Efficacy and safety of splenectomy in immune thrombocytopenic purpura: long-term results of 402 cases

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Background and Objectives. Immune thrombocytopenic purpura (ITP) is an acquired autoimmune disease characterized by platelet destruction. Glucocorticoids are the first-choice treatment, resulting in a complete (CR) or partial (PR) response in 70-80% of cases. In most cases, however, response is transient or glucocorticoid-dependent. For these and for selected patients with acute refractory ITP, splenectomy may produce a good response (CR+PR) in about 60-80% of cases. We report here the long-term outcome of a large cohort of ITP splenectomized patients.

Design and Methods. We retrospectively analyzed the data on 402 patients (137 males, 265 females) who underwent splenectomy for ITP between 1959 and 2002 in 22 different Hematology Centers.

Results. Seventy-nine of the 345 (23%) responsive patients relapsed, in most cases (80%) within 48 months from splenectomy. Sixty-eight out of these 79 patients (86%) were then treated with a good response in 46/68 (68%) cases. Fifty-four of the 57 patients refractory to splenectomy and were then treated, after the surgery, with a good response in 27/54 (50%) cases. Infection and thrombosis did not significantly weigh upon the outcome of the patients. Only three patients died of hemorrhage during follow-up. By multivariate analysis, the number of therapies before (p<0.01) and higher peak post-splenectomy platelet count (p<0.00001) were predictive of a favorable response to splenectomy, whereas only higher post-splenectomy peak platelet count (p<0.001) was predictive of relapse.

Interpretation and Conclusions. This study shows that splenectomy is a safe procedure and effective in approximately two thirds of patients with chronic ITP. Further studies are required to establish whether surgery-sparing treatments of chronic ITP, such as high-dose dexamethasone, anti-D and anti-CD20 immunoglobulins, have similar or even superior efficacy, risk and cost ratios compared to splenectomy.

Key words: immune thrombocytopenic purpura, ITP, splenectomy, long-term follow-up.

Haematologica 2005; 90:72-77

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Immune thrombocytopenic purpura (ITP) is an acquired autoimmune disease characterized by platelet destruction caused by an antiplatelet autoantibody. The complex autoantibody-platelet complex is captured by the reticuloendothelial system, which is particularly prominent in the spleen. Glucocorticosteroids are recommended as the initial treatment for adult patients with acute ITP, resulting in a good response in 70-80% of cases.[1] However, only about one third of these patients shows a satisfactory long-term response.[2] In the common event of refractory thrombocytopenia, many other therapeutic approaches are available, but the results have been unsatisfactory or contradictory and they are sometimes associated with a not negligible toxicity.[3,4] Patients who do not have a partial (PR) or complete remission (CR) after 6 months off steroids are considered to have chronic ITP. For selected cases among these patients, as well as for patients with acute refractory ITP (i.e. severe symptomatic thrombocytopenia refractory to medical treatment), splenectomy produces a good response (CR+PR) in about 60-80% of cases.[5] However, while there is agreement regarding the short-term efficacy of splenectomy, conflicting data on the long-term efficacy and safety have been reported. Some authors[6-8] observed a long-term success rate of about 60%, but others[9] stated that almost all patients would relapse. Moreover, a major concern for patients and physicians is overwhelming pneumococcal septicemia, which may occur even many years after splenectomy. Anti-CD20 antibody[10,11] and anti-D[12] have recently been suggested as alternatives to surgery. Some studies have shown that

they are effective and relatively safe for the treatment of chronic ITP, although the long-term results of these drugs still need to be assessed. For these reasons, further data on the long-term efficacy and safety of splenectomy are needed. Furthermore, it is not clear from the data in the literature which patients will respond to splenectomy and whether there are pre- and/or post-operative parameters able to predict the relapse of disease.[8,10,13-17]

To contribute to these issues, we performed a retrospective multicenter Italian study on a large group of ITP patients who underwent splenectomy. We report their short- and long-term outcomes, as well as the rates of post-splenectomy infection, thrombosis and cancer. We also evaluated a number of pre- and post-splenectomy variables as potential predictors of outcome.

Design and Methods

Study design

We retrospectively analyzed the data, available in the archives of 22 Italian hematology centers, on 402 patients (137 males and 265 females), who underwent laparotomic splenectomy for ITP between 1959 and 2002. A small proportion of these patients have been previously reported on.[18-19] The diagnosis of ITP was based on the presence of isolated thrombocytopenia and on the exclusion of other explanations for thrombocytopenia.[1] The median platelet count at diagnosis was 16×10^9/L (range, 1-100×10^9/L). The median age at diagnosis was 34 years (range, 1-84), whereas the median age at the time of splenectomy was 36 years (range, 6-85). Fifty-three patients were aged ≤16 years and 38 patients were aged ≥60 years at the time of diagnosis. Twenty-four patients were aged ≤16 years at the time of splenectomy.

Four patients were splenectomized at diagnosis, 11 during follow-up without any other previous therapy and 387 after one or more medical treatments (median, 2 treatments; range, 1-4). All 387 patients received steroids as the initial treatment. Twenty percent of patients also received intravenous immunoglobulin before splenectomy. Patients were splenectomized when they had a platelet count <30×10^9/L and/or were steroid-dependent. One hundred and sixty-three (40%) patients were vaccinated before splenectomy (pneumococcal vaccine). All patients underwent open splenectomy.

After splenectomy, refractory or relapsed patients with a platelet count below 30×10^9/L or with bleeding were treated, generally with steroids. In case of failure, steroids were replaced or associated with high dose intravenous immunoglobulins (IVIg), azathioprine, danazol, vinca alkaloids and, less often, drug combinations or investigational drugs. Data on patients who were lost during follow-up were censored at the time of the last visit.

Definition of response to treatment

A complete response and a partial response were defined as a rise of the platelet count above 150×10^9/L and 50×10^9/L, respectively, at least 1 month after surgery, in the absence of steroid treatment. Refractoriness (NR) was diagnosed when the platelet count remained at the baseline value or increased to less than 30×10^9/L within 1 month after surgery. Relapse of ITP was defined as a drop in the platelet count to below 150×10^9/L after CR, below 50×10^9/L after PR, or when medical treatment was required to maintain a safe platelet count. In patients who were refractory to splenectomy or relapsed after it, a good response to medical treatment was considered to be a platelet count that rose above 30×10^9/L.

Statistical methods

Curves for relapse-free survival (RFS) were calculated according to the method of Kaplan and Meier. For comparisons between groups, the Student's t-test and χ^2 test were employed for comparisons between groups. All p values were two-sided and statistical significance was defined as a p value <0.05. Variables influencing response and relapse were compared in logistic regression analyses. All statistical analyses were computed with SPSS software (SPSS, Inc., Chicago, IL, USA).

Results

One hundred and thirteen patients were splenectomized within 6 months and 192 patients within 1 year after diagnosis. The median time from diagnosis to splenectomy was 14 months (range, 1-384). The median pre-operative platelet count was 25×10^9/L (range, 1- 406×10^9/L) (Table 1).

Outcome after splenectomy

Of the 402 patients, 345 (86%) achieved a good response (66% CR and 20% PR), whereas the remaining 57 (14%) were refractory to splenectomy. Three of the 57 refractory patients subsequently achieved a PR spontaneously, within nine months after splenectomy (Table 2). Fifty-four out of the 57 refractory patients were treated after surgery. A good response was achieved in 27 out of 54 (50%) cases; at last follow-up, response was spontaneous or drug-maintained in 19 and 8 cases, respectively. No significant difference was observed in response when patients were subdivided into two groups: ≤16 years and >16 years old (Table 3).

Table 1. Patients' characteristics at the time of diagnosis and at the time of splenectomy.

Number of patients	402
Sex (female/male)	137/265
Median age at diagnosis (years)	34 (1-84)
Median age at splenectomy (years)	36 (6-85)
Time between diagnosis and splenectomy (months)	14 (1-384)
Median number of platelet at diagnosis ($\times 10^9$/L)	16 (1-100)
Median number of platelet at splenectomy ($\times 10^9$/L)	25 (1-406)
Number of patients vaccinated	163 (40%)

Table 2. Response to splenectomy.

	Total	*> 16 years*	*< 16 years*	*p value*
Complete response (CR) + partial response (PR)	345/402 (86%)	323/378 (85%)	22/24 (92%)	0.39
Complete response	271/402 (66%)	253/378 (67%)	18/24 (75%)	
Refractory	57/402 (14%)	55/378 (14%)	2/24 (8%)	0.41
Relapsed	79/345 (23%)	74/323 (23%)	5/22 (23%)	0.39
Median time to relapse (months)	8 (2-236)	7 (2-236)	130 (5-215)	0.98
Relapses 48 months from splenectomy	80%			

Table 3. Clinical outcome of refractory patients.

	Total	*> 16 years*	*< 16 years*	*p value*
Late spontaneous response	3/57 (5%)	3/55 (5%)	0/2	0.73
Further medical therapy	54/57 (93%)	52/55 (94%)	2/2	0.73
Good response to medical therapy	27/54 (50%)	25/52 (48%)	2/2	0.14
Spontaneously maintained	19/27 (70%)	17/25 (68%)	2/2	1
Drug-maintained	8/27 (30%)	8/25 (32%)	0/2	1

Seventy-nine out of the 345 (23%) responsive patients (CR+PR) relapsed, most of them (80%) within 48 months of the splenectomy, with a median time to relapse of 8 months (range, 2-236) (Figure 1). Sixty-eight out of these 79 (86%) patients were

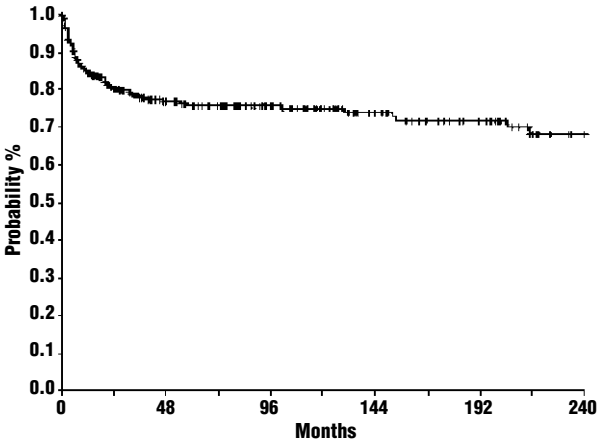

Figure 1. Kaplan-Meier estimate of thrombocytopenia-free survival. The estimated curve for all the patients shows a slowing relapse-rate during the first 48 months and a plateau at a 75% remission rate. The median follow-up was 92 months (range, 1-502), with a median follow-up after splenectomy of 57 months (range, 1-498).

Table 4. Clinical outcome of relapsed patients.

	Total	*> 16 years*	*< 16 years*	*p value*
Further medical therapy	68/79 (86%)	63/74 (85%)	5/5	0.35
Good response to medical therapy	46/68 (68%)	43/63 (68%)	3/5	0.70
Spontaneously maintained	27/46 (59%)	24/43 (56%)	3/3	0.19
Drug-maintained	19/46 (41%)	19/43 (44%)	0/3	0.13

treated. A good response was achieved in 46 out of 68 (68%) cases; at the last follow-up, response was spontaneously or drug-maintained in 27 and 19 cases, respectively. Again no significant difference was observed in relapse when patients were subdivided into groups ≤16 years and >16 years old (Table 4). The median follow-up was 92 months (range, 1-502), with a median follow-up after splenectomy of 57 months (range, 1-498). In 6 (1.5%) patients, perioperative infections, most often pneumonia, occurred. In 33 (8%) patients (11/33 had been vaccinated) infective complications occurred during follow-up. All infections were easily controlled and no case of overwhelming pneumococcal septicemia was observed. During follow-up, 12 (2%) patients experienced thrombosis, which was fatal in 3 cases although platelet counts were normal at the onset of complication. A neoplasm occurred in 13 (3%) patients. Three patients out of 402 (0.7%) died of hemorrhage (all intracranial hemorrhage) at 14, 105 and 139 months after splenectomy. Only one of

them was aged <60 years, and all had refractory severe thrombocytopenia (<30×10⁹/L). These patients represent 6% of the refractory subgroup.

Prognostic factors for post-splenectomy outcome

The correlations between sex, age at diagnosis, age at splenectomy, time to splenectomy, number of treatments before splenectomy, platelet counts before and seven days after surgery and likelihood of response or relapse after splenectomy were studied.

By univariate analysis, patients who had either a complete or a partial response to splenectomy were significantly younger both when considered at diagnosis and at splenectomy (median age 32 vs 46.5 yrs, $p<0.0001$ and 35 vs 49 years, $p<0.0001$, respectively), were previously untreated or had been treated with only one drug ($p<0.0001$), had a higher platelet count at the time of splenectomy (27×10⁹/L vs 11×10⁹/L, $p<0.0001$), and had a higher post-splenectomy peak platelet count (437×10⁹/L vs 73×10⁹/L, $p<0.0001$) than patients who did not respond. By multivariate analysis, only the number of former therapies ($p<0.01$) and higher peak post-splenectomy platelet count ($p<0.00001$) were predictive of a favorable response to splenectomy.

By univariate analysis, only higher post-splenectomy peak platelet count (455×10⁹/L vs 272×10⁹/L, $p<0.001$) correlated with a lower risk of relapse. The same parameter retained statistical significance ($p<0.001$) by multivariate analysis. The five-year actuarial relapse-free survival was 75% (Figure 1).

Forty-nine patients were considered refractory during follow-up, because their platelet count was <30×10⁹/L at the last follow-up regardless of whether they were on or off therapy. The age at diagnosis, age at splenectomy, time to splenectomy, number of treatments before splenectomy, platelet counts before and seven days after surgery were considered in multivariate analysis to distinguish this subset of patients from the others. Patients receiving more than one treatment before splenectomy (≤1 vs ≥2, $p=0.048$), with a lower platelet count at the time of splenectomy (18×10⁹/L vs 30×10⁹/L, $p=0.004$) and lower post-splenectomy peak platelet count (125×10⁹/L vs 448×10⁹/L, $p<0.001$) were more likely to be refractory during follow-up after splenectomy.

Discussion

Immune thrombocytopenic purpura is considered one of the most common indications for splenectomy. However, the fear of complications such as severe infection, hemorrhage or thrombosis as well as the hope of a late remission may induce physicians to delay splenectomy in favor of other treatments, potentially able to induce a sustained response to thrombocytopenia. Among these alternative treatments, high-dose dexamethasone, anti-D and rituximab have been shown to be effective and relatively safe treatments for patients with chronic ITP,[12,20-22] although there are still few data on the long-term results of these drugs. To shed further light on the long-term efficacy and safety of splenectomy, as well as to identify pre and/or post-operative parameters predicting outcome, we performed a retrospective multicenter study on 402 patients who underwent laparotomic splenectomy for ITP. This is one of the largest studies with long-term follow-up reported so far.

Our data confirm the high efficacy of splenectomy at increasing the platelet count to safe levels in patients with chronic ITP, in agreement with what has been reported by other authors.[10,23-27] Eighty-six percent of our patients achieved a good response (CR+PR) after splenectomy. Relapse occurred in 23% of responders, in most cases within 4 years of the splenectomy. The long-term follow-up of our patients allows us to demonstrate the low risk of relapse more than 4 years after splenectomy, confirming the potential of splenectomy to provide long-term control of the disease. Kaplan-Meier analysis showed that the probability of maintaining response for five years after surgery was 75% (Figure 1). These data are, again, in agreement with those reported in the literature. Although in some studies relapses could be observed up to 16 years after splenectomy,[6,8,28,29] we observed only 9 relapses after 5 years. We have no data concerning the possible presence of accessory spleen in refractory and relapsed patients.

In our experience splenectomy seems to be the only treatment capable of producing a sustained response in at least two thirds of cases. Looking from the opposite perspective, however, splenectomy failed in almost 40% of our cohort, if we pool together relapsed and refractory patients (total, 133 cases). Most of them required further treatment(s), and 73 patients (55%) reached a sustained good response, either off or on treatment at the last follow-up. This means that splenectomy often converts refractory patients into responding ones, as already reported by other groups.[34-36] This, in turn, means that splenectomy does not seem to jeopardize the possibility of a second response in relapsing patients. Thus, the prevalence of a true failure after splenectomy is low in our cohort, as only 49 patients (12%) did not respond to any further treatment. Only three of them have since died of bleeding complications (6%).

Among 785 patients splenectomized for ITP reported in the literature,[5,6,8,29,30] only 4 (0.5%) have died from severe infection; 2 of them were not vaccinated. However, the true incidence of severe or fatal infections cannot be calculated because of the lack of long-

term observations and the absence of data on the incidence per patient per year in most of the studies. We observed neither post-operative deaths nor subsequent fatal infections in our cohort of patients, although only 40% of them were vaccinated. These data are, again, in agreement with what has been reported by most other authors.[8,31-33] Twelve patients experienced a thrombotic event during follow-up. This was fatal in three cases, in spite of a normal platelet count. Many factors have been suggested in the literature to have prognostic value, although none conclusively.

Younger age at the time of splenectomy has been suggested as a positive prognostic factor by several authors,[6,14,37-40] whereas others have not confirmed this observation.[41-43] Similarly, a higher post-splenectomy platelet count has been reported to be predictive of a better response by some authors,[14,40,43] in contrast with the findings of Mintz *et al.*[42] Najean *et al.* found the site of destruction of autologous ^{111}In-labeled platelets to be a prognostic parameter.[17] Julia *et al.*[44] performed a comprehensive evaluation of 61 different variables in a group of 138 patients, and found age, post-splenectomy platelet count and severity of hemorrhagic tendency to have predictive value.

We considered several pre- and post-splenectomy prognostic factors. In multivariate analysis, the number of pre-splenectomy treatments and the platelet count seven days after surgery were predictive of a favorable response. Only the platelet count seven days after surgery was predictive of relapse, even though we could not establish a cut-off platelet count that could predict the relapse. In the subset of 49 patients who were refractory during follow-up after splenectomy, more than one treatment before splenectomy, lower platelet count at the time of splenectomy and lower post-splenectomy peak platelet count resulted to be predictive of refractoriness. In conclusion, our study shows that splenectomy is a safe procedure, which potentially provides long-term disease control in approximately two thirds of patients with chronic ITP. The recently emerging wide use of laparoscopic splenectomy is likely to make this procedure even safer and therefore suitable for a larger number of patients. Further studies are required to establish whether surgery-sparing treatments of patients with chronic ITP, such as high dose dexamethasone, anti-D and anti CD20 immunoglobulins, have similar or even superior efficacy, risk and cost ratios as compared to splenectomy.

Appendix

The following members of the GIMEMA actively participated in this study: *A. Levis (Alessandria); G. Quarta (Brindisi); R. Giustolisi (Catania); M. Montanaro (Latina); A.T. Maiolo and A. Zanella (Ospedale Maggiore Milano); Rossi (Ospedale Luigi Sacco Milano); E. Pogliani (Monza); B. Rotoli (Napoli); A. D'Arco (Nocera Inferiore); S. Siragusa (Palermo); Loni (Pietrasanta); Andriani (Roma, S. Giacomo); I. Majolino (Roma, S. Camillo); Persiani (Roma Complesso Ospedaliero); M. Longinotti (Sassari); O. Epis (Sondalo); R. Fanin and F. Zaja (Udine); G. Pizzolo (Verona); F. Rodeghiero and M. Ruggeri (Vicenza).*

NV and TB gave substantial contributions to the conception and design of the study; MG, MGM, ST and MB were responsible for critical revision of the manuscript; AdV was responsible for the analysis and interpretation of data; TI and BG were responsible for data collection.

We thank Simona Soverini for her contribution to editing the manuscript. The authors declare that they have no potential conflicts of interest.

Manuscript received October 22, 2004. Accepted November 5, 2004.

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