Original Article

Immune Thrombocytopenia: A Disease With Many Unresolved Questions

İmmün Trombositopeni: Birçok Çözümlenmemiş Sorusu Olan Bir Hastalık

Samet Yaman, Burcu Aslan Candır, Ersin Bozan, Sema Seçilmiş, Semih Başcı, Bahar Uncu Ulu, Tuğçe Nur Yiğenoğlu, Merih Kızıl Çakar, Mehmet Sinan Dal, Fevzi Altuntaş

University of Health Sciences Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Hematology and Stem Cell Transplantation Service

ABSTRACT

Introduction: Immune thrombocytopenia (ITP) is an autoimmune disease and characterized with isolated low platelet count (<100x10^9). There is no single golden standard test for ITP diagnosis. Treatment is not indicated for all ITP patients. Corticosteroids are the first line of treatment. Rituximab, splenectomy, eltrombopag, azathioprine, cyclosporin, cyclophosphamide, dapsone, mycophenolate mofetil, and vinca alkaloid are some of the other therapeutic options. Here, we aimed to present our experience on ITP patients and treatment outcomes.

Materials and methods: The data of the patients were retrieved from retrospective records between 2015-2021.The study included patients over the age of 18 who had a regular follow-up diagnosis of ITP. Patients with primary hematological malignancy and patients with unavailable data or lost follow-up were excluded from the study

Results: A total of 62 patients with a diagnosis of ITP were included in the study. Treatment was indicated in 51 (82.3%) patients. All of the patients with treatment inclusion were given steroids in the first step. In ten patients who didn't respond to steroid treatment, the factors that predicted resistant treatment were explored. Age, mean platelet volume (MPV), C-reactive protein (CRP), ferritin, B12 and folic acid values were taken for analysis, no predictive factor was detected.

Discussion: While steroid treatment is effective in the initial step, recurrences are common. Factors that predict steroid refractoriness seems to require larger studies. Other step treatments should be evaluated on a case-by-case basis at the time of recurrence. Patients should also be encouraged to participate in clinical trials.

Keywords: Immune thrombocytopenia, ITP, splenectomy, steroid refractory

ÖZET

Giriş: İmmün trombositopeni (ITP) izole trombositopeni (<100x10^9) ile karakterize otoimmün bir hastalıktır. ITP teşhisi için altın standart bir test yoktur. Tüm ITP hastaları için tedavi endike değildir. Kortikosteroidler tedavinin ilk basamağıdır. Rituksimab, splenektomi, eltrombopag, azatioprin, siklosporin, siklofosfamid, dapson, mikofenolat mofetil ve vinka alkaloid diğer tedavi seçeneklerinden bazılarıdır. Burada ITP hastaları ve tedavi sonuçları ile ilgili deneyimlerimizi sunmayı amaçladık.

Gereç ve yöntemler: Hastaların verileri 2015-2021 yılları arasında geriye dönük kayıtlardan toplandı. Çalışmaya, düzenli takibine devam eden 18 yaş üstü ITP hastaları dahil edildi. Primer hematolojik malignitesi olan hastalar ve verisi olmayan veya takipten çıkan hastalar çalışma dışı bırakıldı.

Bulgular: Çalışmaya ITP tanılı 62 hasta alındı. 51 (%82,3) hastada tedavi endikeydi. Tedaviye alınan hastaların tamamına ilk basamakta steroid verildi. Steroid tedavisine yanıt vermeyen on hastada tedaviye direnci öngören faktörler araştırıldı. Analiz için yaş, ortalama trombosit hacmi (MPV), C reaktif protein (CRP), ferritin, B12 ve folik asit değerleri alındı, prediktif faktör saptanmadı.

Tartışma: Steroid tedavisi ilk aşamada etkili olmakla birlikte nüksler sık görülmektedir. Steroid refrakterliğini öngören faktörlerin saptanması için daha büyük çalışmalar gerekmektedir. Diğer tedavi seçenekleri, nüks anında vaka bazında değerlendirilmelidir. Hastalar ayrıca klinik araştırmalara katılmaya teşvik edilmelidir.

Anahtar kelimeler: İmmün trombositopeni, ITP, splenektomi, steroid refrakter

First Received: 28.04.2022, Accepted: 16.05.2022 doi: 10.5505/aot.2022.89166

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease and characterized with isolated low platelet count (<100x10^9). It is also known as idiopathic thrombocytopenic purpura, but this term is less used now, since not all patients have purpura, and the autoimmune mechanism is understood. It appears in both children and adults. Adults are affected at a rate of 1.6 to 3.9 new cases per 100,000 individuals per year. While primary ITP develops due to antiplatelet antibodies, secondary ITP may develop due to another underlying cause, such as infectious or rheumatological diseases. Usually, primary ITP is detected in adults [1,2]. Patients may present with symptoms ranging from asymptomatic to life-threatening bleeding. The risk of serious bleeding is usually low. The risk of venous thromboembolism is approximately doubled compared to the normal healthy population [3].

There is no gold standard test to diagnose ITP. The diagnosis of primary ITP is determined when all other causes of thrombocytopenia have been ruled out. It is determined by the ITP diagnosis timeframe. The terms "new diagnosis" for less than three months, "persistent" for three to twelve months, and "chronic" for more than twelve months are used. Chronic ITP is commonly encountered in the adult population [4].

Treatment is not indicated for all ITP patients. It is usually recommended when the platelet count falls below 20-30 X 10^9 or any ITP associated symptoms such as bleeding. Treatment should be individualized, and the goal of the treatment should be to prevent serious bleeding, maintain the target platelet count, select low-toxicity treatments, and improve quality of life [4,5]. Corticosteroids are the first line treatment. Both standard-dose prednisone and high-dose dexamethasone can provide a long-term response. In individuals who needs a prompt response, high-dose dexamethasone appears to be more efficient. Intravenous immunoglobulin (IVIG) is one of the preferred treatment methods in first-line therapy. It is frequently applied when aim mediate response is desired. Second-line treatment decisions differ depending on the centers' experience and patients' condition. Rituximab, an anti-CD20 monoclonal antibody with a response rate of 28-40%, is an effective choice. Splenectomy is a treatment option that two out of every three patients respond to. Thrombopoietin receptor agonists such as eltrombopag are used as an effective agent that is well tolerated. Azathioprine, cyclosporin, cyclophosphamide, dapsone, mycophenolate mofetil, and vinca alkaloid regimens are some of the other therapeutic options [6-9]. Real world data experience is important for clinicians since mostly the randomized controlled trials are conducted in optimized conditions and usually not reflecting real world data outcomes.

Here, in our study we aimed to present our experience on ITP patients and treatment outcomes.

Patients and Methods

The study was conducted in Ankara Oncology Training and Research Hospital Hematology outpatient clinic. The data of the patients were retrieved from retrospective records between 2015-2021. The local institutional review board approved this study with approval number 2021-09/1392. The study was performed under the ethical principles of the Declaration of Helsinki.

The study included patients over the age of 18 who had a regular follow-up diagnosis of ITP. Patients with primary hematological malignancy and patients with unavailable data

Table-1. Patient demographic and laboratory at diagnosis

Parameters	N, %
Age (median, min-max)	49 (16-75)
Gender (M/F)	22(%35,5)/ 40 (64,5)
Comorbidity (present)	22(%35,5)
Malignancy(present)	5(%8.1)
Laboratory (at diagnosis)	
WBC (x10^{3}cells/uL)	7.25 (2.4-26)
Hgb (g/dL)	13,4 (9.6-18.3)
MCV (fL)	89,3 (61-110)
MPV (fL)	11,8 (7.4-14,6)
Platelets (x10^{3}cells/uL)	11 (1-86)
CRP (mg/L)	4,67 (0.1-31)
B12 (ng/L)	338 (185-2000)
Folate (µg/L)	7.8 (2.85-48)
Ferritin (ng/mL)	45,85 (3.8-262)

Comorbidity: Hypertension, diabetes mellitus, coronary artery disease and chronic renal failure.
WBC: White Blood Cell, MCV: Mean Corpuscular Volume, MPV: Mean Platelet Volume, CRP: C-reactive protein

or lost follow-up were excluded from the study. The study did not exclude patients with solid organ malignancies.

Patients were considered responsive if their platelet count improved by more than 30 x 10^9 after treatment.

At the time of diagnosis, demographic information, comorbidities, and hemogram and biochemistry results were all documented. The patients' therapy and response to treatment, and also their splenectomy histories, were all documented.

The statistical analyses performed with SPSS software (v26, Armonk, NY). The data was summarized by presenting the continuous data as a median (min-max) and the categorical data as a ratio. Logistic regression analysis was used to investigate if any factor influencing steroid refractoriness. Two-sided p value <0.05 was regarded as statically significant.

Results

A total of 62 patients with a diagnosis of ITP were included in the study.22 (35,5%) of the patients were male and 40 (64,5%) of them were female. Demographic data and laboratory findings of the patients are summarized in Table-1.

Treatment was indicated in 51 (82.3%) of the 62 patients followed. All of the patients with treatment inclusion were given steroids in the first step, and the response rate to steroid treatment was 80.3%. Second-line and above treatment options, as well as the proportion of patients who relapsed after response, are summarized in Table-2.

In ten patients who didn't respond to steroid treatment, the factors that predicted resistant treatment were explored. Age, MPV, CRP, ferritin, B12 and folic acid values were taken for analysis. As summarized in Table-3, no predictive factor was detected.

Discussion and Conclusion

In our study, we found that 80,3 % of patients in first line responded to treatment. In patients who did not respond to steroid treatment, no prognostic predictor was found for steroid refractoriness. Splenectomy was performed in 22 patients (35.5%), and the response rate following splenectomy was 86,3%. While 21 (91.3%) of 23 patients who received eltrombopag responded to treatment, patients who received rituximab had a 50% response rate. The response rate was 87.5% when IVIG was used as surgical preparation or rescue therapy.

In the meta-analysis of Siraj Mithoowani et al., standard-dose prednisolone or high-dose dexamethasone treatment was compared. As a result, long-term responses were found to be similar, while less toxicity was observed in the

Table 2. Treatments and outcomes

	N=62, %100	Responders	Relapsed after Response
Observation	11 (%17.7)		
1st line treatment			
Steroid	51 (%82.3)	41(%80.3)	30 (%73,2)
2nd line and other lines			
Eltrombopag	23 (%37.1)	21(%91.3)	11(%52.4)
Splenectomy	22 (%35.5)	19(%86.3)	10 (%52.6)
Rituximab	4(%6.5)	2 (%50)	1(%50)
IVIG	24(%38.7)	21(%87.5)	13(%61.9)
Vincristine	10(%16.1)	6 (%60)	-
Others (CSA, azathioprine)	7 (%11.2)	5 (%71.4)	-

IVIG: Intravenous Immunoglobulin, CSA: Cyclosporine A

Table 3. Predictors of the Steroid Refractoriness

Parameters	OR (95%CI)	P value
Age	0.998 (0.954-1.045)	0.944
MPV	0.963 (0.549-1.689)	0.896
CRP	0.998 (0.852-1.168)	0.978
Ferritin	0.998 (0.983-1.012)	0.736
B12	0,999 (0.997-1.001)	0,403
Folic Acid	0,868 (0,735-1,024)	0,094

MPV: Mean Platelet Volume, CRP: C-reactive protein

Logistic regressionanalysis was used and p value<0.05 was regarded as statistically significant.

group receiving high-dose dexamethasone. On the 14th day, the response rate was higher in the group receiving high-dose dexamethasone, with 79% [6]. In our study, the response rate to steroid treatment was found to be 80.3%, and similar results were obtained with the literature.

In another study, the overall response to steroid treatment was found to be 88.5%. 11.4% of the patients were evaluated as steroid refractory [8]. In our study, the steroid refractory group was found to be 19.6%. We believe our ratio and this ratio is not far, with larger cohort it could be similar. The other reason is that the responses in the group receiving high-dose dexamethasone were higher than the standard-dose prednisolone as we explained above. The use of high-dose dexamethasone in our center has increased in recent years. In previous years, the use of standard dose prednisolone was higher.

Age, serum ferritin level, and positive HbsAg were revealed to be prognostic factors in multivariate analysis by Yu J et al. [10]. In our research, no predicting factor was identified. This could be due to the limited number of steroid-refractory patients we have.

The response rate of IVIG treatment is approximately 80%, but it is generally short [3,11]. The response rate to IVIG treatment was found to be 87.5% in our research, and the available data were determined to be similar to the literature.

In the real-life study of Mishra K et al. with 53 patients, they found the response rate to eltrombopag treatment as 81.1% [9]. In our patient group, this rate was 91.3%. Relapse was detected in more than half of the patients. We do not have high relapse rate after eltrombobag, however our median follow up

was short, this could be explaining the difference.

Response to rituximab treatment has been observed between 40-60% in studies [3]. Two of our four patients who received rituximab responded to treatment. Results similar to the literature were found.

In the study of Al Askar AS et al., the splenectomy rate was found to be 37%. This rate was similar to our study (35.5%). While the recurrence rate after splenectomy was 27.2% in their study, it was 52.6% in our study. Moreover, in the same study, the recurrence rate after rituximab was 15.8%, while in our study this rate was found to be 50%. Splenectomy and rituximab response rates were similar in both studies. The difference in rates can be explained by cohort variation and follow-up time [7]. In another study of Wang T et al., the response after splenectomy was found to be 82.6%, which is similar to our study [13].

Vincristine can be used as an alternative therapy. Response rates of 10-75% have been reported in the literature [11]. In our study, this rate was found to be 60%. Other immunosuppressive drugs can also be used in single therapy and combined therapy.

Our study is valuable in terms of applying a standard strategy because it is a single center study. Our study has limitations as we were unable to mention adverse conditions of the therapies due to missing records. In addition, the small number of patients and the short follow-up period are our other limitations.

In conclusion, while steroid treatment is effective in the initial step, recurrences are common. Factors that predict steroid refractoriness seems to require larger studies. Other step treatments should be evaluated on a case-by-case basis at the time of recurrence. Patients should also be encouraged to participate in clinical trials.

REFERENCES

1. Lambert MP, Gernsheimer TB. Clinical updates in adult immune thrombocytopenia. Blood. 2017; 129(21): 2829-35.
2. Audia S, Mahévas M, Samson M, Godeau B, Bonnotte B. Pathogenesis of immune thrombocytopenia. Autoimmun Rev. 2017; 16(6): 620-32.
3. Cooper N, Ghanima W. Immune Thrombocytopenia. N Engl J Med. 2019; 381(10): 945-55.
4. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019; 3(22): 3780-817.
5. Terrell DR, Neunert CE, Cooper N, et al. Immune Thrombocytopenia (ITP): Current Limitations in Patient Management. Medicina (Kaunas). 2020; 56(12): 667.
6. Mithoowani S, Gregory-Miller K, Goy J, et al. High-dose dexamethasone compared with prednisone for previously untreated primary immune thrombocytopenia: a systematic review and meta-analysis. Lancet Haematol. 2016; 3(10): e489-96.
7. Al Askar AS, Shaheen NA, Al Zahrani M, et al. Splenectomy vs. rituximab as a second-line therapy in immune thrombocytopenic purpura: a single center experience. Int J Hematol. 2018; 107(1): 69-74.
8. Chang H, Tang TC, Hung YS, et al. Immune thrombocytopenia: Effectiveness of frontline steroids and comparison of azathioprine, splenectomy, and rituximab as second-line treatment. Eur J Haematol. 2018; 101(4): 549-55.
9. Mishra K, Pramanik S, Jandial A, et al. Real-world experience of eltrombopag in immune thrombocytopenia. Am J Blood Res. 2020; 10(5): 240-51.

10. Yu J, Xu Z, Zhuo Y, et al. Development and validation of a nomogram for steroid-resistance prediction in immune thrombocytopenia patients. Hematology. 2021; 26(1): 956-63.
11. Kistangari G, McCrae KR. Immune thrombocytopenia. Hematol Oncol Clin North Am. 2013; 27(3): 495-520.
12. Cuker A, Cines DB, Neunert CE. Controversies in the treatment of immune thrombocytopenia. Curr Opin Hematol. 2016; 23(5): 479-85.
13. Wang T, Xu M, Ji L, Han ZC, Yang R. Splenectomy for adult chronic idiopathic thrombocytopenic purpura: experience from a single center in China. Eur J Haematol. 2005; 75(5): 424-9.

Corresponding author e-mail: drsametyaman@gmail.com

Orcid ID:
Samet Yaman 0000-0003-4081-1070
Burcu Aslan Candır 0000-0003-3386-8984
Ersin Bozan 0000-0002-3307-3121
Sema Seçilmiş 0000-0003-2957-2339
Semih Başcı 0000-0003-4304-9245
Bahar Uncu Ulu 0000-0002-6230-9519
Tuğçe Nur Yiğenoğlu 0000-0001-9962-8882
Merih Kızıl Çakar 0000-0003-0978-0923
Mehmet Sinan Dal 0000-0002-5994-2735
Fevzi Altuntaş 0000-0001-6872-3780

Doi: 10.5505/aot.2022.89166

