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Immunomodulatory Second-Line Therapies for Immune Thrombocytopenia

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Abstract

Management of immune thrombocytopenia (ITP) is complex requiring communication between patients and caregivers to establish a mutual understanding of the impact of the patient's disease on quality of life, the current symptoms and risk of morbidity/mortality and the goals of therapy. The currently available second-line therapies for ITP provide potential for management of thrombocytopenia and bleeding symptoms with medical therapy or surgical intervention potentially offering long-term remission. All therapies are associated with potential side effects and necessary monitoring or modifications/risks and careful discussion of these is necessary to determine the optimal therapy for each patient. This review covers second-line therapies for ITP and discusses the currently available information on immunomodulatory second-line treatments for ITP.

Keywords
- autoimmune disease
- platelet
- ITP
- treatment

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease defined by isolated thrombocytopenia (platelets $<100 \times 10^9$/L). Treatment paradigms for ITP have assumed at the onset a fundamental difference between paediatric and adult ITP describing paediatric ITP to be generally self-limited disease with abrupt onset and profound thrombocytopenia while adult ITP is considered a more chronic disease with more insidious onset, moderate thrombocytopenia and higher bleeding risk with platelet counts $<30 \times 10^9$/L and increased morbidity and mortality.[1,2] Recent data suggest that presenting platelet counts are not that different and that the likelihood of bleeding, overall, with platelets of $<20 \times 10^9$/L is low in most patient populations.[3] This study, prospectively following outcomes in approximately 3,360 children and 420 adults with ITP from several countries over several years, also demonstrated a higher than expected remission rate in the adult population (45% at 6 months), although the majority of adults were young adults (250/420 were young adults). Late remission was similar in children and adults (approximately 30% at 12 and 24 months of follow-up).[3]

At the time of the publication of the last guidelines (2009–2011),[4,5] there was little data available on the long-term safety and efficacy of some of the second-line therapies for ITP, in particular for the thrombopoietin receptor agonists (TPO-RAs), such as eltrombopag and romiplostim which are approved for adults and children and lusutrombopag and avatrombopag, which are approved for adults with chronic liver disease. These medications are covered in a separate review in this issue and are not discussed here, but have changed the landscape of second-line therapy for ITP. This review will focus on non-TPO-RA second-line therapy for ITP in patients requiring treatment. Generally, treatment is warranted for adult patients with platelet counts $<30 \times 10^9$/L (although data suggest this number may be higher than necessary), or in patients at risk for bleeding.[4] Often, patient quality of life determines need for therapy, irrespective of bleeding symptoms in both paediatric and adult populations.[6,7] Patients that fail first-line therapy often require second-line therapy, and may progress through multiple second-line therapies.

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Splenectomy

The first splenectomy for ITP was performed in 1916[8] and for decades, surgical splenectomy was the second-line treatment of choice because this is an effective treatment for steroid-refractory or dependent ITP with 50 to 70% of patients achieving a durable remission.[9,10] However, recent data suggest that <25% of patients with ITP undergo splenectomy,[11] despite these excellent durable response rates[12,13] and decades of experience. Declining splenectomy is likely in part due to the risk of infection (5- to 30-fold increase in the first 90 days and 1- to 3-fold life-long increased risk of invasive bacterial infection and sepsis) and emerging data on risk of thrombosis as well as reports of pulmonary hypertension combined with immediate post-operative complications in the setting of available effective medical therapy. Most studies examining risk of mortality in splenectomy do not stratify by indication; however, Thai and colleagues examined the long-term complications of splenectomy in ITP patients in particular,[14] finding that in 93 patients with ITP, 17% of patients had early post-operative complications including haemorrhage, infection and venous thromboembolism (VTE). After a median follow-up of 192 months (range: 0.5–528), 52% had a sustained response and 80% were alive. The rate of VTE in this study was 16% in the splenectomy group versus 2% in the control group (consisting of patients with ITP who had not undergone splenectomy matched for date of diagnosis, age and gender).[14] These included both immediate post-operative VTE and VTE 10, 20 and 30 years post-splenectomy. A second recent long-term follow-up study of 174 adult patients who underwent splenectomy had a 2.9% rate of VTE in their cohort.[15] The smaller study also suggested an increased risk of cardiovascular events compared with control patients (12 vs. 5%), although this did not reach statistical significance ($p = 0.143$).[14] The rates of infection were not significantly different between splenectomy and control; however, the rate of bacterial infection was higher in the post-splenectomy group and these infections were more likely to result in hospitalization (all of the post-splenectomy patients) with an increased risk of sepsis (19%) with three fatalities (vs. 0 for the control group).[14] Other studies have suggested an overall risk of mortality from overwhelming post-splenectomy infection of 0.73 per 1,000 patient years.[13] These data support the overall assessment that splenectomy is relatively safe, but not without risk or potential long-term complications. Generally, splenectomy is deferred at least 12 months if possible (although it is still the treatment for fulminant ITP refractory to intravenous immunoglobulin/corticosteroids especially if there is poor response to TPO-RA).[6] Patients who undergo splenectomy should be vaccinated for pneumococcus, Haemophilus influenzae B and meningococcus C prior to splenectomy whenever possible.[16] Because there is very little data to compare long-term outcome of splenectomy with long-term medical treatment, evidence-based recommendations are lacking and decisions are often based on patient and physician discussion and mutual discussion of patient factors, preferences and goals of therapy.[6,17,18] Patients who prefer to have minimal daily reminders of ITP and are interested in a therapy with high probability of platelet count response who have low risk with undergoing surgical procedure may be good candidates for splenectomy; alternatively, patients who have failed or are not good candidates for medical therapy may have few other options.

Rituximab

As rates of splenectomy declined, use of rituximab increased and initial response rates were promising. Several studies examining the efficacy of rituximab as an alternative to splenectomy in patients with ITP, using the standard dosing of 375 mg/m^2/dose $\times$ 4 doses, resulted in initial response rates of 40 to 60%.[19] Unfortunately, the long-term response rates with rituximab are not as good as splenectomy with sustained response of approximately 20% at 5 years post-initial rituximab treatment.[20] A recent trial in 112 adult patients comparing standard dosing of rituximab and placebo showed no difference in complete response (CR) at 1.5 years.[21] Many patients who initially respond to rituximab can respond to subsequent doses; however, the safety and efficacy of repeated dosing of rituximab has not been systematically evaluated.

In addition, rituximab is associated with significant side effects. Approximately 1% of patients treated are unable to complete a full course because of infusion reactions, while 1 to 2% of patients develop persistent hypogammaglobulinemia post-therapy, which can be associated with infection and development of common variable immunodeficiency.[21] For this reason, it is important to check immunoglobulin levels and B cell recovery after rituximab therapy. Some guidelines recommend following similar practices prior to rituximab therapy as for splenectomy.[22]

Efforts to reduce side effects, but maintain efficacy, have resulted in various dosing regimens that have been used in treatment of ITP including low-dose regimens (100 mg/m^2 weekly or 100 mg weekly) that have been used alone[23,24] or in combination with other medications such as dexamethasone and cyclosporine[25] or recombinant human thrombopoietin.[26]

Other Immunomodulatory Therapies

A recent (2017) systematic review examined the literature published in English for studies using several immunomodulatory treatments that have been reported in clinical studies in small numbers of patients.[27] Some of these options, particularly dapsone and azathioprine, are especially useful in countries where access to some of the more expensive medications such as TPO-RA and rituximab is more limited. Some of the immunomodulatory medications were covered in this systematic review, but others have been used, and the limited data available are presented in ►Table 1.

Dapsone

Dapsone has been studied in both adults and children with persistent and chronic ITP. Approximately 80 adult patients were evaluated prospectively (reviewed in Weber et al.[27])

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Table 1 Alternative non-TPO-RA second-line therapies

Second-line therapy	Dosing	Response rates	Time to response	Duration of response	Major side effects	Adult or paediatric
Dapsone	75–100 mg oral daily; 2 mg/kg	53–63% (overall); complete (21%)	1–2 mo	17–42 mo	Haemolysis, headache, nausea, vomiting, rash, nausea; dapsone-hypersensitivity syndrome (1.4–2.5%)	Both
Interferon α	3,000,000 units SQ 3 × /wk	42% (overall); complete (18%)	Not avail	2 wk to 8 mo	Flu-like syndrome	Both
Danazol	400–900 mg oral daily	58% (overall); complete (29%)	2–3 mo	4–119 mo	Amenorrhea, liver test abnormalities, weight gain, acne, headaches, masculinization, intracranial hypertension	
Hydroxychloroquine	200–600 mg oral daily	50% (overall)	4–6 mo	5 y	No retinal deposits or other side effects observed	Adults
Azathioprine/ 6-mercaptopurine	1–3 mg/kg oral daily	51–64% (overall)	3–4 mo	3–84 mo	Leukopenia, elevated transaminases	Both
Vincristine	1.5 or 2 mg weekly IV × 4	75% (overall)	9 d	6 mo to 1 y	Peripheral neuropathy	Adults
Mycophenolate mofetil	250–1,000 mg oral twice daily	64–80% (overall); 24–46% complete	3–4 wk	4–90 mo	Headache, abdominal pain, nausea, vomiting, hypertension, bone marrow suppression	Both
Cyclophosphamide	1–2 mg/kg/d orally	65% (overall); 23–45% complete	1–4 wk	3–96 mo	Haemorrhagic cystitis, leukopenia, infertility, nausea, vomiting, mouth ulcers, alopecia, diarrhoea, dizziness	Both
Cyclosporine	4–12 mg/kg/d orally in two divided doses	55% (overall); 25–57% complete	3–4 wk	3–86 mo	Hirsutism, acne, hypertension, bone marrow suppression, renal and hepatic toxicity, CNS toxicity	Both

Abbreviations: CNS, central nervous system; IV, intravenous; SQ, subcutaneous.

with an additional 141 patients (both adults and children) reported by retrospective review of medical records after treatment.[28–30] Dosing is generally 75 to 100 mg daily for adults and 2 mg/kg in paediatric patients. In both groups of patients, response rates were 53 to 63% (except the smallest retrospective study, which had a response rate of only 11% in nine patients[28]). Time to response is relatively slow with most patients requiring 1 to 2 months to respond. Duration of response ranged from 17 to 42 months, but responses generally require ongoing therapy.[27]

Side effects are relatively common and included haemolysis without anaemia or methemoglobinemia, haemolytic anaemia, as well as headache, nausea, vomiting and rash.[27] Severe dapsone-induced hypersensitivity syndrome is rare, characterized by generalized skin eruption with one or more of the following: (1) fever, (2) lymphadenopathy or (3) hepatis, and occurs in approximately 1.4% of patients.[31] This reaction may be associated with the HLA-B*13:01 polymorphism among patients of Indian origin (at least in those receiving dapsone for leprosy).[32]

Azathioprine/6-Mercaptopurine

Purine anti-metabolites, azathioprine and 6-mercaptopurine (6MP), were developed as a chemotherapeutic in the 1950s. Azathioprine is slowly but completely metabolized to 6MP and is felt, generally, to have fewer side effects. As suppressors of both B and T lymphocytes, they have been used in both autoimmune haemolytic anaemia and ITP since the 1960s.[33] The anti-metabolites have been used in small series and at least two larger adult series and one paediatric trial demonstrating response rates of approximately 51 to 64% (up to 87% in smaller series and 83% for 6MP in paediatrics[34]). Most commonly reported side effects include leukopenia (and less commonly other cytopenias due to bone marrow suppression) and elevated transaminases (3× upper limit of normal, ULN). Careful attention should be paid to concomitant medications, as several drug–drug interactions can be important. Time to response ranged from 0.7 to 11 months (with a median of 3–4 months)[35] and duration of response was from 3 to 84 months.[35]

Cyclophosphamide

Cyclophosphamide has been used primarily as an adjunct in severe, refractory ITP. First reported in 1971, cyclophosphamide is one of the oldest adjunctive immunosuppressive therapies that have been used.[36] Severe toxicities, such as haemorrhagic cystitis, leukopenia and risk of secondary malignancies limit its routine use (although these are more common with the intravenous dosing). Long-term use may compromise fertility. Even the common toxicities (nausea, vomiting, mucosal ulcers, alopecia, diarrhoea and dizziness) are more onerous than many of the other currently available options, making cyclophosphamide an option for patients with truly refractory disease that fails to respond to other less toxic therapies. Response rates are similar to other treatments with overall response rates of approximately 65% and CR of 23 to 45% with partial response (PR) of 20%.[37] The dose most commonly used is 1 to 2 mg/kg/day (generally

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approximately 100–200 mg for an adult patient) and the drug should be administered after platelet count response for an additional 2 to 3 months and then discontinued.[37] Responses are usually within 2 to 10 weeks after initiation of therapy[36] inducing remissions lasting up to 96 months.

Cyclosporin

Cyclosporin, a calcineurin inhibitor, inhibits production of interleukin 2, which leads to an inhibition of T cell activation. This then suppresses T-cells and modulates the immune response and can lead to improved platelet counts in some patients with ITP. Reponses typically occur in approximately 4 weeks when cyclosporine is administered orally at 4 to 12 mg/kg/day in two divided doses. Side effects include hirsutism and acne, which may be quite distressing to patients. In addition, hypertension, renal insufficiency and hepatotoxicity can be seen and careful monitoring is needed.[38] Finally, patients may also develop myelosuppression and neurologic complications including tremors and seizures (usually due to posterior reversible encephalopathy syndrome, a complication of hypertension). Overall responses, however, are similar to most other second-line therapies for chronic ITP at approximately 55% with PR of 8 to 30% and CR of 57 to 25%.[39–41]

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) was first reported as a potential therapy for steroid-resistant ITP in 2002.[42] MMF works by suppression of T cells, similar to azathioprine and cyclosporine, but by inhibition of inosine-5′-monophosphate dehydrogenase (IMPDH), a key enzyme in the purine biosynthesis pathway resulting in adenine accumulation and relative guanine deficiency ultimately causing cell cycle arrest. Because lymphocytes are dependent upon purine synthesis due to inability to recycle purine nucleotides and because some T cell activation steps are guanosine triphosphate dependent, MMF inhibits T cell activation and proliferation. Since the first report, others have reported on the use of MMF as monotherapy or in combination with corticosteroids for ITP with overall response rates as high as 64 to 80%[38,43–46] and CR of 24 to 46% and PR of 18 to 29%. Patients received between 250 and 1,000 mg twice daily (total dose: 2 g/day). Generally, responses are somewhat delayed, as with some of the other immunosuppressive therapies, taking 3 to 4 weeks to see a response in most patients. Common toxicities include headache, abdominal pain, nausea and vomiting. Hypertension may also be seen and patients should have regular blood pressure monitoring. Finally, because of the effect on purine metabolism, other cytopenias may result as a result of bone marrow suppression (leukopenia, anaemia, and thrombocytopenia).[38]

Other Therapies

Several other immunomodulatory therapies have been used alone or in combination with other treatments as second- or third-line treatment for ITP either after relapse post-splenectomy or in an effort to avoid splenectomy. Some of these therapies are listed in ►Table 1. The majority of these treatments have shown some efficacy in some patient populations. The difficulty is to identify the appropriate patient who is going to respond to any given therapy. This is often a process of trial and observation and can be frustrating for both patient and clinician as they embark on the next treatment. Novel immunomodulatory therapies, including the newly approved spleen tyrosine kinase (Syk) inhibitor, fostamatinib, also demonstrate efficacy in some patients. This medication, which is expected to disrupt Fc receptor signalling and phagocytosis of antibody-coated platelets, resulted in 37 to 48% overall response rates in two recently published phase III clinical trials of adult patients with highly refractory chronic ITP, with stable response rates of 18% (vs. 2% in placebo; $p < 0.001$).[47,48] Side effects included diarrhoea and hypertension requiring monitoring and potentially dose reduction. Additional novel therapies including an anti-neonatal Fc receptor (FcRn) agent (rozanolixizumab) which prevents recycling of the FcRn and may reduce the half-life of circulating anti-platelet antibodies is currently in phase II trials in patients with ITP.[49,50] Monoclonal antibodies targeting CD154 and CD40 to target the interactions of T cells with B cells and prevent the development of autoreactive T cells/B cell populations are also in development and in clinical trials, although enthusiasm has been tempered somewhat by increased risk of thrombosis in early trials.

Summary

In summary, ITP is a complex disease. Second-line therapy for ITP conventionally consists of splenectomy, rituximab or oral immunomodulatory therapy. TPO-RAs have begun to play a major role in second-line therapy (discussed elsewhere in this issue) and direct comparison of outcomes has yet to be performed to establish a true hierarchy to guide clinical management. In the absence of evidence, patient and clinician must establish mutual goals of treatment to optimally determine therapy, and not all patients will choose medical therapy over surgical intervention. Novel therapies are in development and may further shift the current practice from splenectomy, but data comparing outcomes are still lacking.

Authorship and Conflict of Interest

M.P.L. drafted the manuscript and provided revisions. She has received honoraria and provided consultancy to Amgen, Novartis, Shionogi, Sysmex, Educational Concepts in Medicine, DynaMed, and Bayer. She has received research funding from Astra Zeneca, Inc.

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