Splenectomy as a curative treatment for immune thrombocytopenia: a retrospective analysis of 233 patients with a minimum follow up of 10 years

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ABSTRACT

The treatment of choice in steroid-resistant immune thrombocytopenia is still controversial due to the recent advent of new drugs (anti-CD20 antibodies and thrombopoietin mimetics) that have encouraged a generalized tendency to delay splenectomy. Consequently, it is extremely importance to define the efficacy and safety of splenectomy in the long term. We retrospectively analyzed the data of 233 patients affected by immune thrombocytopenia who underwent splenectomy between 1959 and 2001 in 6 European hematologic institutions and who have now a minimum follow up of ten years from surgery. Of the 233 patients, 180 (77%) achieved a complete response and 26 (11%) a response. Sixty-eight of 206 (33%) responsive patients relapsed, mostly (75%) within four years from first response. In 92 patients (39.5%), further treatment was required after splenectomy that was effective in 76 cases (83%). In 138 patients (59%), response was maintained free of any treatment at last contact. No significant association between baseline characteristics and likelihood of stable response was found. Overall, 73 (31%) and 58 (25%) patients experienced at least one infectious or hemorrhagic complication, which was fatal in 2 and 3 patients, respectively. A stable response to splenectomy was associated with a lower rate of infections (P=0.004) and hemorrhages (P<0.0001). Thrombosis developed in 18 patients (8%) and was fatal in 4. Splenectomy achieved a long-term stable response in approximately 60% of cases. Complications mainly affected non-responding patients and were fatal in a minority.

Introduction

Primary immune thrombocytopenia (ITP)[1] is an autoimmune disorder in which thrombocytopenia is caused both by increased peripheral platelet destruction and reduced bone marrow platelet production. In most cases, the production of IgG antibodies directed against platelet membrane glycoproteins is the main causative factor for platelet destruction. Circulating antibody-coated platelets are cleared by mononuclear phagocytic mass present in the spleen, liver and bone marrow.[2-4]

Corticosteroids are the standard first-line therapy of ITP, although durable responses are achieved in only 20-30% of cases.[5] Second-line treatment of ITP patients (at high risk for bleeding or symptomatic) is controversial.[6] Splenectomy has been shown to induce durable responses in a substantial proportion of patients, with an acceptable risk of complications, and was, therefore, long regarded as the gold standard for treatment of chronic ITP patients in need of second-line therapy.[2-5,7,8] However, the recent introduction of new drugs has offered new perspectives of treatment and has enhanced the generalized tendency to avoid or delay splenectomy. Rituximab has been proved to induce responses sustained at five years in approximately 20-30% of cases; its administration should be decided and managed with caution as severe infectious complications have been reported.[9-12] Thrombopoietin (TPO) receptor agonists (TPO-ra) are effective in the treatment of refractory ITP, although treatment has to be continued indefinitely.[13-16] The availability of these new drugs makes it particularly difficult to select the optimal second-line therapy. While the recently published international consensus report[6] left the choice to the discretion of the physician, depending on patients' characteristics and compliance, the American Society of Hematology panel of reviewers indicated splenectomy as the preferable second-line therapy.[8] In order to adequately consider the curative properties of splenectomy, and its risk/benefit ratio compared to available medical treatments, the description of long-term results of surgery becomes essential.

For this purpose, we describe the outcome of a large cohort of patients who underwent splenectomy for ITP, and who

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were observed for a minimum time of ten years, with particular focus on those patients who achieved a stable response during follow up.

Design and Methods

Study design and definitions

This was a retrospective, multicenter study that analyzed the outcome of 233 consecutive ITP patients who underwent open splenectomy between 1959 and 2001 in six European Hematology Centers and who were observed for a minimum of ten years. One hundred and twenty-nine out of 233 (55%) of these patients were previously reported in two different papers describing two separate experiences: one collected in a single-center Swedish study of 61 ITP patients (48 patients, 78%),[17] and one in a multi-center Italian study of 402 patients (81 patients, 20%).[18] These cases were included in the present report after a significant lengthening of their observation time; moreover, some centers participating in the 2005 GIMEMA study were different to those included in the present report. In addition, 104 previously unpublished patients are also reported here. All patients were diagnosed with ITP according to standard criteria (isolated thrombocytopenia, normal or increased megakaryocyte count in an otherwise normal bone marrow aspirate and absence of other causes of thrombocytopenia).[1] The decision to splenectomize patients, even before 12 months from diagnosis, was at the physician's discretion, based on patients' characteristics. After splenectomy, patients were evaluated at one, three, six and twelve months, and at 12-month intervals thereafter. Response to all treatments (front-line corticosteroids, splenectomy and further medical therapy after surgery) was rated and classified according to current guidelines and terminology.[1] In particular, a complete response (CR) required a platelet count over $100x10^9$/L, while a response (R) consisted of a platelet count between 30 and $100x10^9$/L and at least doubling of the baseline count. Patients were classified as stable responders when response (R or CR) was never lost and maintained free of any treatment after splenectomy. Non-responding (NR) patients never achieved a platelet count of more than 30 x 10^9/L or did not double the baseline platelet count. ITP relapse following splenectomy was defined as a drop of platelet count below 30 x 10^9/L in previously responding patients. Hemorrhage was graded according to the WHO scale.[19] The study was approved by the ethics committees of participating centers. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Relapse-free survival (RFS) analysis was conducted according to the Kaplan-Meier method. The Mann-Whitney and χ^2 tests were used for comparisons between groups. All *P* values were two-sided and statistical significance was defined as $P<0.05$. Variables influencing stable response were compared in logistical regression analyses. All statistical analyses were computed with SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics and response to first-line treatments

Overall, 233 patients (66% females) underwent open splenectomy for ITP between 1959 and 2001 in six European Hematology Centers. Patients' characteristics are reported in Table 1. The median age at diagnosis was 30.5 years (range 1-74), with 24 patients (10%) under the age of 16 years, and median platelet count (PLT) was 15 x 10^9/L (range 2-100 x 10^9/L). Splenectomy was performed after failure of one or more therapies in all patients but 8 (3.5%), underwent splenectomy front-line.

First-line therapy was steroids-based in all 225 patients. Overall, 134 patients (59.5%) had a response (R), and 62 patients (27.5%) a complete response (CR). Median time from diagnosis to splenectomy was 13 months (range 0-254). Overall, 67 patients (29%) underwent splenectomy within 6 months from diagnosis, 44 patients (19%) between 7 and 12 months, 48 patients (20%) in the 13-24 month interval, and 74 patients (32%) more than two years after diagnosis. The median age at splenectomy was 33 years (range 6-74). The median pre-operative platelet count was 30 x 10^9/L (range 1-416 x 10^9/L). One hundred and eight (46%) patients were vaccinated against *Pneumococcus*, *Haemophilus influenzae B*, and *Meningococcus* before splenectomy. The rate of vaccination increased over time: among the 127 patients who were splenectomized before 1989, 37 were vaccinated (29%), while in the 106 patients splenectomized after 1989, 70 (66%) were vaccinated. The median follow up is 20 years (range 10-43). In 173 patients (74%), the date of last contact was up-dated until 2010 or later, or until death. The other patients were censored at the time of the last visit, which occurred before 2010.

Response to splenectomy

Of the 233 patients, 26 (11%) achieved a response (R) and 180 (77%) a complete response (CR), for an overall response rate of 88%, whereas the remaining 27 patients (12%) never had a response. Sixty-eight of 206 (33%) responsive patients relapsed after a median time from first response of 15 months (range 1-255) (Table 2). In relapsing cases, no data are available concerning the possible pres-

Table 1. Patients' characteristics.

Characteristics	
N. of patients	233
Male/female, n. (%)	79 / 154 (34% / 66%)
Median age at diagnosis, yr (range)	30.5 (1-74)
Median PLT count at diagnosis, $x10^9$/L (range)	15 (2-100)
Response to front-line corticosteroids*, n. of patients (%)	
CR	62 (27.5%)
R	72 (32%)
NR	91 (40.5%)
N. of patients who underwent splenectomy:	
Front-line	8 (3.5%)
Second-line	123 (53%)
> 2 previous therapies	102 (43.5%)
Median age at splenectomy, yr (range)	33 (6-74.3)
Median PLT count at splenectomy, $x10^9$/L (range)	30 (1-416)
Median time from diagnosis to splenectomy, mos (range)	13 (0-254)
Median follow up from splenectomy to last contact, years (range)	20 (10-43)
N. of patients with prophylactic vaccination	108 (46%)

**225 patients received corticosteroid treatment before splenectomy.*

ence of accessory spleen. Relapses occurred within 12 and 48 months from splenectomy in 50% and 75% of cases, respectively. After ten years of follow up, only 4 sporadic relapses were observed. The relapse rate was significantly lower in CR patients compared to R patients (27% *vs.* 73%, respectively; *P*<0.001). Median time to relapse was also longer for CR patients (20.5 *vs.* 12.1 months; *P*=0.05). The 20-year actuarial relapse-free survival was 67% (95%CI: 61.3-74.1%) for all responding patients, 73% (95%CI: 66.2-79.5%) for CR patients and 27% (95%CI: 10-43%) for R patients (*P*<0.001) (Figure 1).

Overall, in 95 patients response to splenectomy was not satisfactory because of relapse (n=68) or lack of response (n=27) (Table 3). In 3 relapsing patients a spontaneous response was observed. In the remaining 92 patients, further treatment was required after splenectomy because of a platelet count below 30 x 10^9/L or bleeding. A response was achieved in 76 of 92 (83%) cases. Response rate was not affected by the type of response to splenectomy, with non-responding and relapsing patients responding to further treatment in 89% and 81% of the cases, respectively (*P*=0.19).

At last contact, 138 patients (59%) were in response (95%CR: 131 patients) without any additional treatment following splenectomy. Three patients (1%) had gained a spontaneous response after initial relapse. Response was drug-maintained in 25 patients (11%) and chronic therapy consisted in low-dose corticosteroids (n=15; 60%), TPO-ra (n=9, 36%) or azatioprine (1 patient). In 51 patients (22%), a response was maintained after discontinuation of post-splenectomy treatments. Sixteen patients (7%) never obtained a platelet count over 30 x 10^9/L (Figure 2).

Prognostic factors for stable responses to splenectomy

Overall, 138 responsive patients never relapsed during the observation time and maintained the response, free of any treatment, at last contact (stable responders).

The likelihood of achieving a stable response to splenectomy was correlated with several prognostic factors, including sex, response to front-line corticosteroids therapy, time to splenectomy, age and platelet count at splenectomy. By univariate analysis, none of these parameters significantly correlated with the probability of achieving a stable response. Time to splenectomy was analyzed both as a continuous variable and after patients' stratification in 4 groups, depending on the interval from diagnosis to splenectomy. No differences in terms of stable responses were observed. In particular, 111 patients (48%) received splenectomy within the first year from diagnosis, achieving a stable response in 65 cases (58.5%). Among the remaining 122 patients, a stable response was achieved in 73 cases (59.8%; P=0.89). Also, age at splenectomy was analyzed as a continuous variable and after dividing patients into 3 categories: patients aged under 40 years (n=148, 64%), patients aged 40-60 years (n=61, 26%) and patients aged over 60 years (n=24, 10%). Patients achieving a stable response were 61.5%, 61.6% and 41.7% in the three groups, respectively (*P*=0.14). Multivariate logistical regression analysis confirmed that none of the variables was able to predict a stable response.

Table 2. Response to splenectomy.

	No response (NR)	Response (R) (PLT 30-100x10^9/L)	Complete response (CR) (PLT >100x10^9/L)	*P*
N. of patients (no=233) (%)	27 (12%)	26 (11%)	180 (77%)	n.a.
N. of patients (%) who relapsed	n.a.	19/26 (73%)	49/180 (27%)	<0.001
Median time to relapse, months (range)	n.a.	12.1 (1-130)	20.5 (1-255)	0.05

n.a.: not applicable.

Table 3. Outcome of refractory patients.

	Overall	Non-responding	Relapsing
N. of patients (%)	95/233 (41%)	27/233 (11.5%)	68/206 (33%)
Spontaneous response, n. (%)	3 (3%)	0	3 (4%)
Further medical therapy, n. (%)	92/95 (97%)	27/27 (100%)	65/68 (95%)
Median n. of therapies, (range)	2 (1-12)	2 (1-12)	2 (1-11)
Response to post-splenectomy treatments, n. of patients (%)			
CR (PLT>100x10^9/L)	53/92 (58%)	16/27 (59%)	37/65 (57%)
R (30-100x10^9/L)	23/92 (25%)	8/27 (30%)	15/65 (23%)
NR (<30x10^9/L)	16/92 (17%)	3/27 (11%)	13/65 (20%)
N. of patients needing a continuative treatment to maintain a response (R or CR) (%)	25/92 (27%)	9/27 (33%)	16/65 (25%)

Table 4. Long-term complications.

	N. of events (%)	All patients (233)	Refractory patients (95)	Stable responders (138)	*P*
Infections					
Lung	63 (40%)	41 (18%)	23 (24%)	18 (13%)	0.03
Gastrointestinal/ urogenital/skin	41 (26%)	21 (9%)	13 (14%)	8 (6%)	0.06
Other (minor recurrent infections)	53 (33%)	28 (12%)	14 (14.5%)	14 (10%)	0.31
Fatal (sepsis)	2 (1%)	2 (1%)	1 (1%)	1 (0.7%)	1.00
Overall	159 (100%)	73 (31%)	40 (42%)	33 (24%)	0.004
Thrombosis					
Stroke/TIA	4 (15.5%)	4 (2%)	2 (2%)	2 (1.4%)	1.00
DVT/PE	12 (46%)	8 (3.5%)	4 (4%)	4 (2.8%)	0.71
AMI	6 (23%)	6 (2.5%)	4 (4%)	2 (1.4%)	0.22
Fatal (2 strokes + 2 AMI)	4 (15.5%)	4 (2%)	3 (3%)	1 (0.7%)	0.30
Overall	26 (100%)	18 (8%)	10 (10.5%)	8 (6%)	0.21
Hemorrhage					
Grade 1-2	221 (92%)	47 (20%)	41 (43%)	6 (4%)	<0.0001
Grade 3-4	17 (7%)	16 (7%)	13 (14%)	3 (2%)	<0.0001
Fatal (intracranial)	3 (1%)	3 (1.2%)	3 (3%)	0 (0%)	<0.0001
Overall	241(100%)	58 (25%)	49 (51.5%)	9 (6.5%)	<0.0001

TIA: transient ischemic attack; DVT: deep vein thrombosis; PE: pulmonary embolism; AMI: acute myocardial infarction.

Incidence of post-splenectomy complications

Post-splenectomy complications are detailed in Table 4. Overall, 73 patients (31%) experienced at least one infectious complication, for a total of 159 events, most often pneumonia (40%). Forty-three of these patients (59%) had received prophylactic vaccinations. Median time from splenectomy to first infection was 35 months (range 0-355). Infectious complications were significantly more frequent in refractory patients compared to stable responders (P=0.004) but were comparable (P>0.05) in vaccinated and non-vaccinated patients. Two fatal infectious episodes (sepsis and intestinal infection) occurred, after 176 and 318 months from splenectomy. Both patients were stable responders to splenectomy and were 78 and 80 years old, respectively, at the time of death.

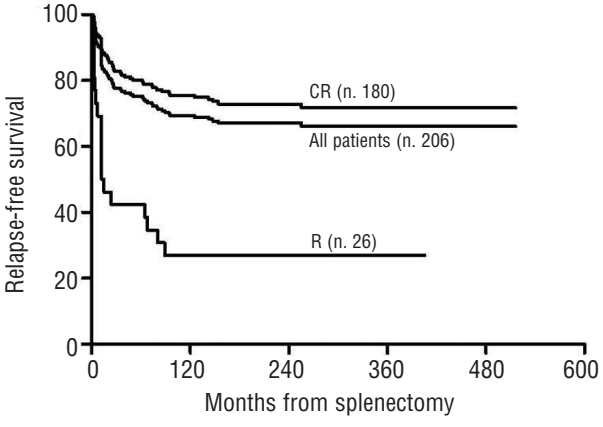

Figure 1. Relapse-free survival (RFS). RFS was 67% (95%CI: 61.3-74.1%) for all responding patients, 73% (95% CI: 66.2-79.5%) for CR patients and 27% (95% CI: 10-43%) for R patients (P<0.001). CR: complete response (PLT>100 x 10^9/L), R: Response (PLT 30-100 x 10^9/L).

Eighteen patients (8%) developed 26 thrombotic events, after a median time from splenectomy of 36 months (range 0-363). Median age at thrombosis was 56 years (range 23-81). In 4 cases, thrombosis was fatal. All patients were aged over 75 years and in response (3 CR, 1 R).

Two hundred and forty-one bleedings occurred in 58 patients (25%) after a median time from splenectomy of 15 months (range 0-300). Among the 241 recorded hemorrhagic events, only 20 (8%) were severe. Three patients died for intracranial bleedings. At the time of the fatal hemorrhage, all patients were aged over 75 years and platelet count was below 30 x 10^9/L. As expected, a stable response to splenectomy was associated with a lower rate of hemorrhages (P<0.0001).

Overall, 37 (16%) patients have died, at a median age of 74 years (range 43-87). Causes of death were: neoplasia (n=6, 16%), other unrelated causes (including liver or pancreatic failure, epileptic crisis, diabetes complications) (n=14, 38%). Death could be strictly related to ITP in the 3 cases of fatal bleeding. Four patients died for thrombotic events and 2 for sepsis. In 8 cases, causes of death could not be reported. However, these 8 deaths occurred after a significant time from splenectomy (median 173 months; range 116-366), and all patients but one were in response and out of treatment.

Discussion

Second-line therapy of steroid-resistant ITP is increasingly controversial. Despite the fact that time-honored data consistently show that splenectomy is able to induce a stable response in a substantial fraction of patients,[17,18,20] the recent availability of new second-line drugs, such as rituximab or TPO mimetics, has offered the possibility of a medical treatment not burdened by surgery-related early and late complications. For this reason, both patients and physicians are increasingly reluctant to proceed to splenec-

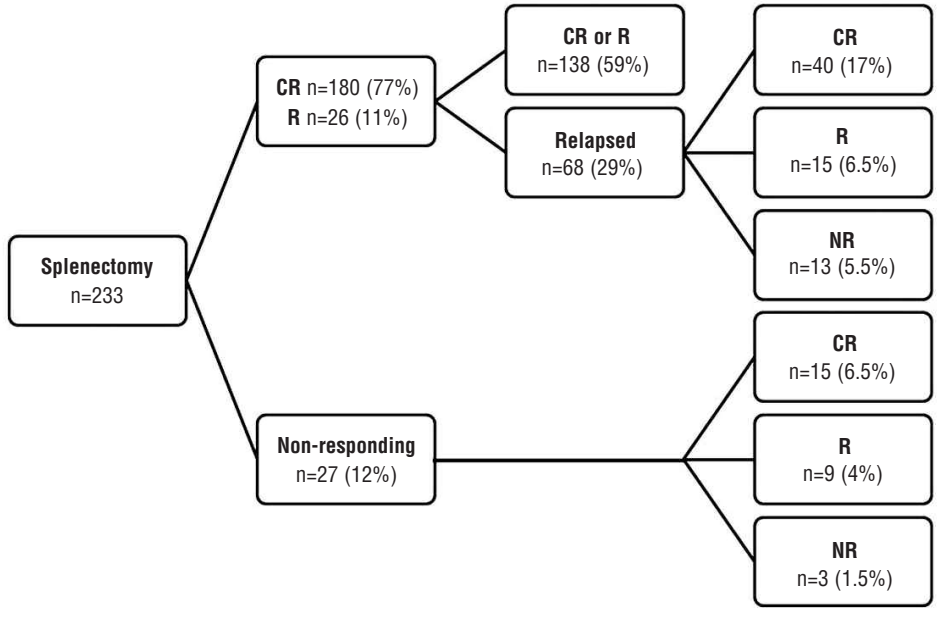

Figure 2. Response to splenectomy and status at last contact. All percentages have been calculated out of 233 patients. All refractory(relapsing and non-responding) patients but 3 received further immunosuppressive treatment.

tomy as second-line therapy, and there is still lively international debate on the therapeutic algorithm of patients failing first-line corticosteroid treatment.[6,8,21]

In this study, we report the largest cohort of ITP patients that was observed for such a long period of time (minimum 10 years) after splenectomy, with a particular focus on stable responders. Unlike previously published experiences, in the present paper, response to treatments was rated and classified according to current guidelines and terminology;[1] this might explain some possible differences in patients' outcome. However, our results confirm the excellent response rate to surgery, with 88% of the patients achieving a response. We also confirm that approximately one-third of the initially responding patients may finally relapse, and that relapse occurs early, mostly within the first four years, with only sporadic relapses after a 10-year follow up. So far, splenectomy represents the only treatment that is potentially curative in a significant fraction of patients, with stable responses in approximately 60% of cases. Indeed, after rituximab administration, only 20-30% of patients maintain the response at five years,[12] with no conclusive data concerning the best timing of its use.[9,21,22] TPO-ra treatment is also effective but needs continuous administration. Moreover, no definitive safety data are available in the use of these agents over 5-6 years.

Despite the large cohort of patients analyzed, no predictors of a stable response were identified among the most commonly evaluated variables,[7] probably due to the fact that most of these features lack a stringent biological or pathogenetic basis. On the other hand, the achievement of a CR after splenectomy was the only factor that identified patients at lower risk of subsequent relapse. In this regard, other prognostic parameters should be explored before splenectomy, particularly radio-labeled platelet scans.[23,24]

The analysis of the 95 patients (41%) who did not achieve a stable response showed that, despite most of them needing multiple lines of further treatments, a new response was achieved in 83% of the cases, confirming that splenectomy can convert refractory patients into responding ones, and does not exclude the possibility of a second response in relapsing patients.[19,20] Indeed, only 16 patients (7%) did not respond to any further treatment and only 3 (1%) died of bleeding complications. Overall, refractory disease correlated to a higher incidence of infectious complications (42 *vs.* 24% in stable responders; P=0.004), probably due to the need for extensive immunosuppressive treatments (Table 3). Indeed, among the 73 patients with infections, the median number of post-splenectomy therapies was 1 (range 0-12; average 1.96) *versus* 0 (range 0-9; average 0.7; P=0.0002) in the remaining patients. Patients with infections received a significantly higher number of therapies also if both pre- and post-splenectomy treatments were considered altogether (median number of treatments 3, range 1-14; average 3.78 *vs.* 2, range 0-11; average 2.28; P=0.0002 in patients with no infections). Hemorrhagic complications were significantly lower in responsive patients (51.5% *vs.* 6.5%; P<0.001). Also, thrombosis occurred slightly more frequently in patients with refractory/relapsed disease, confirming a higher tendency of ITP patients to develop thrombotic complications compared to the normal population. However, splenectomy did not seem to increase the rate of thrombotic complications, compared to medical treatments.[25-30]

Overall, complications were less frequent than in previously reported cohorts, which were fatal in a minority of the cases and mainly affected non-responding patients.[27,29] It is likely that the low incidence of complications in our series was due to the early adoption of splenectomy (median time from diagnosis to surgery 13 months), which meant major pre-splenectomy toxicities were avoided and which was probably justified by the fact that rituximab and TPO-ra were not yet available. Early adoption of splenectomy might also have masked some spontaneous remission, which could have been achieved with a longer follow up even without surgery. However, we could not find any correlation between time to splenectomy and stable responses.

Although studies comparing splenectomy and medical treatments second-line are lacking, our retrospective data indicate that splenectomy should be still considered the therapeutic treatment of choice with the higher curative potential in eligible patients with chronic disease. Studies to identify baseline features, particularly with radio-labeled platelet scans, which might identify those patients most likely to achieve a stable response are needed for a proper selection of optimal candidates for splenectomy.

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