



Factors predicting response to splenectomy in adult patients with idiopathic thrombocytopenic purpura

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ABSTRACT

Background and Objectives. Splenectomy is the treatment of choice in the majority of patients affected by idiopathic thrombocytopenic purpura refractory to corticosteroid therapy, but it is not free from early and late complications. As the available literature does not seem to contain any precise indications concerning possible factors predicting the response to splenectomy, the aim of this retrospective study of 65 splenectomized patients was to attempt to identify potentially predictive clinical or laboratory parameters.

Design and Methods. For the purposes of statistical analysis, the patients were divided into two groups: the first included those with a complete (platelets $> 100 \times 10^9/L$) or partial response (platelets $50-100 \times 10^9/L$) to splenectomy; the second, the non-responders (platelets $< 50 \times 10^9/L$). The non-parametric tests were based on the Kruskal-Wallis method for independent samples, and the independent samples were compared using the Chi-square test according to Pearson.

Results. Univariate analysis did not reveal any significant correlation between successful splenectomy and age, sex, platelet count at diagnosis, anti-platelets antibody positivity, the site of platelet sequestration, the time between diagnosis and surgery, or the response to high intravenous immunoglobulin doses. However, the probability of success was greater in the patients with a complete or partial pre-operative response to steroid therapy ($p < 0.05$).

Interpretation and Conclusions. The factor most frequently associated with the success of splenectomy is the site of autologous platelet sequestration. Our study did not identify any clinical or laboratory parameter clearly predictive of post-splenectomy cure other than a transient response to steroid treatment. This finding needs further confirmation in larger patient populations.

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Key words: idiopathic thrombocytopenic purpura, factors predicting response, splenectomy

Adult idiopathic thrombocytopenic purpura (ITP) is a chronic acquired autoimmune disorder that hardly ever resolves without treatment. The treatment of ITP has not changed substantially over the last few decades: 30% of the affected patients show a long-term response to steroid therapy; splenectomy is the treatment of choice in the remaining 70% of the patients, including the ones who never respond to steroids and those who relapse at withdrawal of steroid therapy (both are considered steroid-refractory).¹ However, the morbidity and mortality rates associated with the operation are not negligible, and adult patients can tolerate a moderate grade of thrombocytopenia (the risk of severe hemorrhages is 2-6%).²⁻⁷ A number of studies have tried to define the factors predicting a response to splenectomy by considering the clinical severity of the disease, the age and sex of the patients, the pre-operative response to corticosteroids, pre- and post-operative platelet counts, the levels of serum and platelet-associated immunoglobulins, the site of platelet sequestration, the size and weight of the spleen, hyperplasia of splenic follicles, the time interval between diagnosis and splenectomy, the presence of an accessory spleen, bleeding time, and the response to high intravenous immunoglobulin (Ig) doses. However, the results of these studies have been contradictory and cannot be used as a means of patient selection.

In this study, age, sex, platelet count at diagnosis, anti-platelet antibody positivity, the site of platelet sequestration, the response to initial steroid treatment, high-dose intravenous immunoglobulin therapy, and the time between diagnosis and surgery (which are all considered to be possible predictive factors of the outcome of splenectomy) were analyzed in 65 patients with chronic steroid-refractory ITP who subsequently underwent splenectomy.

Design and Methods

We studied 65 splenectomized patients with steroid-refractory ITP treated in the Servizio

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Table 1. Patients' characteristics.

	N= 65		
	Mean	Range	Median
Age at diagnosis (yrs)	35	10-68	35
Age at splenectomy (yrs)	37.3	12-68	35
ITP diagnosis/splenectomy time interval (mos)	37.4	1-369	15
<i>No. of platelets (x 10⁹/L)</i>			
On steroid therapy	127	2-436	146
Six months after discontinuing steroids	41.4	1-360	32
Pre-splenectomy	16.7	1-40	15
Before i.v. Ig	17.9	1-36	5
After i.v. Ig (n = 23)	137.9	1-460	107

Autonomo di Ematologia Diagnostica of Ospedale Maggiore, IRCCS, Milan, and the Haematology Division of Ospedale San Gerardo, Monza, in the period 1978-1998. Patients with thrombocytopenic purpura secondary to lymphoproliferative disorders, myelodysplasia, agammaglobulinemia, congenital or hereditary thrombocytopenia, acquired HIV, HBV or HCV infections, autoimmune diseases (SLE) or drug related disease were excluded from the study.

The 65 patients included 20 men and 45 women (a male:female ratio of 0.44). The mean follow-up from the time of ITP diagnosis was 139 months (median 113; range 13-450). The mean age at diagnosis was 35 years, and that at splenectomy was 37.3 years; the mean time between diagnosis and splenectomy was 37.4 months. The mean duration of follow-up after splenectomy was 129.8 months (range 28-482). The general characteristics of the patients are shown in Table 1.

All the patients had been treated with prednisone at an initial dose of 1 mg/kg/day for one month, which was subsequently tapered off until complete withdrawal. The maximum pre-splenectomy platelet count was $40 \times 10^9/L$ (range $1-40 \times 10^9/L$; mean $16.7 \times 10^9/L$). Twenty-three patients received intravenous Ig at a standard dose of 400 mg/kg/day for five consecutive days; nineteen patients underwent second-line medical treatment (vincristine or vinblastine, danazol, azathioprine, cyclophosphamide, etc.) without success before being splenectomized. All the patients received the anti-pneumococcal vaccine.

The response to steroid therapy, i.v. Ig and splenectomy was evaluated as complete (CR = platelet counts $>100 \times 10^9/L$), partial (PR = platelet counts $50-100 \times 10^9/L$) or no response (NR = platelet counts $< 50 \times 10^9/L$). For the pur-

poses of statistical analysis, the patients were subdivided into two groups: CR+PR vs NR.

Anti-platelet antibodies were assayed in 51 patients using the method reported by Von dem Borne.⁸ Antibodies were positive in 25/51 patients.

Platelet survival and the site of platelet sequestration were determined in 59 patients. The mean platelet survival was three days.

The tests were carried out at Ospedale Niguarda, Milan, using the platelet markers ⁵¹Cr (until 1987) or ¹¹¹In (from 1988). The technique used for measuring platelet survival, as well as platelet recovery and organ sequestration, was labeling of isolated, washed platelets with the radioisotope compound ¹¹¹In-oxine. ¹¹¹In was not lost from platelets during activation of *in vitro* storage, and cells labeled with ¹¹¹In had the same *in vivo* recovery and survival as those labeled with ⁵¹Cr.^{9,10} The majority of the patients were not receiving any therapy at the time the test was performed.

Statistical analysis

The data were analyzed using version 6.1 of the SPSS for Macintosh statistics program (SPSS Inc.); the non-parametric tests were based on the Kruskal-Wallis method for independent samples, and the independent samples were compared using the Chi-square test according to Pearson.

Results

Of the splenectomized patients, 44 (67.7%) achieved a CR, seven (10.8%) a PR, and 14 (21.5%) failed to respond. Eighty-five percent of the 20 male patients achieved a CR/PR as against 75% of the 45 female patients ($p=0.4$).

Sixty-nine percent of the 12 patients aged 20 years or less achieved a CR/PR as against 79% of the 53 older patients.

In the first week post-splenectomy, about 88% of the patients had platelet levels of more than $100 \times 10^9/L$, and 84% of them achieved a CR/PR. Of the 12% of patients with platelet levels of $100 \times 10^9/L$ or less, only 37% developed a lasting CR or PR (NR= 63%).

Forty-six percent of the patients underwent splenectomy within one year of the diagnosis of ITP. Of these, 80% subsequently achieved a CR or PR, as against 77% of the patients who were splenectomized more than one year after diagnosis. The relation between the diagnosis/splenectomy time interval and the response to splenectomy was not statistically significant ($p=0.26$).

In 25 patients (42.4%) the sequestration site was prevalently splenic and in six (10.2%) hepatic or mixed; 28 patients (47.4%) showed no

increase in splenic and/or hepatic sequestration. The percentage of CR/PR in these three subgroups of patients was respectively 84% (21/25), 50% (3/6) and 75% (21/28) ($p=0.2$).

Twenty-five (46%) of the 51 patients in whom anti-platelet antibodies were looked for proved to be positive, of whom 80% (20/25) achieved a CR/PR to splenectomy. The percentage of CR/PR in the negative patients was 77% (20/26) ($p=0.79$).

All of the 23 patients who had been treated with i.v. Ig at high doses relapsed within a month of the first treatment cycle: 86% of those who achieved a CR/PR to i.v. Ig (12/14) achieved a CR/PR after splenectomy. Of the nine patients failing to respond to i.v. Ig, four (44%) were complete responders to splenectomy and five (56%) did not respond. There was no statistically significant difference between the response to i.v. Ig and the response to splenectomy ($p=0.09$). (Table 2).

Table 3 shows the characteristics of the patients in relation to splenectomy response.

Discussion

The first-choice treatment of adult ITP is corticosteroid therapy,^{11,12} which leads to a complete or partial response at the time of drug discontinuation in 30% of patients followed up for a maximum mean period of five years.¹ The elective therapy for steroid-refractory patients is splenectomy, which has proved to be effective in two-thirds of cases.¹

Splenectomy is ineffective in 30% of patients. The short-term (5-year) success rate in unselected populations is about 70-85%,^{13,19} but this does not necessarily indicate a long-term response. The majority of relapses occur within the first year and the relapse rate reported in the literature is 10-20%.^{13,18-20} The success rate of splenectomy is higher in more selected populations, reaching 93% in the patients with purely splenic platelet sequestration¹³ or in those who have shown an even transient response to steroids before the operation.¹⁵

A number of published studies have tried to identify factors predictive of successful splenectomy, but their results are not unequivocal. The factors most frequently associated with a response to splenectomy have been the following: i) the site of splenic platelet sequestration;^{14,21-26} ii) the pre-splenectomy response to corticosteroid treatment;^{15,16,25,27,28} iii) a younger patient age (< 50-60 years).^{13,23,25,27-30}

Other variables found to correlate positively with the response to splenectomy have been: a high platelet count after splenectomy,^{23,25,28,29} a low level of PAIg,³¹ the absence³² or presence²⁶ of splenic follicle hyperplasia, and the response to

Table 2. Response to i.v. Ig and splenectomy.

Response to i.v. Ig	No.	Response after splenectomy	
		CR/PR (%)	NR (%)
CR/PR	14	12/14 (86)	2/14 (14)
NR	9	4/9 (44)	5/9 (56)
Total	23	16/23 (70)	7/23 (30)

For definitions see the text.

Table 3. Response to splenectomy.

	Response to splenectomy	
	NR (n=14)	CR/PR (n=51)
Males/females	3/11	17/34
Age (yrs)	40 (10-64)	33.4 (12-68)
Response during steroid therapy (No. of platelets $\times 10^9/L$)	77.9 (10-322)	141.35 (2-436)
Response to i.v. Ig (No. of platelets $\times 10^9/L$)	61 (1-270)	163 (1-460)
ITP diagnosis/splenectomy time interval (mos)	64.5 (4-369)	30 (1-238)

intravenous Ig administration.^{30,33}

The present study considered some of the parameters already evaluated in the literature (the age and sex of the patient, the presence of anti-platelet antibodies, platelet count at diagnosis, the platelet sequestration site, the time interval between diagnosis and splenectomy, and the response to high-dose intravenous Ig or corticosteroid therapy), but only the initial response to corticosteroid therapy was associated with more successful splenectomy ($p < 0.05$).

The results published in the literature are contradictory and mainly based on retrospective studies of small patient series (the largest population was that involved in the study carried out by Najean,¹⁴ which considered 268 splenectomized ITP patients). Furthermore, these studies cannot be compared because of the differences in the characteristics of the patients involved: for example, some of them included pediatric patients,^{14,33} in whom the course of the disease is different and generally more favorable than in adults. The same can be said in relation to the laboratory methods used to evaluate the site of platelet sequestration: some of the studies used ⁵¹Cr, others ¹¹¹In, and others both, but it is known that the ¹¹¹In test is more sensitive even in the presence of very low platelet levels.

It is still not possible to identify any certain

factors predicting the response to splenectomy because some authors sustain that pre-splenectomy parameters have no value in terms of patient selection,^{34,35} whereas others consider that the site of platelet sequestration is an important predictive factor.¹³

Our results and those of other published studies do not indicate any difference in the effects of early and later splenectomy¹⁷ but it seems reasonable to adopt a *wait and see* approach for 8-12 months after diagnosis in the case of patients at low hemorrhagic risk because it has been reported that some of them respond to second-line medical therapies.

In conclusion, the parameter reported as being most frequently associated with the success of splenectomy is the site of splenic sequestration, but we did not find that any studied clinical or laboratory parameter certainly predictive of post-splenectomy cure except for a transient response to steroid therapy. This finding needs further confirmation in larger patient populations.

Contributions and Acknowledgments

FR was responsible for the conception of the study and direct supervision. PF, MG and EG followed the patients, collected clinical data and wrote the paper. EP was responsible for the statistical analysis. EMP, ATM and AC helped to evaluate and interpret the data.

Disclosures

Conflict of Interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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Potential implications for clinical practice

- ◆ The current practice in Italy of offering splenectomy as second-line treatment for ITP³⁶ is appropriate. ITP patients who show a transient response to steroid treatment and subsequently relapse may undergo splenectomy.

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