Evolving treatment modalities for immune thrombocytopenia in adults

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ABSTRACT

The management of patients with relapsed or refractory immune thrombocytopenia (ITP) remains challenging for hematologists. While there are a multitude of drugs available, it is largely an individualized management based on patient preferences, side effects, previous treatment received, and responses to them, comorbidities and cost associated with the treatment. We hereby review the newer approaches in the treatment of ITP.

1. Introduction

The abbreviation ‘ITP’ previously referred to ‘Idiopathic’ Thrombocytopenic Purpura now refers to ‘Immune’ Thrombocytopenia as a mechanism of thrombocytopenia is not completely idiopathic and only a few patients present with the classic ‘purpura’ [1]. There is evidence of immune-mediated destruction as well as impaired production of platelets in patients with ITP [2]. Incidence of ITP is about 1.6–3.9 per 100,000 patient-years with a female predominance [3]. ITP in children is usually self-limited with complete remission in 3–6 months in 80% of the cases whereas the majority of adults develop chronic disease [1–3]. Bleeding is the most common manifestation of ITP ranging from mild/petechiae, purpura, epistaxis, to severe life-threatening bleeding in the GI tract, Urinary tract, or Intracranial Hemorrhage. Fatigue and low quality of life are also of significant concern in patient with ITP [4].

1.1. Evolving treatment of ITP from past to present

The decision to treat can be challenging as there is no clear consensus regarding safe platelet count and the majority of patients are asymptomatic to mildly symptomatic [5]. The current recommendation from American Society of Hematology is to treat ITP in patient with bleeding symptoms or platelet count <30,000 per Microl. irrespective of symptoms [6]. Treatment strategies for ITP are rapidly evolving. Splenectomy and glucocorticoids were considered the first-line treatment, and immunosuppressants drugs like azathioprine, cyclophosphamide, and vinca alkaloids were reserved for ITP refractory to splenectomy and glucocorticoids. Splenectomy was found to have a permanent remission rate of 50–80% [7]. Hence, traditionally, ‘refractory’ ITP has been referred to disease that does not respond to or relapses after splenectomy and that requires treatment to reduce the risk of clinically significant bleeding [8]. While corticosteroids are still in the front-line therapy for ITP, splenectomy has fallen out of favor with the advent of novel nonsurgical treatment options; hence, the definition of ‘refractory’ ITP has evolved to indicate disease refractory or relapsed after initial steroids therapy, requiring further treatment for platelet count <20,000 or bleeding.

2. Treatment of refractory ITP

With multiple therapies available in this arena, there is a lack of clear recommendation for one over the other. The choice of therapy heavily relies on clinical judgment and shared decision-making. Second-line therapy with rituximab, splenectomy, or TPO-A is opted when the patient continues to be thrombocytopenic > 3 months, steroid dependent or steroid nonresponder [6].

2.1. Rituximab

Rituximab Is a monoclonal antibody against CD20 protein on B Lymphocytes. It enhances the elimination of the B lymphocytes by antibody-dependent cytotoxicity, complement mediated cytotoxicity, and induction of apoptosis [9]. Rationale for use in ITP lies in its ability to inhibit the production of autoantibodies leading to long-term improvement. Analysis of uncontrolled studies of rituximab 375 mg per m² every week for four doses used in ITP has shown an overall response rate (ORR) of 62%, with a complete response rate (CRR) of 39.5% [10]. Side effects with rituximab include infusion reactions, reactivation of underlying
hepatitis, tuberculosis, etc., and rare fatal progressive multifocal leukoencephalopathy [11].

2.2. Splenectomy

Splenectomy now holds an important role in second-line therapy. A systematic review in 2004 showed a durable platelet response in 66% of the patients at the end of 153 months after splenectomy, mortality was 0.8%, and total complication rates including bleeding, infection, thrombosis were 12%. Both mortality and complications were significantly lower with laparoscopic surgery compared to laparotomy [12]. Spleen being a vital organ in the human immune system, there is a 5% risk of a lifetime infection in patient after splenectomy despite immunizations and prophylactic antibiotics [13]. Depletion of macrophages and marginal B cell make patients more vulnerable to encapsulated bacterial infection with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. Risk is highest in a few months after the surgery [14]. Immunizations prior to splenectomy and counseling regarding antibiotic prophylaxis following surgery is now included in American Society of Hematology 2019 guidelines for ITP [6]. The accepted recommendation now is to treat ITP with medical management for a year before considering splenectomy [6].

2.3. Thrombopoietin receptor agonists (TPO-A)

Romiplostim given as 1–10 μg per kg injection weekly and Eltrombopag given as 25–75 mg oral daily are two well-studied TPO-A [15,16]. Avatrombopag is a new drug in this group which was recently approved by the FDA [17]. Thrombopoietin being the primary factor stimulating thrombopoiesis, romiplostim induces an overall response in 80% and Eltrombopag in 94% [18]. TPO-A are clinically successful in increasing the platelet count both transiently and in long term for splenectomized and non-splenectomized groups [15,18]. Possible side effects with TPO-A are liver toxicity, thromboembolism, and bone marrow fibrosis [19]. The absence of long-term safety studies and the high cost of TPO-A are other limiting factor for their use [20].

2.4. Immunosuppressants

Immunosuppressants like azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, and Vinca alkaloids are actively used in ITP as steroid-sparing agents in second-line or third-line setting, but lack systematic reviews and controlled trials for their use [6]. Azathioprine when used continuously in reduced doses for refractory ITP showed a CRR of 45% at 18 months [21]. Cyclophosphamide has a variable response between 24%- 85% in refractory ITP patients [22] Though intermittent doses of vinca alkaloids like vincristine and vinblastine might be helpful in ITP patients, they are infrequently used because of peripheral neuropathy [23]. The use of cyclosporine in ITP has been studied both as monotherapy and in combination therapy. With cyclosporine, ORR is 55%, which might be helpful in corticosteroid refractory patient but the toxicities like hypertension, severe headache, and myalgia are high [24]. Mycophenolate mofetil is found to have an ORR of 78% irrespective of the duration of disease [25].

2.5. Novel approaches

2.5.1. Fostamatinib

Fostamatinib is a spleen tyrosine kinase inhibitor that was approved by the FDA in April 2018 for patients with refractory or relapsed at the dose of 100 mg orally two times daily. In phase –3 randomized control study among patients who have failed splenectomy, TPO-A, and/or rituximab, 43% and 18% of the patients responded with a platelet count of >50,000 microl within 12 weeks and 24 weeks, respectively, [26]. It acts by decreasing inflammatory response and phagocytosis by macrophages. Side effects include diarrhea, nausea, hypertension, dizziness, and transaminitis [26,27]. Initial results are alluring, but long-term safety and efficacy are yet to be explored with the ongoing open-label extension study.

2.5.2. Combination therapies

(A) Steroids and TPO-A A case series of 10 patients who had 6 prior lines of therapy for ITP including TPO-A responded with the addition of prednisone to TPO-A (Romiplostim/Eltrombopag). One patient elected to discontinue the treatment whereas nine patients had sustained response with a combination of prednisone (5 mg–10 mg daily) and TPO-A (Romiplostim 5–9 μg/kg q7 days and Eltrombopag 50–75 mg po daily) [28]. Similarly, in a randomized controlled trial high-dose dexamethasone (40 mg IV for 4 days) combined with recombinant thrombopoietin (300 mg s/c for 14 days) compared to dexamethasone only showed a clinically significant response rate of 83% [29]. These studies indicate that the combination of steroid and TPO-A may be more than simply an additive effect and needs further exploration.

(B) Steroids, Cyclosporine, and Rituximab: This combination has been brought forward as a novel triple therapy for ITP. In a small prospective study of 20 patients, who had 2 or more prior lines of therapy, the combination
of oral dexamethasone 40 mg daily for 4 days, oral cyclosporine 2–3 mg/kg/day for 28 days, and IV rituximab 100 mg every week for 4 weeks. The 6-month response rate was 60%, and the treatment was well tolerated. Responders enjoyed relapse-free survivals of 92% and 76%, respectively, at 12 and 24 months of [29] TPO-A and rituximab In a randomized controlled trial, 123 patients with ITP refractory to steroids, were randomized to either Rituximab (100 mg IV weekly for 4 weeks) alone or Rituximab plus human thrombopoietin (300 U/kg Subcutaneous daily for 14 days). Although ORR was not significantly different in either arms (79.2% in the combination group vs 71.1% in the monotherapy group), CRR rate (45.4% vs 23.7%), and the median time to response (7 vs 28 days) were significantly better in combination group [30]. This combination has a potential for use where a rapid response is desired in a patient with corticosteroid resistant or relapsed patients. (C) TPO-A, immunosuppressions, and IVIG A study in a small group of 18 patients with refractory ITP failing an average of 6.5 treatment were given TPO-A (Romiplostim weekly subcutaneous injection/eltrombopag oral daily), immunosuppressant (cyclosporine 5 μg/kg/day/mycophenolate 500–1000 mg two times daily) and IVIG (1 g/kg as a rescue treatment when clinically indicated for severe thrombocytopenia) had a response rate of 72.2% [31].

Combinations like above are small studies with limited patients but suggest the possibility of targeting multiple pathophysiological mechanisms to achieve a higher success rate.

2.6. Novel agents

2.6.1. Sutimlimab

Sutimlimab is monoclonal antibody that inhibits the classical complement pathway, which is one of the pathways for immune-mediated destruction of platelets. Sutimlimab has shown benefit in cold agglutinin disease. From open-label phase-I trial, adult patients with severe and chronic ITP failing two or more prior treatment receiving Sutimlimab had a rapid and sustained response but there was a reoccurrence of thrombocytopenia on discontinuation of drug prompting further study on this novel agent [32].

2.6.2. Decitabine

Decitabine, a hypomethylating agent, is FDA approved for aplastic anemia, myelodysplastic syndrome, and acute myeloid leukemia. Defective methylation of DNA is now considered as proven pathway causing ITP [33]. A multicenter phase 2 study showed low-dose decitabine (3.5 mg/m² for 3 days every 4 weeks, three cycle) in patients not responding/refractory/unwilling to undergo splenectomy had a complete response of 17.7%, the partial response of 33.3% with significant improvement in fatigue and psychological symptoms. Adverse events like GI symptoms, transaminitis, and mild fever were noted in 13% of the patients [34].

2.6.3. Bruton Tyrosine Kinase (BTK) inhibitors

PRN1008 is a BTK inhibitor drug that has orphan drug designation from FDA. It was shown to inhibit B cell activation causing dose-dependent decrease in platelet destruction [35]. In an ongoing phase I/II study, use of oral PRN1008 in refractory ITP patients without alternative treatment, the overall response was 33%. The enrollment of this study is expanding, and further results are awaited [36].

2.6.4. Neonatal Fc receptor antibody

Rozanolixizumab is a monoclonal antibody targeted against human neonatal Fc receptors. Given subcutaneously, in a multiple-dose study to patients with persistent/chronic ITP, there was a clinically relevant improvement in platelet count with a reduction of IgG in all dose groups. It was well tolerated with a common side effect of headache [37]. This result supports the development of the phase III study which is awaited.

2.6.5. Recombinant IL-11

IL-11 has a known role in the maturation of megakaryocytes and is used in the treatment of cancer-related thrombocytopenia [38]. In a retrospective study, the patient receiving oral prednisone 1 mg/kg/day, dose tapered by 10 mg every week for a total of 6 weeks combined with recombinant IL-11 at 50μg/kg body daily for 7–14 days showed a response of 90% in patient with newly diagnosed and severe thrombocytopenia [39].

2.6.6. Bortezomib

Bortezomib, a proteasome inhibitor induces apoptosis of long-lived plasma cells reducing the concentration of antiplatelet antibodies in steroid-resistant or relapsed ITP [40]. There are case reports of successful treatment of refractory ITP with bortezomib alone or in combination [41,42].

2.6.7. PRTX-100

It is a highly purified staphylococcal protein A which modulates the immune system by binding B-cells and monocytes. It has shown efficacy in murine models [43]. An initial dose-escalation study found it to be safe [44]. There is an ongoing higher dose expansion cohort study for this medication.
2.7. Potential areas of future research

- The ambiguity regarding the choice of second-line treatment could be mitigated with larger studies directly comparing splenectomy, rituximab, and TPO-A
- Exploration of dose escalation or deintensification of rituximab to alter the response
- Cost analysis evaluation and patient-related quality of life measures for all newer medications
- Ideal sequencing trials of different available FDA approved therapies
- Exploration of various combination therapies in ITP

3. Conclusion

Our understanding of ITP has broadened over the last four decades, opening avenues for novel therapeutic approaches. Even though the majority of the patients attain remission with first-line corticosteroids, they either relapse or need maintenance therapy and fortunately, many medications with substantial potential are under investigation. Splenectomy has now moved to second-line treatment which can be considered only after trying other medical treatment (Rituximab or TPO-A). Avatrombopag and fostamatinib are new drugs approved by the FDA. Combination therapies are promising but need to be further explored in larger trials. Multiple new medications as above are in different phases of clinical trials.

To conclude the choice of treatment continues to be a shared decision-making process and relies on clinical judgment, patient preferences, cost, and adverse effect profile.

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