review

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Practical considerations for the management of immune thrombocytopenic purpura

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Summary Immune thrombocytopenic purpura (ITP) is a rare hematological disorder with an autoimmune-mediated, often dramatic reduction of platelets in peripheral blood. Thrombocytopenia results from a reduced life span of thrombocytes and an additionally decreased production in bone marrow. For decades, the first-line therapy for ITP has been corticosteroids. As significant thrombocytopenic bleedings occur, the use of additional medication may be needed. Recent updates on therapy guidelines recommend the shortest possible use of corticosteroids. Thrombopoietin-receptor agonists are often used second line. Today splenectomy, which was previously recommended after unsuccessful first-line therapy, is usually considered much later. Patients who do not respond even after multiple lines of therapy continue to pose a major challenge. New drugs for ITP treatment are now available after steroid failure and will be discussed. This review gives a short summary on actual therapy guidelines taking into account newly available therapy options. In addition, comparisons between selected published data and experience at our department are made.

Keywords Rituximab · Corticosteroids · Splenectomy · Thrombopoietin agonists · Fostamatinib · Immunoglobulines

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Immune thrombocytopenic purpura (ITP, synonymous: immune thrombocytopenia, idiopathic thrombocytopenic purpura) is a rare hematological disorder with an autoimmune-mediated decline of platelets in peripheral blood and consequent bleeding complications. In Austria the yearly incidence of ITP in adults is 2–4 cases per 100,000 inhabitants; prevalence ranges between 9 and 26 per 100,000 persons (the incidence rate of pediatric cases is up to 2-fold of adults).

Thrombocytopenia results from a reduced life span of thrombocytes due to predominantly splenic destruction and an additionally decreased reproduction rate in bone marrow. Even megakaryocytes in the bone marrow are affected by this autodestructive process. The detection of autoantibodies (anti-glycoprotein-antibodies, type IgG, rarely IgM and IgA) against platelets is usually not helpful, as the sensitivity of the monoclonal antibody immobilization of platelet antigens test (MAIPA) is only around 60%. Therefore, a negative result does not exclude ITP. Antibodies against HLA-antigens (e.g., after polytransfusions) or certain medical substances are not considered as ITP.

Usually splenomegaly is not associated with ITP and if present should lead to exclusion of other lymphatic or metabolic diseases.

Other autoimmune diseases or infections with concomitant thrombocytopenia should be ruled out before diagnosis of ITP is made.

Laboratory tests of peripheral blood typically show isolated thrombocytopenia, not affecting other blood cell counts. As there is no “gold” standard for diagnosis, the term “ITP” should only be used if platelets drop below 100 G/l and other causes for thrombocytopenia (e.g., pseudo-thrombocytopenia, chronic/acute bleedings, certain hereditary or metabolic diseases) can be excluded.

In the majority of cases, successful immunosuppressive therapy with a prompt rise of platelets is suf-

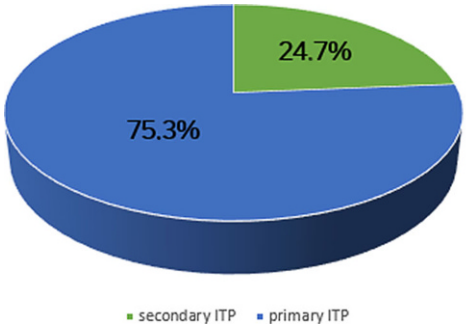

Fig. 1 Ratio of primary to secondary immune thrombocytopenic purpura (ITP) in 93 evaluable patients diagnosed at the 3rd Medical Department, Hanusch Krankenhaus, Vienna, between 2010 and 2020

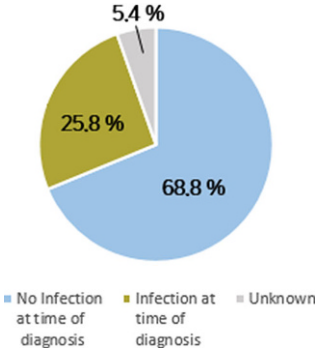

Fig. 2 Documented infection at time of diagnosis in newly diagnosed immune thrombocytopenic purpura (ITP) patients ($n = 93$) at the 3rd Medical Department, Hanusch Krankenhaus, Vienna, between 2010 and 2020

ficient for diagnosis. In a minority of cases (atypical courses of disease, multi-refractoriness, age >60 years, planned splenectomy) bone marrow biopsy needs to be performed to distinguish ITP from other diseases like myelodysplastic disorders, thrombotic thrombocytopenic purpura, etc.

Principally adults of all ages and both sexes can be affected. The median age at our center in 93 evaluable ITP cases is 52 years, roughly corresponding with international data showing a median age of 56 years.

A clearly predisposing pathophysiological process or underlying disease is usually not detectable, meaning that in about 80% of cases the cause of this type of thrombocytopenia remains unknown.

Around 80% of ITP are classified as primary disease, 20% can be seen in the context of other illnesses (Fig. 1).

Acute (less than 3 months of duration) ITP has to be distinguished from intermediate (3–12 months) and chronic (longer than 12 months) ITP courses. There are no known predicting factors for development of acute, prolonged, or chronic disease.

Particularly in children ITP may occur shortly after flu-like (viral) infections; however, bleeding signs are often nonexistent or mild. This explains the often observed seasonal increase in cases with a peak in early spring and late autumn [1].

Acute pediatric ITP (70–80% of pediatric cases) is usually self-limiting; thrombocyte counts mostly recover fully without any therapeutic intervention, meaning that medication is only needed when critical situations (major bleeding signs) occur.

As chronic ITP (less than 10% of cases) is rarely seen in this young patient group, more than 60% of adults show chronic courses of disease; thus, chronic ITP is far more common in adults than children. Spontaneous remissions in adults are rather rare events after the first year of diagnosis. For this reason nowadays splenectomy is considered as a curative intervention after this period of time.

The risk for ITP appears to be higher in people suffering from other autoimmune disorders like rheumatoid arthritis, vasculitis, lupus erythematosus, Hashimoto's thyroiditis or antiphospholipid syndrome. On the other hand, autoimmune cytopenias—and therefore also ITP—can occur in the course of hematologic neoplasms as well (chronic lymphoid leukemia, multiple myeloma, myelodysplastic syndrome and others) [2].

In about 20% of patients with ITP, a positive direct antiglobulin test (direct Coombs test [DAT]) is obtained. In these cases, concurrent autoimmune hemolysis must be assumed and further diagnostic steps added to exclude other disorders.

Inducing factors for ITP are often undetectable. However, in some cases there are hints for previous viral (human immunodeficiency virus, hepatitis, cytomegalovirus, Parvo B19 virus) or certain bacterial infections like Helicobacter pylori (HP). At our center, 25.8% of ITP present with concomitant infections, whereas 68.8% did not show any clinical or laboratory signs (Fig. 2).

Such events can expose immune-reactive cells to antigens that may mimic surface markers of platelets. But there are also several other theories for the development of anti-platelet antibodies under certain conditions. The activation and proliferation of cytotoxic T-lymphocytes (CD8+) and NK cells (CD3–, CD16+, CD56+) in chronic ITP has been known for many years. This gives a possible target for therapeutic interventions, too [3].

Considering the recent coronavirus disease 2019 (COVID) pandemic, it has been shown that immune regulatory activity can be altered during the infection due to increase of proinflammatory mediators. This causes propagation of NK cells, neutrophils and monocytes. Interactions of the different viral proteins (S, M, E, N) influence the inflammatory processes by altering the secretion rates of IL-8, IL-6, and IFN-1. Cross reaction, bystander activation, and hyperinnate inflammatory response may amplify autoimmune processes not only in ITP and are not completely understood yet [4].

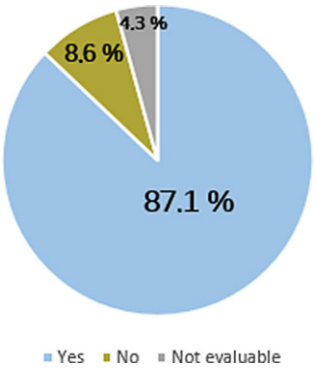

Fig. 3 In 93 patients, 87.1% show initial response to first-line immune thrombocytopenic purpura (ITP) treatment, i.e., corticosteroids ± intravenous immunoglobulines (IvIG)

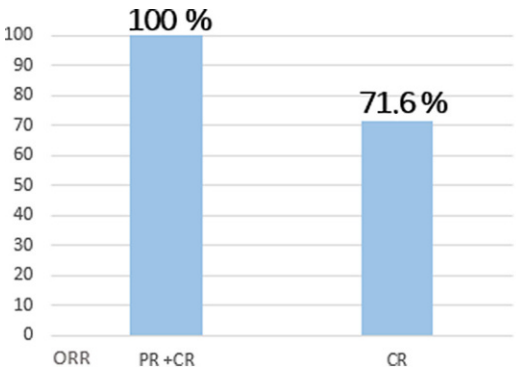

Fig. 4 Breakdown of best response to first-line treatment. 100% of the responding patients ($n = 81$) were able to reach at least a partial remission (PR; platelet count ≥50 G/L) and 71.6% were able to achieve a complete remission (CR; platelet count ≥100 G/L). *ORR* overall response rate

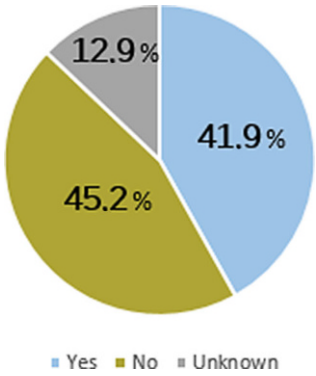

Fig. 5 Percentage of immune thrombocytopenic purpura (ITP) patients able to maintain the best response (partial remission defined as platelet count ≥50 G/L, complete remission defined as platelet count ≥100 G/L) for at least 3 months regardless of the dose change of corticosteroids

Certain clinical situations may be stressful for both patient and medical staff: Beside treatment of pediatric cases, ITP management during pregnancy is often challenging, as this condition itself may be a trigger for development of immune thrombocytopenia. On the other hand, minor thrombocytopenias may be caused by dilutionary and humoral effects on circulation. At the time of delivery, a sufficient number of platelets (>50–80 G/L) is needed in order to reduce the bleeding risk for mother and newborn. In most cases, the child will not be affected, but a number of babies will also have low platelets, needing close monitoring after birth and cooperation of gynecologists, neonatologists and hematologists [5, 6].

Another difficult issue are polymorbid, often elderly persons with the need of antithrombotic medications. In thrombocytopenic patients (e.g., during and after coronary angiography), the necessity of anticoagulative measures must be carefully evaluated and probably dose reductions are required if platelets drop below 50 G/L.

But ITP is not treated only on the basis of platelet counts. In a portion of patients the onset of ITP can be without any bleeding signs, detected only in routine laboratory tests. In the majority of adult cases, clinical signs of ITP comprise mild bleeding symptoms like mucosal and skin petechiae or epistaxis, hematuria or hematochezia, intense menstrual bleedings or even potentially life-threatening hemorrhage (organ or cerebral bleeding). Significant thrombocytopenic bleedings need to be aggressively medicated with immunosuppressive agents and/or other therapeutic interventions (e.g., immunoglobulins, splenectomy).

In clinical routine, first-line treatment consists of systemic corticosteroids (i.v./p.o.). Our data show an overall response rate of 87.1% within 6 weeks of treatment (Fig. 3).

However, sustained response for 3 months (at least platelets ≥50 G/l) can be achieved in 41.9% (Figs. 4 and 5).

In the literature up to 20% of patients do not respond sufficiently. The blood levels of CD8+ CD25+ regulatory T-cells (activated Tregs) in steroid responsive cases are described as being significantly higher, giving predictive information in sensitivity to corticosteroid treatment if examined [7].

Comparative trials for prednisone and dexamethasone in this indication do not give clear reason to prefer one over the other. Nevertheless, some publications suggest that prolonged dexamethasone (2–6 cycles high-dose induction, followed by low-dose maintenance for a limited time) might be superior over standard treatment with a monotherapy of prednisolone or single courses of high-dose dexamethasone. Time to initial response is a useful parameter for prediction of successful therapy, but relapses can occur anytime. Far less than 40% of ITP patients will experience spontaneous recovery within the first year after diagnosis [8].

A large proportion of patients need prolonged immunosuppressive treatment, either alone or in combination with other drugs. Only 20% of patients will not need further treatment after stopping steroids. To avoid long-term toxicity, steroid medication should be

limited to a short period (less than 6 weeks) according to updated international guidelines.

Considering the most recent recommendations early change to consequent options like thrombopoietin receptor agonists (TRAs) or rituximab (not approved for this indication) is recommended [9, 10].

Second-line treatment

Second-line treatment shall at least stabilize platelet counts in a safe range above 20–30 G/l without clinical relevant bleeding signs. The choice of different drugs in this situation is usually not based on head-to-head comparative trials. As there are no known predictors for decision-making and there is no consensus in the sequence of options, chronic ITP treatment must remain an individualized decision (life quality, comorbidities).

An often successful—but surgical—second-line option is splenectomy, with an initial response around 80–90%. As new and effective drugs are available, today splenectomy is considered much later in the course of medical therapies. A delay of 12–24 months is widely accepted to achieve remission on medical therapies before proposing this option to patients. The majority of splenectomized patients will have a sustained rise of platelets, but relapses can occur anytime and some side effects have to be accepted (increased frequency of thrombosis and infections, pulmonary hypertension, need of repeated vaccinations). Around 60% of those patients remain stable long term [11].

Rituximab ("off label") is a monoclonal anti-CD20 antibody that causes peripheral B-cell depletion and reduces immunoglobulin levels. Response can be achieved in about 60% of cases after administration. But relapses are often observed after varying lengths of time. In a meta-analysis only 21% of treated adults vs. 26% of treated children maintained remission at 5 years [12, 13].

In the era of the COVID-2019 (coronavirus disease 2019) pandemic anti-CD20 treatment adds the risk of not responding to vaccination and should therefore be taken into account.

In Europe thrombopoietin receptor agonists (TRAs) are licensed and nowadays widely used for the treatment of adult patients with chronic ITP, first limited to splenectomized patients, refractory to previous treatments (corticosteroids, immunoglobulins). The beneficial effects of these drugs have been shown in many clinical trials, even in pediatric patients. During pregnancy those drugs have been successfully and safely used in critical situations (although long-term safety data are lacking and this substance is not approved for this indication) [14].

Romiplostim (approved 2009) is a peptide that is injected once a week subcutaneously. Eltrombopag has been approved since 2010 and belongs to the class of "small molecules". Avatrombopag is another new, recently approved (2019) small molecule-TRA. Both drugs are taken orally on a daily basis [15, 16].

Published response rates range between 74 and 96%. Under certain circumstances, even exchange of substances within the TRAs can be useful. TRAs are considered a long-term therapy; however, it has been shown that a portion up to 30% are capable to discontinue treatment and stabilize platelet counts without further intervention for a longer period of time if not continuously [17].

The spleen-tyrosine-kinase inhibitor (SYK inhibitor) fostamatinib is another type of "small molecule", orally taken twice daily. This drug was approved in January 2020 in Europe. SYK plays a major role in signal transmission and interactions between immune cells. This substance has been studied in various autoimmune diseases (rheumatoid arthritis, autoimmune hemolysis). When used as second-line therapy, up to 78% of treated patients had an overall platelet response. If used after second-line, response rate dropped to 47% [18].

Other kinase inhibitors are currently being investigated in trials.

The immunosuppressant mycophenolate mofetil (MMF, "off label") has been widely used for many years in ITP as second-line option. This drug has a direct inhibitory effect on T-cells. More than 80% of steroid-refractory patients show an acceptable hematologic response, but the onset of effects can take up to 2 months [19, 20].

First-line data in newly diagnosed ITP (FLIGHT trial, closed March 2020) with a combined steroid and MMF treatment were presented at the December 2020 ASH meeting, giving hints that corticosteroids plus MMF may be a well tolerated and safe option for certain patients. This combination reduced the risk of refractoriness or relapse about 50%. Only limited preliminary data are currently available. Final response data have not yet been published [21].

Tacrolimus (a selective T-cell activation inhibitor, "off label") is reported in quite a few cases of ITP associated with mostly allogenic transplant recipients. A new retrospective single-center study on the effect of tacrolimus in relapsed or refractory ITP showed an overall response rate of 63.6% (>100 G/l: CR: 30.3%; >30 G/l: PR: 33.3%) [22].

Other therapeutic approaches include high-dose i.v. immunoglobulin (mostly used as rescue therapy for a limited time), anti-D-antibody, danazol and several other immunosuppressive agents (e.g., azathioprine, cyclosporine A). These are often recommended as spare medication after multiple relapses. Some other, older substances (dapsone, vincristine, cyclophosphamide etc.) are used in certain countries due to limited access or for financial reasons.

Despite the availability of several new substances, treatment of ITP remains challenging and requires an individual approach in each case.

Conclusions

In the examined patient population at our center ($n=93$; diagnosis between 2010 and 2020), the overwhelming majority of ITP cases (75.3%, $n=70$) presented without any identifiable predisposing autoimmune or neoplastic illness, therefore classified as primary ITP.

In 25.8% ($n=24$), a concomitant infection could be determined. Furthermore, 87.1% of patients ($n=81$) were responsive to first-line steroids (±IVIG) within 6 weeks after start of treatment, of which 71.6% ($n=58$) reached complete hematologic remission (platelet count above 100 G/L).

In all, 28.4% ($n=23$) were categorized best response with partial remission (platelet counts 50–100 G/L within 6 weeks of treatment onset).

Of all responders, 41.9% ($n=34$) were able to maintain best response (PR + CR) for at least 3 months regardless of dose changes in corticosteroid therapy (Figs. 1, 2, 3, 4, and 5).

Conflict of interest M. Fillitz, B. Dixer and F. Keil declare: Involvement in clinical trials in ITP concerning TRA therapies, fostamatinib and other pharmacological products; honoraria and congress participation support.

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