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REVIEW ARTICLE

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Treatment advances in adult immune thrombocytopenic purpura

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Abstract Immune thrombocytopenic purpura (ITP) is an autoimmune disease characterized by autoantibody-mediated destruction of platelets. The disease generally runs a mild clinical course, though significant morbidity and mortality can occur. Steroids and/or splenectomy are effective in treating the disease in approximately 70% of patients. These treatments have been well established with approximately 50 years of clinical experience. While open splenectomy is the traditional surgical procedure, laparoscopic splenectomy, splenic artery embolization, and splenic irradiation are viable alternatives. For patients who relapse after the above therapies, treatment is more difficult and seldom results in a cure. The goals of therapy involve maintaining a safe platelet count while minimizing toxicities from the treatment. Multiple treatment options exist including corticosteroids, androgens, immunomodulatory drugs, cytotoxic chemotherapy, immunoglobulin preparations, bone marrow transplantation, *Helicobacter pylori* eradication, and others. While the standard treatment of steroids and splenectomy has changed little over the past decades, a number of promising new therapies on the horizon may soon join the armamentarium upon which the clinician can draw to fight the disease. In this review, we will examine treatment for chronic ITP in adults in the pre-splenectomy, splenectomy, and post-splenectomy settings.

Keywords Immune thrombocytopenic purpura · Splenectomy

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Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disease in which the body's own immunoglobulins bind to platelets and cause destruction in the reticuloendothelial system, primarily the spleen. The disease can be secondary to other lymphoproliferative, autoimmune, or viral diseases, or can be a primary disease [16]. This review will examine only primary ITP. The disease is relatively common in children with an estimated incidence of 5/100,000 [102]. The incidence in adults may be somewhat lower (2.7/100,000) with a slight female preponderance (1.7:1) [76]. The natural history of the disease in both children and adults is characterized by asymptomatic thrombocytopenia, mild mucocutaneous bleeding, and infrequent life-threatening hemorrhages [19, 164, 204]. Fatal intracranial hemorrhage (ICH) in ITP is extremely rare in both children [102] and adults [134, 204]. Although the disorder is often self-limited in children, the disease in adults is associated with a chronic course, a higher rate of complications, and inadequate response to therapy [19, 48]. Childhood ITP [22, 30, 53, 108, 161], pathophysiology of ITP [16, 143], diagnosis of ITP [79], and ITP during pregnancy [116] have been reviewed elsewhere and will not be examined in this article. The goal of this paper is to review existing treatments and summarize new trends in the management of ITP.

A review of the literature shows that most trials enroll a small number (generally less than 25) of patients, usually non-blinded and at a single institution. These studies generally involve patients with both primary and secondary immune thrombocytopenias, pre- and post-splenectomy, and with a varying number and types of previous therapies. Some include both children and adults. These factors combine to make studying therapies for ITP difficult, especially for generalizing results. Because of these difficulties, the American Society of Hematology (ASH) issued its first practice guideline in 1999 [79], which still remains the "standard of care" for ITP.

Pre-splenectomy treatment

When is treatment indicated?

The first question after diagnosis should be whether to treat the patient or not. ITP runs a varied clinical course, with only 5–9% showing spontaneous remission [79, 188]. Most (85%) will have benign disease with little morbidity and no mortality, though as many as 5% of patients will have a fatal hemorrhage [79]. Those who do not respond to therapy run a fourfold risk of serious illness or death [165]. There is no clear platelet count at which to begin therapy or a goal platelet level. Various factors should be examined for each individual patient including bleeding history, bleeding risk, risk of therapy-related side effects, and concurrent medical problems. Age and a history of a previous hemorrhagic event have been particularly associated with morbidity and mortality [48, 91]. Generally, bleeding is common with platelet counts below 10×10^9/l and rare above 50×10^9/l. The ASH guidelines recommend treatment for all patients with platelet counts less than 20×10^9/l and consideration of withholding treatment (unless significantly bleeding) if platelets are more than 50×10^9/l. With platelet counts between 20×10^9/l and 50×10^9/l, whether to treat or not depends upon the clinical scenario and bleeding status and risk [79]. Response to therapy is also prognostic, with younger patients often responding better to therapy [65, 91].

Initial treatment with corticosteroids

Since the initial description by Damashek et al. in 1958 [50], corticosteroids have remained the treatment of choice for newly diagnosed ITP. They are postulated to work by several mechanisms including decreased platelet clearance by the reticuloendothelial system, decreased antibody production, and possibly through stabilizing capillaries to decrease bleeding [147]. In the largest adult ITP study to date, a favorable response to initial steroid therapy was observed in 65% of 934 patients [164]. Response rates in other adult series were similar and ranged from 74% to 78% [19, 123]. However, a sustained complete remission was seen in only 39% of patients treated within 6 months of diagnosis, and in only 14% of patients with chronic ITP [164]. Other studies have confirmed the relatively low prolonged complete response rate of 20–46% in adults after initial corticosteroid therapy [20, 130]. The correct dosage is not known. Traditionally, 1 mg/kg per day of prednisone has been used, but studies comparing doses ranging from 0.25 mg/kg per day to 1.5 mg/kg per day have shown no clear advantage to higher doses [17, 140]. Another study has shown that patients who fail standard dose prednisone therapy may still respond to high-dose dexamethasone [56], possibly indicating a degree of dose response.

High-dose IVIg

Intravenous immunoglobulin (IVIg) is a polyclonal mixture of immunoglobulins derived from pooled human plasma. Its mechanism of action has traditionally been thought to occur through Fc receptor blockade in reticuloendothelial system tissues, leading to the inability of the spleen and other organs to uptake immunoglobulin-bound platelets. However, the mechanism of action of IVIg is more complicated. It has been shown to interfere with complement activation, modulate cytokine responses, and interfere with B and T lymphocyte function [49, 113]. The treatment is generally well tolerated, but side effects can include allergic reactions, rare viral transmission, fever, renal failure, headaches, aseptic meningitis, and thromboembolic events [49, 79, 113]. IVIg is not felt to be beneficial for the initial management of patients in the non-emergent setting as it does not improve response compared with steroids alone and because its effects are transient [103]. It has long been used in the pre-splenectomy setting, primarily for emergent treatment of ITP-induced bleeding and before splenectomy surgery. It raises the platelet counts within 24 h and the effect can last several days to weeks [46]. Traditionally, the dose has been 2 g/kg intravenously divided over 2 or 5 days. The 2-day regimen is more convenient and maybe slightly more efficacious [124]. The correct dose, however, is unknown. Some evidence points towards a clear dose-related effect, especially when using less than 2 g/kg as the total dose [87], while other studies show equivalence between varying dosages [37, 83]. IVIg has also been used for both pre-splenectomy chronic maintenance therapy, often in an effort to avoid splenectomy. Though a significant minority of patients can maintain adequate platelet counts even after therapy is stopped [34, 35, 83], IVIg for chronic therapy is expensive and often impractical.

Anti-D immunoglobulin

Anti-(Rh) D immunoglobulin has also been used. It generally has the same mechanism of action, except that it binds Rh+ cells before blocking Fc receptors. It is generally safer and cheaper than IVIg, with its main side effect being induction of a Coombs + hemolytic anemia in Rh+ patients. This usually causes a minor, clinically insignificant drop in hemoglobin. The correct dose is uncertain, though 75 μg/kg per day intravenously is often used [157]. As with IVIg, a majority of patients will initially respond to treatment, but platelets ultimately return to baseline in most patients. Chronic maintenance therapy can be used, with a minority of patients achieving complete remission off of therapy [24, 38, 89, 179, 180, 181].

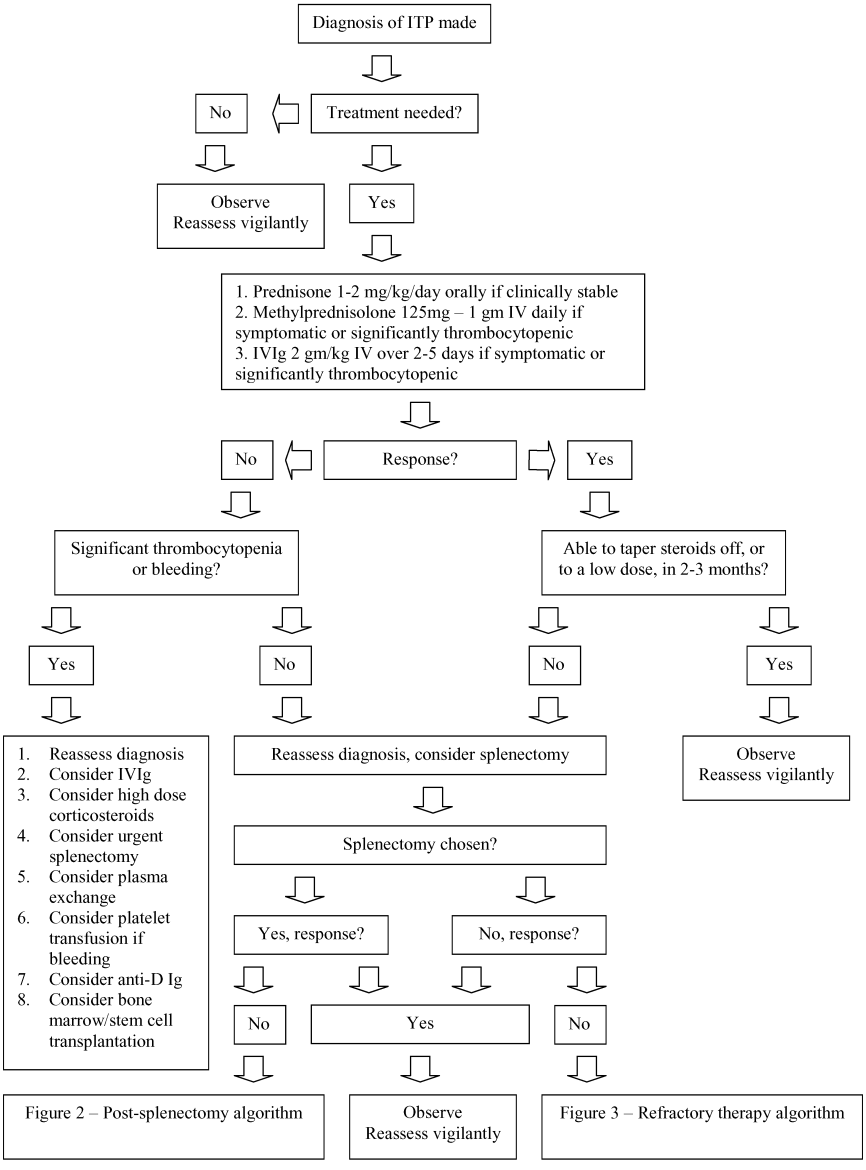

Fig. 1 Pre-splenectomy therapy algorithm

Plasma exchange

Plasma exchange has the advantage of being able to remove the offending autoantibodies from the patient's plasma [33]. It has the potential of working quickly, completely, and safely [33], though it is expensive and time consuming. There is a small risk of transmission of viral diseases or hypersensitivity reactions. Plasma exchange has been shown to work in at least 50% of patients (pre- and post-splenectomy) acutely—even those refractory to steroids and IVIg [21, 33, 36]. Because of expense and logistical difficulties of plasma exchange, IVIg still remains the treatment of choice for quickly raising platelet counts in emergent situations.

Platelet transfusions

Platelet transfusions have generally been thought of as being non-beneficial, though not harmful, in ITP. Concern over immediate sequestration in the reticuloendothelial system by antibody-coated platelets has tempered the enthusiasm for platelet transfusions. Despite this concern, moderate platelet increments have been observed when transfusing ITP patients [41]. Transfusing IVIg immediately prior to platelets has also been shown to be helpful in emergency situations and can improve the platelet increment [15]. In summary, platelet transfusion can be considered for severe, life-threatening bleeding in conjunction with IVIg, steroids, hospitalization, and other aggressive supportive measures [79].

Anti-*Helicobacter pylori* treatment

A recent observation implicates *Helicobacter pylori* as a factor in driving the immune response in ITP. One study involving 51 HIV-negative French Caucasian patients found similar *H. pylori* seroprevalence rates in patients and controls. There was also no difference in the time course, onset, or severity of ITP between patients and controls [148]. Nevertheless, several case reports and series have shown that treating the *H. pylori* infection with a standard 1–2-week cocktail of proton pump inhibitors and antibiotics leads to a platelet response in approximately half of patients, though the range varies widely (13–100%). Most responses are sustained over time [62, 64, 78, 88, 95, 104, 118, 200]. This is a potentially simple and relatively inexpensive way to maintain adequate platelet counts, especially before considering splenectomy.

In summary, the mainstay of pre-splenectomy therapy consists of oral corticosteroids, with IVIg or parenteral corticosteroids given as the urgency of the clinical situation mandates. The other therapies listed above are all considered secondary and to be used in specific scenarios when standard therapy is not effective. Eradication of *H. pylori* is a relatively new therapeutic modality and its role in the management of ITP has yet to be fully defined. Please refer to Fig. 1 for a pre-splenectomy treatment guideline.

Splenectomy

The spleen plays a central role in the pathogenesis of ITP, being involved in the immune response against platelets [144] as well as in their sequestration [90, 155]. Splenectomy as therapy for ITP was initially proposed in 1916 following successful treatment of hemolytic anemia with splenectomy in some patients [114] and used for ITP shortly thereafter [207]. Subsequently, splenectomy remained the treatment of choice until the introduction of corticosteroids in the 1950s [50]. Indications for splenectomy generally include failure to respond to corticosteroids after 4–6 weeks or inability to wean corticosteroids off while maintaining an acceptable platelet count. Steroids should not be maintained for prolonged periods of time due to their well-known side effects including glucose intolerance, weight gain, neuropsychiatric changes, osteoporosis, hypertension, glaucoma, cataracts, change in body habitus, myopathy, etc. Preoperative therapy with corticosteroids or IVIg to maintain a platelet count over 20×10^9/l is appropriate. Platelet counts greater than 50×10^9/l are generally considered adequate for the procedure. Ideally *Haemophilus influenzae* b vaccine, polyvalent (23) *Streptococcus pneumoniae* vaccine, and the quadrivalent *Neisseria meningitidis* vaccine should be given [79].

Traditionally, the open splenectomy has been performed. Over the years, this technique has been perfected and can now be performed with minimal morbidity and almost no mortality. Laparoscopic splenectomy has become the procedure of choice due to its shorter hospitalization times, less blood loss, and less discomfort for the patient. It does require a longer operative time and is technically more demanding for the surgeon [111, 112, 193, 196].

In our experience [123], the overall response rate from splenectomy among 140 consecutive adult patients was 88% (76% complete response and 12% partial response). This is similar to other studies [8, 20, 44, 65, 69, 90, 149, 175, 183, 188]. The response rate of 74% at 12 months post-splenectomy is also similar to what has been reported previously [142]. Approximately 10–20% of complete responders subsequently relapse, generally within 2 years of splenectomy [55]. However, relapses occurring after 9–20 years have been reported [65].

Previous studies have tried to identify factors predicting a favorable response to splenectomy, with mixed results [65, 69, 149, 172, 175]. Many of the earlier studies included both adults and children [149, 183]. We found younger patients had a higher response rate [123], an observation that has previously been made [2, 8, 47, 54, 69]. However, age has not been a consistent predictor for response in other series [90, 149, 175]. A higher post-splenectomy platelet count has generally been predictive of a better response rate in most studies in which it has been evaluated [54, 69, 175]. Rocco et al. found that a platelet count exceeding 60×10^9/l on day 1 after splenectomy was highly predictive for a favorable response [175]. Fenaux et al. in their study observed a similar trend for those with higher day 10 platelet counts [69]. No such correlation was found in another study [149].

We found a higher pre-splenectomy platelet count was predictive when only pre-splenectomy variables were considered. Similar observations have been reported in several other studies. Responsiveness to steroid therapy has been found to be a good predictor of response to splenectomy in several studies [28, 100, 149, 175, 194], whereas others have failed to substantiate the correlation [69, 90, 135, 183]. Patients with a shorter interval between diagnosis and splenectomy may have a better response [2, 54], but most studies have failed to demonstrate such a benefit [69, 90, 149, 175]. As in our patients, a larger spleen size has been found to correlate with better response in one study [23]. Pre-splenectomy response to IVIg has been proposed to be a strong predictor of response [129], though we could not evaluate this variable in our patients. Lack of reliable predictors of splenectomy results is a common theme in most studies [45, 171, 178, 182]. Julie et al. evaluated 61 different variables in their study and found only age and post-splenectomy counts to have a predictive value [106]. We did not find any factors for subsequent relapse after an initial splenectomy.

Some patients may not be able to tolerate splenectomy because of medical comorbidities or refusal of major surgery. Other strategies exist to try to eradicate splenic tissue, including splenic artery embolization and splenic radiation. Initial reports of splenic artery embolization

showed a high rate of complications including splenic rupture and abscess formation. Subsequently, partial splenic embolization was employed as a means of maintaining efficacy while avoiding these complications [152]. This technique can induce a complete response in a significant minority (38% in one study) of patients. These studies include steroid nonresponders and steroid-naïve patients. Most patients had tolerable side effects such as fever, nausea, and vomiting, with a minority experiencing moderate side effects such as pleural effusion and subdiaphragmatic abscess. There were no severe events such as splenic rupture or death [117, 150]. In summary, this is a technique that enjoys moderate success at the expense of moderate morbidity and no mortality in an effort to eradicate splenic tissue while avoiding splenectomy.

Splenic radiation has also been used. Relatively low doses (5–15 Gy) are used and side effects are mild. Subsequent scarring can impede attempts at subsequent splenectomy. Approximately two-thirds of patients can achieve some response with a minority attaining a complete response. Responses are generally short lived, but may respond to subsequent re-irradiation [39, 42].

In summary, splenectomy should be performed in those patients who either do not respond to corticosteroids or who cannot be weaned off of corticosteroids within approximately 2–3 months. While open splenectomy has traditionally been the standard operation, laparoscopic splenectomy has been used extensively and is considered the standard procedure by many now. The other methods of splenic tissue eradication described above have been studied in small cohorts of patients. Not enough information exists to regularly recommend their use. They should be used only in situations where laparoscopic or open splenectomy cannot be performed.

Post-splenectomy treatment

For patients who have failed splenectomy, a variety of treatments can be employed that generally show benefit in a significant minority of patients. Generally the disease is incurable after splenectomy failure, and long-term therapy seeks to minimize treatment side effects while minimizing bleeding episodes by maintaining platelets at satisfactory (though not "normal") levels. Examining the peripheral blood smear for Howell-Jolly bodies, indicating functional asplenism, should be the first step. Patients can have accessory spleens, found in approximately 12–18% of cases [67, 79, 177]. Residual splenic tissue can be imaged with 99-technetium sulfur colloid, 99-technetium heat-damaged red blood cells, or with computed tomographic (CT) scanning [67, 93]. Whether or not accessory splenectomy can lead to a subsequent hematological remission has been the subject of debate. Some case series show complete remissions in greater than 50% of patients [8, 10, 81, 177], while others do not [67]. There has been no proven morbidity or mortality benefit [79]. The role of accessory splenectomy still remains incompletely defined, but should be considered.

Most patients with post-splenectomy failure will require pharmacological therapy. A first priority should be given to avoidance of antiplatelet or anticoagulant agents as well as minimizing trauma and other risk factors for bleeding. Procoagulation adjuncts, such as aminocaproic acid, can be beneficial [14]. A number of immunomodulatory, cytotoxic, and unknown-mechanism agents have been tested. Some studies suggest that immunosuppressive agents may be more effective in splenectomized patients [40, 110]. Response assessment to drugs that are instituted shortly after splenectomy is confounded by the observation that late responses to splenectomy appearing after months to years have been reported [8, 183]. Below, we will summarize the multiple agents that have been used to treat ITP patients who have failed splenectomy. Please refer to Fig. 2 for a therapy algorithm for post-splenectomy failures.

Corticosteroids

As with initial treatment of ITP, steroids are commonly used for post-splenectomy failures [123]. We found that a refractory state prior to splenectomy did not preclude a beneficial response post-splenectomy, with 5 of 31steroid-refractory patients responding to treatment, though 2 of those responses were in combination with vincristine. The response rate in our series for relapsed patients (those that had attained an initial response to steroids) was 81% with a median 7-month duration of response. A sizeable number (44%) of responders maintained their platelet counts off of therapy [123]. Other studies have shown that refractory, pretreated patients can respond to high-dose pulse intravenous or oral steroids [11, 12, 85], though this observation was not universal [51].

Danazol

Danazol, an androgenic steroid, has been tested in several small series with varying levels of success. Results vary wildly, from trials showing up to an initial 80% response rate, a significant minority with prolonged complete remissions, and minimal side effects [4, 7, 31, 60, 120, 137, 156] to a 10% response rate with significant side effects [9, 70, 75, 141, 146]. The balance of available evidence shows that danazol can be a useful agent as long as side effects are monitored and recognized. Dosages varied from 50 mg daily to 800 mg daily, with no clear benefit to higher dosages [6, 119]. Side effects of the therapy include masculinization effects and liver dysfunction. Danazol has been rarely associated with thrombocytopenia when used in the treatment of other disorders [128, 171]. Though most of the aforementioned studies enrolled small numbers of patients, taken as a whole they combine to make danazol one of the most studied agents in ITP. Because of its relatively good success, low

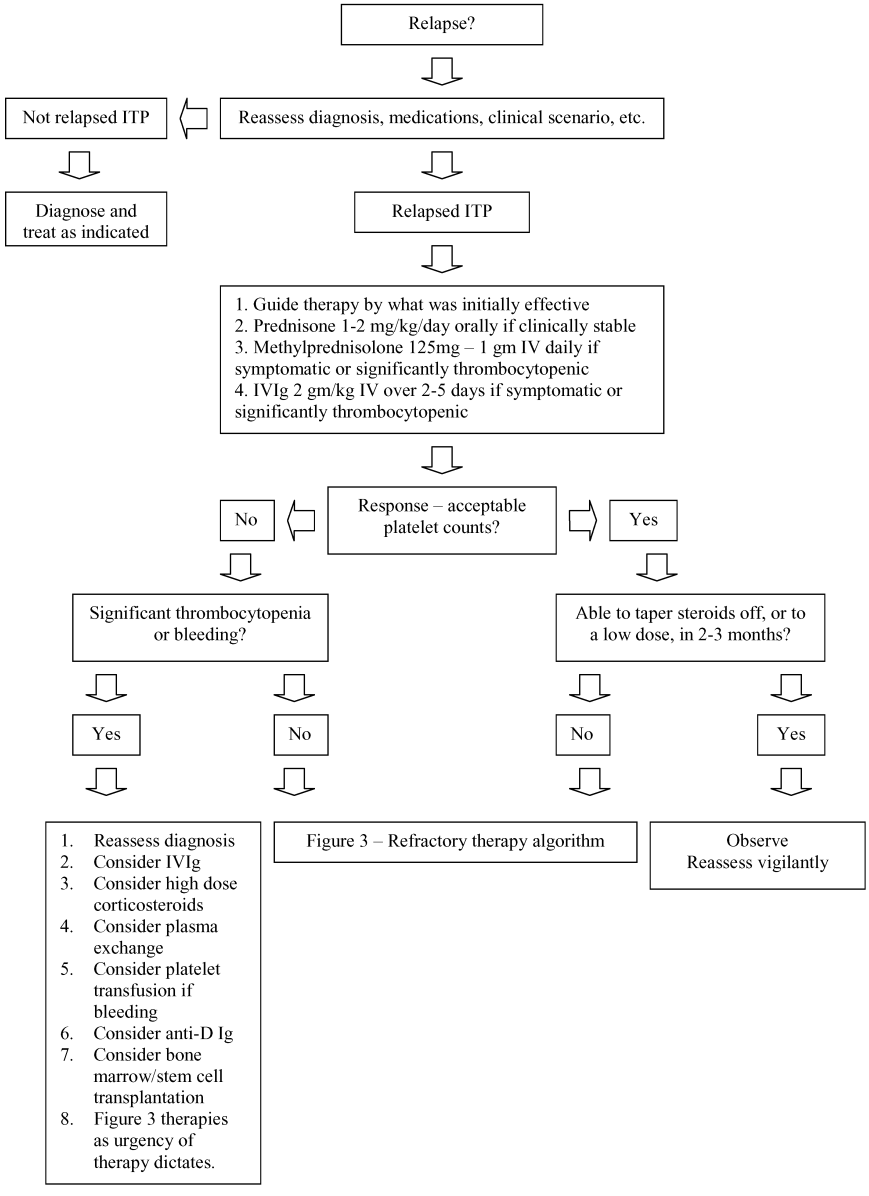

Fig. 2 Post-splenectomy therapy algorithm

toxicity profile, and low cost, danazol should be considered early in the management of patients with post-splenectomy ITP relapse.

Azathioprine

Azathioprine is an antimetabolite immunomodulatory drug that has been used for its steroid-sparing effects in other disorders [210]. Azathioprine has been reported to produce normalization of platelet counts in up to 45% of patients, both pre- and post-splenectomy. In some, this response is maintained even after stopping treatment [170]. Other small series show a majority of patients can obtain at least a partial response [25, 26, 192]. This agent works slowly, so at least 4 months of treatment should be used before considering a patient unresponsive [79]. The drug is generally well tolerated, but can cause bone marrow suppression (mainly leukopenia, but thrombocytopenia is a concern) and increase the risk for neoplasms—especially lymphomas [158]. Dosages usually start at approximately 150 mg/day, but need to be titrated to side effects, most commonly leukopenia. Therefore, doses can vary widely. Azathioprine is less well studied than corticosteroids and adrenal steroids. While it is generally a safe and well-tolerated drug, it does have the potential for second malignancies, other cytopenias, and slow onset of action. These qualities make azathioprine a possibly useful agent after other therapies have failed in the post-splenectomy setting.

Mycophenolate mofetil

Mycophenolate mofetil, another purine nucleotide synthesis inhibitor, has been shown in one small study to have a response in five of six patients, implicating a future role for it [96]. Side effects include dyspepsia, bone marrow suppression, and risk of developing lymphoma [52]. As with azathioprine doses must be titrated, but generally range from 500 mg to 2000 mg daily, split into two doses. This drug, while promising, has not been studied enough to routinely recommend it.

Cyclosporine

Cyclosporine has also been used to treat chronic post-splenectomy ITP by interfering with lymphocyte function. It can have multiple side effects, including hirsutism, risk for neoplasia, gingival hyperplasia, renal insufficiency, and hypertension [199]. Cyclosporine is usually given at a maintenance dose of 3 mg/kg per day with or without prednisone (approximately 0.4 mg/kg per day). The dose is titrated to maintain a level of 200–400 ng/ml. Three studies show that in chronic ITP, both pre- and post-splenectomy, an initial response of approximately 75% can be attained, with approximately 40% of responders staying in remission while off of cyclosporine for several months [61, 63, 109]. The cost, side effects, need for drug levels, and potential for neoplasia make cyclosporine an attractive agent in only highly refractory, heavily pre-treated patients.

Dapsone

Dapsone has also been used as a therapy. It is generally well tolerated, though it can cause nausea, vomiting, headache, methemoglobinemia, and hemolytic anemia, especially in those who are glucose-6-phosphate-dehydrogenase deficient [74]. In one study, 62% of non-HIV patients responded, with a substantial percentage of those maintaining platelet counts after dapsone was stopped [84]. Other series, of both pre- and post-splenectomy patients, show response rates from 40% to 100% with generally mild side effects—most commonly mild hemolytic anemia [58, 86, 94]. Doses generally range from 75 mg to 100 mg daily. The side effects and general lack of familiarity of many physicians with this agent make it difficult to recommend.

Cyclophosphamide

Cyclophosphamide has also been tried, both in oral daily dosages as well as intermittent intravenous pulsing. Cyclophosphamide is an alkylating agent that interferes with DNA function [176]. It increases platelet counts in 55–100% of patients and induces a sustained complete response in a substantial minority for several years after stopping therapy [127, 174, 202, 205]. Cyclophosphamide was used for therapy in four of our patients with a complete response in three. This response was sustained in two with a fourth patient having a partial unsustained response [123]. Cyclophosphamide has a number of potentially troublesome side effects, including bone marrow suppression, hemorrhagic cystitis, infertility, teratogenicity, myeloid dysplasia, and leukemia with prolonged administration [151]. Cyclophosphamide can be given on a daily oral schedule, often at 1–2 mg/kg per day (usually 100–200 mg daily) and titrated to mild leukopenia. For intermittent IV bolus, one study used 1–1.5 mg/m^2 intravenously [174]. While this dose can cause a significant nadir in blood counts, nausea, vomiting, and mucositis, it is generally well tolerated and can be given as an outpatient therapy. While cyclophosphamide is familiar to hematologists, the potential for late toxicities make it difficult to routinely recommend as an initial treatment for post-splenectomy treatment failures.

Vinca alkaloids

Vinca alkaloids have been one of the most studied agents in the management of chronic ITP. The agents inhibit microtubule polymerization and are used widely as cytotoxic chemotherapy. They are attractive agents because they can be given intravenously periodically and are well tolerated, with the possible exceptions of bone marrow suppression with vinblastine and neuropathy with its attendant complications [121]. Different preparations (vincristine, vinblastine, and vinblastine-loaded platelets) have been tested with varying schedules (bolus, continuous infusion). Seven patients in our series received therapy with vinca alkaloids with excellent responses [123]. However, most of these patients were being treated simultaneously with steroids or danazol, making an objective assessment of efficacy difficult. Vincristine, the classic vinca alkaloid, has been tested in chronic ITP in both pre- and post-splenectomy patients. It is generally given as an intermittent intravenous infusion, at least 1 week between infusions at a dose of 1–2 mg. It shows a complete response rate of 25–50% with overall responses of approximately 70%, though many of these are short-lived [1, 5, 32, 43, 133, 136, 138]. Vinblastine shows a similar overall response rate of approximately 67% [68, 71, 185]. Dose is usually 0.1 mg/kg with a maximum of 10 mg per treatment at least 1 week apart. Prolonged (6–8 h) infusions to increase the drug's "area-under-the-curve" have no convincing clinical benefit over bolus dosing for either vincristine [5] or vinblastine [68, 71, 185], though only one study tested modes of delivery head to head [68]. In one study, vinblastine-incubated ("loaded") platelets showed an 82% response rate [3]. Another study, however, showed that 19% of patients had an initial drop in their platelets [115]. The process of "loading" the platelets also took more time and expense than standard intravenous dosing. In summary, the ease of administering bolus doses, lack of long-term side effects

(other than neurotoxicity), familiarity to hematologists, and patient tolerability make vinca alkaloids attractive agents to use. The major drawback is the relatively short-lived responses, necessitating frequent treatment.

Combination chemotherapy

Combination chemotherapy has been used in severe, refractory post-splenectomy cases. In one report, cyclophosphamide- and prednisone-based chemotherapy regimens have shown a 60% complete response rate, with 67% of those responses being durable [73]. A follow-up report confirmed this success [145]. Another chemotherapeutic agent that has been shown to be ineffective is 2-chlorodeoxyadenosine [72]. These agents should only be used in severe, refractory cases of ITP, preferably in a clinical trial setting.

High-dose IVIg

IVIg has also been used in the post-splenectomy setting as chronic maintenance therapy. The details of IVIg's mechanism of action and side effects are described above. In one study of 30 post-splenectomy patients, 37% could stop further treatment with 45% of those maintaining a complete remission [35]. Other studies show that most patients get a good response after each infusion of maintenance IVIg, but ultimately platelet counts return to baseline [162, 197]. Once again, the treatment is expensive and often impractical, due to the need for periodic IV infusions, to be used routinely.

Anti-D immunoglobulin

Anti-(Rd) D immunoglobulin has been tried for chronic maintenance therapy in post-splenectomy adults with little success [38, 180]. In one study, the 11 enrolled splenectomized patients had an overall response rate of 45%, but responses were transient, suboptimal, and required higher doses of anti-D immunoglobulin. The authors concluded it was not an effective treatment in the post-splenectomy patient with ITP [180]. The other study had no responses in the three post-splenectomy patients they enrolled [38]. This agent cannot be routinely recommended at this time.

Plasma exchange

Plasma exchange has also been used for post-splenectomy treatment. A few reports indicate successful treatment, but evidence is generally lacking [27, 36, 101]. Other reports indicate failure of post-splenectomy patients to respond to plasma exchange [139, 206]. Likewise, this agent cannot be routinely recommended at this time.

Interferon

Interferon is another immunomodulatory agent that has been used. Most commonly, interferon-alpha-2B at a dose of 3 million units subcutaneously three times weekly for 4 weeks has been studied. In several small series enrolling both chronic pre- and post-splenectomy patients, initial response rates varied widely from 11% to 100%, with many responses short-lived [18, 57, 77, 97, 99, 122, 166, 167, 168, 184, 203]. Side effects can be noticeable, including fevers, exacerbation of other autoimmune diseases, thyroid dysfunction, asthenia, and bone marrow suppression—particularly thrombocytopenia. These side effects, except for generalized malaise and weakness, were generally manageable at the described doses. While well studied, the significant side effects, expense, and need for frequent dosing make this agent unattractive for the therapy of post-splenectomy ITP.

Staphylococcal protein A immunoadsorption

Immunoadsorption using staphylococcal protein A columns theoretically pulls the offending autoantibody out of the patient's serum during plasmapheresis. The largest series showed an overall response rate of 46% and a complete response rate of 25%, with most responses being durable [187]. In several small series, response rates of 41–100% have been reported in chronic pre- and post-splenectomy patients [13, 66, 92, 169]. Most treatments are complicated by fever, chills, nausea, vomiting, and allergic reactions, which are generally tolerable and partially ameliorated by steroids. Cases of more severe immune complex-mediated reactions, such as leukocytoclastic vasculitis, have been reported [59, 107]. Side effects and the need for expensive, time-consuming apheresis make this an impractical therapy.

Vitamin C

Vitamin C (ascorbic acid) has been tested as a safe, cheap, well-tolerated method to increase platelets both pre-splenectomy and post-splenectomy. While an initial report showed an excellent response to 2 g daily of ascorbic acid [29], multiple subsequent series showed only a 10–15% sustained response rate. These studies had a mix of chronic pre- and post-splenectomy patients [18, 82, 105, 160, 195, 198, 201, 209]. Though safe and inexpensive, general lack of efficacy relegates ascorbic acid to a small role in the management of post-splenectomy ITP.

Colchicine

Colchicine is another inexpensive, well-tolerated treatment that has been minimally studied. One report showed an overall response rate of 29% in 14 patients refractory

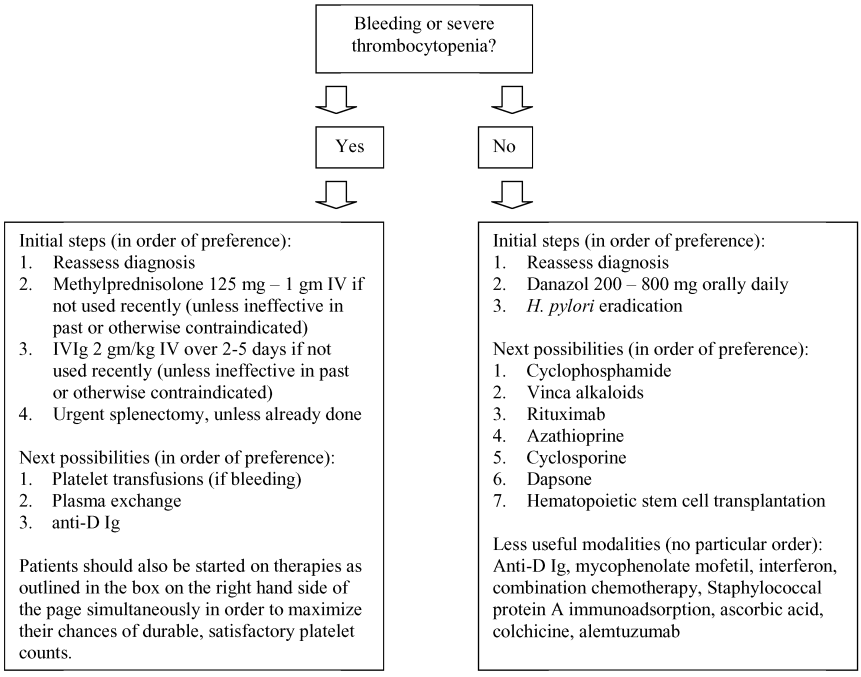

Fig. 3 Chronic, refractory therapy algorithm

to splenectomy and steroids at a dose of 1.2 mg daily for at least 2 weeks [191]. While inexpensive and well tolerated (mild dyspepsia and diarrhea), there is a scarcity of information on this agent to routinely recommend its use.

Rituximab

Rituximab is a humanized monoclonal antibody that targets $CD20^+$ B lymphocytes that ultimately produce antibodies. A large study by Stasi et al. reported on rituximab therapy in 25 chronic ITP patients, 8 of whom had failed splenectomy [189]. Standard dosing would be 375 mg/m^2 IV once weekly for 4 consecutive weeks. Of 25 patients, 13 had a response (5 complete responses, 5 partial responses, and 3 minor responses) with 7 durable beyond 6 months. In a follow-up report, these same investigators reported six of seven additional patients experienced a response to rituximab (four complete responses, two partial responses). Some responses occurred up to 5 weeks after the final rituximab dose with peak counts not coming until 6–12 weeks after the final infusion [190]. In our own experience of 12 adults with ITP treated with rituximab, the complete response rate was 42% (unpublished). Another prospective study of 12 highly pretreated post-splenectomy ITP patients demonstrated a complete response rate of 42% with all complete responses lasting at least 6 months [80]. Stasi et al. have postulated two mechanisms by which rituximab may improve thrombocytopenia in patients with ITP, speculating that early responses are mediated by opsonized B cells blocking Fc receptors in the reticuloendothelial system and late responses are mediated by decreased production of antiplatelet antibodies [190]. Rituximab is generally well tolerated, though is expensive and can cause fevers and severe, sometimes fatal, allergic hypersensitivity reactions. Its role has yet to fully be defined. Though expensive and associated with infusion reactions, the early successes and high rate of durable responses make this an attractive agent for therapy for chronic, refractory post-splenectomy ITP. Future study will determine rituximab's place in the therapeutic armamentarium for ITP. Patients should ideally be treated in a research protocol setting to facilitate this.

Alemtuzumab

Alemtuzumab is a monoclonal antibody against CD52, a pan-lymphoid marker. This antibody has been used as therapy for ITP. In one study of patients with a variety of immune thrombocytopenias, three of five evaluable patients showed a response of at least 4 months duration [131]. Another study of severe, life-threatening immune cytopenias enrolled only one ITP patient, but showed a response in 71% of the patients [208]. Side effects can be significant, including fevers, hypersensitivity reactions, cytopenias, and severe CD4 lymphocyte suppression. Administration can also be inconvenient, with up to three times weekly dosing, given either intravenously or subcutaneously. Dosing usually starts at 3 mg/kg three times weekly and is titrated up to a maximum dose of 30 mg/kg three times weekly for up to 12 weeks as blood counts and infusion reactions allow, though in one study it was given as 10 mg IV daily over 4 h on 10 consecutive days [208]. Compared with rituximab, the need for

frequent dosing, significant immunosuppression, and limited data make alemtuzumab a clearly inferior agent.

Hematopoietic stem cell transplantation

Bone marrow transplant has shown promise as a potentially curative, though radical, treatment of refractory severe ITP. The goals of therapy would primarily involve immunomodulation of the existing host lymphocytes to downregulate antibody production. Autologous CD34(+) selected stem cells have been most frequently tested. One report showed a 57% response rate (n=14) for autologous CD34(+) peripheral blood stem cell transplant (PBSCT) [98]. Other small series with several months worth of follow-up per patient have shown mixed results from sustained complete responses [132] to no response [186]. Nonmyeloablative autologous PBSCT has also been tested with limited success [153]. Initial reports of patients receiving matched related peripheral blood or bone marrow allogeneic transplants have not been favorable, with significant morbidity and mortality [163, 173]. Hematopoietic stem cell transplantation should be undertaken only in highly refractory, severely symptomatic patients in centers familiar with transplantation for this indication. It cannot be routinely recommended at this time.

In summary, the therapy of post-splenectomy treatment failures remains challenging for the clinician as well as the patient. Initial pharmacological therapy should include corticosteroids, especially if initially effective. Other agents to consider early include *H. pylori* eradication, danazol, azathioprine, rituximab, cyclophosphamide, and vinca alkaloids. Agents to consider after that include cyclosporine, mycophenolate mofetil, dapsone, and ascorbic acid. Other agents should be considered only in selected clinical scenarios. Please refer to Fig. 3 for our guidelines to the management of chronic, refractory ITP.

The Future

Other areas of research are ongoing. One involves interfering with the interaction of CD40 on antigen presenting cells and CD154 (CD40 ligand) on CD4(+) T cells by using anti-CD154 monoclonal antibodies. In vitro studies show this might decrease the formation of pathogenic antiplatelet antibodies [125, 126, 154]. Trials with thrombopoietin have also been started. One early report showed a dramatic platelet response, to higher than normal levels, in two of four patients with ITP who were treated with pegylated recombinant human megakaryocyte growth and development factor. The response was transient however [159]. The results of future studies are eagerly anticipated.

Conclusion

The treatment of ITP remains challenging for the clinician. Standard treatment has remained the same for decades, primarily consistent of corticosteroids and splenectomy. Advances are being made primarily in the area of management of patients who fail splenectomy. New treatments are moving away from typical cytotoxic chemotherapeutic agents towards therapies that modulate the immune system. Newer treatments should have the benefit of fewer side effects while equal if not better response rates than traditional therapies. The future of these "targeted" therapies looks bright and results of current trials are eagerly anticipated over the next several years.

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