HOW I TREAT REFRACTORY IMMUNE THROMBOCYTOPENIA

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ABSTRACT

This article summarizes our approach to the management of children and adults with primary immune thrombocytopenia (ITP) who do not respond to, cannot tolerate, or are unwilling to undergo splenectomy. We begin with a critical reassessment of the diagnosis and a deliberate attempt to exclude non-autoimmune causes of thrombocytopenia and secondary ITP. For patients in whom the diagnosis is affirmed, we consider observation without treatment. Observation is appropriate for most asymptomatic patients with a platelet count of $\geq 20-30 \times 10^9$/L. We use a tiered approach to treatment for patients who require platelet-raising therapy. Tier 1 options (rituximab, thrombopoietin receptor agonists, low-dose corticosteroids) have a relatively favorable therapeutic index. We exhaust all Tier 1 options before proceeding to Tier 2, which comprises a host of immunosuppressive agents with relatively lower response rates and/or greater toxicity. We often prescribe Tier 2 drugs not alone but in combination with a Tier 1 or a second Tier 2 drug with a different mechanism of action. We reserve Tier 3 strategies, which are of uncertain benefit and/or high toxicity with little supporting evidence, for the rare patient with serious bleeding who does not respond to Tier 1 and Tier 2 therapies.

KEY WORDS

Immune thrombocytopenia, ITP, refractory, splenectomy, treatment
CASE 1

A 10-year-old male was diagnosed with primary ITP 5 months ago when he presented with epistaxis, petechiae, bruising, and a platelet count of $5 \times 10^9$/L. He responded transiently to intravenous IgG, but epistaxis recurred 2 weeks later. He subsequently received a short course of oral corticosteroids to which he had a temporary response in platelet count and cessation of epistaxis. Since discontinuing corticosteroids, he has had only occasional bruising and petechiae. His platelet count is currently $13 \times 10^9$/L. He states that ITP is not interfering with activities.

INTRODUCTION

Treatment of ITP may be conceptually divided into rescue therapy and maintenance therapy. The objective of rescue therapy is a swift rise in platelet count in a patient with active hemorrhage, a high risk for bleeding, or need for a critical procedure. In selecting rescue therapy, a premium is placed on rapidity of response with relatively less regard for durability of response, patient convenience, or safety and tolerability with long-term use. Maintenance therapy, in contrast, is given with the goal of achieving a sustained platelet response while minimizing short- and long-term treatment-related toxicity. Goals and standard treatment options for rescue and maintenance therapy are summarized in Table 1.

Management of the patient with ITP whose platelet count does not respond to standard therapy (Table 1) can be frustrating and terrifying for clinicians and patients, particularly if there is active bleeding or severe thrombocytopenia. The purpose of this article is to summarize our approach to the management of children and adults with primary ITP who do not respond to or cannot tolerate standard maintenance therapy (i.e. splenectomy). Much of the evidence in this area is
limited to case reports and uncontrolled series. There are few direct comparisons of different treatment strategies. Where evidence is available, it is cited. Suggestions are otherwise based on our experience and opinions.

WHAT IS REFRACTORY ITP?

An International Working Group (IWG) defined refractory ITP as disease that does not respond to or relapses after splenectomy and that requires treatment to reduce the risk of clinically significant bleeding. The American Society of Hematology (ASH) ITP Guidelines endorsed this definition as a means of identifying the most severely affected patients. Given that splenectomy remains the surest means of “curing” ITP with long-term complete platelet response rates of 60-70%, this characterization remains pertinent.

Nevertheless, several limitations of the IWG definition must be acknowledged. First, it may not be applicable to certain patient populations such as children, those with significant comorbidities, and those unwilling to undergo splenectomy. In these patients, avoidance of splenectomy may be desirable or even necessary. Indeed, the IWG acknowledged that it was unable to achieve consensus on the definition of refractory disease in children. Second, the IWG definition stipulates that treatment be deemed necessary for bleeding symptoms or presumed high risk of bleeding. It is conceivable that for some patients the indication for treatment following splenectomy failure might relate to something other than bleeding symptoms, for example improvement in health-related quality of life (HRQoL). HRQoL is a multi-dimensional construct that focuses on the impact of health on physical, mental, social, and emotional functioning. Third, the IWG classification does not include refractoriness to rescue therapy.
Herein, we use a broader definition of refractoriness than the IWG. Among patients refractory to maintenance therapy, we include not only patients who require treatment to mitigate bleeding risk after splenectomy, but also patients who are unable or disinclined to undergo splenectomy and patients in whom the primary objective of treatment is improvement in HRQoL.

**ITP REFRACTORY TO MAINTENANCE THERAPY**

Figure 1 illustrates our approach to the patient who is refractory to or ineligible for splenectomy. Key features include reassessment of the diagnosis, consideration of observation without treatment, a 3-tiered approach to treatment, and the use of combination therapy.

**Reassessment of the diagnosis**

There is no gold standard diagnostic test for ITP. The most compelling evidence for the presence of ITP is a platelet response to standard therapy (Table 1). Non-responsiveness to treatment should therefore prompt reassessment of the diagnosis and a concerted effort to exclude non-autoimmune causes of thrombocytopenia and secondary ITP. The reader is referred elsewhere for a discussion of diagnostic evaluation.\(^3,9,10\) It is likewise imperative that a manual platelet count be performed because automated cell counters may misclassify large or agglutinated platelets, leading to an underestimation of the platelet count and potentially inappropriate treatment decisions.

**Observation**
In accordance with ASH guidelines, we recommend observation without treatment in most asymptomatic adults after splenectomy with a platelet count of 20-30 \( \times 10^9/L \) or greater. In a prospective cohort study, patients who maintained a platelet count above this threshold after splenectomy had no bleeding-related deaths. In contrast, patients with a platelet count less than 30 \( \times 10^9/L \) had a bleeding-related mortality of 36.7\%. In a separate study of 47 patients who failed to maintain a platelet count of 100 \( \times 10^9/L \) after splenectomy, there were 3 deaths over a median follow-up of 7.5 years. All 3 had a baseline platelet count < 20 \( \times 10^9/L \). A platelet count threshold > 30 \( \times 10^9/L \) may be preferred in some patients due to occupation, participation in sports, need for antithrombotic therapy, or control of other symptoms that track with platelet count (e.g. fatigue, HRQoL). Conversely, some patients have little or no bleeding at platelet counts well below 30 \( \times 10^9/L \) and are more concerned about adverse effects of treatment than bleeding. These individuals may elect to defer therapy at lower platelet counts. This is particularly relevant to children, who have low bleeding risk even in the setting of severe persistent or chronic thrombocytopenia. Observation may be appropriate in asymptomatic or minimally symptomatic children, as in Case 1 above, irrespective of the platelet count. We prioritize bleeding symptoms and HRQoL over platelet count in decision-making in this population (Figure 1).

**Tiered approach to treatment**

For patients with refractory ITP who require therapy to maintain a hemostatic platelet count, numerous treatments are available. We divide these options into 3 tiers based on efficacy, safety, and quality of evidence. Treatment options in Tier 1 have a relatively favorable therapeutic
index and are supported by reasonably good evidence. Options in Tier 3, in contrast, have a less auspicious efficacy/safety profile and/or a weak evidentiary basis.

There are no direct comparisons of treatment options within a given tier. We therefore individualize choice of treatment on the basis of age, comorbidities, drug availability, cost, and patient preference. We exhaust options in each tier before proceeding to the subsequent tier. When a durable platelet response cannot be attained with monotherapy, we consider combining agents with different mechanisms of action.

**CASE 1 CONTINUED**

The child has been managed with observation for the past 3 months and is now 8 months from his diagnosis. He continues to have no bleeding symptoms apart from bruising and petechiae. His platelet count has varied between 10 and $30 \times 10^9/L$. Football season will begin shortly and he desires to have a platelet count that is safe for participation.

**Tier 1**

*Low-dose corticosteroids*

Rarely, patients who are highly responsive to corticosteroids at standard rescue therapy doses (e.g. prednisone 1 mg/kg/day, dexamethasone 40 mg daily $\times$ 4) may be able to sustain hemostatic platelet counts at very low maintenance doses of prednisone ($\leq 5$ mg/day). Long-term treatment at such doses is generally well-tolerated, but is not devoid of risk for cumulative toxicities including weight gain, diabetes mellitus, hypertension, decreased bone mineral density, and cataract formation (Table 2). Monitoring for toxicities including periodic bone density
assessment is indicated. Calcium and vitamin D supplementation and regular weight-bearing exercise are recommended to reduce the risk of osteoporosis.

**Rituximab**

Rituximab is a chimeric monoclonal anti-CD20 antibody that depletes B lymphocytes. Its efficacy was evaluated in a systematic review and meta-analysis collectively involving 19 studies and 313 patients, approximately half of whom had undergone splenectomy. A response (platelet count > 50 × 10^9/L) was achieved in 63% of patients. Median time to response was 5.5 weeks and median duration of response was 11 months. In a long-term observational study of 72 adults and 66 children, the response rate to rituximab at 5 years was 21% and 26%, respectively. Published evidence suggests that the likelihood and duration of platelet response are similar in splenectomized and non-splenectomized patients. Complete responders who relapse ≥ 1 year after treatment are likely to respond to retreatment.

The optimal dose of rituximab for ITP treatment is not established. We use 375 mg/m^2 weekly × 4 weeks, but lower doses may be effective (Table 2). Rituximab is generally well-tolerated. Toxicities include infusion reactions, serum sickness and prolonged immune suppression. Patients should be screened for hepatitis B before receiving rituximab due to the risk of viral reactivation. We generally avoid rituximab in patients with hepatitis B, though we consider co-administration of antiviral therapy in patients who do not respond to or are ineligible for all other Tier 1 options. One case of progressive multifocal leukoencephalopathy has been reported in a patient with ITP treated with rituximab. We provide immunizations before beginning treatment because rituximab attenuates response to vaccines for up to 6 months.
Thrombopoietin receptor agonists

Thrombopoietin receptor agonists (TRAs) bind to the thrombopoietin receptor and stimulate megakaryocyte maturation and platelet production. Two TRAs, romiplostim and eltrombopag, have been approved by the FDA. We do not have experience with recombinant human thrombopoietin, which is available in jurisdictions outside the US.

Romiplostim is given as a weekly subcutaneous injection. The starting dose is 1 mcg/kg. The dose is increased by 1 mcg/kg each week (maximum dose 10 mcg/kg) until a platelet count of $\geq 50 \times 10^9/L$ is achieved (Table 2). In a randomized, placebo-controlled trial of 63 splenectomized adult patients, the rate of overall response (platelet count $\geq 50 \times 10^9/L$ at any time during the study) and durable response (platelet count $\geq 50 \times 10^9/L$ for at least 6 of the final 8 weeks of the study) was 79% and 38% in the romiplostim group and 0% and 0% in the placebo group, respectively.\textsuperscript{24} Romiplostim also reduced bleeding and improved health-related quality of life. An extension study enrolled 95 splenectomized patients. A platelet response ($\geq 50 \times 10^9/L$) was achieved in 90% of subjects and persisted for a median 67% of time on study.\textsuperscript{25} Thirty-nine patients with prior splenectomy were enrolled in a French compassionate use program. Many had also received rituximab and other immunosuppressive agents. Despite refractoriness to previous therapies, 45% met criteria for long-term response at 2 years.\textsuperscript{26}

Romiplostim is not approved for treatment of children, but preliminary data suggest that it may be effective and safe in this population. In a randomized controlled trial of children (ages 6 months to 17 years), 15 of 17 subjects allocated to romiplostim and 0 of 5 assigned to placebo
had a platelet response (≥ 50 × 10^9/L × 2 consecutive weeks). Of 6 splenectomized children in the romiplostim arm, 4 demonstrated a platelet response. There were no treatment-related serious adverse events. In a subsequent open-label extension study, romiplostim maintained platelet responses for over 4 years without significant toxicity. The results of a larger placebo-controlled trial (NCT01444417), which completed enrollment in 2015, have not yet been reported.

Eltrombopag is formulated as a daily pill. The starting dose is 50 mg daily (25 mg daily in individuals of East Asian ancestry, with liver impairment, or age 1-5 years). The dose may be increased to a maximum of 75 mg daily to achieve a platelet count ≥ 50 × 10^9/L (Table 2). In a phase III trial, 197 adults were randomized to eltrombopag or placebo for 6 months. Seventy-one of these patients had undergone splenectomy. A durable platelet response (50-400 × 10^9/L for at least 6 of the last 8 weeks on study) was observed in 51% of splenectomized subjects assigned to eltrombopag. Eltrombopag was associated with reduced bleeding and concomitant medication usage. In a 6-week randomized trial, 114 subjects were allocated to eltrombopag or placebo. Among the 45 splenectomized patients in the trial, a platelet response (≥ 50 × 10^9/L at 6 weeks) was more common in the eltrombopag arm than in the placebo group (62.1% vs 15.4%). An open-label extension study included 115 splenectomized patients followed for up to 3 years of treatment with eltrombopag. Eighty percent achieved a platelet count ≥ 50 × 10^9/L at least once during the study. In a real-world retrospective study of 164 Spanish patients taking eltrombopag (104 of whom had undergone splenectomy), 88.5% manifested a response (platelet count ≥ 30 × 10^9/L and doubling from baseline).
Eltrombopag is approved by the FDA for children $\geq 1$ year old with chronic ITP who have not achieved an appropriate response using other medications or splenectomy. Approval was based on the placebo-controlled PETIT trials, which showed that 36-40% of eltrombopag-treated children maintained a platelet count of $\geq 50 \times 10^9$/L for the majority of time on study compared with 0-3% who received placebo. In the open-label extension studies that followed the randomized trials, 80% of patients achieved a platelet count $\geq 50 \times 10^9$/L for at least one time point during the study. Less than 10% of subjects enrolled in the PETIT trials had been previously splenectomized.\textsuperscript{33,34}

The TRAs are generally well-tolerated. In a pooled analysis of 14 trials of adults with ITP treated with romiplostim, bone marrow reticulin was observed in 17 of 921 patients.\textsuperscript{35} In the eltrombopag extension study, 2 of 117 bone marrow biopsies showed moderate to marked reticulin fibrosis.\textsuperscript{36} Systematic investigations of bone marrow fibrosis have not been undertaken in children. TRAs may increase the incidence of thromboembolism in some populations, but a meta-analysis suggested that these agents do not increase thrombosis in patients with ITP compared with placebo.\textsuperscript{37} When TRAs are discontinued, the platelet count generally returns to and may temporarily fall below baseline (rebound thrombocytopenia). Some patients experience prolonged platelet responses after discontinuation of therapy.\textsuperscript{38} Hepatotoxicity may occur with eltrombopag and monitoring of liver function tests is mandatory.

**CASE 1 CONTINUED**

Eltrombopag was initiated to achieve a sufficient platelet count for football season. The platelet count remained between 95 and $200 \times 10^9$/L for 4 months. Following football season,
eltrombopag was discontinued and the patient maintained a platelet count > 150 × 10^9/L without need for further treatment.

**CASE 2**

A 64-year-old man was diagnosed with primary immune thrombocytopenia (ITP) 18 months ago when he presented with epistaxis, petechiae, and a platelet count of 8 × 10^9/L. He had a robust response to corticosteroids, but relapsed when prednisone was tapered. One year ago, he received weekly rituximab 375 mg/m^2 × 4 without response. Six months ago, he underwent laparoscopic splenectomy. Although his platelet count rose briefly after surgery, it subsequently fell to 10 × 10^9/L. Trials of eltrombopag and then romiplostim produced intermittent spikes in the platelet count, but did not lead to a sustained response or permit reduction in the dose of prednisone. He remains dependent on prednisone 20 mg daily to maintain a platelet count of 20-30 × 10^9/L. He complains of insomnia, weight gain, and dysphoria on corticosteroids. A bone density scan shows osteopenia.

**Tier 2**

If a patient is not able to maintain a hemostatic platelet count with single agent therapy using the options in Tier 1, we encourage participation in a clinical trial. If a suitable clinical trial is not available, we proceed to Tier 2 agents. We frequently prescribe Tier 2 agents not as monotherapy but in combination with a Tier 1 or another Tier 2 drug. A myriad of multiagent regimens exist, few of which have been formally studied. We prefer to combine drugs with different mechanisms of action, allowing for potential synergy between agents. For example, we often use a TRA to boost platelet production in combination with a drug that interferes with platelet
clearance (e.g. low-dose prednisone, danazol) or autoantibody production (e.g. azathioprine, mycophenolate mofetil). This approach may induce a more rapid increase in the platelet count than monotherapy given the delayed time to response of many Tier 2 agents (Table 3).

Vinca Alkaloids

Evidence for vinca alkaloids (VAs) is drawn mostly from studies conducted in the 1970s and 1980s with few reports from the modern era.\textsuperscript{48-57} Published studies vary in which VA was used (vincristine vs. vinblastine), the dose and number of infusions, use of maintenance dosing, and definition of response. While initial reports were promising, relatively poor durability of response has dampened enthusiasm for VAs. In an early report of 21 patients, two-thirds achieved a platelet count $\geq 50 \times 10^9$/L.\textsuperscript{55} Several subsequent studies showed similar response rates. However, later studies found that most responses were transient.\textsuperscript{48-51,53} In a prospective trial, 35% of patients treated with vincristine achieved a platelet count $> 100 \times 10^9$/L, but a 40% decline in the platelet count was observed as soon as 8 weeks following completion of three infusions.\textsuperscript{51} The fleetingness of response to VAs must be balanced against their toxicities, which include vesication, constipation, and peripheral neuropathy (symptoms generally arise after cumulative vincristine doses of 30-50 mg).\textsuperscript{48,49,51-55} Because of their relatively short time to response (5-7 days), we consider VAs in patients who require a rapid rise in platelet count and do not respond to standard rescue therapy (Table 1). They are generally not a good option for induction of long-term remission.

Dapsone
Dapsone was first discovered as a potential agent for ITP in 1988 when it improved the platelet count in a patient with systemic lupus erythematosus.\(^5^8\) There are no randomized clinical trials of dapsone in ITP. Its use is based on prospective and retrospective cohort studies.\(^5^9\)-\(^6^1\) In one of the largest series, 66 patients with chronic ITP were treated with oral dapsone at a dose of 75-100 mg. A platelet count > 50 × 10\(^9\)/L was achieved in 33 subjects (50\%), 20 of whom continued to respond for a median duration of 12.5 months.\(^5^9\) In a literature review of dapsone, overall response rates ranged from 40-75\%.\(^6^2\)

Toxicities of dapsone include include methemoglobinemia, agranulocytosis, aplastic anemia, hypersensitivity, gastrointestinal complications, and hemolysis in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency.\(^6^2\) We screen males for G6PD deficiency before beginning dapsone.

**Danazol**

Danazol is an attenuated androgen. Response rates vary widely between studies from 10 to 70\%.\(^6^3\)-\(^6^9\) One factor that may account for this variation is heterogeneity in dosing with some studies investigating low dose danazol (50 mg PO daily)\(^6^4,6^5\) compared with conventional dosing (400-800 mg divided into 2-4 daily doses).\(^6^3,6^6,6^7,6^9\) The effect of danazol appears to be greatest when patients are able to remain on therapy for a prolonged period. In a series of 96 patients, 7 of the 10 patients (70\%) in whom danazol therapy was discontinued relapsed within 6 months. Responses were more durable for patients who remained on therapy for at least one year.\(^6^9\)
It has been our observation that danazol is more likely to elicit a response in patients who respond well to corticosteroids. Therefore, we use corticosteroid-responsiveness as a criterion for selecting danazol. Liver function tests must be monitored regularly. We rarely use danazol in women because of its virilizing effects.

**Cyclophosphamide**

Cyclophosphamide may be given intravenously (500-1000 mg/m² every 3-4 weeks × 2-3 courses) or orally (1-2 mg/kg daily). Evidence for its use in ITP is limited to two early studies, which showed complete or excellent responses in 50% of subjects and partial responses in an additional 20% of patients.⁷⁰,⁷¹ While these response rates compare favorably to other Tier 2 agents, we use cyclophosphamide infrequently because of a paucity of data and the potential for serious long term sequelae including malignancy and infertility. Patients receiving cyclophosphamide should drink at least 2 L of fluids daily to prevent hemorrhagic cystitis and blood counts should be monitored weekly.

**Antimetabolites**

The antimetabolites, azathioprine, 6-Mercaptopurine, and Mycophenolate Mofetil (MMF) have been studied in patients with refractory ITP. Azathioprine demonstrated an overall response rate of 64% in a study of 53 adult patients. When the drug was discontinued, 42% remained in remission for a variable follow-up of 7-43 months.⁷² Smaller series also showed favorable results.⁷³,⁷⁴ One study of 6-mercaptopurine in pediatric autoimmune cytopenias has been published. In this series of 29 patients, there was an 83% response rate, yet only four children (two with ITP) remained in remission without additional immunosuppressive therapy.⁷⁵ Major
toxicities of azathioprine and 6-mercaptopurine include myelosuppression, hepatotoxicity, and pancreatitis.

A greater number of studies have investigated MMF.\textsuperscript{76-82} We begin MMF at a dose of 500 mg PO twice daily and increase the dose to 1000 to 1500 mg twice daily after 2 weeks. Protocols using this approach have demonstrated overall response rates of 50-60\%.\textsuperscript{76-81} Durability of response following discontinuation of therapy is variable.\textsuperscript{77,79,82} MMF is generally well-tolerated; principal side effects include headache and gastrointestinal symptoms.

\textit{Cyclosporin A}

Several small studies highlight the effectiveness of cyclosporine A for the management of refractory ITP.\textsuperscript{83-85} In the largest study of 20 patients, response rates were 50-60\%. Side effects, which include hypertension and nephrotoxicity, led to discontinuation in 6 (30\%) patients.\textsuperscript{85} A study of 14 children reported a response rate of approximately 30\% and one life-threatening fungal infection.\textsuperscript{84} Patients require regular monitoring of blood pressure, renal function, and drug levels.

\textbf{CASE 2 CONTINUED}

Danazol was initiated at a dose of 200 mg twice daily and increased to 400 mg twice daily while the patient remained on romiplostim 10 μg/kg weekly and prednisone 20 mg daily. The patient tolerated danazol well without transaminitis or other toxicities. Three months after beginning danazol, his platelet count was $60 \times 10^9$/L. Over the ensuing 6 weeks, prednisone was tapered off. The patient remains on danazol and romiplostim with a platelet count of 40-50 $\times 10^9$/L.
**Tier 3**

In the rare patient with serious bleeding who does not respond to or is ineligible for all Tier 1 and Tier 2 treatment options including combination therapy, we recommend enrollment in a clinical trial. If a suitable trial is not available, we consider Tier 3 approaches (Figure 1). Tier 3 options are characterized by low response rates and/or high toxicity. Many studies of Tier 3 agents are small and include a mix of patients with newly diagnosed and intractable disease, clouding interpretation of response rates in refractory ITP. Given their weak evidentiary basis and unfavorable therapeutic index, we reserve Tier 3 treatments for severely refractory patients with a history of serious or life-threatening bleeding. Table 4 summarizes these approaches, highlighting evidence from studies of \( \geq 10 \) patients.\textsuperscript{86-100}

**CONCLUSION**

Refractory ITP is challenging to treat and may be associated with poor outcomes.\textsuperscript{11,12} Our approach to management involves confirmation of the diagnosis, consideration of observation, and a tiered treatment strategy for those who require therapy (Figure 1). With recent advances in treatment including rituximab and the TRAs, a greater proportion of patients than ever before are able to maintain hemostatic platelet counts with acceptable tolerability and safety. Still, a subset of highly refractory patients is failed by current therapeutic options. For these individuals, new treatments are sorely needed. Novel agents including an anti CD40 ligand (BMS-986004) and splenic tyrosine kinase inhibitor (fostamatinib) as well as a number of repurposed drugs (e.g. decitabine, oseltamivir, sirolimus, thalidomide) are currently in clinical trials. We encourage
patients and physicians to participate in clinical trials to support development of new treatments so that the number of patients with truly intractable disease may continue to wither.

AUTHORSHIP CONTRIBUTIONS
AC and CEN searched the literature and wrote the manuscript.

DISCLOSURE OF CONFLICT OF INTEREST
AC has served as a consultant for Amgen, Bracco, CSL Behring, and Genzyme; has received research support from Spark Therapeutics and T2 Biosystems; and has provided expert witness testimony related to ITP. CEN has served as a consultant for Genzyme.
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**TABLES**

Table 1. Goals and standard treatment options for rescue and maintenance therapy.

<table>
<thead>
<tr>
<th>Goals of treatment</th>
<th>Rescue therapy</th>
<th>Maintenance therapy</th>
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<tbody>
<tr>
<td></td>
<td>Rapid platelet response</td>
<td>Durable platelet response</td>
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<td></td>
<td>Short-term safety</td>
<td>Long-term safety and tolerability</td>
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<td></td>
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<td>Patient convenience</td>
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<tr>
<td>Desired time to response</td>
<td>Hours to days</td>
<td>Days to weeks</td>
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<tr>
<td>Standard treatment options</td>
<td>Corticosteroids</td>
<td>Splenectomy</td>
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<td></td>
<td>IVIG</td>
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<tr>
<td></td>
<td>Anti-D&lt;sup&gt;a&lt;/sup&gt;</td>
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</tbody>
</table>

IVIG, Intravenous IgG

<sup>a</sup>Indicated only in Rh(D)-positive, non-splenectomized patients
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Response rate</th>
<th>Time to response</th>
<th>Selected toxicities</th>
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</thead>
<tbody>
<tr>
<td>Low-dose prednisone</td>
<td>≤ 5 mg PO daily</td>
<td>&lt; 10%</td>
<td>N/A²</td>
<td>Weight gain</td>
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<td></td>
<td></td>
<td></td>
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<td>Hyperglycemia</td>
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<td>Hypertension</td>
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<td>Osteoporosis</td>
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<td>Cataracts</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m² IV weekly × 4 (lower doses may be effective)</td>
<td>60% overall 40% complete 20-25% at 5 years</td>
<td>1-8 weeks</td>
<td>Infusion reactions Serum sickness HBV reactivation PML (rare)</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>1-10 μg/kg SC weekly</td>
<td>80% overall 40-50% persistent</td>
<td>1-4 weeks</td>
<td>Reticulin fibrosis Rebound thrombocytopenia Thrombosis</td>
</tr>
<tr>
<td>Eliotrombopag</td>
<td>25-75 mg PO daily</td>
<td>80% overall 40-50% persistent</td>
<td>1-2 weeks</td>
<td>Reticulin fibrosis Rebound thrombocytopenia Thrombosis Hepatotoxicity</td>
</tr>
</tbody>
</table>

HBV, hepatitis B virus; PML, progressive multifocal leukoencephalopathy

¹Studies vary in their definition of response.

²In patients who are responding to intermediate or high doses or prednisone, we taper to low-dose prednisone. We do not start low-dose prednisone de novo.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Response rate</th>
<th>Time to response</th>
<th>Selected toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-mercaptopurine</td>
<td>50-75 mg/m² PO QD</td>
<td>83%</td>
<td>Not reported</td>
<td>Hepatotoxicity, Neutropenia, Infection, Pancreatitis</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1-2 mg/kg PO QD (maximum 150 mg/day)</td>
<td>40-60%</td>
<td>3-6 months</td>
<td>Hepatotoxicity, Neutropenia, Infection, Pancreatitis</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>5-6 mg/kg/day PO divided twice daily (titrate to blood levels of 100-200 ng/mL)</td>
<td>30-60%</td>
<td>3-4 weeks</td>
<td>Nephrotoxicity, Hypertension, Tremor, Parathesias, Gingival hyperplasia</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>0.3-1.0 g/m² IV repeated every 2-4 weeks × 1-3 doses 50-200 mg PO daily, once response achieved dose tapered to 50mg</td>
<td>24-85%</td>
<td>1-16 weeks</td>
<td>Neutropenia, Nausea/Vomiting, Infertility, Secondary malignancy</td>
</tr>
<tr>
<td>Danazol</td>
<td>50-800 mg/day PO divided 2-4 times daily</td>
<td>10-70%</td>
<td>3-6 months</td>
<td>Hepatotoxicity, Virilization, Amenorrhea</td>
</tr>
<tr>
<td>Dapsone</td>
<td>75-100 mg PO QD</td>
<td>40-75%</td>
<td>3 weeks</td>
<td>Hemolysis (in patients with G6PD deficiency), Rash, Nausea, Methemoglobinuria</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>250-1000 mg PO BID</td>
<td>11-80%</td>
<td>4-6 weeks</td>
<td>Headache, Diarrhea, Nausea, Anorexia, Infection</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>Vincristine: 1-2 mg IV weekly × 3 weeks</td>
<td>10-75%</td>
<td>5-7 days</td>
<td>Peripheral neuropathy, Vesication at infusion site, Constipation, Fever, Neutropenia</td>
</tr>
<tr>
<td></td>
<td>Vinblastine: 10mg IV weekly × 3 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 4. Tier 3 treatment options.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Response rate</th>
<th>Selected toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA(^{86})</td>
<td>10 mg PO TID</td>
<td>29%</td>
<td>Retinoic Acid Syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Flu-like Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Musculoskeletal pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nausea/Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Autologous HSCT(^{87})</td>
<td>Cyclophosphamide 50 mg/kg IV QD × 4 days (conditioning)</td>
<td>43%</td>
<td>Neutropenic fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infection</td>
</tr>
<tr>
<td>Colchicine(^{88})</td>
<td>1.2 grams PO QD</td>
<td>21%</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neuritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nausea/Vomiting</td>
</tr>
<tr>
<td>Interferon α(^{89-92})</td>
<td>Various</td>
<td>0-36%</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Influenza-like symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Plasma exchange(^{93-95})</td>
<td>One plasma volume exchange QD × 1-8 days</td>
<td>29-80%</td>
<td>Hypocalcaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anaphylactoid reactions</td>
</tr>
<tr>
<td>Protein A immunoadsorption(^{96})</td>
<td>Average of 6 treatments (0.25 to 2.0 L plasma per treatment) over 2-3 weeks</td>
<td>21%</td>
<td>Hyper-sensitivity reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nausea/Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiopulmonary complications</td>
</tr>
<tr>
<td>Vitamin C(^{97-100})</td>
<td>2 grams PO QD</td>
<td>0-82%</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nausea/Vomiting</td>
</tr>
</tbody>
</table>

ATRA, all-trans retinoic acid; HSCT, hematopoietic stem cell transplant
FIGURE LEGENDS

Figure 1. Approach to the patient with refractory ITP.

We begin by reassessing the diagnosis of immune thrombocytopenia (ITP) and excluding non-autoimmune causes of thrombocytopenia and secondary ITP. After ITP has been affirmed, we consider whether treatment is indicated. For most adults with a platelet count > 20-30 × 10^9/L and no bleeding or impaired health-related quality of life (HRQoL) and for most children without bleeding or impaired HRQoL, observation alone is appropriate. For patients who require treatment, we treat with a Tier 1 agent (see Table 2 for a list of Tier 1 agents). We select an agent based on age, comorbidities, drug availability, cost, and patient preference. In patients who do not respond to or cannot tolerate a Tier 1 agent, we move on to another Tier 1 agent. In patients who have exhausted all options in Tier 1, we consider enrollment in a clinical trial. If a suitable trial is not available, we initiate a Tier 2 agent (see Table 3 for a list of Tier 2 agents). We often use Tier 2 agents not alone but in combination with Tier 1 or other Tier 2 agents with different mechanisms of action. For the rare patient with serious bleeding who does not achieve an acceptable response with Tier 2 agents, we again consider enrollment in a clinical trial or initiation of a Tier 3 treatment (see Table 4 for a list of Tier 3 treatments).
Reassess diagnosis

Alternative diagnosis identified

Primary ITP affirmed

Adult patient

Platelet count > 20-30 × 10^9/L, no bleeding, no impaired HRQoL

Observation, No treatment

Platelet count < 20-30 × 10^9/L or bleeding or impaired HRQoL

Treat (Tier 1 agent)

Platelet count > 20-30 × 10^9/L, No bleeding

Observation, No additional treatment

Platelet count < 20-30 × 10^9/L or bleeding

Clinical trial or Treat (Tier 2 agent)

No bleeding

Observation, No additional treatment

Bleeding

Clinical trial or Treat (Tier 3 agent)

Pediatric Patient

Bleeding or impaired HRQoL

Consider observation, No treatment

No bleeding, no impaired HRQoL

No additional treatment
How I treat refractory immune thrombocytopenia

Adam Cuker and Cindy E. Neunert