How I treat immune thrombocytopenia (ITP): the choice between splenectomy or a medical therapy as a second-line treatment

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Abstract

The paradigm for managing primary immune thrombocytopenia (ITP) in adults has changed with the advent of rituximab and thrombopoietin receptor agonists (TPO-RAs) as options for second-line therapy. Splenectomy continues to provide the highest cure rate (60-70% at 5+ years). Nonetheless, splenectomy is invasive, irreversible, associated with post-operative complications, and its outcome is currently unpredictable, leading some physicians and patients towards postponement and use of alternative approaches. An important predicament is the lack of studies comparing second-line options to splenectomy and to each other. Furthermore, some adults will improve spontaneously within 1-2 years. Rituximab has been given to more than 1 million patients worldwide, is generally well tolerated and its short-term toxicity is acceptable. In adults with ITP, 40% of patients are complete responders at one year and 20% remain responders at 3-5 years. Newer approaches to using rituximab are under study. TPO-RAs induce platelet counts >50,000/μl in 60-90% of adults with ITP, are well-tolerated, and show relatively little short-term toxicity. The fraction of TPO-RA-treated patients who will be treatment-free after 12-24 months of therapy is unknown but likely to be low. As each approach has advantages and disadvantages treatment needs to be individualized, and patient participation in decision-making is paramount.
Background

Consult: A 34 year-old patient presents with a platelet count of 10,000/µL accompanied by petechiae, ecchymoses, and epistaxis. Work-up leads to the diagnosis of ITP. Treatment with prednisone is initiated with good clinical and platelet response and the drug is reasonably well tolerated. However, the platelet count falls and bleeding symptoms recur when the dose is tapered below 10 mg daily. Prednisone is reinitiated at a high dose and tapered more slowly, but the platelet count again falls to <20,000/µL when the dose reaches 10 mg daily. It is now 5 months since diagnosis. What is the appropriate therapy? Specifically, is splenectomy indicated or should it be reserved and other treatments tried first?

Introduction

Splenectomy has been the standard second-line treatment for adults with ITP for decades and remains the option that provides the highest cure rate. Careful choice of patients, widespread adoption of a laparoscopic approach, peri-operative thromboprophylaxis, and better approaches to prevent and mitigate sepsis have helped reduce morbidity, costs and possibly mortality. Concurrently, important advances have been made in understanding the pathogenesis of ITP accompanied by development of novel treatments, including anti-CD20 antibodies and thrombopoietin receptor agonists (TPO-RAs). This has led to increased uncertainty as to when splenectomy is advisable as the standard next step. It has also become clear that some adults improve over time either spontaneously or as a result of treatment, leading some to recommend deferring surgery for one to several years. Moreover, increased clinical awareness and use of laboratory testing now identifies concomitant illnesses in patients who otherwise meet diagnostic criteria for ITP (“cryptic” secondary ITP), including some, e.g. hepatitis C and common variable immune deficiency (CVID), that mitigate against splenectomy.

It is our distinct impression that information of variable validity widely available on the Internet has increased the number of patients who wish to avoid splenectomy. The introduction of new therapies and increased awareness of late remissions in ITP have resulted in physicians tending to avoid or defer splenectomy, which is increasingly viewed as the last resort, particularly in the United States and some European countries. This is evidenced by a decrease in the rate of splenectomy for ITP from 50–60% in previously reported cohorts to 20–25% more recently.
Two recent reviews of treatment for ITP have been published. The International Consensus document used both published studies and the accumulated experience of 22 international experts, somewhat akin to the process used to develop the initial ASH guidelines, though with less formal integration of expert opinion. In contrast, the revised ASH guidelines focused on evidence-based medicine, with half of the writing group having expertise in trial-methodology and data-analysis, the remainder in ITP. Both groups considered splenectomy, and both recommended it as a second-line therapy. However, the International Consensus gave it equal place among a number of options, whereas the ASH guidelines gave splenectomy its highest grade of recommendation based on its curative effects and the extensive published experience. Additional guidelines that consider the role of splenectomy in second line treatment are summarized in Supplemental Table 1.

This article on “How I Treat ITP” investigates the question: What is the optimal second line treatment for adults with ITP? Splenectomy is considered in the context of the two most commonly employed, newer approaches to second line therapy: rituximab and TPO-RAs. Since no comparative evidence-based recommendations can be made, our focus is to consider and balance the potential benefits and relative contraindications of each option to help inform individualized care.

What is ITP?

ITP is an autoimmune disease characterized by isolated thrombocytopenia (platelet count <100,000/µl) resulting from accelerated clearance and destruction of antibody-coated platelets by tissue macrophages, predominantly in the spleen. Anti-platelet antibodies also target antigens on megakaryocytes and pro-platelets, variably suppressing platelet production. Plasma thrombopoietin (TPO) is generally normal or only minimally elevated, primarily because of accelerated clearance via megakaryocytes and platelets. Activated cytotoxic CD8 positive T cells may contribute to thrombocytopenia in certain patients. A potential underlying etiology giving rise to secondary ITP, such as infection with hepatitis C, human immunodeficiency virus (HIV) or Helicobacter pylori, and co-existence of systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS) or common variable immunodeficiency
(hypogammaglobulinemia, CVID), is identified in approximately 20% of patients with immune thrombocytopenia. Discovering an underlying cause is important since it may impact the efficacy and safety of splenectomy and other approaches (see below). Moreover, patients such as in the case example are often not thoroughly evaluated for secondary ITP and an underlying etiology may not be apparent on presentation.

**Who should be treated?**

Treatment is generally confined to patients who are bleeding or are perceived to be at significant risk of bleeding. The risk of bleeding is multi-factorial and its assessment is complex. For the most part, bleeding is related to a decreased platelet count, increasing age, co-morbidities (including their treatments), risk of trauma, and previous history of bleeding. Although a platelet count of &lt;30,000/µl is often used as a surrogate marker, lower (10-20,000/µl) or higher (50,000/µl) thresholds are pursued depending on the risk of bleeding, the presence of co morbidities, patient’s lifestyle and risk of trauma, all of which need to be weighed against the likely benefits and the risk of treatment-related side effects. Some therapies may improve health related quality of life (HRQoL), especially fatigue, although this issue is infrequently considered or invoked as a reason to treat. Comparative outcome studies are lacking here as well.

**When should splenectomy be considered among second-line therapies?**

The frequency of complete remission after a course of first line therapy with corticosteroids ranges from 10-30% with daily oral prednisone to as much as 60-80% with high-dose, pulsed dexamethasone (HDD). However, the latter remains to be confirmed in controlled trials and currently available evidence does not establish the superiority of HDD. In the absence of such evidence, we do not routinely use multiple cycles of HDD to induce remission in patients who have failed a course of prednisone. Patients may develop hemostatic platelet counts by one year (Figure 1) or occasionally after many years of severe disease without additional treatment. Accordingly, the International Consensus statement suggests deferring splenectomy until the chronic phase (&gt; 12 months), if possible, unless an adequate count cannot be maintained with medical therapy, adverse reactions to medical alternatives develop, or there is compelling patient preference, e.g. because of life-style or employment.
The management of patients who fail corticosteroids is challenging, as there have been no comparative trials of treatment options in this setting. The International Consensus report lists more than 10 second-line therapeutic options, including splenectomy, without indicating a preference. The revised ASH guidelines recommend splenectomy (Grade-1B evidence) for patients who failed corticosteroid therapy while suggesting treatment with TPO-RAs and rituximab pre-splenectomy (Grade 2C evidence). What follows is our analysis of the factors to be considered when choosing amongst the three most common options (Table 2; Figure 2). We recognize that other approaches, including watchful waiting may be appropriate in many patients. Also, other treatments widely used in some countries, such as dapsone and immunosuppressive agents, are not commonly employed as second line treatments in our practice.

Splenectomy
Splenectomy has been employed for decades as the primary option in patients who require additional treatment after a course of corticosteroids.

What are the Pros of Splenectomy?

1- Splenectomy is “curative”
Splenectomy “cures” ITP by removing both the primary site of platelet destruction and an important site of anti-platelet antibody production in an uncertain but large proportion of patients. Platelet counts rise rapidly in 85% of patients. Relapses are encountered, especially in the first 2 years after surgery, but 60-65% of patients remain in clinical remission 5-10 years after splenectomy, an outcome unmatched by any other therapy (Figure 3). A systematic review of 135 case-series published between 1966 to 2004 revealed a complete response rate of 66% with a median duration of follow-up of 28 months (range 1 to 153 months). A recent systematic review of 23 articles and 1,223 patients post-laparoscopic splenectomy recorded a success rate of 72% at 5 years. Responding patients require relatively little follow-up e.g. yearly platelet counts and repeated vaccinations, except in pregnant women who are at risk for having a fetus with thrombocytopenia.
2- Splenectomy failure does not jeopardize response to most medical treatments

It has been thought for some time that some patients who fail splenectomy may be managed with lower doses of corticosteroids than were required before surgery. However, strong evidence is lacking. TPO-RA and rituximab are equally effective in splenectomized and non-splenectomized patients. The only therapies known to be less effective after splenectomy are IV anti-D, and probably dapsone.

3- Advantages of laparoscopic splenectomy

Laparoscopic splenectomy is widely used as the preferred approach because it is less traumatic, engenders less post-operative pain, and is associated with fewer wound infections and other complications leading to shorter hospital stays, more rapid convalescence, and more rapid return to work, all of which contribute to lower costs. Cosmesis is improved compared with the open approach. Laparoscopy does not increase the frequency of missing accessory spleens. Consequently, laparoscopic splenectomy has been embraced as the “Gold Standard,” but should only be performed by experienced operators. The conversion rate to open laparotomy ranges from 5-15%. As with open splenectomy, it is important to elevate platelet counts preoperatively to >20,000/µl to avoid longer hospital stay, blood transfusions, and other complications.

4- Splenectomy has a well-characterized safety profile and generally preventable complications

Perioperative complications of splenectomy include bleeding, infection, and thrombosis. Long-term complications include overwhelming sepsis by encapsulated bacteria and vascular/thrombotic events. Most complications are infrequent and either preventable or treatable (see Splenectomy “Cons”). Surgical expertise combined with proper patient selection and preparation is key to reducing complication rates and involves: excluding patients with serious co-morbidities for general surgery and “older” patients (age cut-offs for those in otherwise excellent health is debated), optimizing platelet counts perioperatively, and judicious use of antibiotics and thromboprophylaxis. We recommend Pneumococcal, Meningococcal, and Haemophilus influenzae vaccination prior to splenectomy and periodically every 5 years or according to titers.
5- Splenectomy reduces cost
Prior to TPO-RA, the annual cost of treating severe chronic ITP was estimated to be $40,000 \textsuperscript{45}, although comprehensive cost-effectiveness studies are lacking in adults. However, the cost of TPO-RAs ranges from $2500-$4000 per month, and each 4-infusion course of rituximab costs $10,000-$50,000, whereas the estimated total procedural cost of splenectomy is not more than $20,000. These cost estimates apply only to patients who respond. The societal cost of failed splenectomy includes the cost of surgical complications and subsequent therapy.

6-Pregnancy
Women with ITP who contemplate pregnancy may opt for splenectomy because most options for management of the maternal platelet count, including TPO-RA and rituximab, may not be safe for the fetus. \textsuperscript{46,47} However, women in remission post-splenectomy may relapse during pregnancy and the fetus/neonate may develop thrombocytopenia even if the splenectomized mother remains in remission. \textsuperscript{48}

What are the Cons?

1- Removal of a “healthy” organ
Splenectomy is irreversible and consequently leads to the loss of its multiple hematologic and immunologic functions e.g. elimination of abnormal blood cells, cell particles and organisms from the blood and production of antibodies to blood-borne antigens. \textsuperscript{49}

2- Unpredictability of response
The response to splenectomy cannot be predicted using readily available clinical criteria, e.g. previous response to steroids or IVIG, other than “older” age, which is ill-defined. \textsuperscript{2} In a retrospective review of \textsuperscript{111}In-labeled autologous platelet sequestration studies, the complete response rate after splenectomy was 87% (median 3.8 years follow up) in patients having predominantly splenic sequestration as opposed to 35% in those with “mixed” or hepatic sequestration (OR 5.39; 95% CI 1.3–21.6). \textsuperscript{50} Confirmatory studies are needed. Major limitations include restricted availability and technical difficulty. \textsuperscript{51}
3- Post-Splenectomy Mortality and Morbidity

Splenectomy is an invasive procedure associated with near-term complications primarily related to general anesthesia and surgery and long-term complications from loss of splenic functions.

a- Overall Mortality

The 30-day mortality and complication rates after laparoscopic splenectomy (0.2% and 9.6%) are reported to be lower than after open splenectomy (1% and 12.9%).² A Danish cohort study compared 3,812 patients splenectomized for various indications between 1996 and 2005, 8,310 non-splenectomized patients with matched underlying conditions, and 38,120 controls. Ninety-day mortality was elevated in the splenectomized cohort as a whole and in the sub-cohort with ITP (n=269) (Adjusted Relative risk (RR) 33.6; 95%CI 7.9-143) compared to the general population. However, for patients with ITP, the difference in mortality during the first year after splenectomy was not significant when compared to the non-splenectomized cohort. Interestingly, after one year, the RR of death in the splenectomized ITP patients was significantly lower than in the matched ITP controls treated otherwise (RR 0.4; 95% CI 0.2-0.7).⁵² However, the assessment period preceded the introduction of TPO-RAs and extensive use of rituximab; therefore data in the non-splenectomized ITP cohort was derived from an era when patients typically underwent prolonged exposure to high doses of corticosteroids and other immunosuppressives not widely used and/or no longer considered safe or appropriate in this setting.

b- Risk of infection

Since 1952, it has been evident that asplenic subjects are at increased risk of life-threatening infections.⁵³ The Danish cohort study identified a 14-fold higher RR of sepsis in splenectomized ITP patients (n=269) during the first year after splenectomy and a 4-fold higher RR after 1 year compared to the general population. Importantly, compared to non-splenectomized ITP patients, a higher rate of sepsis was observed only during the first 90 days.⁵³ Interestingly, enteric organisms were the predominant cause of early and late postsplenectomy bacteremia; encapsulated bacteria, such as pneumococci, meningococci, and Haemophilus influenzae were rarely encountered in the splenectomized cohort, perhaps a result of widespread vaccination and early intervention with antibiotics (see below). No sepsis-related mortality was reported in two Italian
studies that included 612 splenectomized ITP patients.\textsuperscript{31,54}

Repeated patient education is vital because the rarity of sepsis predisposes to non-compliance. Med-alert bracelets may be helpful. Guidelines for preventing sepsis and/or improving the outcome, when it occurs, vary but may include: a) repeat vaccination every 5-10 years or when antibody titers (especially to pneumococcus) fall; b) measurement of body temperature at the onset of any illness and urgent emergency room evaluation for a fever of 101°F or higher with initiation of IV antibiotics such as ceftriaxone (absent allergy); and c) consideration of penicillin 250-500 milligrams twice a day for life (however, the incidence of pneumococcal penicillin resistance currently approaches 30%). Exposure to infections with known worse outcomes in splenectomized patients, e.g. malaria and babesiosis, should be avoided if at all possible. Table 3 summarizes pre- and post-operative recommendations to minimize post splenectomy infectious complications.

**c- Vascular complications**

Splenectomy may increase morbidity from venous thromboembolism (VT) or atherosclerosis. Increased pro-coagulant derived microparticles,\textsuperscript{55} platelet activation, disturbance and activation of the endothelium, altered lipid profiles and persistent thrombocytosis have been implicated in hypercoagulability in ITP.\textsuperscript{44}

VT is reported to occur in up to 10% of patients with hematologic diseases undergoing splenectomy.\textsuperscript{2,38,42,56} The risk of VT is highest in the first year post-splenectomy, but even thereafter the rate of VT in splenectomized ITP was 2.7-fold (95% CI 1.1-6.3) higher than in age-matched controls.\textsuperscript{57} However, these studies did not include a non-splenectomized ITP cohort. In a more recent French study of 275 patients given thromboprophylaxis who underwent laparoscopic splenectomies for various hematological disorders (76% with ITP), only 1% developed VT.\textsuperscript{42} Portal vein thrombosis is a known early complication of open or laparoscopic splenectomy. Systematic screening for portal vein thrombosis with doppler ultrasound or CT scan revealed a high incidence (8-37%), but symptomatic cases are rare (<2%),\textsuperscript{57,58} making the value of routine post-operative surveillance unproven. Secondary pulmonary arterial hypertension has been reported after splenectomy in patients with hemolytic anemia, e.g. spherocytosis and thalassemia, but only anecdotally after splenectomy for ITP.\textsuperscript{59} There is insufficient information to know
whether splenectomy predisposes to other reported vascular complications, (e.g. multi-infarct dementia and acute coronary syndrome).\textsuperscript{60}

**Summary.** Splenectomy offers the greatest opportunity for cure and societal costs appear favorable. There is little evidence to suggest increased long-term mortality and morbidity compared with medical treatment options if patients are managed appropriately, especially with regard to selection, pre- and peri-operative management, laparoscopy by an experienced surgeon, and prophylaxis of and attention to sepsis and thrombosis.

On the other hand, data comparing splenectomized and non-splenectomized ITP patients, which suggest little difference in adverse outcomes (e.g. sepsis), were acquired in patients with extensive steroid exposure before the current era of TPO-RA and rituximab. Furthermore, the long-term consequences of splenectomy remain ill defined. Delaying the decision for 12 months or more appears to lessen the need for surgery in a substantial proportion of patients. If this approach is adopted more widely, it may affect subsequent analyses, because restricting splenectomy to third-line “salvage” therapy will likely reduce not only the need but also the response rate.

**Primary Alternative Therapeutic Options including Factors Determining the Choice of Treatment**

**Rituximab**

**a. Pros.** Rituximab is appealing because of its curative potential and relative safety and because hematologists are familiar with its use in treating lymphoma. Four once-weekly IV infusions at 375 mg/m\textsuperscript{2} induce complete remission (CR) in 44% of patients.\textsuperscript{61} In one study, splenectomy was deferred by two years in 40% of the patients who were treated with rituximab.\textsuperscript{62} Patients with CRs generally persist at least 1 year; those with PRs usually relapse within 6 months.\textsuperscript{3} In adults, the CR rate falls to approximately 20% by 2-5 years after a single 4-infusion course.\textsuperscript{62,63} More durable remissions might be induced by adding 1-3 cycles of HDD or using maintenance rituximab.\textsuperscript{64,65} First infusion reactions induced by clearance of anti-CD20-coated B cells by macrophages and direct cytotoxicity to B cells is generally preventable by slowing the rate of infusion and pre-administration
of IV methylprednisolone (100-1000 mg), IV diphenhydramine (25-50 milligrams) and acetaminophen.

b. Cons. Toxicities primarily involve first infusion reactions, serum sickness, which is more common (5-10%) in children, and a series of rare complications, including fulminant hepatitis B and progressive multifocal leukoencephalopathy (primarily in the setting of profound immunodeficiency such as when rituximab is used along with intensive chemotherapy), delayed neutropenia (more common when rituximab is combined with chemotherapy), hypogammaglobulinemia, and diverse idiosyncratic reactions. Toxicities primarily involve first infusion reactions, serum sickness, which is more common (5-10%) in children, and a series of rare complications, including fulminant hepatitis B and progressive multifocal leukoencephalopathy (primarily in the setting of profound immunodeficiency such as when rituximab is used along with intensive chemotherapy), delayed neutropenia (more common when rituximab is combined with chemotherapy), hypogammaglobulinemia, and diverse idiosyncratic reactions.  

Persistent perturbations in the T- and B-cell repertoires and impaired response to specific antigens have been reported in non-ITP populations and in animal models, but their clinical significance is uncertain. Immunizations, such as pneumovax, should be given prior to rituximab, as response is reduced for 4-6 months until B cells return. This may be especially important if the patient subsequently requires splenectomy. While safety issues exist, more than one million patients have been treated for a variety of malignant and autoimmune indications since the 1990’s with limited long-term serious toxicity documented to date.

c. Additional considerations. Because large randomized studies have not been completed, Rituximab has not received FDA or EMA approval for ITP although it is currently reimbursed for this purpose in many countries. Currently the drug is administered IV, although subcutaneous administration has been performed with two other anti-CD20 antibodies, one in ITP. The longest follow-up for which data is more than anecdotal is 3-5 years compared with 5-20 years for splenectomy. Dosing is empiric. Infusions of lower doses, e.g. 100 mg, showed comparable but delayed short-term benefit. There is no mechanism or treatment effect that can be used to individualize dose or frequency of administration, other than depletion of peripheral blood B cells. Repeat administration has been used effectively in a few patients. Anecdotal information, which suggests that Rituximab administered closer to the time of diagnosis is more effective, needs to be formally demonstrated. Outcomes may be improved by use in combination with HDD. The single reported study combining one cycle of HDD followed by Rituximab in previously untreated ITP patients yielded a combined PR and CR rate of 63% at 6 months; of those, 15-25% relapsed by 20 months. In a pilot study of 42 previously treated patients, a combination of Rituximab with 3 cycles of HDD
yielded a CR + PR of 71% and lasting responses in 57%.

**d. Summary.** Rituximab has been used widely and appears to be relatively safe to date. It provides long-term CR comparable to any therapy other than splenectomy. However, the long-term outcome after 4 standard-dose infusions is somewhat disappointing. Additional benefits from co-administering dexamethasone and maintenance therapy appear promising and are under investigation.

**Thrombopoietin receptor agonists (TPO-RAs)**

TPO-RAs are the only second-line therapy validated by randomized, controlled trials; however, thus far, the comparator arm was placebo. Two TPO-RAs, Romiplostim and Eltrombopag, are approved for use in over 80 countries. In the USA, Romiplostim is administered as subcutaneous weekly injections, which, at the time of this writing, must be administered by a health care provider. Eltrombopag is an oral agent given daily that must be taken at least 2 hours apart from ingestion of food and 4 hours apart from calcium-containing products (e.g. dairy) and supplemental iron.

**a. Pros.**

The reported response rates to TPO-RAs range from 59-88%. responses are generally sustained as long as treatment continues. The short-term safety and tolerability of both TPO-RAs have been carefully documented and both were monitored closely for 3 years in the US, as part of post-marketing surveillance by the FDA. In one long-term study, 5% of the patients discontinued therapy because of side effects. Only a few patients lose responsiveness once a stable platelet count has been attained. In responders, doses can be individualized to attain hemostasis and in many patients the dose can be increased temporarily to raise platelet counts further in advance of elective surgery. Many patients are able to discontinue or reduce the dose of concomitant ITP treatments such as corticosteroids. Decreased bleeding, less need for other (rescue) treatments, and increased HRQoL have been seen in responders. A number of patients, after months to years of treatment, appear able to discontinue treatment and maintain an adequate platelet count.
b. Cons.

The major disadvantage of these agents compared to splenectomy and rituximab is the indefinite duration of treatment. As TPO-RAs are potentially life-long treatments, compliance may be a real issue. The current requirement for a healthcare professional to administer romiplostim and the alimentary requirements to ensure effective dosing of eltrombopag are cumbersome. TPO-RAs require at least 1-2 weeks to take effect (in responders) and therefore play at most a supplementary role in managing urgent conditions. Patients may experience mild-moderate headache, myalgias and gastrointestinal disturbances.\(^\text{46}\) Eltrombopag carries a black-box warning for hepatotoxicity. Neither should be used during pregnancy or lactation. “Rebound” thrombocytopenia occurs infrequently after abrupt discontinuation of TPO-RAs, which can be prevented by tapering the drugs and/or using rescue treatment, if needed.\(^\text{22}\) An increase in bone marrow reticulin has been observed in several patients.\(^\text{75,77,78}\) However, current evidence does not indicate progressive bone marrow fibrosis with prolonged exposure.\(^\text{77}\) TPO-RAs have not been shown to induce malignancy or myelodysplasia in patients with ITP thus far,\(^\text{77}\) but they are not indicated in patients with myelodysplasia due to the potential risk of acute myeloid leukemia (romiplostim carries a warning). Although, it seems these agents have acceptable short and intermediate term safety profiles, long-term safety data beyond 5 years is limited.

c. Additional considerations: Relapse occurs in a large majority of patients when treatment is interrupted.\(^\text{74,75,79}\) An increase in regulatory T-cells (Tregs) is seen and a few patients appear to maintain adequate platelet counts off therapy.\(^\text{80}\) In contrast to splenectomy and rituximab, TPO-RAs have only been in use for 7 years in trials and 3 years in general practice; hence experience in patients who were not eligible for inclusion on protocols is limited.\(^\text{81}\) It is difficult to discern if there is an increase in the rate of VT compared with other successful interventions; it is important to take the underlying risk of arterial or venous thrombosis into consideration in patients with ITP and to consider use of aspirin in those at risk once the platelet count has entered a safe range, e.g. \(\geq50,000/\mu\text{L}\). Additional detailed analyses of toxicity have been reported in primary studies\(^\text{4,5,22,34,35,74,75}\) and in reviews.\(^\text{82}\) These agents are not approved for use pre-splenectomy in Europe unless surgery is contraindicated.
d. Summary: TPO-RAs are highly effective before and after splenectomy, rituximab, and other agents. Toxicity appears limited, although surveys and studies are ongoing involving patients treated in the United States and elsewhere to better define complication rates (especially thrombosis and marrow fibrosis) in larger numbers of patients followed for longer times. There is no evidence at this time that there is any major difference in efficacy or toxicity between the two agents, although eltrombopag requires monitoring of liver function tests every 1-2 months, which may occasionally lead to at least temporary discontinuation, if abnormal. Anecdotal evidence suggests that infrequently one agent will be effective when the other is not.

Factors that influence the choice of treatment

1-Patient and physician preference: The patient is a critical protagonist in the decision to undergo or defer splenectomy. Increasing awareness of medical alternatives, input of patient advocacy groups, impact of the internet, inability to predict with certainty the response to a surgical procedure,83 and rare but dramatic adverse outcomes have changed the landscape with respect to the patient’s perspective. In turn, this decreases the breadth of experience of hematologists and surgeons with the procedure and its relative long-term advantages. The recent demonstrations that a substantial fraction of patients may not require treatment beyond 1-2 years after diagnosis further lessens physician enthusiasm for splenectomy as initial second line management. “If, however, response becomes predictable based on sequestration of labeled platelets and such testing becomes more widely available, then there may be a resurgence in the use of splenectomy.”

2-Co-morbidities:
Co-morbidities (e.g. serious cardiopulmonary disorders) increase the risk of general anesthesia and post-surgical complications. A higher rate of surgical complications and a lower response rate is reported in most studies of patients over 45-70 years of age84 2,85,86 and in those with various secondary forms of ITP15,87. Care must be taken when considering options for patients with a history or serious risk of thrombosis,
3-Restrictions imposed by health funding authorities

National health services in many European countries restrict the use of TPO-RA and rituximab. After application for permission, the cost may only be covered in splenectomized patients or if splenectomy is contraindicated, but the situation is liberalizing rapidly in some countries.

Deciding which option to pursue

Before considering treatment options, it is important to exclude inherited thrombocytopenias and secondary ITP that might not have been evident on presentation. A search should be made for conditions that may contribute to or co-exist with persistent thrombocytopenia including infections such as human immunodeficiency virus and hepatitis C (even if initially excluded), H. Pylori and possibly cytomegalovirus, thyroid disorders, immunodeficiency, low-grade lymphoid neoplasms or other lymphoproliferative disorders, and systemic autoimmune conditions. The lack of clinical findings, e.g. no history of infection, does not exclude CVID, which might nonetheless be clinically significant in the post-splenectomy setting and which is more amenable to treatment with rituximab.17 If a substantial, albeit transient, response has not been achieved by prior ITP treatments, a bone marrow examination should be performed to exclude other conditions, particularly myelodysplasia.

The patient’s prior history, anticipated course, and relevant pros and cons of each option are discussed in a personalized way with each patient and participating family members. The patient’s goals, fears, individual capacities (e.g. memory, frailty), family support, proximity to medical care and likely tolerance of each approach are considered in addition to outcomes. The appropriate therapy for two individuals with essentially identical clinical presentations, duration of disease and response to other therapies may differ based on these additional medical and psychosocial factors.

At one end of the spectrum, splenectomy has the highest cure rate and may therefore be the preferred option for younger patients, who have the best response and lowest complication rates, engage in physically challenging sports or professions, are potentially non-compliant with protracted daily treatment, and who do not wish to continue to “deal
with their ITP. Recommendations would be influenced by the results of platelet isotopic distribution studies (if confirmed and if available).51

At the other end of the spectrum, we try to avoid splenectomy in patients over 65-70 years of age (depending on their physical condition) not only because of higher complication rates, but also lower response rates. The same considerations apply to the very frail, those with significant surgical co-morbidities, history or risk of thrombosis, those with obligatory exposure to malaria or babesia, or who have secondary ITP. Questions may be raised about post-splenectomy infection in teachers, veterinarians, healthcare providers, travelers to certain areas, or others with increased exposure to infectious conditions.

It is far more difficult to make recommendations for or against splenectomy to the majority of patients with ITP who do not meet these criteria and have no contraindications to surgery. Although splenectomy is recommended after the failure of steroids, there is an argument to be made for waiting one year or more after diagnosis before proceeding. We generally follow the recommendations of the International consensus,8 and often lean towards either rituximab (lower response rate, modest likelihood of cure) or TPO-RA (higher response rate, less likelihood of cure) after considering the many factors mentioned above based on personal clinical experience and patient preference. This difficulty is exemplified by the responses of each of the authors to how they would advise the patient presented in the case report:

Consult: We would proceed by excluding causes of secondary ITP and by assessing the risk of bleeding. This patient’s course to date is consistent with the initial diagnosis of ITP, which is best substantiated by the response to prednisone and the absence of new evidence of an underlying cause of secondary ITP. Each of the four authors recommend therapeutic intervention as opposed to “wait and watch”, since the patient had experienced bleeding with a platelet count below 20,000/µl. The probability of responding to low dose or alternate day corticosteroids was considered as remote. All authors proceeded to second-line treatment. Three different approaches were adopted. These were: a) 4 weekly infusions of rituximab at conventional doses (WG and BG), b) 4 weekly infusions of rituximab combined with 3 cycles of HDD (JBB), c) a TPO-RA for a limited period, i.e. 6 months (DC). None of the authors considered splenectomy as initial next
step in this patient with “persistent” disease. TPO-RA was recommended as the next option if rituximab-based therapy fails, and rituximab would be considered if treatment with a TPO-RA failed or the patient wanted an option that might lead to cure. All authors would consider splenectomy if an adequate response was not achieved by one year.

Conclusions

The last decade has seen the introduction of new exciting suitable second-line medical approaches to manage adults with ITP. Each approach has unique benefits, limitations, and risks, and none have been subjected to head-to-head comparisons. Nor have quality of life or long-term comparative effectiveness analyses been performed to inform decisions. It is unlikely any comparative studies will hold interest for the pharmaceutical industry. Even consortia of major academic centers will have difficulty pursuing these studies because of the relatively low frequency of disease, cost and reimbursement issues, and the duration of studies needed to address critical concerns. Therefore, optimal treatment will continue to involve a personalized approach to therapy that combines the art of medicine with the science through close collaboration between patients and health-care providers for the foreseeable future.

AUTHORSHIP

All 4 authors wrote and edited the article extensively.

CONFLICTS OF INTEREST

W.G. has received research grants from Roche and Amgen, consultancy and lecture honoraria from Amgen and Glaxo Smith Kline (GSK).

B.G. has participated in advisory boards and symposia for Amgen, Roche, GSK and LFB and has received research funding from Roche.

D.C is Ad hoc member of medical advisory board for Amgen, GSK and Eisai.

J.B. currently receives clinical research support from the following companies: Amgen, Cangene, GSK, Genzyme, IgG of America, Immunomedics, Ligand, Eisai, Inc, Shionogi and Sysmex. His family owns stock in Amgen and GSK. He has participated in Advisory Boards for Amgen, GSK, Ligand, Shionogi, Symphogen and Eisai. He had a one day consult with Potola.
References


Table 1  Comparison between various national and international guidelines in regard to splenectomy in the treatment of ITP.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Year</th>
<th>Language</th>
<th>Publication site</th>
<th>Timing, indication and restrictions for splenectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASH</td>
<td>2011</td>
<td>English</td>
<td>Blood</td>
<td>Deferred &gt; 6 mo 2nd line therapy after steroids- grade of recommendation IB.</td>
</tr>
<tr>
<td>International</td>
<td>2010</td>
<td>English</td>
<td>Blood</td>
<td>Deferred &gt; 6-12 mo One of the second-line therapies without preference.</td>
</tr>
<tr>
<td>Consensus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>French</td>
<td>2009</td>
<td>French</td>
<td><a href="http://www.has-sante.fr">www.has-sante.fr</a></td>
<td>Deferred &gt;12 mo 2nd line after steroids but TPO-mimetics or rituximab should be considered in some patients.</td>
</tr>
<tr>
<td>Norwegian</td>
<td>2011</td>
<td>Norwegian</td>
<td><a href="http://www.legeforeningen.no/hematologi">www.legeforeningen.no/hematologi</a></td>
<td>Deferred &gt; 6-12 mo 2nd line after failure of steroid and/or rituximab.</td>
</tr>
<tr>
<td>German</td>
<td>2010</td>
<td>German</td>
<td>Onkologie</td>
<td>Deferred &gt;12 mo 2nd line after steroids but TPO-mimetics or rituximab should be considered in some patients.</td>
</tr>
<tr>
<td>British</td>
<td>2003</td>
<td>English</td>
<td>British Journal of Haematology</td>
<td>NG 65? 2nd line after failure of steroids</td>
</tr>
<tr>
<td>Swedish</td>
<td>2010</td>
<td>Swedish</td>
<td><a href="http://www.sfhem.se">www.sfhem.se</a></td>
<td>NG NG 2nd line after failure of steroid in the absence of contraindication</td>
</tr>
</tbody>
</table>

NG = not given
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Efficacy and response prediction</th>
<th>Safety</th>
<th>Contraindications</th>
<th>Mode of application and follow-up</th>
<th>Grade of ASH 2011 guidelines recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomy</td>
<td>Highest cure rate; short-term response 80% and long-term response 60-70% at 5-10 years. Response hard to predict (see text)</td>
<td>Surgery-related mortality and morbidity (bleeding, infections, thrombosis); lifetime risk of overwhelming infection. Possible AE: venous thrombosis, pulmonary hypertension, atherosclerosis, dementia</td>
<td>Patients with co-morbid conditions that increase the risk of complications. Relative: elderly patients over 60-70 because high rate of complication and lower response; patients with immunodeficiency and secondary ITP e.g. CVID, hepatitis C, neutropenia, possibly SLE</td>
<td>Invasive procedure usually performed laparoscopically. Requires pre- and post-operative preparation and care and regular vaccination</td>
<td>well-established treatment for ITP ASH-1B after failure of steroids/</td>
</tr>
<tr>
<td>TPO-RA</td>
<td>A maintenance treatment; 60-80% achieve platelet elevation; sustained response in 70-90% in those entering long-term treatment studies</td>
<td>Headache, rebound thrombocytopenia, weekly injection Possible AE: Bone marrow reticulin fibrosis, aterial and venous thrombosis, risk of malignancy (if MDS)</td>
<td>Pregnancy and lactation, MDS Relative: past history of venous or arterial thrombosis</td>
<td>Weekly s.c. injections; requires dose-adjustment and regular CBC</td>
<td>Approved treatment for ITP; ASH-2C after failure of steroids before splenectomy/</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>A maintenance treatment; 60-80% achieve platelet elevation; sustained response in 70-90% in those entering long-term treatment studies</td>
<td>Headache, rebound thrombocytopenia, elevated liver enzymes Possible AE: Bone marrow reticulin fibrosis, aterial and venous thrombosis; nausea, vomiting in small percent; cataracts (very infrequent if at all)</td>
<td>As with Romiplostim Requires monitoring of liver tests but used successfully in large studies of patients with liver disease secondary to hepatitis C</td>
<td>Daily ingestions; requires dose-adjustment and regular CBC and liver tests</td>
<td>same</td>
</tr>
<tr>
<td>Eltrombopag</td>
<td>A maintenance treatment; 60-80% achieve platelet elevation; sustained response in 70-90% in those entering long-term treatment studies</td>
<td>Headache, rebound thrombocytopenia, elevated liver enzymes Possible AE: Bone marrow reticulin fibrosis, aterial and venous thrombosis; nausea, vomiting in small percent; cataracts (very infrequent if at all)</td>
<td>As with Romiplostim Requires monitoring of liver tests but used successfully in large studies of patients with liver disease secondary to hepatitis C</td>
<td>Daily ingestions; requires dose-adjustment and regular CBC and liver tests</td>
<td>same</td>
</tr>
<tr>
<td>Anti-CD20</td>
<td>May be curative treatment; initial response in 50-60%; sustained response 3-5 years in 20%; retreatment gives the same pattern of response as observed after the first course in complete responders. Cannot predict response</td>
<td>Infusion-related side effects (chills, fever, dyspnea), neutropenia, Possible AE: increased risk of infection and viral reactivation, hypogamma globulinemia, serum sickness (especially in children), multifocal leukoencephalopathy (PML)</td>
<td>Active hepatitis B virus, known clinically significant allergy including past serum sickness with anti-CD20, or anti-mouse antibody Pregnancy and lactation</td>
<td>Weekly IV infusions for 4 weeks; CBC required depending on the response</td>
<td>Not approved for ITP – only off-label use. ASH-2C after failure of steroids/</td>
</tr>
<tr>
<td>Rituximab</td>
<td>May be curative treatment; initial response in 50-60%; sustained response 3-5 years in 20%; retreatment gives the same pattern of response as observed after the first course in complete responders. Cannot predict response</td>
<td>Infusion-related side effects (chills, fever, dyspnea), neutropenia, Possible AE: increased risk of infection and viral reactivation, hypogamma globulinemia, serum sickness (especially in children), multifocal leukoencephalopathy (PML)</td>
<td>Active hepatitis B virus, known clinically significant allergy including past serum sickness with anti-CD20, or anti-mouse antibody Pregnancy and lactation</td>
<td>Weekly IV infusions for 4 weeks; CBC required depending on the response</td>
<td>Not approved for ITP – only off-label use. ASH-2C after failure of steroids/</td>
</tr>
</tbody>
</table>

*See text for more complete description of the issues in this table.*
Table 3. Pre-and post-operative measures to reduce and/or prevent complications after splenectomy

<table>
<thead>
<tr>
<th>Prior to splenectomy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient education regarding risk of overwhelming sepsis</strong></td>
<td>Early administration of oral antibiotic therapy that covers S. pneumoniae and H. influenzae in case of fever (amoxicillin-clavulanate, cefuroxime axetil, or levofoxacin) AND immediate travel to a hospital for assessment and IV antibiotics.</td>
</tr>
<tr>
<td>Vaccination</td>
<td>Vaccination against S. pneumoniae, meningococcus, and H. influenzae type b. ideally at least 14 days prior to scheduled splenectomy</td>
</tr>
<tr>
<td>Elevation of platelet count</td>
<td>Elevation of platelets to &gt;5x10^9/L by steroids or IVlg or another treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>After splenectomy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic prophylaxis</td>
<td>Post-operative antibiotics prophylaxis until the risk of infection is abated</td>
</tr>
<tr>
<td>Thromboprophylaxis</td>
<td>Early mobilization, good hydration and early initiation of prophylactic anticoagulants once hemostasis is ensured if any risk of thrombosis</td>
</tr>
<tr>
<td>Discontinuation of other treatments</td>
<td>Gradual tapering of steroids, discontinuation of TPO-RA (provided that counts are good)</td>
</tr>
<tr>
<td>Re-vaccination</td>
<td>Vaccination against S. pneumoniae every 5 years and annual flu vaccine</td>
</tr>
<tr>
<td>Regular follow-up</td>
<td>Responding patients require platelet count every 3 months for one year and no less than annually thereafter. Patients need to be reminded of precautions. Pregnancy requires reevaluation.</td>
</tr>
</tbody>
</table>
Figure legends

Figure 1. Probability of first complete remission according to the type of onset (insidious or acute). Kaplan-Meier curves show that remissions continued to occur with or without treatment with low-dose steroids between 6 months and 3 years and that remissions occurred earlier and at higher rates in patients with an acute onset of symptoms as opposed to those with an insidious onset. Splenectomized patients were censored at time of splenectomy. Obtained from *Haematologica* (http://www.haematologica.org) and reprinted from Sailer et al.⁶

Figure 2. Suggested treatment algorithm for ITP

Footnotes:

*: These are overall factors that go for or against splenectomy without distinguishing between TPO-RA and rituximab.

†: Based on recommendations to defer splenectomy for 1 year, if possible.

‡: Alternative option is rituximab and wait for 12 months prior to conception.

§: Anticipated poor compliance is also applicable to splenectomy although post-splenectomy management, e.g. repeat vaccination, management of febrile illness, and f/u re platelet count would probably also be at risk.

Figure 3. Probability of thrombocytopenia-free survival after splenectomy. The estimated relapse-free survival for all patients during plateaus at 75% after 48 months. Obtained from *Haematologica* (http://www.haematologica.org) and reprinted from Vianelli et al.⁳¹
Figure 1

Probability of a first remission

$\rho=0.0003$

- Acute $n=44$
- Insidious $n=67$

Years from diagnosis
Figure 2

ITP requiring treatment

First-line therapies
Corticosteroids/IVIg/Anti-D

No response, requires high dose or relapse after Corticosteroids

Choose a second-line treatment based on the following factors

Restrictions on use of TPO-RA/rituximab by health funding authorities.

1- Contraindication to splenectomy, e.g. comorbidity. *
2- No restrictions on use of TPO-RA/rituximab.

Other factors:
1- Old age (>60-70y depending upon physical condition).
2- Mixed or hepatic platelet sequestration on radioisotope study.
3- Newly diagnosed (0-3 mo) or persistent (3-12 mo) ITP. †
4- Exposure to malaria, babesia or other infections cleared by the spleen.

Other factors:
1- Chronic ITP (>1 year).
2- Patient prefers Rx with high cure rate and/or no maintenance therapy.
3- Wish to become pregnant. ‡

1- Patient refuses splenectomy but prefers Rx with curative intent.
2- High risk of art. or ven. thrombosis.
3- Anticipated poor compliance. §
4- Reliability/cannot cope with dietary restrictions (eltrombopag).

1- Patient/physician seeks Rx with high response rate.

Splenectomy  Rituximab  TPO-RA
Figure 3

The graph shows the probability of an event occurring over a period of months. The probability decreases over time, with a significant drop in the first few months, followed by a slow decline thereafter. The x-axis represents the number of months, and the y-axis represents the probability percentage.
How I treat immune thrombocytopenia (ITP): the choice between splenectomy or a medical therapy as a second-line treatment

Waleed Ghanima, Bertrand Godeau, Douglas B. Cines and James B. Bussel