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Long-Term Follow-Up of Adult Patients with Idiopathic Thrombocytopenic Purpura after Splenectomy

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Key words: idiopathic thrombocytopenic purpura; splenectomy; follow-up; response rate.

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Abstract

Background: Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease characterized by isolated thrombocytopenia and the absence of any underlying cause for thrombocytopenia. Corticosteroids are the standard first line treatment for patients with symptomatic disease, but in many cases, steroid tapering or withdrawal is followed by a decrease of platelet count and the need for additional treatment. Splenectomy is still the standard salvage therapy in cases refractory to corticosteroid therapy.

Aim: The aim of this study was to evaluate the long-term outcome of splenectomized patients with ITP.

Materials and Methods: We retrospectively analyzed medical records of 38 patients with ITP that underwent splenectomy after first-line steroid treatment. All patients were followed for at least one year.

Results: According to the results at the time of the last control, 28 patients had complete response (CR), but from those 28 patients only 22 (58%) were without therapy and 6 (22%) were receiving prednisone, azathioprine or both. These results indicate that only 22/38 (58%) of patients had long-lasting CR without therapy, 12 patients (31%) were receiving therapy and 4 patients (11%) had partial response without therapy.

Conclusion: In conclusion, splenectomy may be considered as safe and effective treatment for patients with ITP who failed to respond to firs-line treatment with corticosteroids.

Introduction

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by accelerated destruction of platelets due to the presence of platelet (Plt) autoantibodies and impaired production of platelets [1, 2]. The etiology of ITP remains unclear, but both genetic and environmental factors are thought to play role in the development of the disease. ITP in adults is a chronic condition with insidious onset and varying severities of thrombocytopenia, more common in women than in men (2:1).

According to the recent international consensus report [3], ITP is characterized by isolated thrombocytopenia, defined as platelet count <100 x 10^9/L and the absence of any underlying cause for thrombocytopenia. It can be classified by duration into newly diagnosed, persistent (3-12 month duration) and chronic (>1 year duration). Because severe bleedings are rare in patients with ITP and they occur when platelet counts are <10 x 10^9/L, the main goal of therapy is to maintain a safe platelet count (not necessarily a normal count) to prevent major bleeding and to avoid adverse

effects of therapy [4].

Glucocorticosteroids are the standard first line treatment for patients with symptomatic disease, inducing platelet count recovery in 70-80% of patients; but in many cases, steroid tapering or withdrawal is followed by a decrease of platelet count and the need of additional treatment [5]. Splenectomy is still the standard salvage therapy in cases refractory to corticosteroid therapy. About 40% of splenectomized patients do not respond or relapse after surgery [6], approximately 10% of patients have perioperative or delayed infections, and some develop surgical complications, although rarely fatal.

In case of relapse or refractory to corticosteroids ITP, other immunosuppressive drugs can be used like azathioprine, cyclosporine A, cyclophosphamide, danazol, mycophenolate mofetil, but all with marginal efficacy [7-11]. Intravenous immunoglobulin's (IVIG) and anti-D are also used in the treatment of ITP, especially when rapid improvement of platelet count is needed (in case of life-threatening bleeding or prior to splenectomy or other surgical procedures). However, neither modality induces a long-term remission [12]. Recently, romiplostim and eltrombopag, two new thrombopoetin receptor agonists, have shown potent activity in ITP, but these agents do not act on the underlying disease mechanism, and therapeutic efficacy is dependent on continual administration [13, 14]. Rituximab is a monoclonal anti-CD20 antibody and it has been used in the past decade for the treatment of several autoimmune diseases and ITP [15-19]. Rituximab is relatively safe agent and it induce overall early responses in 40-70% of patients with chronic ITP, with complete response rate of 20 to 50% [18,19].

Management of patients with immune thrombocytopenia (ITP) refractory to standard first-line treatment with corticosteroids and splenectomy remains a problem, because the response rate to all available treatments at the moment are low and are not long-lasting.

The purpose of this study was to evaluate the outcomes of 38 patients with ITP after splenectomy and to evaluate the results of additional therapy in patients that didn't respond to splenectomy.

Materials and Methods

Retrospectively we analyzed 38 patients with ITP that underwent splenectomy in the period 1980-2009 and have been followed for at leas 12 months. All patients met the diagnostic criteria for ITP a) platelet count below 100 x 10^9/L in peripheral blood, b) normal or increased megakaryopoesis on bone marrow examination, and c) the absence of clinically apparent associated conditions or causes of thrombocytopenia. The medical records of these patients were reviewed for the clinical and laboratory information regarding their diagnosis, initial treatment, splenectomy and after treatment follow-up. The severity of thrombocytopenia was classified into: severe (platelets < 30 x 10^9/L); moderate (platelet count 30-50 x 10^9/L) and mild (platelets > 50 x 10^9/L). Data collected from medical records were age at diagnosis, gender, symptoms and type of bleeding, platelet count at diagnosis, platelet count after treatment and at the last recorded check up, treatment modality, time of follow-up after splenectomy in months, and response to different treatments. The data was analyzed using standard statistical test in Microsoft Office Excel 2003.

Therapy and definitions of response

First-line treatment consisted of oral prednisone (1 mg/kg/d) for 3-6 weeks, followed by a tapering off period of maximally 1 year with subsequent withdrawal. Indications for splenectomy were no platelet response after at least 6 weeks of prednisone, one or more recurrences after withdrawal of prednisone, or requirement of maintenance prednisone treatment. Second line treatment was given if no response occurred after splenectomy. Most common prednisone was reintroduced in therapy or other immunosuppressive therapies were used (azathioprine, cyclophosphamide, rituximab). Intravenous gama globulins (IVIG) were reserved for interventions during serious bleeding episodes or to raise platelet count before splenectomy or other surgery.

The response criteria to treatment were defined as: complete response (CR), platelet counts >100 x 10^9/L without therapy for at least 2 months, partial response (PR) platelet counts >30 x 10^9/L without therapy for at least 2 months, response to maintenance therapy as a platelet count of more than 30 x 10^9/L during drug therapy, and no response as platelet count of fewer than 30 x 10^9/L with or without therapy. The same criteria were used to define CR and PR after splenectomy. No response to splenectomy was defined as platelet count bellow 30 x 10^9/L at any time after splenectomy and requirement for additional therapy. Relapse after splenectomy was defined as a decrease in platelet

counts bellow 30 x 10^9/L. Refractory ITP was defined as platelet count lower than 50 x 10^9/L despite treatment with standard dose of corticosteroids and splenectomy.

Results

1. Characteristics of patients at diagnosis

The median age at diagnosis was 28 years (range: 14-57 years). Twenty nine 29 (76%) patients were females and 9 (24%) were males (Table 1). Seven (18.4%) were asymptomatic, 27 (71%) had minor skin or mucosal bleeding and 4 (10.6%) had significant bleeding from gastrointestinal or genitourinary system. None of the patients had severe, life threatening bleeding symptoms. The median platelet count at diagnosis was 18 x 10^9/L (range: 0-91 x 10^9/L). Number of patients with severe thrombocytopenia at diagnosis was 28 (74%), with moderate thrombocytopenia was 7 (18%) and with mild 3 (8%). Bone marrow examination was performed in 33 (87%) of patients. Direct antiglobuline test (DAT or Coombs test) was positive in 2 (5.2%) patients and 1 (2.9%) patients had hemolytic anemia (Fisher Evans Syndrome).

2. Initial response to treatment before splenectomy

Corticosteroids were initial treatment for all 38 (100%) patients and 12 patients (32%) were treated with steroids and intravenous immunoglobulin's (IVIG). Complete response to initial treatment with steroids ± IVIG was achieved in 16 (42%), partial response in 19 (50%) and no response in 3 (8%) Table 1.

3. Characteristics of patients at splenectomy

The median age at the time of splenectomy was 30 years (range 17-60 years). The median follow up from splenectomy was 21 months (range 12-348 months). The median duration from diagnosis to splenectomy was 20 months (range 2-194 months). Twenty-nine patients (76.4%) underwent splenectomy because they didn't respond to corticosteroids or were dependent to steroid therapy, 4 (10.5%) patients had severe side effects from steroid treatment, and 4 (10.5%) patients had poor compliance and in 1 (2.6%) patient splenectomy was performed during cholcystectomy. Four patients had perioperative complications in a form of infections; bronchopneumonia (n=1), tonsillopharingitis (n=1), flu-like syndrome (n=2).

Table 1: Characteristics of splenectomized ITP patients at diagnosis.

Characteristics	N=38
Age (years), median (range)	28 (14-57)
Gender	
Male	9 (24%)
Female	29 (76%)
Median follow up from diagnosis-months (range)	53 (12-384)
Clinical presentation	
No hemorrhagic symptoms	7 (18.4%)
Hemorrhagic symptoms	
Skin or mucosal bleeding	27 (71%)
GIT or genital bleeding	4 (10.6%)
Platelet count at diagnosis, median (range)	18 x 10^9/L (0-91 x 10^9/L)
Severe (Plt <30 x 10^9/L)	28 (74%)
Moderate (Plt 30-50 x 10^9/L)	7(18%)
Mild (Plt > 50 x 10^9/L)	3 (8%)
Treatment	
Prednisone	38 (100%)
IVIG	12 (32%)
Other	14 (37%)
Response to initial treatment (Prednisone ± IVIG)	
CR	16 (42%)
PR	19 (50%)
No response	3 (8%)

Abbreviations: ITP, idiopathic thrombocytopenic purpura; GIT, gastrointestinal tract; Plt, platelets; IVIG, intravenous immunoglobulin's; CR, complete remission; PR, partial remission.

4. Response and treatment after splenectomy

The median platelet count at last control was 240 x 10^9/L (range: 15-704 x 10^9/L). At the last follow up, number of patients with severe thrombocytopenia was 1 (2.6%), with moderate thrombocytopenia was 2 (5.3%), with mild 7 (18.4%) and with platelet count >100 x 10^9/L was 28 (73.7%). At the last control 26 (69%) patients were without therapy for ITP, 5 (13%) were still receiving prednisone, 2 (5%) azathioprine, 5 (13%) were receiving both low doses of prednisone and azathioprine. Two patients were also treated with Rituximab after splenectomy. Overall response rate to splenectomy after 1 year of follow up was 89%, with CR in 23 (60%), PR in 11 (29%), no response or relapse in 4 (11%). According to the results at the time of the last control, 28 patients had CR, but from those 28 patients with normal platelet count only 22 (58%) were without therapy and 6 (22%) were receiving prednisone (2 patients), azathioprine (2 patients) and both drugs (2 patients). These results indicate that only 22/38 (58%) of patients had long-lasting CR without therapy, 12 patients (31%) were receiving therapy and 4 patients (11%) had PR without therapy (Table 2).

We have observed higher response rate in patients under 40 years of age 17/23 (73.9%) than in older ones 5/15 (33.3%), p=0.032. Complete remission

Table 2: Characteristics of patients after splenectomy, response to splenectomy and additional therapy.

Characteristics	N=38
Age (years) at splenectomy, median (range)	30 (17-60)
Median follow up from splenectomy in months (range)	53 (12-348)
Median time from diagnosis to splenectomy in months (range)	20 (2-194)
Platelet count at last control, median (range)	240x10^9/L(15-704 x10^9/L)
Severe (Plt < 30 x 10^9/L)	1 (2.6%)
Moderate (Plt 30-50 x 10^9/L)	2 (5.3%)
Mild (Plt > 50 x 10^9/L)	7 (18.4%)
Normal (Plt > 50 x 10^9/L)	28 (73.7%)
Treatment at last control	
Prednisone	5 (13%)
Azathiprine	2 (5%)
Prednisone + Azathioprine	5 (13%)
No therapy	26 (69%)
Response to splenectomy	
CR*	22 (58%)
PR#	10 (26%)
No response	6 (16%)

Abbreviations: ITP, idiopathic thrombocytopenic purpura; GIT, gastrointestinal tract; Plt, platelets; IVIG, intravenous immunoglobulin's; CR, complete remission; PR, partial remission.

after splenectomy was achieved in 14/16 (87.5%) of patients that were at CR after initial treatment with corticosteroids ± IVIG compared to 8/22 (36.4%) of patients that were at PR or NR after initial treatment, p=0.005. Sex didn't influence the outcome after splenectomy in our group of patients. Complete remission after splenectomy was achieved in 3/9 (33.3%) of males comparing to 13/29 (44.8%) of females, p=0.82. In our group of patients better results after splenectomy were associated with younger age and better response to initial treatment with corticosteroids ± IVIG.

Discussion

Idiopathic thrombocytopenic purpura is an autoimmune disease characterized by thrombocytopenia due to the presence of platelet autoantibodies specific for platelet membrane glycoproteins, such as GPIIb/IIIa, GPIb/IX and GPIa/IIa [1]. These autoantibodies cause an accelerated destruction of autoantibody-opsonized platelets by FcγReceptor bearing phagocytic cells in the reticuloendothelial system [2]. Spleen is the major site of removal of opsonized or damaged platelets that contribute to the thrombocytopenia in patients with ITP. For this reason, splenectomy has been used as therapeutic approach in patients with ITP who were not responsive to corticosteroid treatment [5, 20].

The initial response rate referred in other studies was 75-85% but it decreased to 50-60% after follow-up longer than 1 year [21-23]. Some studies reported higher long-term response rate of 70-89%, but this can be due to shorter follow-up period, differences in patient characteristics, and higher percentage of patient with severe ITP [6, 24, 25]. Elezovic et al. [25] reported that 111/147 (75.5%) splenctomised patients were in remission during follow up of median 62 months. Ninety nine (67%) were in CR, 12 in PR, and 36 patients (24.5%) were relapsed. Our results indicate 58% long-term response rate in adult ITP patients and 31% of patients were receiving therapy at the time of last control. In our patients better results after splenectomy were associated with age less than 40 years (p=0.032) and better response to initial treatment (p=0.005), similar to the results in the study of Elezovic et al. [25].

Patients that did not respond or relapsed after splenectomy were resistant and had a low response rate to additional therapy (like azathioprine, rituximab, cyclophosphamide, mycophenolate mophetil etc). Response rate to mycophenolate mophetil was 69%, but only 5/11 responders (45%) had sustained remissions [26] and results were independent of patients age, gender or prior splenectomy. Management of patients with immune thrombocytopenia (ITP) refractory to standard treatment with corticosteroids and splenectomy is difficult, because the response rate to all available treatments at the moment are low and are not long-lasting [23, 24, 26].

Splenectomy is relatively safe surgical intervention with postoperative complication rate of 13% in the study by Kojouri et al [6] up to 33% in the study of Portielje et al. [4]. We didn't have any severe complication or death due to splenectomy and postoperative morbidity was 10%. We had only four patients that experienced moderate infective complications after splenectomy.

In conclusion, splenectomy may be considered as safe and effective treatment for patients with ITP who failed to respond to firs-line treatment with corticosteroids. Management of patients who do not respond or relapse after splenectomy represent an important problem for further treatment due to low response rate to other treatment options.

References

1. McMillan R. Chronic idiopathic thrombocytopenic purpura. N Eng J Med. 1981;304:1135.

2. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. N Eng J Med. 2002;346:995-1008.

3. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113:2386-2393.

4. Portielje Je, Westendorp RG, Kluin-Nelmand HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. Blood. 2001;97:2549-54.

5. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood. 1996;88:3-40.

6. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systemic review to assess long-term platelet count responses, prediction of response, and surgical complication. Blood. 2004; 104:2623-2634.

7. Quiquandron I, Fenaux P, Caulier MT, et al. Re-evaluation of the role of azathiprine in the treatment of adult chronic idiopathic thrombocytopenic purpura: a report of 53 cases. Br J Haematol. 1990;74:223-228.

8. Kappers-Klunne MC, van't Veer MB. Cyclosporine A for the treatment of patients with chronic idiopathic thrombocytopenic purpura refractory to corticosteroids or splenectomy. Br J Haematol. 2001;114:121-125.

9. Verlin M, Laros RKJr, Penner JA. Treatment of refractory thrombocytopenic purpura with cyclophosphamide. Am J Hematol. 1976;1:97-104.

10. Maloisel F, Andres E, Zimmer J, et al Danazol therapy in patients with chronic idiopathic thrombocytopenic purpura: long term results. Br J Haematol. 2004;116:590-594.

11. Provan D, Moss AJ, Newland AC, Bussel JB. Efficacy of mycophenolate mofetil as a single agent therapy for refractory immune thrombocytopenic purpura. Am J Hematol. 2006; 81:19-25.

12. Blanchette VS, Luke B, Andrew M, et al. A prospective, randomized trial of high dose intravenous immune globulin G therapy, oral prednisone therapy, and no therapy in childhood acute immune thrombocytopenic purpura. J Pediatr. 1993; 123:989-995.

13. Kuter DJ, Bussel JB, Lyons RM et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura : a double-blind randomized controlled trial. Lancet. 2008;371: 395-403.

14. Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med. 2007;357:2237-2247.

15. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350:2572-2581.

16. Ahmed ER, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. N Engl J Med. 2006;355:1772-1779.

17. Zecca M, Nobili B, Ramenghi U, et al. Rituximab for the treatment of refractory autoimmune hemolytic anemia in children. Blood. 2004;103:2925-2928.

18. Arnold DM, Dentali F, Crowther MA, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med. 2007;146:25-33.

19. Zaja F, Baccarani M, Mazza P, et al. Dexamethason plus rituximab yields higher sustained response rates than dexamethasone monotherapy in adults with primary immune thrombocytopenia. Blood. 2010;115:2755-2762.

20. British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and pregnancy. Br J Haematol. 2003;120:574-96.

21. Schwartz J, Leber MD, Gillis S, et al. Long-term follow-up after splenectomy performed for immune thrombocytopenic purpura (ITP). Am J Hematol. 2003;72:94-8.

22. Vianelli N, Galli M, deVivo A, et al. Efficacy and safety of splenectomy in immune thrombocytopenic purpura: long-term results of 402 cases. Haematologica. 2005;90:72-7.

23. Han JJ, Baek SK, Lee JJ, et al. Long-term outcomes of a 5-year follow up of patients with immune thrombocytopenic purpura after splenectomy. Korean J Hematol. 2010;45:197-204.

24. Mazzucconi MG, Arista MC, Peraino M, et al. Long-term follow-up of autoimmune thrombocytopenic purpura (ATP) patients submitted to splenectomy. Eur J Haematology. 1999;62:219-22.

25. Elezovic I, Boskovic D, Colovic M, Tomin D, Suvajdzic N, Gotic M, Colovic R, Popovic M. Late results of splenectomy in patients with chronic immune thrombocytopenic purpura. Acta Chir Iugosl. 2002; 49:29-34.

26. Colovic M, Suvajdzic N, Colovic N, Tomin D, Vidovic A, Palibrk V. Mycophenolate mophetil therapy for chronic immune thrombocytopenic purpura resistant to steroids, immunosuppressants, and/or splenectomy in adults. Platelets. 2011;22:153-6.