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PRIMARY IMMUNE THROMBOCYTOPENIA IN ADULTS - A NEW CONCEPT

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Summary

Primary immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by isolated thrombocytopenia (< 100 x10^9/L) in the absence of known causes. It is characterized by mucocutaneous bleeding and has a chronic and unpredictable course. Diagnosis of ITP is based on exclusion criteria. Its pathogenesis involves both increased destruction of platelets opsonized by antiplatelet autoantibodies and impaired platelet production. The majority of patients with ITP are either asymptomatic or have mild to moderate bleeding, while only the few with severe symptoms undergo treatment of unpredictable duration and effectiveness. Not until 2009 was the international consensus report on terminology, definitions and outcome criteria provided for ITP. Factors to be considered during treatment include bleeding, comorbidities, activity and lifestyle, individual tolerance of side effects, patient preferences and concerns, and finally the platelet count. The overall mortality rate of 1-5% and morbidity may be attributed equally to bleeding and to treatment-related infections. While there is general agreement about treatment of newly presenting adults with ITP, few evidence-based studies direct therapies in relapsed and refractory patients. Thrombopoietin receptor agonist targeting impaired platelet production represents a revolution in the treatment of refractory ITP.

Key words: immune thrombocytopenia, pathophysiology, therapy

INTRODUCTION

Primary immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by isolated thrombocytopenia (< 100 x10^9/L) in the absence of conditions known to cause thrombocytopenia. It is characterized by skin and mucosal bleeding and has a chronic and unpredictable course. In the absence of a "gold-standard" test, diagnosis of ITP is based on exclusion criteria [1,2].

Terminology, classification, definitions and demographics

It was not until 2009 that the International Working Group (IWG) on ITP provided a consensus report on terminology, definitions and outcome criteria for this disease [1]. A new staging scheme was also proposed by the IWG, defining the following stages of ITP: 'newly diagnosed' (diagnosis to 3 months), 'persistent' (4-12 months) and 'chronic'(≥ 12 months duration). The term 'severe ITP' stands for patients with major bleeding, while 'refractory ITP' is defined as severe ITP after splenectomy. ITP is a relatively rare disorder in adults with an estimated incidence of 1-4/100.000 persons. Historically, it is typically seen in women in the reproductive period. However, recent epidemiologic data showed that the incidence increases with age with the maximal age-specific incidence in the 8th and 9th decades. The median age at diagnosis is 56 years. Prevalence in elderly female patients ≥ 65 years old and males of a similar age was equal [3,4].

Pathophysiology

The mechanisms of thrombocytopenia in ITP involve both increased platelet destruction and impaired platelet production. The emergence of antiplatelet autoantibodies remains the central pathogenic mechanism. These antibodies are directed against a restricted number of dominant epitopes on glycoproteins (GP) IIb/IIIa and Ib/IX. Autoantibodies opsonize platelets, which are taken up and destroyed by macrophages predominantly in the spleen. They also bind to bone marrow megakaryocytes, thereby impairing megakaryocyte maturation and platelet production [5,6]. T-cells are also involved in the pathogenetic process in ITP. Namely, expansion of oligoclonal T-cells together with platelet- and megakaryocyte- reactive cytotoxic T-cells and suppressed regulatory T-cells have been identified in ITP patients. The emergence of antiplatelet autoantibodies and antiplatelet cytotoxic T-cells is a consequence of loss of immunological tolerance for self antigens. In some patients response to *Helicobacter pylori* and hepatitis B and C infection may generate antibodies that cross-react with platelet antigens. In addition, genetic factors might contribute to the predisposition to develop ITP or influence the natural history of ITP and treatment response. Such a complex pathophysiology of ITP explains its clinical heterogeneity [6].

Signs and symptoms

The majority of ITP patients are either asymptomatic or with mild to moderate bleeding, typically mucocutaneous. The intensity of bleeding correlates with the severity of thrombocytopenia and the patients' age, with the highest rate of severe or fatal hemorrhage in patients > 60 years old and those with platelet counts < 10 $x10^9$/L

[7,8]. Addressing this issue the IWG proposed that bleeding symptoms should be measured by a validated scale and expressed in bleeding scores [1,9]. Spontaneous remission is a rare phenomenon occurring in less than 10% of patients. Moreover, only a minority of patients exhibit severe ITP and the overall mortality rate of 1-5% could be attributed either to bleeding or to treatment-related infections. [7,8,10,11].

The diagnosis is based on exclusion of myriad causes of isolated thrombocytopenia such as: pseudothrombocytopenia, inherited thrombocytopenia, thrombocytopenia in pregnancy, cyclic thrombocytopenia, drug-induced thrombocytopenia, infections, various bone marrow diseases, autoimmune systemic diseases, lymphoproliferative disorders, liver disease, common variable immune deficiency, posttransfusion purpura and thrombotic microangiopathy syndromes [2].

Essential investigations in ITP include: history and physical examination, complete blood cell counts including reticulocytes, examination of a peripheral blood film, determination of immunoglobulin concentration, blood group Rh (D) typing, direct antiglobulin test and testing for *Helicobacter pylori,* and hepatitis B and C infection. A bone marrow examination should be considered in patients older than 60 years, in those with systemic symptoms and before splenectomy [2].

ITP is not considered a minor disease any longer, because the patients exhibit an impaired health-related quality of life (HRQoL) comparable to that observed with other serious chronic diseases (hemophilia, arthritis, diabetes, cancer) [12]. In addition, patients with primary ITP are at an increased risk for venous thromboembolic events compared to those without ITP [13]. Moreover, patients with primary ITP have a substantially enhanced long-term risk of infections, hemorrhagic episodes requiring hospitalization, hematologic malignancies and mortality [14].

Management

In general the treatment should be tailored to the individual patient and in line with current guidelines [2,15]. The therapeutic goals are as follows: to provide a safe platelet count to prevent or stop hemorrhages, to avoid overtreatment and to ensure a satisfactory HRQoL. Factors to be considered include: whether the patient is bleeding, comorbidities, activity and lifestyle, individual tolerance of side effects, patient preferences and concerns, and finally the platelet count. Treatment should not be based solely on platelet counts, but is prescribed according to the individual bleeding risk. In general, treatment is initiated in patients with a platelet count < 30 $x10^9$/L and rarely in those with higher counts (if bleeding or with risks for bleeding) [2,15]. In addition, activity restriction and avoidance of non steroid antirheumatic and intramuscular injections are advised.

Corticosteroids at a dose of 0.5-2 mg/kg for 2-4 weeks are the standard initial treatment. Up to 75% of patients respond but only 10-30% of them obtain a sustained higher platelet count. The mechanisms of corticosteroid action encompass suppression of macrophage function, inhibition of antibody binding to platelets and reduction of antibody production. Notable side effects of corticosteroids are infections, hypertension, glaucoma, cuchingoid appearance, diabetes mellitus, anxiety, osteoporosis and avascular necrosis of the hip. Intravenous immunoglobulin (IVIg) is also an effective treatment for ITP with nearly 80% responders for a period up to 3-4 weeks after therapy initiation. IVIg is administered at a dose of 2 mg /kg but is usually reserved for emergency treatment. The mechanisms of IVIg action are various: Fc receptor blockade, anti-idiotype antibodies in IVIG reaction with epitopes on the patients' autoantibodies. Among IVIg toxicities, headache, nausea, chills, allergic manifestations are common phenomena, while aseptic meningitis, thrombosis, hemolytic anemia and renal failure are rare.

Splenectomy (a second-line treatment) is an efficient therapy offering a sustained response in about 65% of patients [2,16]. Splenectomy removes the major site of destruction of antibody-sensitized platelets and also the major place of antibody synthesis. ITP guidelines recommend suspension of splenectomy for at least 6 months after diagnosis [2] due to the possibility of attaining spontaneous remission [2,15]. The relapse rate increases with time and 10% of relapses are due to hypertrophy of accessory spleens. Actually, the rate of splenectomy in primary ITP patients has dropped from 50-60% to 20-30% in the last decade due to the emergence of new drugs and the fact that splenectomized patients are immunocompromised for life.

For the 25-35% of refractory ITP patients, treatment options are TPO-receptor agonists (TPO-RA) [2,15]. TPO-RA are a new class of drug, eltrombopag being a non-competitive and romiplostim a competitive agent. They both activate the same signal pathway as endogenous TPO. They have the potential to increase the platelet count, to decrease bleeding manifestations and to improve the HRQoL in 80% of ITP patients, both splenectomized and non-splenectomized. Thus the use of TPO-receptor agonists has become the cornerstone of treatment for chronic refractory ITP [17, 18]. Eltrombopag is an oral non-peptide small molecule administered daily, while romiplostim, an Fc-peptide fusion protein (or 'peptibody'), is administered as a weekly subcutaneous injection. Several extensive, randomized, placebo controlled long-term clinical studies using both drugs showed that there were no important drug toxicities. Upon cessation of treatment, most patients returned to their basal platelet level [2,17,18]. However, cases of durable remissions after TPO-RA discontinuation in adult ITP have been reported recently [19].

CONCLUSION

Although guidelines provide the treating physician with the best current evidence relating to the diagnosis and management of ITP, we should remember that no diagnostic or treatment algorithm is suitable for all. Since guidelines always fall behind new research data, it is up to the physician to follow the principal medical literature.

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Sažetak

Primarna imunološka trombocitopenija u odraslih - suvremeni pristup

Primarna imunološka trombocitopenija (ITP) je stečena autoimuna bolest koja se odlikuje izoliranom trombocitopenijom nižom od 100x10⁹/L i odsustvom svih stanja i bolesti koje mogu dovesti do trombocitopenije. Karakterizirana je sklonošću krvarenju po koži i sluznicama, ima kronični tijek a ishod bolesti je nepredvidiv. Dijagnoza ITP se postavlja isključivanjem. Etiopatogeneza ITP je kompleksna i podrazumijeva prijevremenu razgradnju trombocita obloženih autoantitijelima kao i neefikasnu megakariocitopoezu. Većina bolesnika prikazuje slabo do umjereno izražene simptome, a samo manjina zahtjeva liječenje koje je dugotrajno i nepredvidivog ishoda. Tek 2009. godine provedena je standardizacija kako terminologije tako i definicija stadija bolesti i kriterija terapijskog odgovora kod ITP. Odluka o započinjanju liječenja se donosi na osnovu intenziteta i lokalizacije krvarenja, prisustva dodatnih faktora rizika za krvarenje, komorbiditeta, individualnog toleriranja neželjenih efekata liječenja i broja trombocita, a uvažavajući želje pacijenata. Stopa smrtnosti je 1-5% i posljedica je krvarenja i infekcija nastalih tijekom liječenja. Za razliku od liječenja novodijagnosticirane ITP, za liječenje refraktorne ITP, zasada ne postoje jasne preporuke. Revoluciju u liječenju refraktorne ITP predstavljaju agonisti trombopoetinskih receptora koji popravljaju neefikasnu megakariocitopezu.

Ključne riječi: imunološka trombocitopenija, patofiziologija, liječenje

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