Desafíos actuales en Púrpura Trombocitopénica Idiopática

Current Challenges in the Management of Immune Thrombocytopenia

Nichola Cooper

Consultant haematologist - Hammersmith Hospital - Du Cane Road - London

n.cooper@imperial.ac.uk

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Introduction

The management of immune thrombocytopenia has changed dramatically over the last 20 years. Establishing terminology and definitions of ITP has helped to compare treatments and establish response criteria[1]. While an increasing number of treatment options has improved patient care. However many challenges remain. Despite the identification of a serum derived factor causing thrombocytopenia and isolation of anti-platelet antibodies, there is still no sensitive or specific diagnostic test for ITP, which remains a diagnosis of exclusion[2]. The precipitating cause for ITP is not known and the contribution of T cell or antibody mediated effects in individual patients is not known. When to start treatment is also not clear, with a poor understanding of the effects of low platelet count. If treatment is required, there are a number of treatment options, with few comparative studies to help guide treatment decisions. There is a real need for a better understanding of the pathogenesis of ITP, development of diagnostic tests and comparative studies of established treatments.

Diagnosis and pathogenesis

There is no diagnostic test for ITP and the diagnosis remains one of exclusion of other causes of thrombocytopenia. This partly relates to a poor understanding of the pathogenesis of the disease. Although primarily thought to be an antibody mediated disease, up to 40% of patients with ITP have no detectable anti-platelet antibodies and

responses to treatment remain variable. T cell disease has been noted in some patients, but the establishment of disease types has not been made. Abnormalities in T cells include skewing to a Th1 phenotype, features of Th17 mediated disease and a reduced numbers of and function of regulatory T cells. In addition to a peripheral mediated platelet destruction, it is also clear that in some patients platelet production is inhibited[3].

Decision to treat

Treatment requirement is not clear. Not all patients require treatment even with low platelet counts. Patients with ITP have a heterogeneous disease and very few experience serious bleeding. Deciding which patients are at risk of bleeding and need treatment can be difficult. For example, many children receive no treatment, but without an increase incidence of intracranial haemorrhage (ICH). Whilst the majority of adults are treated based on the platelet count rather than on bleeding symptoms. This partially reflects increased risks of ICH with increasing age but may also reflect that some adults are unnecessarily treated[4]. Newer methods of assessment of bleeding may help.

Treatment options

Newly Diagnosed ITP (0 to 3 months)

What treatment to use for first or second line therapy has little evidence base, limiting the development of guidelines[2, 5]. High dose oral prednisolone, high dose dexamethasone and IVIG are all treatment options for first line treatment. Although studies of high dose dexamethasone suggest higher rates of remission at 12 months[6], there is little comparative data to help guide which therapies will result in the best long-term outcome.

Persistent ITP (3 to 12 months)

Second line treatments, for patients who do not go in to an immediate remission following a course of IVIG or steroids are listed in alphabetical order in the current ITP guidelines[2, 5]. Although randomized controlled studies have provided high-grade evidence for the newer agents, there is little other high-grade evidence and few comparative trials to allow development of evidence based guidelines. Common treatment options for those who do not go into a remission with first line therapy include immunosuppression with azathioprine or mycophenolate mofetil (MMF), rituximab therapy and thrombopoietin receptor agonists (romiplostim and eltrombopag). All are well tolerated and in the short term have few toxicities. For all agents, some patients (approximately 30%) will go into remission after a period of time yet there is no clear indication which patients will go into remission and which agents may be more likely to induce a remission in individual patients. Co-morbidities will influence the treatment options. Patients with associated immunodeficiency may have a better outcome with thrombopoietin-receptor agonists (TPO-RAs). While patients with co existing thrombotic risks, including ischemic heart disease (IHD) may have a better outcome with rituximab or immunosuppression, although there is little data to guide this.

Chronic ITP (greater than 12 months)

For those patients who do not go into remission within the first year, consideration will be made to the potential long term toxicity of treatments. MMF has been used in patients with other autoimmune conditions, although it is unclear what the risk of secondary malignancies are. Regarding rituximab, although using it on a single occasion appears to have limited toxicity, the majority of patients relapse within 5 years of treatment. Although many patients will respond to repeated infusions of rituximab, a proportion will develop hypogammaglobulinaemia. TPO-RAs have only been used for > 10 years in a handful of patients. They appear safe so far, but there may be increased risks of thromboembolic phenomena in susceptible patients, and the long term effects of persistent bone marrow stimulation is not known. Other treatments used in the long term treatment of ITP include danazol, dapsone and hydroxychloroquine. All have limited efficacy.

What is the role of splenectomy in ITP

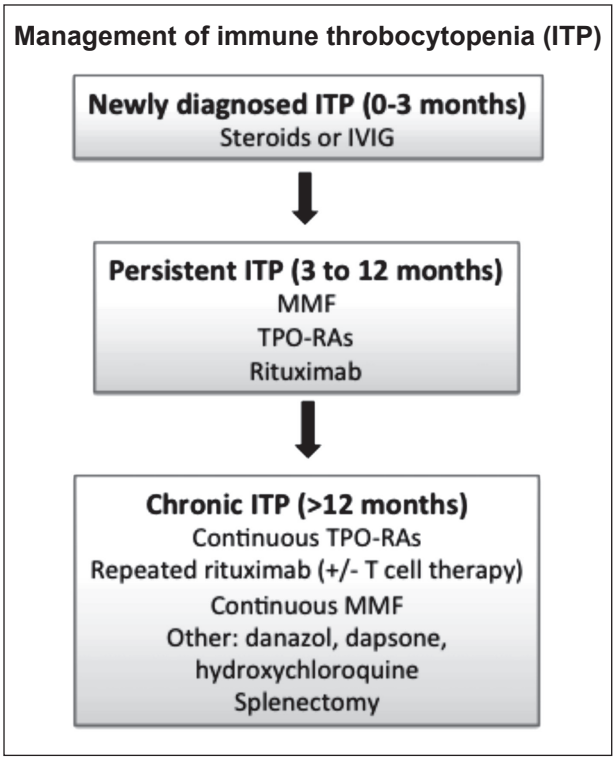
Overall, splenectomy has a lesser role in the management of ITP, but it remains an important treatment option. It still gives patients the greatest chance of remission and minimizes long-term treatment toxicities. Complications of splenectomy include a continued risk of septic shock and an increased risk of thrombosis[7]. These risks have been well established in longitudinal studies from a number of groups. What is not known is how these risks compare to other potential treatments such as repeated rituximab or long term TPO-RAs. Patients should be offered splenectomy if they have refractory disease, or require long term medication. Splenic destruction scans may help to predict which patients are more likely to respond.

Management of refractory disease

For those patients who do not go into remission and require long term therapy, minimizing long-term toxicity is required. For those few who are refractory to standard therapy, treatment options are limited and this has a big impact on health related quality of life (HRQoL). Better understanding of the cause of disease may help to guide novel therapies.

Summary

Overall, there is little understanding of the cause of ITP. The impact of this is a limit to the diagnosis of ITP and subsequent potential to misdiagnosis and there are no biomarker to direct treatment. While the majority of patients are asymptomatic and do not need treatment, a proportion of patients will require long term treatment. For these individuals, there is a need to better understand which treatments are more likely to put patients into a long term remission, and which agents are least likely to result in toxicity. There is an urgent need for more basic science to understand the cause of disease, development of biomarkers to help direct treatment and comparative studies to understand which agents cause the best long-term outcome. There is also a need to develop novel treatments for patients with refractory severe disease.



Declaración de conflictos de interés:

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