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Management of Adult Immune Thrombocytopenia: Review Article

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Immune thrombocytopenia (ITP) is an acquired autoimmune disorder defined by isolated thrombocytopenia and the exclusion of other causes of thrombocytopenia.Although the underlying pathophysiology of ITP has been known for more than five decades, therapy has remained empirical. ITP guidelines were published by the American Society of Hematology 15 years ago (updated in 2011) and the British Committee for Standards in Hematology 8 years ago. The primary treatment goal is to prevent severe bleeding rather than achieve normal platelet counts**.** Nowadays, new therapeutic agents have changed strategies for ITP treatment. In this review,we discuss criteria for treatment, the role of splenectomy and other treatment options along with their side effects, and the treatment of ITP during pregnancy.
Key Words: Primary; Immune; Thrombocytopenia; Treatment; ITP.

Erişkin İmmun Trombositopeni ve Tedavisi: Derleme

İmmün trombositopeni (İTP) diğer trombositopeni yapan nedenlerin olmaması ve izole trombositopeni ile seyreden edinilmiş otoimmün hastalıktır. İTP'nın patofizyolojisi 50 yıldan daha uzun süredir bilinmesine rağmen tedavi empirik olarak kalmıştır. İTP kılavuzu 15 yıl önce Amerikan Hematoloji Derneği(2011 de güncellenmiştir) ve 8 yıl önce de Hematoloji Standartları İngiliz Komitesi tarafından yayınlanmıştır. Tedavinin başlıca amacı normal platelet sayısına ulaşıncaya kadar ciddi kanamayı engellemektir. Günümüzde İTP'de yeni ilaçlarla tedavi stratejileri değişti. Bu derlemede erişkin İTP'de tedavi kriterlerini, tedavi yaklaşımlarını, splenektominin rolünü, yan etkileri ile birlikte diğer tedavi seçeneklerini ve gebelikteki İTP'nın tedavisini tartıştık.
Anahtar Kelimeler: Primer; Immün; Trombositopeni; Tedavi; İTP.

Introduction

ITP, has variably been defined as "immune thrombocytopenic purpura," "idiopathic thrombocytopenic purpura," and, most recently, "immune thrombocytopenia.[1]

Immune thrombocytopenia (ITP) is a common hematologic disease characterized by persistant thrombocytopenia, caused by a circulating antiplatelet autoantibody that binds to platelet membrane glycoproteins mediating the destruction of platelets in the reticuloendothelial system, particularly the spleen and liver.[2]

An expert panel established in 1996 by the American Society of Hematology (updated in 2011)and the British Committee for Standards in Hematology in 2003 published practical guidelines.[3,4] Furthermore, an International consensus reported in 2010.[5]

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ITP can be classified based on patient age (adult or childhood ITP) and duration of thrombocytopenia (acute or chronic). The clinical features of ITP in adults are different from those in childhood. In children, ITP is usually an acute, self-limiting disease, often occurring 2-3 weeks after a viral infection or immunization. In contrast, ITP in adults typically has an insidious onset, no preceding viral or other illness and has a chronic course. Using a lower-threshold platelet count of 50×10^9/l. The annual incidence of ITP among adults was reported to be 1.6-3.2 cases per 100,000 per year. The median age at diagnosis is 56 years, with a female predominance in those younger than 60 years and equal proportions between sexes among older patients.[6]In adults, the symptoms and signs are highly variable and range from completely asymptomatic to massive bleeding from any region, the most serious of which is intracranial, although their prevention remains the main goal of management.[7] The aim of this article was to provide an updated review of ITP in adults and on the evolving therapeutic modalities for chronic refractory ITP.

Pathophysiology

Pathophysiology of ITP, a disorder in which autoantibodies against cell-specific glycoproteins (GPIIb-IIIa, GPIb-IX and others) accelerate platelet destruction. These autoantibodies are produced by a limited number of B-cell clones. Platelet antibodies may also impair megakaryocyte development and platelet turnover. Thromobopoietin levels are normal or only moderate increased. Patients may show impaired immune regulation manifested by increased proliferation of helper T lymphocytes. Cytotoxic T lymphocytes from patients can lyse platelets in vitro. This mechanism may contribute to decreased platelet level.[6] Polymorphisms in the Fcγ-RIIIa gene may correlate with response to certain forms of therapy and similar genetic approaches may help to identify subsets of patients that differ in their natural history and response to various interventions.[8]

Diagnosis of immune thrombocytopenia

An important component of patient management is accurate diagnosis, documenting that the patient has idiopathic rather than a secondary form of thrombocytopenia. For this reason a full history must be obtained. The patient should be questioned on the type of bleeding, attempting to distinguish platelet-type mucocutaneous bleeding from coagulation-type bleeding and assessing the severity, extent, and duration of bleeding. The history should be used to determine the presence of other medical disorders that may give rise to thrombocytopenia, recent transfusion, a history of excess alcohol consumption or a family history of thrombocytopenia. The presence of splenomegaly should be noted; if present it probably indicates a diagnosis other than ITP, since ITP is not typically associated with splenic enlargement.[9]Approximately 1% of patients have coexisting immune hemolytic anemia (Fisher-Evans syndrome) and a smaller percentage have immune neutropenia, which confer a less favorable prognosis. Up to 5% to 10% of patients eventually meet criteria for systemic lupus erythematosus or another cause of secondary immune thrombocytopenia. Myelodysplastic syndrome is a relatively common condition in elderly patients in which, like ITP, the marrow is typically hypercellular in conjunction with marked peripheral cytopenia.[10]

The three key diagnostic criteria for ITP are; (i) isolated thrombocytopenia with otherwise normal peripheral complete blood count and smear; (ii) absence of hepatosplenomegaly and lymphadenopathy on physical examination; and (iii) platelet response to classicITP therapy (usually intravenous immunoglobulin, IV anti-D, and possibly steroids). It is not necessary for the diagnosis of bone marrow examination.

In case with splenectomy planned and patients over the age of 60,bone marrow aspiration and biopsy can be done. There is no "gold standard" test that can reliably establish the diagnosis.[1,5]

Most ITP patients experience only minor bleeding symptoms, such as petechiae, epistaxis, and bruising. Severe bleeding events, such as intracranial hemorrhage, protracted epistaxis, hematuria, hemoptysis, and gastrointestinal bleeding are rare[11] (Table 1).

Table 1. Characteristics of 168 patients with ITP as initial diagnosis.[11]

	Female	Male	Total
n (%)	115 (68,4%)	53 (31,6%)	168
Median age (range)	35 (15-80)	31 (15-91)	33 (15-91)
Platelets (10^9/l), median (range)	7 (1-132)	7 (1-99)	7 (1-132)
Hemoglobin (g/dl), (mean±SD)	12.1±2.2	13.9±1.3	12.6±2.3
Leucocyte (10^9/l) (mean±SD)	11.3±21.5	9.2±4.6	10.7±18.1
MVC (fl) (mean±SD)	81±8,2	83±4,9	82±7,3
Traumatic skin bleeding	7 (6,5%)	6 (12,5%)	13 (8,4%)
Spontaneous skin bleeding	41 (28,3%)	16 (33,3%)	57 (36.8%)
Mucosal bleeding	16 (15%)	10 (20,8%)	26 (16.8%)
Skin and mucosal bleeding	31 (29%)	12 (25%)	43 (27.7%)

Morbidity and mortality in adults with immune thrombocytopenia

Morbidity and mortality in adult patients with ITP was rarely studied systematically. The several patient series reported in the literature comprise different types of patients, differ in follow-up, and therefore do not permit drawing conclusions on morbidity and mortality in the overall patient population with ITP. Most studies are primarily concerned with the success or failure of different therapies to increase platelet levels, which is a surrogate marker of morbidity. Moreover, although many studies address hemorrhagic events and deaths during follow-up, the complications of medical and surgical therapies of the disease have not been consistently taken into account, and therefore morbidity and mortality of ITP may have been underestimated.[12,13] (Table 2).

Table 2. Mortality of immune thrombocytopenia (ITP) in adults.[13]

Reference	Patient accrual (years) design	Number of patients	Median follow up	Mortality related to ITP (%)
Neylon et al.	1993-1999 Prospective study in a population-based cohort	245	60 months	1.6
Vianelli et al.	1963–1997 Retrospective bicentric cohort	310	121 months	0.3
Portielje et al.	1974–1980 Retrospective monocentric cohort	138	126 months	4
Pamuk et al.	1984–2000 Retrospective monocentric cohort	150	30 months	0
Zimmer et al.	1985–1994 Retrospective monocentric cohort	201	1.7-84 months	1.5
Bourgeois et al.	1985–1994 Prospective monocentric cohort	183	90 months	1.6
Vianelli et al.	1959–2002 Retrospective multicentric cohort	402	92 months	0.7
Kumar et al.	1985–1998 Retrospective monocentric cohort	140	37.5 months	2.9
Balague et al.	1993–2003 Prospective monocentric cohort	119	33 months	0.9
McMillan et al.	1986–1998 Prospective monocentric cohort	105	142 months	12
Kaya et al.+	1994-2005 Retrospective monocentric cohort	168	27 months	0.006

+ This study has been added in the original table.

Management of immune thrombocytopenia

The goal of management for ITP is to increase the platelet count and prevent serious hemorrhage, and at the same time minimizing treatment-related toxicity.
In generally, patients who have platelet counts greater than 30 x 10^9/L with no bleeding require no treatment unless they have a particular risk, such as undergoing an invasive procedure. Treatment is suggested if platelets are less than 30 x 10^9/L and/or any bleeding symptoms are presents that regardless of platelets count in ITP patients.[1,4]

First-line treatment
Corticosteroids

The conventional standard practice is to initiate treatment of ITP with oral prednisolone 1-2 mg/kg per day. Treatment regimens used, duration of full-dose treatment (3-4 weeks) and the mode of tapering (fast or slow), however, are diverse. A short-term response to corticosteroids is observed in approximately 65-85% of patients but only around 10-30% show a prolonged response.[14] The appropriate dose of corticosteroids is uncertain and uncontrolled studies suggest that high-dose intravenous methylprednisolone may induce a more rapid increase and is more effective than oral prednisone. Additionally, in ITP patients, oral high-dose methylprednisolon treatment is more effective than the conventional dose of prednisolone in cases with bleeding and prior to emergent surgery where platelet number should be raised quickly.[15,16] In a study of 95 previously untreated patients (adults and children), 4-day pulses were administered every 14 days for four cycles. Initial response rates were around 85%, with response maintained long term in 74.4% (lasting for a median of 8 months), and the treatment was well tolerated.[17] Prednisone is usually given at 0.5 to 2 mg/kg/d until the platelet count increases (30-50x10^9/L), which may require several days to several weeks. To avoid corticosteroid-related complications, prednisone should be rapidly tapered and usually stopped in responders, and especially in non-responders after 4 weeks. Parenteral administration of high-dose methylprednisolone has been used in various regimens to treat patients failing first-line therapies, with 80% response rates. Administration of dexamethasone 40 mg/day for 4 days produced sustained response in 50% of newly diagnosed adults with ITP. Pulsed high-dose oral dexamethasone 40 mg/d for 4 days is an alternative to standard IV or oral methylprednisolone.[5] ASH recommend longer courses of corticosteroids (eg, prednisone 1 mg/kg orally for 21 days then tapered off) over either shorter courses of corticosteroids (eg, dexamethasone 40 mg orally for 4 days). Because, this treatment provides a sustained response than others.[1]

Intravenous immunoglobulin

The mechanisms of action of IVIG are complex and not clearly understood. Recent work has shown that IVIG slowed the antibody-coated platelet destruction by increasing the expression of inhibitory FcRγRIIb on splenic macrophages. Other mechanisms include the saturation of FcRn with IVIG, thereby increasing the clearance of autoantibodies.[18]In current practice the standard dose is 1 g/kg per day for one to two days. IVIG is effective in elevating the platelet count to more than 50×10^9/l in approximately 80% of patients. In more than half of responders, the platelet count becomes normal (>100×10^9/l). IVIg recipients are more likely to attain a platelet increase within 24 hours at a dose of 1 g/kg (1-2 infusions over 2 days) compared with the historical treatment regimen (0.4 g/kg/d over 5 days).[5]Platelet counts may begin to increase after one day and usually reach peak levels within one week after treatment. However, response is

generally transient, lasting no longer than 3-4 weeks, after which the platelet counts decrease to pretreatment levels. Thus, IVIG therapy is ideal when a rapid increase in platelet count is desired in patients with life-threatening bleeding and can also be combined with steroids and platelet transfusions in these situations. IVIG is well tolerated but side effects include allergic reactions, fever, renal failure (with some sucrose-based formulations), headache, aseptic meningitis and thromboembolic events. The optimal dose and regimen are unclear.[6]

Anti-D

Anti-D is recommended only in patients who are Rh-positive, negative direct antiglobulin test (DAT), and non splenectomized. It should be avoided in those with autoimmune hemolytic anemia, to avoid exacerbation of hemolysis.[1] Anti-D is a polyclonal antibody against the Rho(D) blood antigen. More than 25 years ago studies demonstrated that Rh immune globulin infusion induced an increase in platelet count in Rh(D)-positive patients with ITP.There are no extensive studies regarding the mechanism of action of anti-D. A direct interaction with macrophage FcγRs, thereby hampering destruction of platelets, is probably involved and is in agreement with the fact that anti-D is not effective after splenectomy. Another effect might be the increased levels of inflammatory and other cytokines which may be observed immediately after anti-D infusion.[6]The response rate to intravenous antiD50 μg/kg was 70% in the largest series published to date. The increase in platelet count occurred after 72 hours and lasted more than 21 days in 50% of the responders. At doses of 75 μg/kg, anti-D not only increases the platelet count more rapidly, and for a longer duration compared with the standard dose of 50 μg/kg, but platelet responses within 24 hours occur in the majority of patients, faster than those that have been reported with corticosteroids and as fast as those reported with IVIG. Furthermore, anti-D infusions may be an effective maintenance treatment for nonsplenectomized patients with chronic ITP[13]. Premedication with paracetamol/acetaminophen, or corticosteroids is recommended to reduce the risk of fever/chill reactions especially with the higher dose.[5]

Second-line treatment
Splenectomy

Many years ago it was recognized that the spleen played a major role in the removal of damaged platelets and hence contributed to the deficiency of circulating platelets. Splenectomy is traditionally considered second-line treatment in adults with ITP in whom achieving a safe platelet count with initial prednisone therapy has failed. Generally accepted criteria for splenectomy include severe thrombocytopenia ($<10x10^9$/l), high risk of bleeding with platelet counts less than $30x10^9$/l, or the requirement of continuous glucocorticoid therapy to maintain safe platelet counts. The results of splenectomy are better below the age of 40. The effectiveness and safety of splenectomy are confirmed by a high remission rate, and the general absence of haemorrhagic and infective complications.[19] 80% of patients respond to splenectomy, and response is sustained in 66% with no additional therapy for at least 5 years. Many patients without a complete response can still expect a partial or transient response. Approximately 14% of patients do not respond and approximately 20% of responders relapse weeks, months, or years later.[5]

Recent studies showed that laparoscopic splenectomy was as effective as conventional splenectomy for increasing the platelet count in patients with ITP. Although surgical time and anesthesia exposure time are longer, laparoscopic splenectomy offers a shorter hospital stay, earlier return of gastrointestinal function, less postoperative analgesia and smaller incisions.[20,21]

The major risk of splenectomy is bacterial sepsis, which occurs in <1% of adults with uncomplicated ITP. Immunization with polyvalent pneumoccocal, *Hemophilus influenzae* Type B, and quadrivalent meningococcal polysaccharide vaccines, depending on age and immunization history, should be given at least two weeks prior to splenectomy.[22] The number of reports on splenectomy for ITP, across many decades and many countries with consistent results provides adequate evidence for its benefits and risks.[23] (Table 3).

Table 3. Long-term outcomes following splenectomy: results of a systematic review of published case series.[23]

CR (Complete remission)	3506/5087 (69%)
CR in case series with ≥5 years of follow-up	779/1159 (67%)
Relapse following CR	15%
Surgical complications (Death)	
Laparotomy	48/4955 (1.0%)
Laparoscopy	3/1301 (02%)
Surgical complications (Others)	
Laparotomy	318/2465 (12.9%)
Laparoscopy	88/921 (9.6%)

Rituximab

Rituximab, a monoclonal anti-CD20 antibody that induces transient depletion of B cells, was originally

introduced for the treatment of non-Hodgkin lymphoma and is now emerging as an effective and relatively safe therapeutic option for patients with refractory ITP. New insights into the mechanism underlying response to rituximab in ITP indicate that, in parallel with B-cell depletion, significant changes occur in the T-cell compartment in patients who respond to rituximab with an increase in platelet count but not in the nonresponders. One important caution is that the optimal dosing regimen for rituximab in ITP has never been formally established. Rituximab is given as an intravenous infusion of 375 mg/m^2 weekly for four doses (days 1, 8, 15 and 22) in most studies. However, the optimal dose, frequency of administration and duration of treatment remain unclear.[24,25]

In a large, systematic review of the efficacy and safety of rituximab treatment in 313 patients with ITP, 62.5% of patients had a platelet response (platelet count ≥50x10^9/l). A complete response (platelet count >150x10^9/l) occurred in 46.3%, and a partial response (platelet count 50-150x10^9/l) in 24%. Preliminary data available in abstract form indicated that approximately 1/3 of the complete responders following initial therapy remained in remission for more than 1 year and around half of these patients continued their response for at least 5 more years. However, this finding derives from uncontrolled studies that also reported significant toxicities, including death in 2.9% of cases. These data suggest that providers should avoid indiscriminate use of rituximab and that randomized, controlled trials of rituximab for ITP are urgently needed.[26] Responses generally occur after 1 to 2 weeks to 6 to 8 weeks and last from 2 months in partial responders to 5 years or longer in 15% to 20% of initially treated patients. Most patients with a durable (>1 year) complete response will respond to repeat treatment if they relapse.[5] Zajaet al reported that dexamethasone plus rituximab was an effective salvage therapy in 56% of patients refractory to dexamethasone. The combination of dexamethasone and rituximab improved platelet counts compared with dexamethasone alone. Combination therapy may represent an effective treatment option before splenectomy. [27] Progressive multifocal leukoencephalopathy has recently appeared as a complication of rituximab treatment; reports suggest this complication is rare in patients with ITP treated with rituximab. Rituximab may be suggested for patients at risk of bleeding who have failed one line of therapy such as corticosteroids, IVIg, or splenectomy.[1]

TPO mimetics

Recent studies have provided evidence that the pathophysiology of ITP is more complex, and impaired platelet production has emerged as one of the mechanisms contributing to thrombocytopenia. On these grounds, second-generation thrombopoietic agents have been used in clinical trials to stimulate platelet production in ITP patients who are not responsive to standard treatments. These new molecules bear no structural resemblance to thrombopoietin (TPO) but still bind and activate the TPO receptor. Studies were completed for two TPO receptor agonists: romiplostim (formerly AMG 531) and eltrombopag (formerly SB497115). Romiplostim is a recombinant protein defined as a peptibody. Results of phase I-II trials published recently demonstrated that romiplostim given as a weekly subcutaneous injection (0.2–10 μg/kg) for 1-6 weeks resulted in doubling of platelet counts and with an increase to >50 x10^9/L in most treated patients with minimal adverse effects. Eltrombopag is an orally available, small organic compound. In a randomized, double-blind, placebo-controlled phase III trial, ITP patients were given daily oral treatment with placebo or eltrombopag 50 mg. Platelet responses were observed in 59% of eltrombopag-treated patients and in 16% of patients in the placebo arm. No significant adverse events were observed.[28] Phase III trials in patients with severe and refractory chronic ITP indicated that treatment with romiplostim results in a platelet count of ≥50×109/L in approximately 80% of patients. 88% of non-splenectomised and 79% of splenectomised patients achieved the target range of 50–200×109/L for at least 4 weeks.[29] Other thrombopoietic agents in development, such as AKR-501 (formerly YM 477), appear promising in healthy volunteers. Ongoing phase III clinical trials will reveal the potential of these agents in the management of ITP prior to splenectomy and for long-term maintenance therapy, as well as their relative benefit compared with standard of care treatment.[28]

Treatment of chronic refractory ITP

Patients can be defined as chronic refractory ITP if splenectomy fails and the patients require additional therapy. About 20-30% of adult patients with ITP may belong to this category. The goals of therapy for refractory ITP are clearly different from those for patients at initial presentation because the chance of inducing a durable, complete, and sustained remission is much lower. The objective of treatment for patients with refractory ITP is to achieve stable adequate platelet counts (>20 to 30 x 10^9/l) while minimizing the adverse side effects of medication.[1,5]

Cyclophosphamide and azathioprine

Response rates to these two immunosuppressive agents are similar. They reduce the number of T and B lymphocytes and suppress their function. They are often administered orally to the refractory ITP patient together with steroids. Response rates are about 50%

with perhaps a third achieving full longstanding remission. Oral cyclophosphamide 2 mg/kg has a response time of 2±8 weeks. Pulse intravenous cyclophosphamide therapy (1±1.5 g/m^2) was also used in patients with refractory ITP and may be of value in elderly patients in whom the long-term risk of malignancy and sterility are less of a concern than in younger patients, as well as in those for whom splenectomy is a high-risk procedure. In vivo, azathioprine is almost completely converted, albeit not instantaneously, to 6-mercaptopurine, resulting in a steady slow action. If azathioprine therapy is selected, a starting dose of 150 mg/day in adults is reasonable and a trial of at least 4 months is recommended since responses are often delayed. The combination of azathioprine and oral corticosteroids may be synergistic and azathioprine therapy may allow a reduction in the dose of corticosteroids. As with cyclophosphamide, the known complications of this drug should be anticipated and monitored.[30]

Cyclosporin A

Cyclosporine A (CyA) suppresses the T-cell function, inhibits antigen-induced activation of CD4+ T lymphocytes and the production of interleukin 2 and other cytokines. Recently prospective studies including six to 20 patients mostly splenectomized, confirmed that cyclosporine could be useful in refractory patients. An overall response was observed in 45-84% and a sustained response after cessation of the treatment in 24% of patients with a follow-up period of 6-48 months. The frequency of initial response appeared similar for splenectomized and nonsplenectomized patients, but a randomized study reported that the response in nonsplenectomized patients was frequently transient and nine of the 10 nonsplenectomized patients ultimately underwent splenectomy. In this study, 30% of the patients discontinued cyclosporine because of side effects, mainly hypertension, severe headache and muscle pain. These data suggest that cyclosporine treatment does not avoid the need for splenectomy in chronic ITP. A sustained response can be obtained in splenectomized patients but treatment toxicity must be considered.[12] Emilia et al. reported the results of long-term treatment with CyA (median, 40 months) and follow-up (median, 36.8 months) in 12 adult patients with resistant ITP.CyA used in relatively low doses (2.5-3 mg/kg of body weight per day) led to clinical improvement in 10 patients (83.3%). Five had a complete response (41.1%), 4 complete response to maintenance therapy (33.3%), and one partial response (8.3%). Two patients had no response. Most patients with a response (60%) had a long-term remission (mean, 28.6 months) after discontinuation of CyA. One patient had a relapse of ITP 4 years after CyA therapy was stopped. Side effects were moderate and transient, even in patients dependent on continued CyA treatment.[31]

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a purine nucleotide synthesis inhibitor initially developed to prevent acute rejection of solid organ transplants. It is now widely used for the treatment of autoimmune diseases. Uncontrolled prospective studies including six to 21 patients have controlled effectiveness of MMF in patients with chronic ITP. A response was observed in 39-83% of patients and the treatment was well tolerated. The response, however, was sustained after cessation of the treatment in only three cases, with a follow-up period of 6 months. The overall findings suggested that MMF could be used as a second-line agent for the treatment of refractory patients with good tolerance. The ability of the treatment to yield sustained response after its interruption remains unknown.[32,33,34]

Danazol and dapsone

Only few studies with limited patient populations were conducted and the published results may probably not apply to refractory patients. In their extensive review of literature published from 1966 to 2003 addressing the treatment of ITP patients refractory to splenectomy, Vesely et al. found 11 articles reporting 90 patients treated with danazol who were eligible according to the methodology of their study. Fifty-nine percent of the patients attained a platelet count of 50x10^9/l and 71% attained 30x10^9/l, but no information was given concerning the long-term outcome. There was only one complete response, defined as a normal platelet count that was maintained while the patient received no treatment for at least 3 months and through follow-up.[35] The response rates to dapsone may be similar to those for danazol but the number of uncontrolled retrospective studies reported is smaller. It is likely that many patients included in the retrospective studies that focus on treatment of ITP with dapsone and danazol did not have severe ITP. The rate of response with these two drugs in refractory patients may have been overestimated. The response seems to be dependent on continuation of the treatment and the response rate was lower in splenectomized patients and in patients with very low platelet counts.[36,37]

Alkoloids

Vinca alkaloids (vincristine and vinblastine) stimulate thrombocytopoiesis and suppress humoral and cellular immunity. Recenty published studies suggest that vinca alkaloids may produce a transient increase in platelet counts lasting 1 to 3 weeks in two thirds of patients, but a sustained normal platelet count occurs in fewer than 10% of patients.[38,39]

High-dose cyclophosphamide

High-dose cyclophosphamide therapy is administered 1.0-1.5 g/m^2 at 4-week intervals. Therapy should be stopped if there is no response after two courses and responding patients should receive at least three courses even if the platelet count has normalized. A high fluid intake is mandatory (3-4 liters daily, either orally or intravenously, during therapy and for at least 3 days afterwards). Frequent blood counts are required during the first two weeks and at least weekly thereafter because neutropenia is common.[40]

Interferon

Several case series have shown that 25% of patients with refractory ITP achieved a platelet count greater than 100 x 10^9/L for 1 week to 7 months following short-course interferon therapy.[2,3] The rationale was that this therapy might modulate the effector B cells involved in the autoimmune process and alter the macrophage behavior responsible for platelet destruction. In a prospective study of 21 splenectomized adults with refractory ITP, complete responses occurred in only 2 patients, and transient responses in 8 patients. The median time to reach maximal platelet count was 5 weeks, with a range of 1 to 30 weeks. One partial responder was retreated at relapse and achieved a complete response of more than 24 months.[41]

Combination chemotherapy

The use of aggressive lymphoma-like chemotherapy regimens for chronic refractory ITP was reported.Immune thrombocytopenic purpura was associated with Hodgkin disease in one case and with chronic lymphocytic leukemia in another. All 12 patients had a history of prior treatment with corticosteroids and all had undergone splenectomy. The duration of thrombocytopenia ranged from 5 to 110 months and all patients had platelet counts of less than 5 × 10^9/L unless they were receiving some form of platelet-enhancing therapy. The chemotherapy regimen consisted of up to 6 cycles of cyclophosphamide and prednisone plus one or more other agents (vincristine, procarbazine, and/or etoposide). Seven patients had a complete response, which was sustained in 4 patients for 60 to 150 months, and 2 had a partial response.[42]

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody against CD52, a molecule expressed by both B and T lymphocytes. In one study, 124 treated 6 patientswith refractory ITP (3 patients had an underlying lymphoproliferative disease). A response occurred in 4 of 5 patients available for assessment and in 3 of these; the response lasted more than 4.9 months. In most patients, between 4 and 6 weeks were needed for a response to occur. Adverse effects were notable and included rigors and fever during the infusion and marked lymphopenia (<0.1×10^9/L) in all patients treated. Worsening of thrombocytopenia was noted in 2 patients during therapy. A more recent study investigated the use of Alemtuzumab in patients with various cytopenias. A response was obtained in 15 and was maintained in 6 patients at the expense of notable adverse effects.[42]

H. pylori Eradication

The pathogenetic mechanisms underlying the relationship between *H. pylori* infection and ITP are still to be elucidated, but some data suggest that the effect of bacterium eradication may depend on genetic factors of the host, country-related factors, or *H. pylori* strains.[43]In the last few years, several studies, primarily from Italy and Japan, found that the eradication of *H. pylori* in infected patients with chronic ITP led to a substantial and persistent increase in platelet count in more than half of treated patients.[44,45] However, a recent prospective study in the United States showed no increased incidence of *H. pylori*in ITP patients and no platelet response after its eradication.[46]
Characteristics of the treatments used in chronic ITPare shown on Table 4.

Hematopoietic stem cell transplantation

Remissions have been induced in some patients with chronic refractory ITP using autologous or allogeneic hematopoietic stem cell transplantation. However, potentially fatal toxicities such as neutropenic fever, cerebral hemorrhage, andsepticemia may ocur.[5]

Immune thrombocytopenia in pregnancy

The American Society of Hematology (ASH) and British Committee for Standards in Hematology (BCSH) guidelines indicate that at platelet counts below 70×10^9/l or 80×10^9/l, respectively, causes of thrombocytopenia other than gestational thrombocytopenia should be considered. The ASH guidelines indicate that for severe thrombocytopenia or thrombocytopenic bleeding in the third trimester, intravenous immunoglobulin is an appropriate first-line agent. No consensus was reached concerning the use of intravenous immunoglobulin or corticosteroids as first-line therapy at other gestational periods. Splenectomy is considered acceptable for patients with refractory ITP and severe thrombocytopenia with bleeding only in the second trimester. Laparoscopic splenectomy can be safely performed during pregnancy. The BCSH guidelines are consistent with contemporary practice in

recommending that the mode of delivery of a pregnant patient with ITP should be determined based on maternal indications.[47] Mothers with ITP require monitoring during pregnancy and may require intervention with agents to raise the platelet count. For most women, however, pregnancy is uncomplicated and even those with severe thrombocytopenia during pregnancy have good outcomes. Fetal loss of approximately 1-2% continues to occur in ITP and remains, so far, unavoidable.[48]

Conclusion

Management of ITP is similarly difficult with many therapies posing potential risks that may be worse than the disease. It is generally agreed that bleeding-not platelet count-should be the rationale for treatment. Despite the absence of prospective, controlled studies, there is consensus that bleeding risks are significantly greater in patients with platelet counts <20 x 10^9 - 30x10^9/L, and therefore treatment is indicated for these patients; for those with higher platelet counts, but still <50 x 10^9/L, treatment is also indicated if accompanied by substantial mucous membrane bleeding. The standard initial treatment for ITP is oral corticosteroids to increase platelet counts. Intravenous immunoglobulin or anti-D immunoglobulin can also increase platelet counts and are particularly useful for

Table 4. Characteristics of the treatments used in chronic immune thrombocytopenia.[40]

Therapy	Dose	Response time	Common side effects
Prednisone	1–1.5 mg/kg PO qd	1–4 weeks	Hypokalemia, gastric upset, sodium and fluid retention, hyperglycemia hypertension, myopathy, osteoporosis infection risk, psychosis
Dexamethasone	40 mg PO qd × q4 weeks	1–4 weeks	Same as for prednisone
IVIG	1-2 gr/kg/gdIV	1-4 weeks	Aseptic meningitis and thromboemboliallergic reactions, fever, renal, headache
Anti-D	50-75 μg/kg	1-4 weeks	Mild hemolytic anemia, chills, nausea
Rituximab	375 mg/M2 IVq4 weeks × 4	3–4 weeks	Infusional symptoms: fever, chills, headache, bronchospasm, severe B cell reduction and potentialfor infection
Eltrombopag+	50-75mg PO gd	4-8 weeks	vomiting, dyspepsia, menorrhagia, paresthesia, ecchymosis, myalgia, cataracts, conjunctival hemorrhage, increasedliver functiontests.
Danazol	200 mg PO qid	3–6 months	Weight gain, fluid retention, seborrhea,hirsutism, vocal changes, amenorrhea,acne, headache, liver toxicity, thrombocytopenia
Colchicine	0.6 mg PO tid	4–8 weeks	Diarrhea (may limit therapy), nausea, vomiting
Dapsone	75–100 mg PO qd	4–8 weeks	Hemolysis, agranulocytosis, aplastic anemia, exfoliative dermatitis,toxic hepatitis, choleostaticjaundice, peripheral neuropathy
Cyclophosphamide	150 mg PO qd	6–8 weeks	Cytopenias, hemorrhagic cystitis,GI symptoms, sterility, secondary malignancies
Azathioprine	150 mg PO qd	2–10 months	Cytopenias, GI symptoms, secondary malignancies
Cyclosporine	1.25-2.5 mg/kg PO bid	3-6 months	Variable renal insufficiency,hirsutism, gum hyperplasia hepatotoxicity, hypertension, tremor, hypomagnesemia, secondary malignancies
Mycophenolate mofetil	0.5-1.0 g PO bid	3–4 weeks	Diarrhea, leukopenia, headache, secondary malignancies
High-dose cyclophosphamide	1.0-1.5 g/M^2 IV q 4 weeks	1–4 weeks	Cytopenias, hemorrhagic cystitis, GI symptoms, alopecia, sterility, cardiomyopathy, secondarymalignancies
Combination chemotherapy	Several combinations	1–4 weeks	Cytopenias, hemorrhagic cystitis,alopecia, dermatitis, anaphylaxis,GI symptoms, sterility, cardiomyopathy
Vincristine	1–2 mg IV/week	7–10 days	Peripheral neuropathy, alopecia,constipation, local corrosiveeffects if extravasated
Vinblastine	5–10 mg IV/week	7–10 days	Leukopenia, alopecia, constipation, local corrosive effects if extravasated

Eltrombopag+:This drug has been added in the original table.

Abbreviations: PO, per oral; IV, intravenous; SC, subcutaneously; qd, daily; bid, 2 times daily; tid, 3 times daily; qid, 4 times daily; GI, gastrointestinal.

stimulating rapid platelet increases before planned procedures. Splenectomy is traditionally considered the second-line treatment in adults with ITP in whom achieving a safe platelet count with initial prednisone therapy has failed. However, splenectomy is an invasive procedure with some patients relapsing even after several years. Very rare cases of life-threatening or lethal infections may also occur at any time after splenectomy and thus physicians and patients are increasingly reluctant to advise or agree to this treatment approach. Rituximab is an effective treatment for many people with ITP. Other treatments have also been evaluated for chronic refractory ITP, including immunosuppressive agents, alkaloids, mycophenolate mofetil, cyclosporine and danazol in a few randomized, placebo-controlled studies and they cannot currently be recommended, as their efficacy and safety remain unclear. Antiviral therapy is useful in patients with HIV or hepatitis C infection, but no consensus has been reached as to the efficacy of antibiotics to eradicate *Helicobacter pylori*. Thrombopoietin receptor agonists are currently under clinical investigation for the treatment of ITP and may represent an alternative treatment option in the near future.

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