13 *Management of Immune Thrombocytopenic Purpura in Adults*

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Abstract: Primary immune thrombocytopenic purpura (ITP) is a heterogenous disease with variable severity and clinical course. It is unpredictable in its response to treatment. Not all patients require treatment. However, treatment is clearly indicated for those with severe bleeding or platelet count < 10,000/cmm. Those who can be managed with corticosteroids or splenectomy do not pose difficult problems. However, the rest require careful evaluation of disease severity, risk of bleeding and adverse effects related to treatment. Various experimental treatments are under clinical trials and these will add more tools to our armamentarium. A logical and structured approach to the clinical management of adult ITP forms the content of this write up.

INTRODUCTION

Primary immune thrombocytopenic purpura (ITP) is an organ-specific autoimmune disorder in which antibody-coated or immune complex-coated platelets are destroyed prematurely by the reticulo-endothelial system, resulting in thrombocytopenia. The clinical features of ITP in adults are different from those seen in children (Table 13.1).[1] Adult ITP usually has an insidious onset and a chronic course. Many cases are diagnosed incidentally on routine blood counts. The clinical course is highly variable and ranges from asymptomatic patient with mild bruising to life-threatening intracranial or GI hemorrhage. The diagnosis is one of exclusion where all other conditions known to cause thrombocytopenia have to be ruled out.[1]

Who should be Treated ?

This may appear a very innocent question. However, it is one of the most difficult one to answer. Not all patients with ITP require treatment. The goal of treatment is simple. Treating doctor has to provide a safe platelet count which can prevent significant bleeding with minimum treatment-related morbidity. Here, disease-related and patient-related factors are important so that treatment can be tailored to the individual patient. Spontaneous remissions, unlike children, are rare in adults. Still, as the disease has asymptomatic or mild course in majority of adults, treatment can be avoided in most.[2] Over a follow-up of 3-7 years, < 10% of patients required treatment.[2] Ten percent of chronic adult ITP patients remitted spontaneously while an equal number required some sort of therapy to improve the platelet count.[2] This percentage could vary as there are many clinicians who will give initial corticosteroid trial to majority of patients.

Does one Know the Mortality risk Attributable to ITP?

Cohen, et al[3] reviewed data involving 1817 patients and showed that the rate of fatal hemorrhage is between 0.016 and 0.039 cases per patient-year at risk. Portielje, et al[2] studied the relationship between disease-related and treatment-related mortality. During the follow-up period, 6 patients

died, 2 from hemorrhage and 4 from infection, most of which could be attributed to treatment. *This makes it clear that the treatment of ITP is even more dangerous than the disease itself. All of us are over-treating some of our patients. Interestingly, in another study by Neylon, et al,[4] 27 of 245 patients (11%) died, and only 3 (1.2%) of these deaths could be attributed to bleeding (ITP). Only 1 (0.4%) was due to overwhelming sepsis (post-splenectomy). All the remaining deaths were unrelated to ITP or its treatment.*

Is there a Relationship between Platelet Count and a Risk of Bleeding?

A count above 30,000/cmm is usually considered safe for patients living a sedentary lifestyle.[5] *What is unclear is whether patients with platelet count between 10,000 and 30,000/cmm are also equally safe. Lacey and Penner[6] showed that spontaneous major bleeding in adults with ITP was rare and occurred in less than 5% of patients with platelet count > 10,000/cmm. They also showed that bleeding occurred in 40% of patients with count under 10,000/cmm. Still, an experienced hematologist is aware of the fact that platelet count is a poor predictor of bleeding risk.* Circulating platelets in ITP are younger and possess better hemostatic activity.[7] This explains lack of bleeding despite very low platelet count. Nevertheless, platelet dysfunction in ITP is well-described. This is due to antiplatelet antibodies affecting platelet function.[8] Similarly, antibodies against megakaryocytes can impair platelet production. In contrast, some antibodies can cause platelet activation and promote thrombotic complications.[9]

Is Age Important?

Several studies have shown that age is an important parameter with respect to clinical bleeding in patients of adult ITP. Cortelazzo et al[10] reported that the rates of severe hemorrhagic complications in patients above or below 60 year's age were 10.4% and 0.4% per patient-year respectively. Similar rates of 13.0% and 0.4% per patient-year was shown by meta-analysis carried out by Cohen, et al.[3]

What are the Other Determinants?

There are other determinants of bleeding as well. Fever, uremia, chronic liver disorders, NSAID-abuse can all be associated with impaired platelet function increasing the risk of bleeding. Sedentary vs active lifestyle also makes a difference. Those engaged with physical jobs must have a stable platelet count above 50,000/cmm. Those performing contact sports may be unsafe up to platelet count of 80,000/cmm. Table 13.2 enlists the values of the platelet counts considered to be safe by British Committee for Standards in Hematology.[5] Table 13.3 enlists variables that are considered important in decision-making with respect to treatment of chronic adult ITP. Table 13.4 enlists ITP patients into four treatment categories:
1. Those who **must** be treated
2. Those who **should** be treated
3. Those who **might** be treated
4. Those who do **not** require treatment (usually).

I may reemphasize that there are young patients of chronic long-standing ITP with no clinical bleeding where platelet count is persistently less than 10,000/cmm and one may still follow a wait-and-watch policy so as to avoid long-term toxicities associated with treatment.

Emergency Treatment

Three groups of patients require emergency treatment:
1. Those with internal bleeding
2. Those with widespread mucocutaneous bleeding
3. Those needing emergency surgery.

The appropriate treatment includes:[1,5]
1. Intravenous immunoglobulin (IVIg): 1 g / k/ d × 2 days
2. Intravenous methyl prednisolone: 1 g / d × 3 days
3. Platelet transfusion: 2 U / h or 6 U every 6 hours

In addition, craniotomy may be required after platelet count has been raised to 100,000/cmm. Emergency splenectomy, antifibrinolytic agents and rFVIIa (NovoSeven) may be needed in occasional patients.[1,5] Anti-D (vide infra) and even Inj. Vincristine are of some help. IVIg and anti-D have synergistic or at least additive effect and hence both can be used simultaneously. They differ in their mechanism of action and the receptors that they blocked.[1,5] In view of these treatments, plasmapheresis may only have to be done occasionally.[11]

Initial Treatment

If life is not threatened, corticosteroids form the standard initial treatment.[1] I give IVIg only to those patients who are unresponsive to corticosteroids. Anti-D is another alternative to IVIg provided blood group is Rh (D) Positive and spleen is intact.[1] Results of treatments using corticosteroids, IVIg, anti-D and splenectomy are summarized in Table 13.5.[12-17]

Corticosteroids

Corticosteroids do not alter the natural history of ITP. It allows you to buy time until patient develops spontaneous recovery (acute ITP) or continues to remain thrombocytopenic and needs additional therapy. Approximately, 66% of patients show partial or complete response to steroids. Most of these responses are visible by the end of first week of treatment.[1] There is no consensus with respect to nature of steroid (prednisolone, methyl prednisolone, dexamethasone), route of administration (oral or intravenous), dosage (variable), duration of full-dose treatment (2-6 weeks) and mode of tapering (fast or slow). Majority will prefer to taper and discontinue steroids by four weeks after achieving a normal platelet count. Some of the studies have evaluated the long-term outcome of corticosteroid as the only treatment in the initial management of adult ITP.[2,12] There is a high early relapse rate (within first 6 months) and thereafter a slower but continuous relapse rate up to 6 years. Less than 20% of patients achieve complete remission which is lasting. Insidious disease and elderly age predict poor response to steroids.[18]

How do steroids work in ITP? This remains unclear. They impair the clearance of antibody-coated platelets by tissue macrophages, inhibit antibody production and increase platelet production by inhibiting phagocytosis of platelets by intramedullary macrophages. Steroids also have a direct effect on vascular integrity.[19,20]

Intravenous Immunoglobulin (IVIg)

IVIg is effective in 85% of patients, with 65% achieving normal platelet count.[21] Platelet counts start increasing within a day. Peak levels are reached by 7th day. The effect does not last longer than 4 weeks, after which the count decreases to pre-treatment levels.[21] *There is no difference in efficacy between the two commonly used dosing schedules of 400 mg/k/d × 5 days vs 1 g/k/d × 1-2 days.*[22] *However, a recent study has favored 1 g/k/d x 1-2 days as a more effective regime and it should now be considered as a standard-of-care.*[15] The adverse effects of IVIg are negligible, provided the infusion is given slowly over several hours. They include headache which can occasionally be severe, fever, chills and lethargy. Renal impairment has occurred with a higher incidence with certain sucrose-containing products.[23] It is more common in those with pre-existing renal insufficiency, diabetes mellitus, and age above 70 years.[24]

IVIg works by blocking Fc receptors on reticulo-endothelial cells, suppressing antibody production and binding (Fig. 13.1). The response to IVIg is quicker than with IV methyl

prednisolone, however, remission rate at one year is not different.[25] IVIg is more expensive and hence it should be used with certain reservations, i.e. when a rapid response is required (for treatment of life-threatening bleeding or before surgery), during pregnancy (where potentially teratogenic drugs should be avoided), where corticosteroids are contraindicated and when corticosteroid-resistance has developed.

Anti-D Immunoglobulin

The anti-D Ig is effective only in Rh (D) positive non-splenectomised patients. It binds to D antigen on RBC membrane. Immune-mediated clearance of the opsonized erythrocytes via the Fc receptors of the reticulo-endothelial system results into minimizing removal of antibody-coated platelets.[26] As against IVIg anti-D can be administered safely over a few minutes. The response rate is 70% and the increments last for over 3 weeks in 50% of responders.[16] The toxicity profile is similar to that of IVIg. In addition, there is slight but significant drop in Hb. The increment in platelet count can occur despite no significant drop in Hb. The standard dose is 50-75 mg/k × 1 day. It requires up to 72 hours to produce a significant increase in platelet count.[27] The higher dose schedule, i.e. 75 mg/k has quicker and higher response. It has been shown that 2/3rd of the patients repeatedly respond to anti-D therapy. Hence, it can be used for delaying splenectomy and sometimes, splenectomy can be totally avoided.[28] However, in view of slow onset of action, anti-D Ig is not recommended as first-line therapy in emergency situations.

The advantages of anti-D Ig over IVIg include its lower cost (although, still much more expensive than corticosteroids) and the convenience of administration. The disadvantages include the dose-limiting toxicity of anti-D in the form of hemolytic anemia, with a mean drop in Hb of 1.0 g/dl and its slower onset of action and hence not the best drug to be used in an emergency situation. Of course, its of no use in those who are Rh (D) Negative and also in those without intact spleen.

Table 13.6 enlists the differences between IVIg and anti-D in ITP.

SECOND-LINE TREATMENT

Rituximab

Increasingly, experts are advocating the use of rituximab (MabThera, anti-CD20 chimeric fab) as a first or at least second-line treatment for ITP.[29,40] The regimen used was identical to that used in follicular lymphomas, i.e. 375 mg/m^2 weekly for four consecutive weeks. The overall response rate is greater than 50%, with 30% sustained complete responses. Responses were observed both early during treatment and several months (even up to 4 months) after the last infusion. Splenectomised and non-splenectomised patients responded equally well. The toxicity profile is favorable. Most adverse effects are grade 1 to 2 first-infusion reactions.[29] The mechanism of action of rituximab are not fully investigated. It induces a profound B-cell depletion which may involve the auto-reactive B-cell clone. However, a mechanism of macrophage blockade by opsonized B-cells has also been proposed and this may explain the early responses.[29,40]

Splenectomy

Splenectomy is the standard and traditional second-line treatment for adults with chronic ITP where steroid therapy has failed to achieve a safe platelet count. However, there are certain issues:
1. Optimal time for splenectomy
2. The predictors of response
3. Selection of the surgical procedure (laparotomy vs laparoscopy)
4. Long-term efficacy
5. Safety.

Hence, the decision to do splenectomy has to be individualized. The factors to be taken into account include: age, duration of the disease, co-morbid conditions, efficacy and adverse effects of steroid therapy and preferences of the patient.

Approximately 75% of patients undergoing splenectomy achieve complete remission.[12] Most relapses occur within first 2 years after splenectomy, however, a small percentage of patients continue to relapse. Approximately, 60% of responders never relapse up to 10 years (Fig. 13.2). In those who relapse, an accessory spleen may be detected and its removal may bring about a second complete remission.[30] Search for accessory spleen may be done using CT scan, ultrasonography or radionuclide imaging. If radionuclide methods are used, the intraoperative use of a hand-held isotope detector probe can help to locate an accessory spleen.

Post-splenectomy complications are common (30%) resulting in prolonged hospitalization or readmission.[31] This is specially so in elderly, obese and those with co-morbid conditions. This is why, the decision to do splenectomy is always taken late. Most important indication for splenectomy is only after all other therapeutic modalities have been exhausted, patient's platelet count remains below 25,000/cmm and he keeps facing significant bleeding.

Can the response to splenectomy be predicted? Splenic sequestration of indium-labelled platelets is a good prognostic factor (Fig. 13.3).[32] However, these studies are difficult to perform and available only in few centers. Also, the specificity is not high enough to recommend it strongly.

Advanced age is also a poor prognostic factor. Response to IVIg is a controversial prognostic factor. Same applies to a good response to prednisolone. Presence of antibodies and the time to splenectomy have also been discussed but not very reliable prognostic factors. Taken together, indium-labelled platelet study appears to be the most accurate predictor.

Splenectomised patients have a small but definite risk of overwhelming infections. The estimated mortality is 0.73 per 1000 patient-years.[33] Splenectomy is usually avoided below the age of 5 years. Immunization for *S. pneumoniae, H. influenzae B* and *N. meningitides* is done at least two weeks before splenectomy. Postoperative antibiotic prophylaxis is not the standard of care in the US, however, it is recommended for life in UK guidelines.[34]

There is no consensus on the minimal platelet count regarded as sufficient to perform splenectomy. Laparoscopic splenectomy has become the preferred method during the past decade. It can be done with shorter hospital stay and even in the presence of co-morbid conditions. However, it is technically more difficult. It is also difficult to search for accessory spleens and to achieve hemostasis. It also takes a longer operative time. It is safe in the hands of an experienced surgeon.[35]

In those with high risk for surgery, splenic radiation[36] or partial splenic embolization[37] have been used with reasonable success.

Treatment after Splenectomy Fails

These patients where splenectomy fails are usually called "chronic refractory ITP". Approximately 30% of adult chronic ITP patients belong to this category. These are difficult patients and hence the goals of treatment are modified. A common strategy is to balance the risks and advantages of a treatment. Commonest treatment used in this situation is low-dose prednisolone, often 5.0 or 7.5 mg/d. Even this dose significantly increases the risk of osteoporotic fractures.

There are patients who require higher doses of prednisolone to maintain a safe platelet count. High-dose corticosteroids have been used, e.g. 40 mg/day of dexamethasone by oral or intravenous route × 4 days, repeated every 4 weeks. This approach, however, is now being shown to produce success in only sporadic cases[39]. No algorithm based on evidence can be proposed as standard of care for such chronic refractory ITP patients.[38] Many agents, various combinations and various procedures have been proposed as shown in Tables 13.7 and 13.8.

Azathioprine

It is one of the most popular immuno-suppressive agents. Approximately 20% of patients normalize their platelet count and the response is sustained for many months to years, even after treatment is discontinued.[40] An additional 30% achieve partial response. Median time to response ranges between 2 and 4 months. Treatment must be continued for 6 months before being deemed a failure. The usual dose is 2 mg/k/d. The dose is modified as per leukocyte count. Although safer than cyclophosphamide, the risk of developing a hematological malignancy is real.

Cyclophosphamide

It can be given as a daily oral dose or as intravenous pulse once every month. Oral dose is 1-2 mg/k/d and once again, it is adjusted as per leukocyte count. Intravenous pulse dose is 1.0 / m^2. Responses occur between 2 to 10 weeks and can persist after therapy is stopped.[41] Twenty to sixty percent of patients achieve partial or complete response. Adverse effects are more than with Azathioprine and include bone marrow suppression, hemorrhagic cystitis, infertility, teratogenicity and development of secondary malignancy. Hence, azathioprine is preferred over cyclophosphamide in younger patients.

Vinca Alkaloids

Both vincristine and vinblastine have been used for refractory ITP. The response is independent of the agent used and the mode of administration which could be intravenous bolus or a prolonged infusion.[42] Responses occur in 40-50% of patients, however, they are ill-sustained. Adverse effects include constipation and peripheral neuropathy and hence more than 3-4 doses are rarely used. The mechanism of action may be related to inhibition of phagocytic cell function.

Combination Chemotherapy

Lymphoma like combination chemotherapy has been used with variable success. This is not necessarily only in patients of ITP secondary to lymphoma or chronic lymphocytic leukemia. Even patients with refractory primary chronic ITP have responded.[43]

Campath-1H

Campath-1H is a humanized monoclonal antibody against CD52, a molecule which is expressed by both B and T-lymphocytes. Usually, it takes 4-6 weeks for the response to occur. The response has lasted for more than 5 months. Adverse effects were notable and included infusional toxicity like rigors and fever. Marked lymphopenia (below 100/cmm) was seen in all patients. Sustained responses were seen in some patients.[44,45]

Cyclosporine A

Cyclosporine A (0.6 mg tds), either alone or with prednisolone has been shown to improve platelet counts. The dose of cyclosporine A has varied from 1.5- 3.0 mg/k/d. Variable but well-sustained response have been noted which have persisted even after stopping the therapy.[46] Adverse effects are significant and often result into discontinuation of therapy.

Mycophenolate Mofetil

It has been used in small studies with partial response in 3-4 weeks. The dose has been 500 mg to 1 gm twice a day orally.[47]

Dapsone

Dapsone has been used in doses up to 100 mg/day orally, especially in older patients where long-term prednisolone is not preferred. Male patients must be screened for G6PD deficiency. Responses may take up to 2 months to occur. They are often ill-sustained.[48]

Danazol

Danazol is an attenuated androgen which was initially formulated for the treatment of endometriosis. It has been used in male patients and non-pregnant female patients with ITP. Ahn, et al recently reviewed 25 publications regarding efficacy of danazol in chronic ITP.[49] Pooled data show that extremely few patients with severe chronic refractory ITP respond to danazol. The standard dose is 400-800 mg/d and the mechanism of action involves impairment of macrophage-mediated clearance of antibody-coated platelets via decreased Fc receptor expression.[50] It is not easy to tolerate danazol in such doses for prolonged period. Adverse effects are frequent and include headache, nausea, breast tenderness, rashes, weight gain, alopecia, liver dysfunction and amenorrhea. Rare cases of hepatic peliosis and hepatomas have occurred.[49]

Eradication of *Helicobacter pylori* Infection

Recently, it has been suggested that *H. pylori* infection causes autoimmune diseases including ITP (Fig. 13.4). Studies describing the prevalence of *H. pylori* infection in ITP have generated conflicting results. Prevalence is ranged from 21.6% in the American study[51] to 71.4% in the Spanish study.[52] These discrepancies may be due to different socioeconomic conditions. A recent review[51] suggested that very few, if any, of responders had severe chronic ITP.

Staphylococcal Protein A Immuno-absorption

Snyder, et al[53] used Staph-A column to treat 72 patients and 25% had good responses. However, these results could not be reproduced by other workers. There is significant toxicity which includes fever, chills, rashes, diarrhea, respiratory distress. A minimum of three treatments are recommended.

Colchicine

Colchicine in the dose of 0.6 mg PO tds has been tried with variable effects.[54] It should be continued for a minimum of 2 months before its full effects occur. Unfortunately, its use is limited because of gastrointestinal adverse effects. Also, the effects are ill-sustained. There is not much experience with this modality of treatment.

Etanercept

In a recent report[55] three consecutive patients with chronic refractory ITP showed complete response to treatment with etanercept, an inhibitor of tumor necrosis factor-alpha. Some of these patients had failed 6-10 previous treatments. A clinical trial has been initiated and the results are awaited with interest.

Autologous Hematopoietic Stem Cell Transplantation

Stem cell transplantation has been tried in a limited number of patients with chronic severe refractory ITP with some success. In a recent study by Huhn et al,[56] 14 patients underwent this procedure and 6 had good durable responses. The procedure was fairly well-tolerated with only a few untoward events in the form of febrile episodes or bleeding. There were no deaths.

Platelet Growth Factors (AMG 531)

AMG 531 is a novel thrombopoietic agent. It binds and activates the thrombopoietin receptor. The results are encouraging. In a double-blind placebo-controlled study, 21 patients received AMG 531.[57] In some patients, the platelet count rose 450,000/cmm. Other studies have also confirmed good response to this agent.[58,59] Similar studies have been carried out using pegylated megakaryocyte growth and development factor. A study has used new orally active thrombopoietic drug, i.e. SB497115. It showed a dose-dependent increase in platelet counts of healthy volunteers.

Miscellaneous

Several other therapies have been tried in patients of chronic refractory ITP. These include ascorbic acid,[60] interferon-α,[61] 2-chlorodeoxyadenosine[62] and liposomal doxorubicin.[63] Number of patients in all these studies are small and the responses were transient, inconsistent and unimpressive. Mostly, patients with less severe ITP respond.

Other Experimental Therapies

These include a monoclonal antibody against FcγRI (MDX-33).[64] CTLA-4 immunoglobulin[65] or anti-CD40 ligand. Daclizumab, a humanized monoclonal antibody directed against CD25 (Interleukin-2 receptor), which has been used primarily to prevent rejection of solid organ transplants, has also been tried.[66]

ITP in Pregnancy[67]

Mild to moderate thrombocytopenia is common in healthy women with normal pregnancy. This is gestational thrombocytopenia which requires no treatment and which is not associated with fetal or neonatal thrombocytopenia.[68] It is, sometimes, difficult to differentiate this innocuous entity from ITP in pregnancy which requires consideration of both the mother and the fetus as the IgG antibodies cross the placenta and may produce profound thrombocytopenia in the neonate. Asymptomatic pregnant women with platelet count greater than 30,000/cmm do not require treatment until delivery is imminent. Platelet counts greater than 50,000/cmm are safe for normal vaginal delivery. Counts over 80,000/cmm are preferred for epidural anesthesia and cesarean section.

The major treatment options include IVIg and corticosteroids. However, IV anti-D and azathioprine have also been used.[69,70] Vinca alkaloids, androgens (danazol) and most immunosuppressive drugs should be avoided during pregnancy. The response rate to various agents are similar to non-pregnant state. Splenectomy during pregnancy, if absolutely essential, is best carried out in the second trimester and this can be successfully performed laparoscopically.

Incidence of fetal thrombocytopenia with platelet count of less than 50,000/cmm is 10% while that with platelet count of less than 20,000/cmm is 5%. There is no accurate, risk-free method of determining fetal platelet count. Both cordocentesis and fetal scalp blood sampling are rarely used in present times[71]. Also, there are no differences in the rate of complications including CNS bleeding in the neonate, with cesarean section compared with vaginal delivery. Hence, it is now agreed that the mode of delivery in ITP is purely determined by obstetric indications.[72]

After delivery, the newborn's platelet count often declines during the 1st week and this needs careful monitoring. IVIg is the treatment of choice for those newborns who have severe thrombocytopenia or mucosal bleeding.[72] If platelet support is needed, it should be eradiated and cytomegalovirus negative.[72]

CONCLUSION

Autoimmune thrombocytopenic purpura is an organ specific common hematological disorder, which is usually diagnosed by exclusion of other causes of thrombocytopenia. Many asymptomatic patients do not require treatment. The primary goal of treatment is to maintain platelet count at a safe level with minimal side-effects. Steroids, IVIg and IV anti-D with or without rituximab form the primary line of treatment. Splenectomy is the single most effective treatment for ITP and it is usually recommended for those who have a symptomatic disease after 3-6 months and where steroids are undesirable due to significant side effects. The refractory patients who fail splenectomy form management dilemma. Various therapeutic options are available (Fig. 13.5). However, many of them are potentially toxic. Chances of sustained response are low. Observation with no active treatment is a reasonable option for some. With availability of thrombopoietic agents in the future, there is a good prospect of keeping the platelet count of these refractory patients at a safe level. Pregnancy with ITP has special considerations and needs careful management.

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