splenectomy infection (OPSI) and thrombosis are major risks associated with splenectomy. Consequently, the use of splenectomy as a second-line treatment is declining in favour of thrombopoietin receptor agonists (TPO-RAs) and immunosuppressive agents.[1,4]

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Romiplostim and Eltrombopag, two TPO-RAs, have been in clinical use since 2008. TPO RA leads to increased platelet production via the activation of the JAK2/STAT5 signaling pathway. These drugs have overall response rates ranging from 50 to 90%. Nevertheless, their use is limited by potential side effects, such as reversible bone marrow reticulin fibrosis, risk of venous thromboembolism (VTE), and high treatment costs in middle-income countries such as Pakistan.[4]

Methodology

After Approval by the ethical committee (IRB-024/AFBMTC/2022) at Department of Clinical Hematology and Bone Marrow Transplant, National University of Medical Sciences, Rawalpindi, Pakistan, a cohort of 40 patients was selected, between 2019 and 2023. All patients diagnosed with ITP were included in the study. The diagnosis of ITP was based on a complete blood count, viral serology (including Hepatitis B, Hepatitis C virus, and HIV), and stool for H. pylori, antinuclear antibody, RA factor, Complement C3 and C4 levels, and a bone marrow examination. The sample size was calculated using OpenEpi with a confidence interval of 95%.

We included all patients, irrespective of age and sex, who had failed first-line treatment with steroids and were managed with second-line treatment (i-e Splenectomy + Eltrombopag). Patient with thrombocytopenia due to secondary causes, gestational thrombocytopenia and those with missing clinical records were excluded. Data variables, including demographics such as age, sex, and disease variables, included the date of diagnosis, WHO bleeding score, white blood cell count, haemoglobin level, and platelet count at the initiation of second-line treatment until the last follow-up.

A simple five-point scale was used to assess the bleeding score, in which 0 was scored for patients with no bleeding, as grade 1, mild blood loss as grade 2, blood loss requiring blood transfusion as grade 3, and massive hemorrhagic with hemodynamic instability as grade 4. Response assessment was performed according to the American Society of Hematology (ASH) 2009 International Working Group Report. Platelet counts < 30,000/mm3 were considered as no response, > 30,000/mm3 as response, and > 100,000/mm3 as complete response.

Results

A total of 40 patients were included in the study, with a mean age of 24.8 years (Range 2–64 years) and a male-to-female ratio of 1.5:1. The selected patients were divided into two groups: N=20 in the Splenectomy group (Cohort 1) and N=20 in the Eltrombopag group (Cohort 2).

The combined bleeding episodes in both cohorts included epistaxis in 18 patients (45%), purpura in 16 (40%), gum bleeding in 15 (37.5%), menorrhagia in 12 (30%), and hematuria in 1 patient (2.5%). Five female patients (12.5%) had both menorrhagia and purpura, two (5%) had epistaxis with purpura, and another two (5%) had epistaxis and menorrhagia. No life-threatening bleeding events, including intracranial hemorrhage, were observed in either group.

Seven patients (17.5%) with significant bleeding requiring RCC transfusions were administered platelet transfusions as emergency management. All patients received oral steroids at a dose of 1 mg/kg as the first-line therapy. Before steroid initiation, the median WBC count was 9.20 ×10⁹/L (IQR: 6.52–12.52), the mean haemoglobin level was 12.94 ± 2.18 g/dL (range: 7.50–18.40), and the median platelet count was 16.00 ×10⁹/L (IQR: 7.25–21.75).

Initial response to steroid was assessed on day 14. An initial response was observed in 13 patients (32.5%), whereas 27 (67.5%) showed no response. At day 14, the median WBC count was 12.90 ×10⁹/L (IQR: 9.20–15.00), the median haemoglobin was 13.00 g/dL (IQR: 12.00–13.95), and the median platelet count was 21.50 ×10⁹/L (IQR: 12.75–38.25). A platelet count >30 ×10⁹/L (response) was achieved in 11 patients (27.5%) and >100 ×10⁹/L (complete response) in two patients (5%). However, these patients subsequently lost their response to steroid tapering. Of patients who had an initial response to steroid therapy when assessed at 4 weeks, 39 (97.5%) had no response, and only 1 (2.5%) responded to steroid therapy. At 4 weeks, the median WBC count was 12.00 ×10⁹/L (IQR: 8.90–14.00), the median haemoglobin was 12.25 g/dL (IQR: 11.92–13.00), and the median platelet count was 20.50 ×10⁹/L (IQR: 12.00–25.00). All patients required second-line therapy.

Response to second-line treatment was evaluated by the platelet count on day 28. There was a statistically significant association between age and the treatment

response (p = 0.02). The detailed associations between demographics, bleeding symptoms, and responses are presented in Table I.

Table I: Association of demographics and bleeding manifestations with response.

		Response		
		Yes	No	
		n (%)	n (%)	p value
Age (Mean ±*SD)*		27.86 ± *14.65*	16.91 ± *9.43*	0.02
Gender	Male	27.86 ± *14.65*	16.91 ± *9.43*	0.24
	Female	19 (65.5)	5 (45.5)	
Gum bleeding	Yes	10 (34.5)	6 (54.5)	0.41
	No	12 (41.4)	3 (27.3)	
Menorrhagia	Yes	17 (58.6)	8 (72.7)	0.81
	No	9 (31)	3 (27.3)	
Epistaxis	Yes	20 (69)	8 (72.7)	0.16
	No	15 (51.7)	3 (27.3)	
Purpura or bruises	Yes	14 (48.3)	8 (72.7)	0.06
	No	9 (31)	7 (63.6)	
Hematuria	Yes	20 (69)	4 (36.4)	0.53
	No	1 (3.4)	0 (0)	

Note: Chi- square and One way Anova were applied, ***p < 0.05*** *is significant*

Overall, 29 patients (72.5%) responded to second-line therapy, while 11 (27.5%) had no response. The mean age of responders was 27.86 ± 14.65 years (min-max: 2–64), with 19 (65.5%) males and 10 (34.5%) females. Of those who responded, 17 (58.6%) were in Cohort 1 and 12 (41.4%) in Cohort 2.A significant association was found between platelet counts before and after second-line treatment. (Table II).

All patients in Cohort 1 received preoperative vaccination and prophylactic antibiotics. No major complications or cases of overwhelming post-splenectomy infection (OPSI) were reported. Patients in Cohort 2 were treated with Eltrombopag at 50 mg/day. Only 4 patients (10%) experienced relapse after second-line therapy. At the last follow-up, the median platelet count was 122.50 ×10⁹/L (IQR: 20.75–245.25). No deaths reported in any group.

Table III: Associations of second line treatments with type of responses.

		Response		
		Yes	No	
		N (%)	N (%)	p value
Type of Response with Splenectomy	No response	0 (0)	3 (100)	0.001
	Response	2 (11.8)	0 (0)	
	Complete response	15 (88.2)	0 (0)	
Type of Response with Eltrombopag	No response	0 (0)	8 (100)	0.001
	Response	2 (16.7)	0 (0)	
	Complete response	10 (83.3)	0 (0)	
Relapse	Yes	4 (13.8)	0(0)	0.19

Note: Chi- square was applied, p < 0.05is significant

Discussion

Present study provides valuable insight into the treatment responses and outcomes of 40 patients treated with second-line therapies such as Eltrombopag or Splenectomy after initial corticosteroid therapy. The patients in our study included a relatively younger population with a mean age of 24.84 than the typical ITP adult population with a mean age of 40 to 50 years.[7] Similarly, higher incidence of bleeding manifestations such as epistaxis, gum bleeding, and purpura and low incidence of events such as intracranial bleeding, hematuria and the presence of combined bleeding symptoms in some patients also aligns with the general ITP presentations; however, some patients had multiple presentations. [8]

All the patients included in the study received oral

Table II: Association of pre and post treatment blood counts with response.

		Response		P- value
		Yes	No	
Steroids therapy	WBC	9.83 ± 5.45	10.85 ± 4.75	0.37
	Hb	13.14 ± 1.82	12.401 ± 2.96	0.34
	Plt	18.45 ± 13.87	17.36 ± 19.45	0.30
Before starting 2nd line treatment	WBC	12.44 ± 3.96	10.74 ± 3.54	0.22
	Hb	13.03 ± 1.48	11.86 ± 2.42	0.20
	Plt	33.14 ± 29.81	78 ± 142.06	0.22
At 2nd line treatment	WBC	12.26 ± 4.43	10.65 ± 3.46	0.28
	Hb	17.45 ± 26.8	11.86 ± 1.99	0.49
	Plt	23.83 ± 13.04	12.18 ± 9.62	0.007
After 2nd line treatment	Plt	245.76 ± 222.84	12.36±6.78	0.001

Note: one way Anova and kruskal-wallis test were applied, p > 0.05 is significant

corticosteroid (1mg/kg) as first-line treatment according to the international guidelines.[9] The initial response rates and complete response rates in this study were lower (2.5%) than the response rates reported by some studies, such as Provan et al. [10] This low response rate can be attributed to the differences in age, disease severity and response criteria. When treated with steroids, the platelet count increased initially, but then a decreasing trend was seen by 14 days when steroids were tapered and necessitated the use of second-line therapies in the study cohort.[9]

For second-line treatment, patients received either Eltrombopag or underwent splenectomy. The overall response rate (ORR) was 17 (58.6%) in cohort 1, of which 88.2% had a complete response (CR). Similarly, the ORR in cohort 2 was 12(41.4%), of which 83.3% achieved CR, which is comparable to the EXTEND trial, which reported a response rate of 85.8%. [11] The slightly higher response rates in the splenectomy cohort can be attributed to the fact that it reduces platelet destruction, whereas Eltrombopag enhances platelet production and requires ongoing long-term treatment to maintain response.[12] Notably, the effects of Eltrombopag wean off over time without proper dose optimization, which underscores the need for further studies with longer follow-ups to assess overall response rates and sustained response in these patients.[13]

The significant association of age with response rates in patients undergoing second-line treatments (p=0.02) can be due to better immune system dynamics and fewer comorbidities in the younger population as compared to adults.[14]

There were no deaths reported and the relapse rate in our study cohort after second-line therapy was 10% which is far less than the relapse rate reported in real-world data by Mishra et al who reported a 5-year relapse rate of 47.7% in patients on Eltrombopag therapy whereas Vianelli et al reports a relapse rate of 33% in patients undergoing splenectomy.[15,16] Lack of long-term follow-up data prevents conclusions about late relapse or sustained remission.

The findings from present study underscore the need for larger multicenter studies, particularly in young ITP populations, to assess the efficacy of second-line treatments. The low steroid response rate also suggests a need to investigate alternative first-line therapies and factors affecting response to steroids. The efficacy of these second-line treatment approaches can be improved by proposing individualized treatments and the use of predictive models using clinical and laboratory parameters to predict treatment responses.

Conclusion

Both splenectomy and Eltrombopag are effective second-line treatment options for steroids-refractory ITP, with a higher proportion of patients achieving complete responses in the splenectomy group when compared to the Eltrombopag group. Age was found to be significantly associated with the treatment response. There were minimal complications, and the overall relapse rate was low.

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