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Original Article

Rituximab versus Splenectomy in Chronic Primary ITP: Experience of a Single Hematology Clinic

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Abstract. ***Background*: Immune thrombocytopenia (ITP) is an acquired immune-mediated disease that lacks an underlying etiology. Steroids are the main first-line treatment of ITP, while the second-line treatment consists primarily of splenectomy and rituximab. This study aimed to assess and compare the response to rituximab and splenectomy.**
Methods: This retrospective comparative study reviewed ITP patients treated at a single private hematology clinic from 2007 to 2019. Seventy-four ITP patients were recruited, 27 were on rituximab, and 47 had undergone splenectomy. The initial platelet counts and bleeding symptoms were recorded, and initial and long-term responses to treatment were evaluated based on the American Society of Hematology guidelines.
Results: The mean age of the patients was 42.1 years with a male-to-female ratio of 1:1.8. The initial mean platelet count was comparable between the rituximab and splenectomy groups (p = 0.749). The initial complete response (CR) differed significantly between the rituximab and splenectomy groups (44.4% versus 83%, p = 0.002). The five-year response rate was significantly higher in the splenectomy than in the rituximab group (74% versus 52%, log-rank 0.038). Splenectomy was the only significant predictive factor for long-term response (OR = 0.193, p = 0.006).
Conclusion: The overall response revealed that splenectomy appeared superior to rituximab as a second-line treatment of ITP. Splenectomy was the only positive prognostic indicator of sustained response.

Keywords: ITP; Rituximab; Splenectomy; Complete response; Second-line therapy.

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Introduction. Immune thrombocytopenia (ITP) is an acquired hematological disorder characterized by a shortened platelet life span, attributed to autoimmune destruction, and impaired thrombopoiesis, resulting in

isolated thrombocytopenia with an increased risk of bleeding.[1,2] Patients with ITP may be asymptomatic or experience varying severity of bleeding, ranging from mild mucocutaneous bleeding to life-threatening hemorrhage.[3,4] The annual incidence of ITP among adults ranges between 1.6 and 3.9/100,000, with women being slightly more affected than men.[5]

ITP in adults is usually chronic, lasting for more than 12 months. The principal goal of treatment is achieving a safe platelet count to prevent major bleeding rather than correcting the platelet count. Major bleeding in ITP patients is possible with a $<30 \times 10^9$/L platelet count. Steroids are the standard initial treatment option for ITP. They usually achieve a response in 60-80% of patients.[4] Nevertheless, some ITP patients experience relapse during dose tapering or following the cessation of steroids, necessitating further treatment.[6] Over the past three decades, splenectomy has been the primary second-line treatment for relapsed and steroid-refractory ITP patients. Although splenectomy has an outstanding response rate, it is associated with nearly 1% surgical mortality and a lifelong higher risk of infections. Moreover, ITP recurs in approximately one-third of splenectomized patients; thus, due to ongoing debates over the procedure, a trend has emerged to avoid or delay splenectomy.[7] With the development of various medical treatments, there is a tendency toward exhausting all possible therapeutic options before undergoing such an irreversible procedure. Consequently, the splenectomy rate has dropped from more than 60% to approximately 20% in ITP treatment.[7]

Rituximab is a monoclonal antibody medication directed against CD20, an antigen found on the surface of B-lymphocytes, which are known to play a significant role in the development of ITP by producing anti-platelet glycoprotein antibodies.[8] It was originally developed to treat B-cell lymphoma and effectively treats various autoimmune illnesses by reducing circulating B-cell levels through three different mechanisms: antibody-dependent cellular cytotoxicity, complement-mediated cytotoxicity, and induction of apoptosis in the target cell. Furthermore, it has been found that rituximab increases regulatory T-cell activity. In ITP, rituximab showed a response rate of up to 60%, making it a good alternative to splenectomy with fewer side effects.[9] However, studies have reported that the effect of rituximab is better in newly diagnosed ITP than in persistent or chronic ITP. Thus, strategies to improve its efficacy in chronic ITP are of value.[8,6]

Many studies have assessed and compared the response of chronic ITP patients managed via variable treatment regimes, including rituximab, TPO-RA, and splenectomy. The debate on the efficacy of rituximab or splenectomy outcome in chronic ITP remains unresolved. In this study, we assessed the efficacy of rituximab compared to splenectomy as a second-line treatment option for chronic ITP by determining the initial and long-term response rates in the enrolled patients.

Patients and Methods. This retrospective study reviewed records of ITP patients who were registered at a single private hematology clinic in Erbil, northern Iraq. From 2007 to 2019, 356 patients were diagnosed with ITP at this center, of which 214 had chronic ITP. The diagnosis of ITP was made based on the International Working Group criteria: platelet count $<100 \times 10^9$/L without any other causes of thrombocytopenia. Chronic ITP was defined as ITP lasting more than 12 months.[10] Cases of secondary ITP and those who received steroids only or had been treated with multiple agents, such as rituximab with immunomodulators and/or TPO-RA, prior to splenectomy were excluded. Only 74 cases fulfilled our inclusion criteria and were analyzed. Access to patient data extended from January to the end of April 2023, and data were fully anonymized before being accessed. The study was approved by the ethics committee of Hawler Medical University.

The patients' demographic, clinical, and laboratory data were retrieved from the medical records. The platelet count at the time of diagnosis and the initial bleeding symptoms before treatment were recorded. Bleeding symptoms were categorized as skin bleeding, including petechiae and ecchymosis; mucosal bleeding, including nasal, gingival, GIT, GUT, and vaginal bleeding; CNS bleeding; and bleeding from multiple sites. The WHO bleeding scale was adopted for grading bleeding.[11] The patients were treated based on the American Society of Hematology guidelines for managing chronic ITP.[12] All patients received steroids as a first-line therapy. Intravenous immunoglobulin was additionally used in 13 cases. The second line of therapy included rituximab, which was used in 27 patients, while open splenectomy was performed for the remaining 47 patients. The majority of the rituximab-treated ITP patients received 4 to 6 cycles of therapy; each cycle comprised intravenous rituximab 375mg/m^2 weekly for four weeks, followed by 8 weeks off therapy.

Response to treatment was evaluated based on the platelet count and bleeding events. Complete response (CR): platelet count $>100 \times 10^9$/L, response (R): platelet count $30\text{-}100 \times 10^9$/L, and no response (NR): platelet count $<30 \times 10^9$/L.[10] The overall response rate (ORR) included both CR+R. The initial response was assessed eight weeks after the initiation of therapy for the rituximab-treated group and ten weeks after the surgery for the splenectomy group. The long-term response was checked in the follow-up with the platelet counts of all patients within both groups.

Statistical analyses were performed using SPSS version 25. Numerical variables were expressed as mean (SD). Comparisons between numerical variables were made using the student's t-test. Categorical variables

were compared using chi-square and Fisher's exact tests. The Kaplan-Meier test was performed to assess the long-term response, and the log-rank was used to determine the difference in long-term responses between the two groups. Regression analysis using a binary logistic regression table was used to predict factors associated with sustained CR. A p-value of ≤0.05 was considered statistically significant.

Results. Seventy-four patients with chronic ITP were enrolled in this study; 27 received rituximab, and 47 underwent splenectomy as second-line treatment. The mean age of the patients was 42.10 years; females constituted 64.9% with a male-to-female ratio of 1:1.8. The mean age of the patients within the two groups was comparable (p = 0.703), while the gender difference was significant between the two groups (p = 0.005). The bleeding pattern and grades showed no significant difference within the groups. **Table 1** shows the demographic and bleeding characteristics of the studied groups.

The patients' mean platelet count at diagnosis was 14.8 $\times 10^9$/L (±11.54). The mean platelet count of the rituximab-treated and splenectomy groups showed no significant variation, 15.37±12.43 and 14.47±11.12, respectively; p=0.749. Twenty-eight patients (37.8%) had platelet counts <10 $\times 10^9$/L and 71 patients (95.9%) had platelet counts <50 $\times 10^9$/L. The mean baseline platelet counts were not different within the two groups (p=0.215). The mean duration from diagnosis to commencement of second-line therapy was significantly longer in the rituximab-treated group than in the splenectomy group (p <0.001). The average number of cycles of the rituximab-treated patients received was 4.2, ranging from 2 to 8. Regarding the initial and long-term responses, the splenectomized ITP patients showed

Table 1. Demographic and bleeding characteristics of the studied group.

		All (n = 74)	**Rituximab** (n= 27)	**Splenectomy** (n=47)	**p value**
Age (yrs)	Mean (SD)	42.10 (15.36)	43.00 (19.39)	41.57 (12.68)	0.703
	Range	19-90	19-90	25-71	
Age at diagnosis (yrs)	Mean (SD)	33.23 (15.34)	36.07 (18.45)	31.60 (13.18)	0.229
	Range	15-80	15-80	15-61	
Gender	Male No. (%)	26 (35.1)	15 (55.6)	11 (23.4)	0.005
	Female No. (%)	48 (64.9)	12 (44.4)	36 (76.6)	
Bleeding sites	Skin No. (%)	45 (60.8)	17 (63.0)	28 (59.6)	0.111
	Mucosal No. (%)	8 (10.8)	4 (14.8)	4 (8.5)	
	CNS No. (%)	2 (2.7)	2 (7.4)	0 (0.0)	
	Multiple sites No. (%)	19 (25.7)	4 (14.8)	15 (31.9)	
Bleeding scale	Grade 0	0 (0.0)	0 (0.0)	0 (0.0)	0.264
	Grade 1	24 (32.4)	8 (29.6)	16 (34.0)	
	Grade 2	48 (64.9)	17 (63.0)	31 (66.0)	
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	
	Grade 4	2 (2.7)	2 (7.4)	0 (0.0)	

Table 2. Platelet counts and response to treatment in the rituximab and splenectomy groups.

		All (n = 74)	**Rituximab** (n = 27)	**Splenectomy** (n = 47)	**p-value**
Platelet count at diagnosis ($\times 10^9$/L)	Mean (SD)	14.80 (11.54)	15.37 (12.43)	14.47 (11.12)	0.749
	Range	2-59	2-59	2-55	
Baseline platelet count ($\times 10^9$/L)	Mean (SD)	9.54 (5.54)	8.48 (4.42)	10.15 (6.04)	0.215
	Range	2-31	2-19	2-31	
Duration from diagnosis to therapy (yrs)	Mean (SD)	1.42 (1.52)	2.24 (2.18)	0.94 (0.59)	<0.001
	Range	0.2-9	0.2-9	0.2-3	
Initial response	CR No. (%)	51 (68.9)	12 (44.4)	39 (83.0)	0.002
	R No. (%)	12 (16.2)	7 (25.9)	5 (10.6)	
	NR No. (%)	11 (14.9)	8 (29.6)	3 (6.4)	
Long-term response	CR No. (%)	46 (62.2)	10 (37.0)	36 (76.6)	0.001
	R No. (%)	24 (32.4)	13 (48.1)	11 (23.4)	
	NR No. (%)	4 (5.4)	4 (14.8)	0 (0.0)	

Table 3. Predictive factors of sustained complete response.

	B*	p-value	OR*	95% CI for OR	
				Upper	Lower
Age (yrs) (<60 vs >60)	0.567	0.462	1.763	0.389	7.999
Gender (male vs female)	-0.242	0.673	0.785	0.255	2.418
Duration from Diagnosis to therapy (yrs) (<1 vs >1)	-0.171	0.808	0.843	0.212	3.343
Therapy (rituximab vs. splenectomy)	-1.646	0.006	0.193	0.060	0.619

B: Beta coefficient. OR: odds ratio.

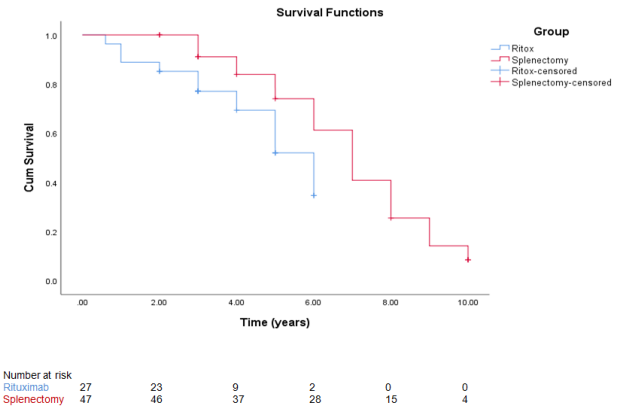

Figure 1. Kaplan-Meier analysis for probability of complete response over time (yrs) for splenectomy (red line) and rituximab (blue line).

significantly higher CR than the rituximab-treated group; p values 0.002 and 0.001, respectively (**Table 2**).

The Kaplan-Meier analysis showed that the splenectomized ITP patients maintained a response significantly higher than the rituximab-treated group as the 5-year CR reached 74% and 52%, respectively, with the log-rank difference being significant (p=0.038) (**Figure 1**).

Table 3 shows the factors that predict sustained CR. Among the four analyzed predictive parameters of age, gender, delay in commencing therapy, and treatment options, only splenectomy emerged as a statistically significant predictive factor of CR (OR =0.193, 95% CI = 0.060-0.619, p = 0.006).

Discussion. Achieving a safe platelet count to evade bleeding is the main aim of treating ITP.[8] The first-line treatment of ITP relies mainly on steroids, which have a good initial response but a high relapse rate, necessitating second-line treatment. Formerly, splenectomy was the only second-line treatment option for chronic and refractory ITP cases. Nevertheless, surgery is not recommended in the early phase of the disease, and the concern of potential surgical complications has caused clinicians to postpone the surgical approach. Accordingly, treatments such as rituximab and TPO-RA have emerged to provide new treatment options for ITP.[13]

In the current study, 27 ITP patients were treated with rituximab, while 47 had undergone splenectomy. The majority of the splenectomized patients (36/47) were old ITP cases who were diagnosed between 2007 and 2012 and had no or very limited opportunity to be treated with rituximab or the TPO-RAs. The recent ITP cases are consistently treated with either rituximab or a TPO-RA when they require second-line therapy unless the patient disagrees. The mean age of the enrolled patients was 42.1 years, comparable to many other studies.[1,13,14] In our cohort, nearly two-thirds of the patients were females, and most had undergone splenectomy. Female predominance is a consistent finding across studies[13,15] because the disease affects more women than men, which is mostly attributed to the role of sex hormones in immune system disorders, thereby increasing susceptibility to ITP in women.[16]

All ITP patients experienced symptoms ranging from minor skin bleeding to severe intracranial hemorrhage. More than half of the patients had skin bleeding, and a considerable proportion had bleeding in multiple sites. Platelet transfusions were carried out for only two patients with intracranial hemorrhage prior to treatment with rituximab. In general, bleeding symptoms are less noticeable in ITP than in other forms of thrombocytopenia, and platelet count is not a reliable predictor of bleeding because other factors, such as age and comorbidities, might contribute to bleeding risk. In some cases, autoantibodies react with platelet glycoproteins, resulting in impaired adhesion or aggregation, thereby causing severe bleeding for the level of platelet count.[17] Concerning immunodeficiency-related side effects during the disease, none of our enrolled ITP patients encountered any significant immunodeficiency-related side effects. It is worth mentioning here that all splenectomized patients received prophylactic pneumococcal vaccination. In literature, many studies on ITP patients reported variable immunodeficiency complications, though such complications are rarely observed in this locality. The exact reason for this inconsistency is unknown, but in addition to prophylactic vaccination, environmental factors may be contributing. Two ITP patients developed portal venous thrombosis following splenectomy; they were treated with anticoagulants for six months with no long-term consequences.

The mean initial platelet count at diagnosis was 14.8 $\times 10^9$/L; the mean platelet count prior to starting second-line therapy, baseline count, was even less (8.9 $\times 10^9$/L). The difference in platelet counts between the rituximab and splenectomy groups were not significant. At diagnosis, 95.9% of the patients had a platelet count <50 $\times 10^9$/L which is slightly more than what was reported by Koylu et al., who reported that 82.6% of ITP patients had a platelet count of <50 $\times 10^9$/L.[1]

Considering the response to treatment, the initial response of the splenectomy arm showed significantly higher CR than that of the rituximab arm (83% versus 44.4%; p=0.002). The overall response rate (ORR) was also higher among the splenectomy group (93.6% versus 70.3% for the splenectomy and rituximab groups, respectively). Moulis et al. reported that CR after splenectomy was significantly higher than rituximab (82.8% versus 39.5%, p <0.001).[18] Koylu et al. reported 87.7% initial CR in splenectomized patients, while the initial CR to splenectomy in an Indian study was 74.4%.[1,15] On the other hand, a study in France revealed that patients on rituximab had a CR of 56.4%, which is higher than in our cohort; however, their overall response was similar to ours (71.8%).[19] An American study reported approximate response figures;[20] one meta-analysis over 368 patients showed a CR of 41% after rituximab with an ORR of 57%.[7] In the current analysis, the long-term response was significantly higher in the splenectomy group than in the rituximab group (CR = 76.6% versus 37%; p value =0.001). A study by Chater et al. found that the CR after 30 months was significantly higher in splenectomy than in rituximab (75.7% versus 30%, p = 0.001).[21] In contrast, a study by Alaskar et al. found that the sustained response did not differ significantly between rituximab and splenectomy (p=0.549).[2] In this study, the probability of maintaining CR five years after splenectomy was 74% but only 52% for the rituximab-treated patients. Two studies reported comparable results; Ahmed et al. reported 76.5% 5-years of sustained CR after splenectomy,[15] and Zaja et al. estimated the 5-year sustained response rate after rituximab at 41%.[14] However, Patel et al., who reviewed data from 17 published studies including 376 adult ITP patients, found less impressive long-term outcomes following rituximab as the 5-year response rate was only 21%.[22]

In our study, splenectomy was the only significant predictor of sustained CR. Other factors, including age, gender, and duration between diagnosis and inception of second-line therapy, did not significantly influence the outcome. Chater et al. reported that female gender and splenectomy, as second-line treatment, were significant predictive factors of CR in the univariate analysis, while only splenectomy reached statistical significance in the multivariate analysis.[21] Other studies have reported that splenectomy and younger age are positive prognostic factors for a long-lasting response.[14,18]

In the current cohort, relapse following treatment with rituximab and splenomegaly was encountered in four patients: three patients in the rituximab arm and one patient in the splenectomy group. They were all treated with steroids and later with a TPO-RA. Based on our observations, which were consistent with most prior studies, the splenectomy outcome was superior to that of rituximab. Despite rituximab's impressive results when administered earlier in the course of the disease, its long-term effect is not promising, as it acts exclusively on B-cells without affecting other immune cells, such as T-cells and plasma cells, causing either persistence of long-lived plasma cells in the spleen and bone marrow or abnormal activation of T-cells.[9] Accordingly, some studies revealed that combining rituximab with other medications was intriguing in terms of targeting plasma cells and T-cells in addition to B-cells. The addition of dexamethasone to rituximab was investigated in a cohort of 67 ITP patients, resulting in an initial response rate of 75% and a nearly 50% long-term response rate at five years.[8] Another study explored adding cyclosporine to rituximab with dexamethasone in 20 patients to target plasma cells and T-cells in addition to B-cells, revealing a higher response rate at six months (60%).[23] All of these findings point to the possibility of utilizing rituximab early in the disease course as a pre-splenectomy alternative, particularly for patients at risk for surgical complications or unwilling to undergo surgery.[14]

Conclusions. Although rituximab is an effective second-line treatment for ITP, splenectomy still has better outcomes. However, early administration of rituximab in the disease course may provide a better outcome. The only positive predictive factor of sustained response was splenectomy. Larger multicenter studies are recommended to assess and compare the outcomes of splenectomy and rituximab as second-line treatment options in ITP.

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