

Chronic ITP: Analysis of various factors at presentation which predict failure to first line treatment and their response to second line therapy

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Abstract

Objective: To observe the significance of various factors in chronic idiopathic thrombocytopenic purpura (ITP) which predict the response of first line (corticosteroids) and second line therapy (splenectomy) and to evaluate their response to second line therapy.

Methods: This was a descriptive, prospective study conducted from August 2004 till January 2006. Patients of all age groups and both genders with diagnosis of chronic ITP were included. Treatment protocol and criteria for response assessment was explained.

Results: During 17 months period, 86 patients with chronic ITP were analyzed. Non-responders to first line therapy were 74 patients who ultimately required splenectomy. Complete response (CR) was had in 37 (50.7%) patients, 10 (13.7%) and 27 (36.5%) had partial response (PR) and no response (NR) respectively. Analysis of variables like younger age, sex and low platelet count at presentation failed to show any significant influence on response to first line treatment. However response to splenectomy was found to be higher in patients who had initial complete or partial response with steroids and later relapsed and the platelet count was more than $300 \times 10^9/L$ on day 14 of surgery.

Conclusion: Splenectomy remains the most effective treatment of chronic ITP. No significant factor was identified which predicted initial response to first line treatment. However patients who initially responded to steroids and had platelet counts above $300 \times 10^9/L$ about a fortnight after splenectomy showed promising results post-operatively ($p=0.003$ and $p=0.001$) (JPMA 57:126;2007).

Introduction

Idiopathic thrombocytopenic purpura (ITP) is an acquired autoimmune disease characterized by platelet destruction caused by an anti-platelet autoantibody. The autoantibody-platelet complex is captured by the reticuloendothelial system, which is particularly prominent in the spleen.^{1,2}

Once the decision to treat patients with ITP has been made, corticosteroids are the standard initial treatment.³⁻⁶ Patients who fail to respond to steroids after six months are considered to have chronic ITP1.

Splenectomy has been the single best option for those who fail to respond to first line treatment (corticosteroids), or relapse afterwards; it results in complete or partial remission requiring no further therapy in two-thirds of patients.^{2,6,7}

Splenectomy is often cited as first line therapy but seldom used and considered as second line therapy.^{6,8} The timing of the procedure depends on disease severity, responsiveness and side effects of medical treatment and patients and doctor preferences.⁵

Furthermore, pre and/or post-operative parameters that are able to predict the response to splenectomy are not fully recognized.^{1,9-11} Multiple patients and disease charac-

teristics have been reported, but the findings are inconsistent. The principal site of platelet sequestration determined by Indium-labelled autologous platelet scanning appears to be the most sensitive indicator⁹ to date; however few studies have not shown a significant association.¹²

Similarly little is known about the factors which predict the response to steroids. No comparable data is available in this regard on regional basis.

To contribute to these issues; we performed an analysis on patients with chronic ITP to determine the overall outcome of splenectomy. We also evaluated the significance of various factors which predict the initial response to steroids and splenectomy.

Patients and Methods

This was a descriptive prospective study conducted over a period of 17 months extending from August 2004 till January 2006. Patients of all age groups and both genders with diagnosis of chronic ITP who visited the haematology out-patient clinic, or underwent splenectomy during the study period were included. Patients with secondary causes of thrombocytopenia or with concomitant autoimmune hemolytic anemia i.e. Evans syndrome were excluded.

The diagnosis of idiopathic thrombocytopenic purpura was made on isolated thrombocytopenia and on the exclusion of other causes of thrombocytopenia and that was confirmed by bone marrow aspirate.

The patients were managed according to guidelines provided by British Society of Hematology⁶ which state that:

* No treatment is required in case where platelet counts are than $30 \times 10^9/L$ or patient has no signs and symptoms of bleeding unless they are undergoing any surgical procedure which is likely to induce blood loss.

* When required; first line treatment is given with steroids (prednisone 1mg/kg/day for 2-4 weeks, tapering off over several weeks) in case when platelet counts dropped further or patient had haemorrhagic symptoms.

* Intravenous immunoglobulin (IVIg) is considered as first line therapy, however responses are transient.

* Splenectomy as second line agent was indicated in all patients with chronic ITP who failed to respond to steroids, or required higher doses of steroids (prednisone more than 10mg/day) to maintain platelets count greater than $30 \times 10^9/L$.

The following criteria were used to assess the response to therapy.¹³⁻¹⁵

Complete response (CR): Achievement of normal platelet counts i.e. greater than $150 \times 10^9/L$ atleast two months after surgery.

Partial response (PR): Achievement of platelet count greater than $50 \times 10^9/L$ atleast two months after surgery, or greater than $30 \times 10^9/L$ only without continued drug administration.

No response (NR): Failure to achieve platelet count above $30 \times 10^9/L$.

Relapse was defined as a drop in the platelet count to below $150 \times 10^9/L$ after CR.

All statistical analysis was computed with SPSS statistical software (version 13.0.1). Data was presented as mean or median values; and percentages. The following variables were studied for their prognostic value on the achievement of response: young age, sex, disease duration, initial response to corticosteroids, platelet count at presentation and after surgery. Differences between responders and non-responders were evaluated by using the chi-square. A p-value of less than 0.05 was considered to be statistically significant.

Results

A total of eighty six patients with chronic ITP were studied. Of these 31 (36%) were males and 55 (64%) were females, with a mean age at the time of diagnosis of 25.5 years (range: 2-65 years). At the time of diagnosis, 33

(38.3%) patients were less than 15 years of age, while at the time of splenectomy 23 (26.7%) patients were found in this age group. Patient characteristics are summarized in Table 1

First line treatment with steroids was required in 83 patients, while three had platelet counts greater than $30 \times 10^9/L$. Although intravenous immunoglobulin (IVIg) was considered as first-line treatment but it was not used as initial treatment modality in our series.

Table 1. Patient characteristics at the time of diagnosis (n=86) and splenectomy (n=74).

Sex (male/female) (%)	31(36%) / 55 (64%)
Mean age at time of diagnosis (years)	25.5
Range	(2-65)
Mean age at time of splenectomy (years)	27
Range	(5-60)
Median time between diagnosis and splenectomy i.e. disease duration (months)	19.1
Range	(6-660)
Median number of platelets at time of diagnosis	$9 \times 10^9/L$
Range	(1-65 $\times 10^9/L$)
Median time of remission Post-splenectomy (months)	27.6
Range	(11-127.2)
Median time of relapse post-splenectomy (months)	12
Range	(2-24)

Table 2. Comparison of the factors which affect initial response to steroids.

	Responders (CR+PR) (n=35)	Non- responders (n=48)	P-value
Age < 15 years	16	17	0.53
Male/Female	13 / 22	17/ 31	0.90
Platelet count at presentation < $20 \times 10^9/L$	31	46	0.2

The response with steroids was complete (CR) in 15 (18.1%) patients, 20 (24.1%) and 48 (57.8%) patients showed partial (PR) and no response (NR) respectively. When the response to steroid therapy was correlated with the patient age, sex and platelet count of less than $20 \times 10^9/L$ at presentation no significant association was noted (p-value 0.53, 0.9, 0.2 respectively) (Table 2).

Out of 48 patients who were refractory to steroids; 45 ultimately required splenectomy, 2 were lost to follow-up and the remaining one patient was not fit for general anaesthesia. Of the 35 patients who had initial complete or partial response to steroids; 29 ultimately underwent splenectomy due to disease relapse.

Hence a total of 74 (86%) patients with chronic ITP were subjected to splenectomy. At the time of splenectomy, 48 patients had disease duration of around one year. After splenectomy, 37 patients (50%) had complete recovery, 10 (13.5%) went into partial remission, and 27 (36.5%) showed no response. Four (5.4%) of the responders subsequently relapsed after a median interval of 12 months (2-24 months).

Table 3. Significance of factors predicting splenectomy response.

	Responders N=47	Non-responders N=27	p-value
Mean age (years)	24.7	31.4	
Age <15 years (n=23)	16 (56.5%)	10 (43.5%)	0.58
Male/ female (26 / 48)	16 / 31	9/18	0.92
Disease duration (less than 1 year) (n=48)	30 (62.5%)	18 (37.5%)	0.89
Platelet <20 x10 ⁹ /L at time of diagnosis (n=69)	43 (62.3%)	26 (37.6%)	0.73
CR+PR to steroids (n=29)	25 (86.2%)	04 (13.8%)	0.003
Platelet count >300 x10 ⁹ /L on day 14 of surgery (n=27).	25 (92.5%)	2 (7.5%)	0.001

CR = Complete Response
PR = Partial Response

To see the significance of various factors which can predict response of splenectomy, the patients were grouped into responders (CR+PR) and non-responders. It was observed that younger age, gender, low platelet count at time of diagnosis, time duration from diagnosis to splenectomy did not significantly influence the splenectomy outcome.

However, out of 29 patients with previous complete or partial response to steroids, 25 (86.2%) attained CR or PR with splenectomy while four (13.8%) patients did not respond (p=0.003).

Twenty seven patients had platelet counts greater than 300x10⁹/L on day 14 of surgery. Of these; 25 (92.5%) were responders to splenectomy- CR (n=23) and PR (n=2) (p=0.001) (Table 3).

Only one patient died of gram negative sepsis which she developed within two months of surgery.

Discussion

The ultimate outcome of chronic ITP is unpredictable.¹⁰

In our series, initial treatment with steroids resulted in CR in 17% of cases, which is comparable with previous studies.^{12-13,16} In contrast to this, considerable higher response rate with steroids (41% and 47%) was observed in other studies.^{17,18}

Comparable to previous data¹⁶⁻¹⁸, younger age, sex and platelet count at presentation were not associated with better response to steroids in our group.

Splenectomy remains the treatment of choice in chronic ITP showing CR in 50%, the results compared favorably with those of Chen et al.¹⁹ However even higher response rates had been reported by various studies.^{1,18, 20}

The prognostic factors of successful splenectomy in ITP have been of much interest for decades. Many studies failed to demonstrate any such prognostic parameter.¹¹

In the present study, an initial complete or partial response to corticosteroid was statistically significant in predicting response with splenectomy. Similar prognostic correlation has been reported in the past²¹ and some recent studies.¹⁸ Some studies failed to show a significant association.^{6,10,22}

Similarly high platelet counts within two weeks

post-operatively showed a favorable outcome in our series. There are consistent with other reports.^{1,23,24}

Contrary to previous reports¹¹, we were not able to identify young age^{19,23}, sex; disease duration and low platelet count at presentation to be prognostic parameters for a successful splenectomy. Our results are comparable with some other study results.^{10,25}

Indium-labelled autologous platelet scanning for detecting principal site of platelet sequestration is the most sensitive indicator to predict the response of splenectomy. This was not utilized in our study due to non availability of the test.

It is worth noting that splenectomy caused no significant morbidity. In previous reports; the overall mortality of splenectomy ranged from 0.2-1.5%²⁰, however we experienced only one (0.01%).

Conclusion

Splenectomy remains an effective and safe treatment for chronic ITP. No factor has been identified to help in predicting response of first line treatment. However, prior stable response with steroids and high post-operative platelet count, were associated with CR after splenectomy.

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