Role of splenectomy for immune thrombocytopenic purpura (ITP) in the era of new second-line therapies and in the setting of a high prevalence of HIV-associated ITP

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Background. New agents are being used as second-line treatment for immune thrombocytopenia (ITP) and have brought into question the relevance of splenectomy for steroid-resistant ITP.
Methods. We retrospectively analysed 73 patients who underwent splenectomy for ITP at our institution over an 11-year period. The median follow-up period was 25 months; patients with follow-up of <1 month were excluded. The outcomes of splenectomy were compared in HIV-positive v. HIV-negative patients.
Results. The rate of complete response was 83%, and response was sustained for at least 1 year or until latest follow-up in 80% of patients. Twelve patients were HIV-positive. Splenectomy was laparoscopic in 43 patients (62%) with an overall 16% complication rate. The 90-day mortality rate was 1.38%. There was no statistically significant difference in response or complication rate in the HIV-positive patients. There was a statistically significant (p=0.017) poorer response to splenectomy in the patients with steroid-resistant ITP.
Conclusion. Splenectomy is effective and safe irrespective of HIV status and remains an appropriate second-line treatment for ITP. Further research is needed to corroborate our finding of lower response in patients who are steroid-resistant, as this might be a subgroup of patients who may benefit from thrombopoietin agonists as second-line therapy.

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Immune thrombocytopenia (ITP) is an autoimmune disorder characterised by immunological destruction of platelets (primarily due to the production of platelet-reactive autoantibodies), along with an inability to compensate by increasing production of platelets as a result of immune-mediated megakaryocyte damage and dysfunction.[1] In ITP a platelet count of >30 × 10^9/L is generally the goal of treatment, but the decision to treat should be based on the patient's risk of bleeding, side-effects of medication and patient preference.[2] First-line treatment for ITP is with oral glucocorticoids. Splenectomy has traditionally been employed as second-line treatment, but newer drugs such as rituximab and thrombopoeitin (TPO) agonists have brought the role of surgery into question.

Thrombocytopenia is a common problem in HIV owing to cross-reactivity of antibodies to HIV with glycoprotein GPIIb and/or GPIIIa on the platelet surface or talin within the platelet cytoskeleton.[3,4] Treatment of HIV-associated ITP is with antiretroviral therapy (ART). The use of glucocorticoids is common but is based purely on expert opinion, since there are no trials of glucocorticoids in HIV-associated ITP. Zidovudine was the first antiretroviral to show response in treating HIV-related thrombocytopenia. However, owing to the risk of generating resistance with monotherapy, combination antiretroviral therapy (cART) is preferred (not necessarily including zidovudine) and has been shown to be as effective.[5] Splenectomy for ITP in HIV has been reported mainly in the pre-ART era and its role in HIV-associated ITP in the current era of ART needs to be studied further.[6]

Splenectomy has been reported to have a complete response (CR) rate of 85%, but up to 25% of patients relapse during a 5-year period.[7-9] The most concerning late complication of splenectomy is overwhelming post-splenectomy infection, the risk of which is estimated to be 0.23 - 0.42% per year, with a lifetime risk of 5%.[10]

Rituximab is a monoclonal antibody directed against epitopes in B lymphocytes and has been studied in treatment-resistant ITP, but has shown poorer outcomes compared with splenectomy, with a 4.4-fold lower probability of CR at 1 year and a response rate of only 20% at 5 years.[11,12] In a systematic review of 306 ITP patients treated with rituximab, 3.7% experienced severe or life-threatening events and 2.9% (9 patients) died.[13]

More recently, recognising that platelet underproduction and megakaryocyte dysfunction play a substantial role in the pathophysiology of ITP, TPO receptor agonists such as romiplostim and eltrombopag have become available. They are costly, and as they have little influence on the immune destructive process they need to be taken indefinitely. These TPO agonists have nevertheless been associated with responses (platelet count >50 × 10^9/L at 6 - 8 weeks) in up to 92% of patients, continuing as long as treatment is maintained.[14] TPO agonists are well tolerated, with a 5-year follow-up study for romiplostim reporting an 8% rate for serious adverse events and 5% mortality.[14] Rituximab and TPO agonists have not yet been studied systematically in HIV-associated ITP.

Considering these non-invasive treatment options, the role of splenectomy continues to be debated. We therefore undertook to investigate response rates to splenectomy in patients with ITP, some of whom were HIV-positive and who had been pretreated with steroids in an era when cART was available. To our knowledge this is the first study reporting outcomes after splenectomy in Africa, in a context of high infectivity with HIV.

Methods

Patient selection

Seventy-three consecutive patients who had undergone splenectomy for ITP during the period 1 January 2001 - 31 December 2011 were retrospectively identified using surgical and histological records. Patients with primary ITP as well as patients with secondary ITP due to HIV, hepatitis and connective tissue disease were included, but patients with lymphoproliferative disease were excluded. Patients who had platelet counts lower than response ($<30 \times 10^9$/L) on high-dose steroids or who relapsed after steroid treatment and weaning were referred for splenectomy.[2] All patients met the diagnostic criteria reported by the American Society of Hematology Practice Guidelines.[2] This record review was approved by the ethics committee of the University of Cape Town.

The medical records of these patients were analysed for their clinical and laboratory data with regard to diagnosis and initial management, comorbidities, response to treatment, recurrence of thrombocytopenia, salvage therapy, operative type of splenectomy, follow-up platelet counts and complications following splenectomy.

After splenectomy the platelet counts at 1 month, 6 months, 1 year or at latest follow-up (up to September 2013) were recorded to assess response. All platelet counts were checked and if there was any platelet count in the follow-up period $<100 \times 10^9$/L this was specifically noted. The correlations between HIV status, hepatitis B positivity, antinuclear antibody (ANA) positivity (signalling connective tissue disease), gender, age and the likelihood of a CR after splenectomy were analysed.

Definitions

Response to medical treatment

Steroid resistance. Platelet count of $>30 \times 10^9$/L never recorded despite treatment with prednisone at a minimum dose of 1 mg/kg for at least 6 weeks.

Steroid dependence. Platelet count dropping to $<30 \times 10^9$/L within 6 months from weaning off steroids.

Response to splenectomy

We used the definitions of response as previously described in the literature, with the addition of 'sustained response' as defined.[7]

CR. Achievement and maintenance of a platelet count $>100 \times 10^9$/L for all measurements 30 days or longer after splenectomy and with no additional treatment for ITP, except for the tapering of glucocorticoids.

Partial response. A platelet count of $>30 \times 10^9$/L for all measurements 30 days or longer after splenectomy, with or without other treatment, excluding patients who qualify for CR. All patients who relapsed after initially achieving a normal platelet count were therefore considered to have a partial response.

No response. The platelet count never increased to $>30 \times 10^9$/L for any measurement 30 days or longer after splenectomy.

Sustained response. A platelet count of $>100 \times 10^9$/L for all measurements for at least 1 year or until last follow-up if follow-up lasted longer than 1 year.

Definition of hepatitis B-positive and ANA-positive

Patients were regarded as having chronic hepatitis B if the surface antigen was positive or if there was a recorded viral load on polymerase chain reaction on the National Health Laboratory Service system. Over the time period of the study, ANA was reported as positive if it was above the laboratory reference range.

Statistics

Microsoft Excel 2010 (Microsoft Corporation, USA) was used for database and data input. Statistical analyses were performed using STATA statistical software, version 12.0 (STATA Corporation, USA). Descriptive characteristics of the patients were analysed, and means (standard deviations) were used for normally distributed data and medians plus interquartile ranges (IQRs) for non-normally distributed data. Survival analysis was based on the Kaplan-Meier estimate and the log-rank test was used for survival comparisons. To assess the association between variables and CR, the prevalence ratio (PR) was calculated (since the prevalence of the 'CR' was >10% and in this situation odds ratios (ORs) overestimate the magnitude of risk) and the p-value was calculated by logistic regression. Continuous and categorical variables were compared using the χ^2 test, and when the expected frequencies in any cell of the contingency tables were <5 Fisher's exact test was used. All p-values were considered significant at $p<0.05$. To compare means, if the data were normally distributed (tested by doing a Shapiro-Wilk test), a t-test was performed; if the data were non-normally distributed, a Wilcoxon-Mann-Whitney test was performed.

Results

Patient characteristics (Table 1)

The median age at splenectomy was 33 years (IQR 22 - 44). There was a female preponderance with a ratio of 3:1; 56 patients (77%) were female. Twelve patients were HIV-positive (16%); in 15 the HIV status was unknown. Of the 36 patients for whom the hepatitis B status was known, 5 were positive (14%). Two patients were pregnant, and one patient underwent splenectomy while pregnant.

Table 1. Patient characteristics at diagnosis (N=73)

Variables	
Age (yrs), median (range)	33 (16 - 70)
Gender, *n* (%)	
Male	17 (23)
Female	56 (77)
HIV status, *n* (%)	
Positive	12 (16)
Negative	46 (63)
Unknown	15 (21)
Hepatitis B status, *n* (%)	
Positive	5 (7)
Negative	31 (42)
Unknown	37 (51)
ANA, *n* (%)	
Positive	19 (26)
Negative	20 (27)
Unknown	34 (47)
Comorbidities, *n* (%)	
Diabetes	8 (11)
SLE	9 (12)
TB	10 (14)

SLE = systemic lupus erythematosus; TB = tuberculosis.

Medical treatment prior to splenectomy

Of the patients for whom details regarding treatment prior to splenectomy were available (n=66), 54 (82%) were steroid dependent and 12 (18%) were steroid resistant. All patients had received glucocorticoids at a dose of at least 1 mg/kg/d, and in 27 patients the dose had been 2 mg/kg/d. Prior to splenectomy, azathioprine was prescribed to 23 patients (33%) (Table 2).

HIV-positive population

Of the HIV-positive patients, 7 were female and 5 male and the median age was 36 years (IQR 27 - 40). The median CD4 count at diagnosis of ITP was 253 cells/μL (IQR 163 - 458); 7 (58%) patients had counts <300 cells/μL, 2 had counts >700 cells/μL, and 1 patient had a count of 458 cells/μL. The CD4 count was unknown in 2 patients.

cART was given to 11 patients prior to splenectomy (for ITP regardless of CD4

Table 2. Treatments given and response type to glucocorticoids (*N*=66)

	n (%)
Response to oral steroids	
Steroid dependent	54 (82)
Steroid resistant	12 (18)
Treatment	
Prednisone	66 (100)
Azathioprine	23 (33)
Polygam	6 (9)
IVI dexamethasone	5 (7)
Plasmapheresis	5 (7)
Cyclophosphamide	2 (3)
Dapsone	1 (1)
Danazol	1 (1)

IVI = intravenous infusion.

count) for a median duration of 12 months (range 2 - 60). All patients on cART were on a regimen comprising two nucleoside reverse transcriptase inhibitors (a combination of two of zidovudine, lamivudine and stavudine) and a non-nucleoside reverse transcriptase inhibitor (either nevirapine or efavirenz). Three patients were being treated with cART prior to developing ITP and the other 9 patients developed ITP and were subsequently put onto cART (*n*=7) or AZT monotherapy (*n*=2).

Operative information

Of the 69 patients for whom operative details were available, 26 patients (38%) had their splenectomy by open laparotomy and 43 (62%) by laparoscopy, with an increasing number of laparoscopic procedures performed in the later years. The median platelet count at splenectomy was 187 × 10^9/L (IQR 125 - 172). Patients were actively treated preoperatively with platelet transfusions (*n*=4), intravenous dexamethasone (*n*=4) and intravenous immunoglobulin (*n*=4) to raise the platelet count in the short term.

The median time from presentation to splenectomy at our institution was 4.7 months (IQR 2.6 - 13) (HIV-negative and positive). In the HIV-positive population it was 3.2 months (IQR 2.1 - 5.9) (*p*=0.138). This short time to splenectomy is explained by the fact that many patients were referred after initially being managed at a secondary-level hospital. The time from initial diagnosis could not be established in 15 patients.

Median time to discharge was on the 3rd postoperative day (IQR 2 - 4 days); for HIV-positive patients it was day 3 (IQR 2 - 3 days; *p*=0.5). The intraoperative complication

Table 3. Operative information

Type of splenectomy (*N*=69), *n* (%)	
Open laparotomy	26 (38)
Laparoscopic	43 (62)
Intraoperative complications (*N*=60*), *n*	
Mortality	-
Adhesions (converted to open splenectomy)	3
Bleeding (converted to open splenectomy)	2
Conversion to open splenectomy, reason not found	2
Postoperative complications (*N*=60*), *n*	
Death	1
Intra-abdominal sepsis	5
Wound infection	2
Thrombosis	2
Drip site sepsis	1
Subacute small-bowel obstruction	1

*Data missing for 9 patients.

rate for splenectomy was 10% and included conversion to open splenectomy for bleeding (*n*=2), and intra-abdominal adhesions (*n*=3). There was no intraoperative mortality.

There were 11 postoperative complications in 10 patients (16% all-cause complication rate). The most common postoperative complication was infection (Table 3). Two patients developed postoperative thrombosis: one patient presented 8 days after surgery with a pulmonary embolism, and the other developed thrombus in the mesenteric vein. Both patients had normal platelet counts at presentation with thrombosis.

Operative bleeding in two patients was associated with surgical difficulties (damage to abdominal vessels) and was not spontaneous or secondary to usual surgical technique; in both, there were no further complications after conversion to open splenectomy.

There was no statistically significant difference in postoperative complications according to method of splenectomy. The complication rate in the HIV-positive patients was non-significantly higher than in the HIV-negative patients (18% and 16%, respectively; *p*=0.59).

There was one postoperative death at 10 weeks post surgery, giving a 90-day mortality rate of 1.38%. This patient was HIV-positive, had an uncomplicated splenectomy and was discharged on day 2 post operation. She presented again 10 weeks later in septic shock (with an unidentified organism) and required inotropic support and dialysis. Her platelet count remained <30 × 10^9/L and she died within 24 hours of admission. Of note, this patient had received the 23-valent pneumococcal vaccine as an inpatient the day before her surgery.

Response to splenectomy

Patients were followed up for a median period of 25 months from splenectomy (IQR 12 - 69). Among the patients for whom platelet counts were known for at least a month and could be included in the analysis (*n*=65), the CR rate was 83% (*n*=54); 11% (*n*=7) had a partial response and 6% (*n*=4) no response. Details for up to 1 year were known for a total of 55 patients, revealing that the sustained response rate was 80% (*n*=44). At 1 year there was no statistically significant difference between HIV-positive and negative patients' platelet counts (*p*=0.69). The group of patients for whom HIV status was unknown had a 90% CR that was non-statistically different from those with known HIV status (*p*=0.46).

Eleven patients did not have a CR. Of these, 7 had a partial response (the median platelet count at 1 year was 113 × 10^9/L, but response was defined as partial owing to fluctuation) and 4 had no response to splenectomy. All 11 patients were retreated with steroids, and 4 were treated with azathioprine. Of the 7 patients with a partial response, 6 later achieved platelet counts of >100 × 10^9/L and were weaned off all therapies.

Predictors of response

For an association between variables and CR, a PR was calculated (Table 4). Only one variable showed a statistically significant poorer response to splenectomy. This was steroid-resistant ITP (PR 0.62; *p*=0.003).

Morbidity and mortality

Seven patients (5 males and 2 females) died in the follow-up period. The total patient follow-up time was 3 710 months, with a mortality rate of 1.89/1 000 patient months (confidence interval (CI) 0.90 - 3.96). Six patients with recorded deaths were HIV-negative and one was HIV-positive. There was no statistically significant difference in mortality rate in the groups by gender (*p*=0.37) or HIV status (for the HIV-positive group 1.7 deaths/1 000 patient months and for the HIV-negative group 2.4 deaths/1 000 patient months; *p*=0.96).

There was a statistically significant difference in mortality rate (*p*=0.001) between

Table 4. Variables and rate of CR with calculated PRs and ORs

Variables	*N*	CR *n* (%)	PR	OR	CI (for OR)	*p*-value
Gender						
Male	16	12 (75)	0.88	0.5	0.11 - 2.76	0.44
Female	49	42 (85)				
HIV status						
Positive	12	9 (75)	0.89	0.58	0.11 - 4.23	0.38
Negative	43	36(84)				
Hepatitis B						
Positive	5	4(80)	1.05	0.78	0.06 - 43.7	0.61
Negative	29	22(76)				
ANA						
Positive	19	17 (89)	0.95	0.5	0.01 - 10.7	0.52
Negative	18	17(94)				
Diabetes						
Yes	8	7(88)	1.06	1.4	0.14 - 70.0	0.62
No	54	45(83)				
TB						
Positive	10	6(60)	0.69	0.21	0.03 - 1.36	0.06
Negative	55	48(87)				
Azathioprine						
Yes	23	17(74)	0.82	0.22	0.03 - 1.26	0.06
No	33	30(90)				
Steroid resistant						
Yes	11	6(54)	0.62	0.24	0.29 - 0.89	0.017
No	51	46(87)				
SLE						
Yes	8	6 (75)	0.89	0.59	0.09 - 6.9	0.42
No	55	46(84)				

TB = tuberculosis; SLE = systemic lupus erythematosus.

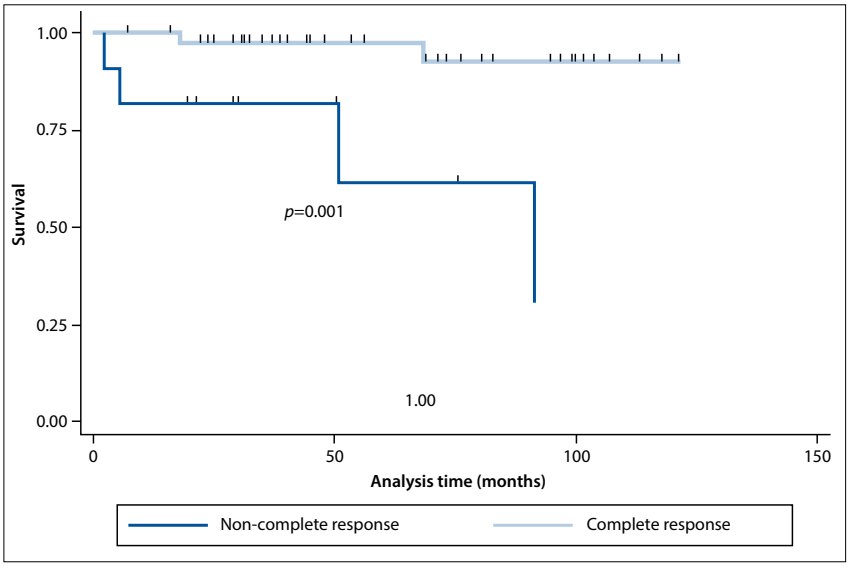

Fig. 1. Kaplan-Meier survival estimates by CR.

the group that had achieved CR following splenectomy (2 deaths; 0.87/1 000 patient months) and the group that had not had a CR (5 deaths; 13.6 /1 000 patient months) (Fig. 1).

Four deaths may have been directly related to the splenectomy: 3 were secondary to sepsis (being asplenic may have contributed to excess mortality risk from sepsis) and 1 from a cerebrovascular accident which may have been attributable to rebound thrombocytosis (this patient's platelet count was 1 214 × 10^9/L at the time of readmission). All four patients were on further immunosuppressive therapy (steroids or azathioprine), which may have contributed to their increased risk of sepsis. One death was related to the underlying disease (thrombocytopenia) and one unrelated and due to prostate cancer (Table 5). There was 100% mortality in the non-responders, with all four patients with no response to splenectomy dying in the follow-up period.

Discussion

In our analysis, CR was seen in 83% and was sustained in 80%, which is similar to that reported in the literature.[7,8,15] Of those who achieved partial response, with the addition of glucocorticoids and/or azathioprine 86% (*n*=6) later progressed to CR, which was maintained for the duration of follow-up. This is in keeping with other studies showing that a partial response is also consistent with a favourable long-term outcome.[7] In our experience, the CR rate to splenectomy (platelet count >100 × 10^9/L) and duration of response appear higher than that reported for rituximab and similar to that of the TPO agonists (with maintenance of treatment).[11,14] There was a 100% (*n*=4) mortality rate in the patients who showed no response following splenectomy; however, only one death was secondary to bleeding. Continued immunosuppression is likely to have contributed to their overall mortality.

In the HIV-positive patients, the CD4 count at diagnosis of ITP demonstrated the typical bimodal distribution showing ITP early in HIV with CD4 counts >700 × 10^6/L, and in late disease with CD4 counts <300 × 10^6/L. In our small (*n*=12) HIV-positive cohort the treatment response was favourable and outcomes were not significantly different from the HIV-negative cohort. These observations need to be confirmed in a larger population, but they are in keeping with the only large-scale study looking at splenectomy in HIV-associated ITP, where the response rate to splenectomy was 92% and a favourable long-term (6-month response) outcome was seen in 82%.[6] The complications, morbidity and mortality asso-

Table 5. Causes of mortality

Gender	Age, years	Months post splenectomy	Cause of death
Male	24	17	Pneumococcal sepsis
Male	70	6	Prostate cancer*
Female	50	5	CVA (rebound thrombocytosis)
Female	32	2.5	Sepsis (pathogen unknown)
Female	23	68	Sepsis (ruptured appendix)*
Female	26	91	Intracerebral haemorrhage (platelet count $<10 \times 10^9$/L)
Female	24	52	Unknown*

CVA = cerebrovascular accident.
*Patients with no response to splenectomy.

ciated with splenectomy were not statistically different in the HIV-positive compared with HIV-negative cohorts. While the complication rate in our cohort was slightly higher than previously reported, this is difficult to interpret since other publications did not define what they considered to be 'complications', while we included minor complications such as drip site sepsis.[2]

We speculate that the unfavourable response to splenectomy in patients with steroid-resistant disease is possibly due to greater megakaryocyte dysfunction, in addition to increased peripheral consumption. If proven, this could be an important finding as it may help to identify patients who would benefit from TPO agonists rather than pursuing measures that aim to decrease peripheral consumption.

Conclusion

The conclusions from this study are encouraging and support the view that because of its effectiveness, splenectomy should remain the second-line treatment for ITP in most patients, including HIV-positive patients. We have also identified a patient population with a statistically significant poorer outcome to splenectomy, and further research is needed to distinguish patients whose ITP is primarily due to peripheral consumption (the majority of patients with ITP), and who would therefore be likely to benefit from immunosuppression (such as glucocorticoids and splenectomy), from those whose ITP reflects megakaryocyte dysfunction predominantly and who would benefit from TPO agonists. This may be the first step towards generating more patient-specific, and mechanism-driven, treatment strategies for the second-line treatment of ITP.

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