Sequence of treatments for adults with primary immune thrombocytopenia

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Management of adults with primary immune thrombocytopenia (ITP) has changed dramatically in the past 10 years. New regimens of corticosteroids for first-line treatment have been introduced and are currently being evaluated in a randomized clinical trial. Many patients may not have durable remissions with initial corticosteroid regimens and may require additional, second-line, treatment. For these patients, rituximab has been increasingly used, as it has for other autoimmune disorders, and new thrombopoietin (TPO)-receptor agonists have been developed. Although splenectomy was the first effective and remains the most effective treatment for ITP, inducing durable complete remissions in 66% of patients, rituximab and TPO-receptor agonists are now additional options for second-line treatment. For patients who continue to have severe and symptomatic thrombocytopenia following failure of multiple treatments, including splenectomy and rituximab, the TPO-receptor agonists are effective as third-line treatment for maintaining safe platelets counts to prevent bleeding symptoms in most patients. Am. J. Hematol. 87:S12–S15, 2012.

Introduction

Evolution of treatment for adults with primary immune thrombocytopenia

Until 10 years ago, the sequence of treatments for adults with primary immune thrombocytopenia (ITP) was rarely discussed. Corticosteroids were the initial (first-line) treatment, typically with a prednisone regimen of 1 mg/kg/day. Initial treatment was considered to be appropriate for all adult patients with severe thrombocytopenia, often defined as a platelet count less than 30,000/μL, because it was assumed that ITP in adults was typically a chronic, persistent disorder, in contrast to young children in whom ITP is expected to spontaneously resolve in most patients [1]. If corticosteroids did not induce a response, or if symptomatic thrombocytopenia recurred when they were tapered and discontinued, then splenectomy was considered to be the next appropriate (second-line) treatment [1]. Splenectomy had a 60-year record of success for achieving durable remissions, defined by a normal platelet count with no requirement for additional treatment, in approximately two-thirds of patients [2,3]. In fact, before the availability of corticosteroids in 1950, splenectomy had been the first-line treatment for ITP [2]. Following failure of splenectomy, many different immunosuppressive agents and combination regimens were used (third-line), often with unsatisfactory results and substantial toxicities [4].

The change of management of adults with ITP during the past 10 years has been dramatic. For first-line treatment, alternative regimens of corticosteroids were proposed for initial treatment and were reported to have greater efficacy for achieving durable responses [5,6]. For second-line treatment, rituximab began to be used as an alternative for splenectomy [7–9] Two thrombopoietin (TPO)-receptor agonists, romiplostim (Nplate®), and eltrombopag (Promacta®) have been studied in randomized clinical trials during the past 10 years in both splenectomized and nonsplenectomized adults with ITP, and have been documented to be effective for increasing platelet counts and decreasing need for other therapies [10–15]. Both agents were approved by the FDA in the United States and the EMEA in Europe for treatment of adults with ITP in 2008. In the United States, the approval was for "adults with insufficient response to corticosteroids, immunoglobulins, or splenectomy"; in Europe, the approval was more restrictive, for "splenectomized adults who are refractory to other treatments. May be considered second-line for non-splenectomized adults where surgery is contraindicated". Although the most important clinical benefit of the TPO-receptor agonists was for patients who had failed to respond to splenectomy and rituximab (third-line treatment), it has also become an option (in the United States) as a second-line treatment, as an alternative to splenectomy and rituximab. A summary of the current common sequence of treatment options is presented in Table I.

First-line treatment for adults with ITP

The decision between the two current corticosteroid regimens for first-line treatment is not critical; both are effective in most patients; either may have an advantage for individual patients. Daily prednisone and pulses of high-dose dexamethasone are currently being compared in a randomized, double-blind, placebo-controlled clinical trial by the Transfusion Medicine/Hemostasis Clinical Trials Network of the National Heart, Lung, and Blood Institute (NCT00991939). A recent report described a comparison between pulses of high-dose dexamethasone with or without rituximab as first-line treatment [16]. Dexamethasone plus rituximab had more frequent and more durable responses. However, rituximab is not mentioned as an appropriate first-line treatment by two recent systematic reviews and guidelines for management of ITP [17,18].

Third-line treatment for adults with ITP

Similarly the decision for third-line treatment is also not critical. TPO-receptor agonists appear to have the best

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TABLE I. Sequence of Treatments for Adults with ITP

Indication for treatment	Treatment
First-line treatment Platelet count <30,000/μL, or symptomatic bleeding	Corticosteroids: daily oral prednisone, or dexamethasone, 40 mg/d x 4 days IVIg or anti-D: appropriate additional treatment for patients with overt bleeding
Second-line treatment (after failure of initial corticosteroid treatment) Platelet count <20,000/μL, or symptomatic bleeding	Splenectomy Rituximab TPO-receptor agonists
Third-line treatment (after failure of splenectomy and rituximab) Platelet count <20,000/μL, or symptomatic bleeding	TPO-receptor agonists Immunosuppressive agents: as adjunctive treatment if TPO-receptor agonists are insufficiently effective, or as alternative treatment if no response to TPO-receptor agonists

The current common sequence of treatment of adult patients with ITP is presented. The platelet count indications for treatment are empirical, considered to be the approximate threshold for risk for clinically important bleeding symptoms. The platelet count indication for second-line and third-line treatment is lower, because the treatments may have greater risk.

record for benefit and may also have the least risk, although long-term clinical experience is still limited. Regimens of combined immunosuppressive agents may be beneficial if the response to TPO-receptor agonists is not sufficient to prevent symptoms or if an attempt to induce a remission is considered [19].

Second-line treatment for adults with ITP

Therefore this discussion focuses on the options for second-line treatment of adults with ITP. Because many adults will fail to achieve a durable remission with corticosteroids and may have severe and symptomatic thrombocytopenia, and because the long-term side effects of corticosteroids are unacceptable [20,21], second-line treatment will be required in most patients. The distinctions between the three principal options are great. Table II describes the advantages and disadvantages, the benefits and risks for each of the three options: splenectomy, rituximab, and the TPO-receptor agonists. The first distinction is between treatments that can induce a remission, hopefully a durable complete remission, by modifying the disease process (splenectomy, rituximab) and treatments that provide symptomatic benefit by maintaining higher platelet counts as long as treatment is continued to prevent bleeding symptoms without modifying the disease process (TPO-receptor agonists). If disease-modifying treatment is selected, then the second distinction is between splenectomy and rituximab.

Splenectomy. The potential benefits of splenectomy are clear. Splenectomy was the first effective treatment and is still the most effective treatment for ITP [3]. The biologic rationale for the principal role of the spleen in the pathogenesis of ITP was documented 50 years ago in studies of infusions of ITP plasma into normal subjects to induce thrombocytopenia [22]. Subjects who had had a splenectomy required six-fold more plasma to achieve the same degree of thrombocytopenia [22]. In a systematic review of all 130 articles reporting 15 or more consecutive patients who had splenectomy for ITP across 58 years, splenectomy consistently achieved a complete remission (defined as a normal platelet count requiring no further treatment for the duration of observation, 1–153 months; median 29 months) in 66% of patients; a partial response occurred in an additional 22% of patients; recurrence of ITP was uncommon, documented by consistent rates of complete remissions across all case series regardless of the duration of follow-up [3]. No presurgical parameter other than age predicted the response to splenectomy; younger patients responded better [3]. A recent report suggested that ^{111}In-labeled autologous platelet scanning can predict which patients will not respond to splenectomy [23], but a systematic review of all reports of ^{111}In-labeled autologous platelet scanning concluded that the results did not provide sufficient evidence to support a decision to proceed with or withhold splenectomy [24]. Surgical complications are less common with current practice of laparoscopic procedures, but are still significant. Surgery-related mortality in 29 reports of laparoscopic splenectomy for ITP was 0.2% (3 of 1301 patients); complications requiring additional treatments occurred in 9.6% of patients [3]. The long-term risks of infection and thrombosis have been emphasized as an important reason to avoid splenectomy. Although overwhelming and fatal sepsis with *Streptococcus pneumoniae* and related microorganisms can occur, it is extremely rare and may be prevented by appropriate immunizations and immediate treatment with appropriate antibiotics kept at home. Beyond 1 year after splenectomy for ITP, the increased relative risk for severe infection among splenectomized patients compared to ITP patients without splenectomy was not significant, 1.4 (95% CI, 1.0–2.0) [25]. An additional concern is the long-term risk for thrombosis [26]. Although the relative risk for venous thrombosis among patients who had had a splenectomy for ITP compared with appendectomized patients in a population-based cohort study was 2.6, the difference was not significant (95% CI 0.9–7.1) [27].

Rituximab. Less data are available to document the frequency of durable remissions and the frequency of side effects of rituximab than are available for splenectomy. A systematic review reported that a complete platelet count response (platelet count more than 150,000/μL) was achieved in 44% (95% CI, 30–58%) of patients and an overall response (platelet count more than 50,000/μL) was achieved in 63% (95% CI, 53–73%) of patients [8]. Median response duration was only 10.5 months [8]. Other studies have reported response rates of 31% [7] and 33% [9]. The data on risks from rituximab treatment of patients with ITP are not conclusive. The systematic review reported that 10 (3.7%) of 306 patients had severe or life-threatening toxicities and 9 (2.9%) died. A study of rituximab treatment of 36 children and adolescents with chronic ITP reported that two (6%) children developed serum sickness and one (3%) developed primary varicella infection [7]. A study of 60 adults reported one patient (2%) who developed serum sickness; this was the only patient who was required to discontinue treatment [9]. A rare but devastating side effect of rituximab is progressive multifocal leukoencephalopathy. One report described 57 patients who developed progressive multifocal leukoencephalopathy at a median time of 5.5 months after their last dose of rituximab; 90% died; one of the 57 patients had been treated for ITP [28].

TPO-receptor agonists. The TPO-receptor agonists are very effective for achieving durable increased platelet counts but this requires continuous treatment [10–15]. Patients treated with TPO-receptor agonists compared to

TABLE II. Advantages and Disadvantages of the Principal Options for Second-Line Treatment of ITP

Second-line treatments	Advantages	Disadvantages
Splenectomy	1. The first effective treatment for ITP, with over 60 years of experience 2. The most effective treatment for ITP, with 66% durable complete remissions and an additional 22% partial remissions	1. Surgical procedure has a 0.2% mortality and 10% frequency of complications 2. Rare occurrence of overwhelming pneumococcal sepsis years after splenectomy 3. Possible increased risk for arterial or venous thrombosis
Rituximab	1. Nonsurgical treatment 2. Extensive experience since first reported use for ITP, 1999 3. Initial platelet count response in 31–63% of patients; responses at 2 years with no additional treatment in 31%	1. Reported follow-up durations are short; 10–20% of patients may relapse within 2 years. 2. Severe toxicities (anaphylactic, serum sickness, pulmonary, infectious) in 2–6% of patients
TPO-receptor agonists	1. Nonsurgical treatment 2. Daily oral agent, or weekly subcutaneous injection with the potential for self-administration 3. Platelet count response in approximately 80% of patients, including patients who have failed splenectomy and rituximab	1. Long-term, perhaps permanent, treatment is anticipated; platelet count is supported but clinical course of ITP is apparently not modified 2. Long-term risks have not been sufficiently documented. 3. Potential risks are marrow fibrosis and thrombosis; hepatic and ocular toxicities have been reported with eltrombopag

Data for splenectomy: durable complete remissions defined as a normal platelet count (more than 150,000/μL) on no additional treatment for the duration of observation; partial response defined as a platelet count more than 50,000/μL for at least 30 days; adverse events previously described [3]. Data for rituximab: good response defined as a platelet count more than 50,000/μL with no additional treatment; adverse events described [7–9]. Data for TPO-receptor agonists adapted from [10–15].

"standard of care" (without splenectomy) had more sustained platelet count responses, less bleeding and fewer transfusions, decreased requirement for other treatments including splenectomy, and improved quality-of-life [14]. TPO-receptor agonists are promoted as safer treatments that can avoid the toxicities of splenectomy and rituximab. Data from the clinical trials of romiplostim and eltrombopag support the safety of these agents, but the duration of their broad community use is not long, and since TPO-receptor agonists are maintenance treatments which require continued, perhaps permanent, use, more experience will be required to provide confidence of safety.

Recommendations of guidelines for treatment of ITP

The choice among these three options for second-line treatment of adults with ITP has been addressed in two recent guidelines, an International Consensus guideline [17] and the updated American Society of Hematology (ASH) guideline (Table III) [18].

Splenectomy. In the Consensus guideline [17] splenectomy was given a recommendation grade of C (evidence Level IV), the lowest level of recommendation and evidence. However, the basis for this recommendation was unclear. The statement with this recommendation was a sentence recommending to "wait at least 6 months from diagnosis before performing splenectomy due to the chance of spontaneous remission". However no articles in the evidence tables addressed the timing of splenectomy. The previous sentence stated that "splenectomy remains the treatment option with by far the highest likelihood of producing cure", but this sentence was not followed by a recommendation grade. The citations listed for splenectomy would correspond to a recommendation Grade of B, not a Grade of C. The ASH guideline [18] gave a strong recommendation (Grade 1) for splenectomy as the treatment for patients who have failed initial corticosteroid therapy supported by an intermediate level of evidence (Level B).

Rituximab. The Consensus guideline [17] gave a recommendation grade of B for treatment with rituximab, without distinction between patients who have or have not had a splenectomy. The ASH guideline [18] gave a weak recommendation rituximab (Grade 2) supported by a weak level of evidence (Level C). Both guidelines cited the same systematic review [8]. The weak recommendation for rituximab by the ASH guideline was based on the relatively poor durable response rate and the relatively high frequency of adverse effects.

TABLE III. Second-line and Third-Line Treatments for ITP: Recommendations of the International Consensus Report and the American Society of Hematology Practice Guideline

	Strength of recommendation	
Treatments	Consensus report	ASH guideline
Second-line treatments		
TPO receptor agonists	A	2C
Rituximab	B	2C
Splenectomy	C	1B
Third-line treatment		
TPO receptor agonists	A	1B

For the International Consensus Report (Consensus guideline), [17] the levels of evidence and recommendations were linked together: A, strong recommendation based on evidence from randomized clinical trials (RCT); B, intermediate recommendation based on evidence other well-designed studies; C, weak recommendation based on expert opinion and clinical experience. For the ASH Practice Guideline (ASH guideline), [18] the levels of evidence and recommendations were assessed according to the GRADE system [29] and were not linked; strong (grade 1) or weak (grade 2) recommendations could be associated with any level of evidence: level A, RCT or exceptionally strong observational studies; level B, RCT with important limitations or strong observational studies; level C, RCT with serious flaws or weaker observational studies. Therefore in the ASH guideline, 1A is a strong recommendation supported by the strongest evidence; 2C is a weak recommendation supported only by the weakest evidence.

TPO-receptor agonists. The Consensus guideline [17] gave a recommendation Grade of A for treatment with TPO-receptor agonists for patients either before or after splenectomy, based on randomized clinical trials evaluating romiplostim and eltrombopag compared to placebo in patients receiving standard of care, with or without previous splenectomy (evidence Level I) [11–13]. The ASH guideline, citing the same randomized clinical trials [11–13], distinguished between patients who have not had a splenectomy and patients who relapse after a splenectomy or in whom a splenectomy is contraindicated. The ASH guideline gave a weak recommendation (Grade 2) supported by a weak level of evidence (Level C) for patients who have not had a splenectomy. The basis for the weak recommendation was infrequent sustained remissions when treatment with TPO-receptor agonists is discontinued and the lack of long-term follow-up for adverse events. For patients who relapse after a splenectomy or in whom a splenectomy is contraindicated, TPO-receptor agonists were given a strong recommendation (Grade 1) supported by an intermediate level of evidence (Level B).

Summary

The data and recommendations of current guidelines demonstrate the great variability of opinion and interpretation of current data for treatment of adults with ITP. The important lesson from these guidelines is that management must be adapted to the patient's condition and that decisions must be shared by both physician and patient.

References

1. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: A practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996;88:3–40.
2. Doan CA, Bouroncle BA, Wiseman BK. Idiopathic and secondary thrombocytopenic purpura: Clinical study and evaluation of 381 cases over a period of 28 years. Ann Int Med 1960;53:861–876.
3. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: A systematic literature review to assess long-term platelet count responses, prediction of response, and surgical complications. Blood 2004;104:2623–2634.
4. Vesely SK, Perdue JJ, Rizvi MA, Terrell DR, et al. Management of adult patients with idiopathic thrombocytopenic purpura after failure of splenectomy. A systematic review. Ann Int Med 2004;140:112–120.
5. Cheng Y, Wong RSM, Soo YOY, et al. Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. New Eng J Med 2003;349: 831–836.
6. Mazzucconi MG, Fazi P, Bernasconi S, et al. Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patinets affected by idiopathic thormbocytopenic purpura: A GIMEMA experience. Blood 2007;109:1401–1407.
7. Bennett CM, Rogers ZR, Kinnamon DD, et al. Prospective phase I/II study of rituximab in childhood and adolescent chronic immune thrombocytopenic purpura. Blood 2006;107:2639–2642.
8. Arnold DM, Dentali F, Crowther MA, et al. Systematic review: Efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Int Med 2007;146:25–33.
9. Godeau B, Porcher R, Fain O, et al. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura: Results of a prospective multicenter phase 2 study. Blood 2008;112:999–1004.
10. Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. New Eng J Med 2007;357: 2237–2347.
11. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: A double-blind randomized controlled trial. Lancet 2008;371:395–403.
12. Bussel JB, Provan D, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: A randomized, double-blind, placebo-controlled trial. Lancet 2009;373:641–648.
13. Bussel JB, Kuter DJ, Pullarkat V, et al. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. Blood 2009;113:2161–2171.
14. Kuter DJ, Rummel M, Boccia R, et al. Romiplostim or standard care in patients with immune thrombocytopenia. New Eng J Med 2010;363:1889–1899.
15. Cheng G, Saleh MN, Marcher C, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): A 6-month, randomized, phase 3 study. Lancet 2011;377:393–402.
16. Zaja F, Baccarani M, Mazza P, et al. Dexamethasone plus rituximab yields higher sustained response rates than dexamethasone monotherapy in adults with primary immune thrombocytopenia. Blood 2010;115:2755–2762.
17. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168–186.
18. Neunert CE, Lim W, Crowther MA, et al. The American Society of Hematology 2011 evidenced-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190–4207.
19. Arnold DM, Nazi I, Santos A, et al. Combination immunosuppressant therapy for patients with chronic refractory immune thrombocytoenic purpura. Blood 2010;115:29–31.
20. Guidry JA, George JN, Vesely SK, et al. Corticosteroid side-effects and risk for bleeding in immune thrombocytopenic purpura: Patient and hematologist perspectives. Eur J Haematol 2009;83:175–182.
21. Guidry JA, Watson SP, George JN, et al. Addendum to corticosteroid side effects and risk for bleeding in immune thrombocytopenic purpura: Patient perspectives. Eur J Haematol 2009;83:497–498.
22. Shulman NR, Weinrach RS, Libre EP, Andrews HL. The role of the reticuloendothelial system in the pathogenesis of idiopathic thrombocytopenic purpura. Trans Assoc Amer Phys 1965;78:374–390.
23. Sarpatwari A, Provan D, Erquo S, et al. Autologous ^{111}In-labeled platelet sequestration studies in patients with primary immune thrombocytopenia (ITP) prior to splenectomy: A report from the United Kingdom ITP Registry. Br J Haematol 2010;151:477–487.
24. Cuker A, Cines DB. Evidence-based mini-review: Is Indium-labeled autologous platelet scanning predictive of response to splenectomy in patients with chronic immune thrombocytopenia? Hematology Am Soc Hematology Educ Program 2010;385–386.
25. Thomsen RW, Schoonen WM, Farkas DK, et al. Risk for hospital contact with infection in patients with splenectomy. A population-based cohort study. Ann Int Med 2009;151:546–555.
26. Crary SE, Buchanan GR. Vascular complications after splenectomy for hematologic disorders. Blood 2009;114:2861–2868.
27. Thomsen RW, Schoonen WM, Farkas DK, et al. Risk of venous thromboembolism in splenectomized patients compared with the general population and appendectomized patients: A 10-year nationwide cohort study. J Thromb Haemost 2010;8:1413–1416.
28. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: A report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009;113:4834–4840.
29. Guyett GH, Cook DJ, Jaeschke R, et al. Grades of recommendation for antithrombotic agents: American College of chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:123S–131S.