DOI: 10.4274/tpa.1659

Changes in chilhood ITP treatment and follow-up in 2011

Tiraje Celkan

İstanbul University Cerrahpaşa Medical Faculty, Department of Pediatrics, Division of Pediatric Hematology-Oncology, İstanbul, Turkey

Summary

Immune thrombocytopenic purpura (ITP) is the most frequent hemorrhagic disease in children. The shortened life of platelets because of immunologic damage (antibodies absorbed by platelets) and insufficient compensatory increased function of the bone marrow result in reduced number of platelets in the peripheral blood. There are three forms of ITP: acute, chronic and persistent. The acute form occurs in 80-90% of cases with bleeding episodes lasting a few days or weeks, but no longer than 6 months. The new 2011 ASH guideline increased this period to one year. It is typical for the phenomenon of bleeding that it starts suddenly and without any other sign of illness. The most frequent acute form appears between the second and fourth year and it usually occurs after acute viral infections. Children older than 10 years of age, like adults, often have the chronic form associated with other immunologic disorders. Hemorrhagic manifestations include: petechiae, purpura, epistaxis, gastrointestinal and genitourinary bleeding. They depend on the grade of thrombocytopenia, although there is no strict correlation between the number of platelets and volume of bleeding.

In cases of acute ITP in children, usually there are two therapeutic options or therapies of choice: corticosteroids and high doses of intravenous immunoglobulin. There are also immunosupressive therapy, anti Rh(D) immunoglobulin, cyclosporine, cytostatics, danazol, rituximab, and TPO receptor agonists. In cases of distinctive hemorrhagic syndrome, there are also indications for platelet transfusion. Nowadays splenectomy is more restricted, because one third of cases are unsuccessful. *(Turk Arch Ped 2012; 47: 8-17)*

Key words: ITP, childhood, new therapies, guideline

Introduction

Immune (idiopathic) thyrombocytopenic purpura (ITP) is an acquired disease which develops as a result of shortening of platelet life span by autoantibodies produced against platelets and is characterized by thrombocytopenia clinically. In immune thrombocytopenic purpura, destruction of peripehral thrombocytes is tried to be balanced by increase in megacariocytes in the bone marrow. However, antithrombocyte antibodies can also affect the production of thrombocytes and thus the number of megacariocytes may be decreased or production of thyrombocytes may be disrupted in the bone marrow. Bleeding findings (frequently purpuric skin lesions, mucosal bleedings) develop according to the degree of thyrombocytopenia (1).

Immune thyrombocytopenic purpura usually occurs acutely in children after an infection or vaccination and tends to improve spontaneously in a short time. However, ITP is usually a chronic disease in adults. Therefore, treatment approach is different in adults and children (2-4). Currently, there is no laboratory test which is diagnostic for ITP. Therefore, the diagnosis of ITP is usually made by excluding other causes of thyrombocytopenia (4-9).

Immune thyrombocytopenic purpura is the most common reason for thyrombocytopenia in children. The actual incidence is not known, since the disease is frequently transient. In studies performed in North America, the incidence in the 1-14 age group is reported to be 7,2-9,5/100000 (1,3). In a recent study performed by Kurata et al.(10), it was reported that the incidence was 1,9/100000, made a peak between the ages of 2 and 5 years and occured more commonly in boys before the age of 4. ITP has a seasonal course and it occurs more frequently in winter and in the early spring period. Race and gender difference is not prominent (11). In 544 patients for whom we obtained adequate information in the files in our first 32-year series (1978-2011), the mean age was found to be 5.3±3.6,

Address for Correspondence: Tiraje Celkan MD, İstanbul University Cerrahpaşa Medical Faculty, Department of Pediatrics, Division of Pediatric Hematology-Oncology, İstanbul, Turkey
E-mail: tirajecelkan@yahoo.com **Received:** 12.06.2011 **Accepted:** 12.16.2011

male/female ratio was found to be 1.1, the rate of becoming chronic was found to be 9,3% and the rate of presentation with wet purpura was found to be 28%. While we could not find any significant seasonal difference, we found a slightly higher rate of presentation in the spring and autumn (12).

In 2011, the American Hematology Association compiled its recommendations about ITP in a guideline. According to this guideline (8):

1) The abbreviation of ITP: Purpura or red blots had been inspired from "porphyra" from the time of Hippocrates and the time of Galen and means purple fish (13). Since purpura are not present in a great part of patients, the term immune thrombocytopenia is recommended to be used instead of idiopathic thrombocytopenic purpura.

2) The limit of thrombocytopenia has been accepted as 100 x109, because the risk of severe thrombocytopenia was found to be 6,9% in a 10-year follow-up of adults with a thrombocyte count of 100-150 x109. When the distribution of thrombocytes in normal individuals were examined in some African-Asian countries, the upper limit was found to range between 100 x109 and 150 x109. In addition, this upper limit was found to be more appropriate to exclude pregnancy-related thrombocytopenia.

3) Etiological evaluation in immune (idiopathic) thrombocytopenic purpura: It is divided into two groups as primary and secondary ITP according to the factors which play a role in the etiology:

a) Primary ITP: Primary ITP is an autoimmune disease characterized by thrombocytopenia alone ((<100 x109). The diagnosis of primary ITP is a diagnosis of exclusion. A definite diagnosis of ITP can not be made clinically or by laboratory findings. The absence of other causes of thrombocytopenia should be manifested.

b) Secondary ITP: All thrombocytopenies other than primary ITP are in this group. When it is described, the cause is recommneded to be written in parentheses (SLE-related).

4) Periods of immune (idiopathic) thrombocytopenic purpura: Previously, ITP was classified as acute, recurring and chronic according to the time of thrombocytopenia. In new guidelines, these definitions are grouped as follows:

a) Newly diagnosed ITP: Acute ITP is a retrospective description and the period before the presentation of the patient can not be known. Therefore, the term" newly diagnosed ITP" was accepted instead of acute ITP. It was found to be appropriate to cover the first three months after the diagnosis.

b) Persistent ITP: This covers the patients who are within the 3-12th months of the diagnosis and who have still no remission or who do not stay in remission when the treatment is discontinued. Spontaneous remission is still possible in this period.

c) Chronic ITP: Patients with ITP lasting 12 months or longer are described in this group. In the old literature, thrombocytopenia lasting for more than 6 months was considered as chronic ITP. However, a significant part of the group defined a chronic ITP between 6 and 12 months previously was shown to achieve normal values at approximately the first year. Therefore, this period was prolonged to one year. In addition, the probability of spontenous improvement in chronic ITP is 30% at the fifth year and 44% at the 10th year (14).

5) The severity of immune (idiopathic) thrombocytopenic purpura was previosly classified as mild, moderate and severe according to the degree of thrombocytopenia. Final guidelines recommend that only the subjects with clinically significant hemorrhage findings should be classified as severe ITP. Since there is no scale evaluating hemorrhage findings, this definition is based on the decision of the physician (Table 1).

a. Definition of response to treatment: for a positive response clinical findings should be improved definetely.

b. Complete response: thrombocyte count>100x109

c. Response: patients with a thrombocyte count of 30-100x109 and patients who reached at least a two-fold increase over the baseline thrombocyte count.

d. Irresponsive: patients with a thrombocyte count of <30x109 and patients who could not reach at least a two-fold increase over the baseline thrombocyte count.

e. Corticosteroid dependence: Patients with a thrombocyte count of>30x109 or patients who should use corticosteroids continiously or intermittantly at least for 2 months to prevent

Table 1. Tests recommended in the American 2011 Guideline for the diagnosis of ITP

1. **Tests which should be done**
   - History of the patient
   - Familial history
   - Physicial examination
   - Complete blood count and reticulocyte count
   - Peripheral smear
   - Quantitative immunglobulin measurement
   - Bone marrow aspiration (in selected cases)
   - Blood group (including Rh)
   - Direct Coombs test
   - *H.pylori*
   - HIV
   - HCV
2. **Tests which may be beneficial in the management of the patient**
   - Specific antibodies against thrombocyte glycoprotein
   - Antiphospholipid antibodies
   - Anti-thyroid antibodies and throid functions
   - Antinuclear antibodies
   - PCR for Parvovirus and CMV
3. **Tests with unknown or unproved benefits**
   - TPO
   - Reticular thrombocytes
   - PaIgG
   - Thrombocyte life studies
   - Bleeding time
   - Serum complement level

bleeding. This may apply to other drugs (e.g azathioprine dependent, etc.). These patients should be accepted as irresponsive. This condition which is observed rarely in children lead to problems in adults.

f. **Refractory ITP:** There are two conditions for this definition. The first condition is splenectomy. The second condition is clinical findings requiring treatment or hemorrhage findings in the patient with thrombocytopenia after splenectomy. This definition is usually used for adults.

Pathogenesis

When Harrington (13) gave 9-10ml blood taken from a patient with ITP to a healthy person in 1951 for the first time, thrombocyte counts was shown to be decreased in hours. Before this Dameshek and Miller (13) examined bone marrow aspirates of patients with ITP in 1946 and suggested that there was a factor which disrupted thrombocyte production by affecting megacariocytes of these patients. As a result of culture of the plasma of a patient with ITP with a sample of bone marrow of a healthy person in 1980's, disruption in growth of megacariocytes and production of thrombocytes and a moderate increase in TPO level in contrast to what is expected were observed. It was found that the life time of thrombocytes which is 9,9 days normally was shortened up to 48-230 minutes by tracking of radiolabeled thrombocytes in the body. In these patients, thrombocyte production rate is increased by 4-9 fold (15). In chronic ITP, it was shown that thrombocyte destruction was minor, but production was inadequate and the life span of the thrombocytes which are produced in the bone marrow and transferred to the peripheral blood was close to normal people. Studies found that thrombocyte increase obtained with use of cortisone in patients with chronic ITP arised from trasfer of thrombocytes to the circulation rather than decrease in destruction. After invention of thrombopoetin in 1994 it was proved that TPO was bound to its receptor found on the membran of megacariocyte (c-Mpl) and provided thrombocyte production and maturation by phosphorilation of JAK-2, STAT-5 and MAPK. When trombocyte count is high in the peripheral blood, TPO is taken by thrombocytes and few TPO remains in the circulation. However, TPO entering into the thrombocyte is decreased and its amount is increased in the peripheral blood, when thrombocyte count is decreased. TPO stimulates megacariocytes and increases thrombocyte production and maturation. Thus, the desired thrombocyte count is tried to be obtained (15). Among thrombocytopenias, the highest TPO level is obtained in amegacariocytic thrombocytopenia, as expected. The lowest TPO level is found in chronic ITP. Anti TPO antibodies are usually not present in patients with ITP. However, antibodies against TPO receptor have been shown both in patients with ITP and in patients with systemic lupus. Immune (idiopathic) thrombocytopenic purpura is a heterogeneous disease with a complex pathogenesis. An acute infection is frequently the first triggering factor of the disease (15). Possible mechanisms:

1. Destruction related to antibodies

Antibody-coated thrombocytes are destructed by activated Fc receptors on reticuloendothelial cells frequently in the spleen (recognition of IgG Fc part by antithrombocyte antibodies). Most of the defined autoantibodies are produced against thrombocyte membrane glycoproteins (GpIIb/IIIa, GpIb/IX, GpIa/IIa). These antithrombocyte antibodies have no marked effect on thrombocyte function.

2. Disrupted thrombocyte production

Antibody and cellular cytotoxicity affect the rate and amount of production. In the etiology of immune (idiopathic) thrombocytopenic purpura, inadequate production has been noted in recent years and has been demostrated with thrombocyte kinetic studies (indium labeled autologous thrombocytes). Thrombopoetine levels were not found to be increased with the expected rate (16).

3. T cell acitivity

CD4+ T helper cells regulate B cells which release antithrombocyte antibodies. However, glycoprotein-specific antibodies are absent in 20-40% of patients with ITP. Genes involved in cell-related toxicity (granzime, perforin) (CD3+CD8+ T cell) are upregulated.

History and clinical findings

In children, the diagnosis of ITP is made by excluding other causes of thrombocytopenia. Even in typical cases, complete blood count and peripheral smear should be repeated at regular intervals until the diagnosis is definite or improvement occurs. If thrombocytopenia is present from the early period of life, familial history is positive or marked findings are present, hereditary thrombocytopenia should be suspected. In patients with multiple autoimmune cytopenias, other autoimmune diseases including systemic lupus (SLE), CVID (variable immune deficiency), ALPS (autoimmune lymphoproliferative syndrome) should be considered. In older children, the rate of tendency to chronic disease is higher.

In 50-80% of patients with newly diagnosed ITP (approximately 60%), there is a history of infection (mostly viral) during the last 1-3 weeks. Non-specific upper respiratory infections is the most common reason in patients with ITP which develops after infection. In 20% of the patients, a specific infection like rubella, measles, varicella, pertussis, mumps, infectious mononucleosis, cytomegalovirus, hepatitis A, B, C, parvovirus or bacterial infection can be found. There are studies about ITP after vaccination (16). The mechanism is not explained fully. While the most common vaccine responsible is reported to be measles, rubella and mumps (MMR) vaccine, recent publications reported that ITP also developed after hepatitis B vaccine. Although ITP develops in the first 6 weeks after vaccination, sometimes this period can prolong up to 9 weeks. Another point which should be paid attention in a child with immune thrombocytopenic (idiopathic) fpurpura is how to

continue the vaccination program in a child who had received intravenous immunglobulin or steroid treatment and who had recovered. Although no definite data are available on this subject, it is reported that at least one month would be a safe interval between live vaccine and the end of corticosteroid treatment, when prednisolone at a dose of 20 mg/day is administered for longer than 2 weeks. If IVIG had been used for treatment, live vaccine is recommended to be administered for at least after 8 months if the dose is low as 400 mg, after 10 months if the dose is 1 gram and after 11 months if the dose is 2 grams (17,18).

Petechiae, ecchymoses and mucosal bleedings are associated with ITP. Physical examination is normal other than purpura. Mild findings are present in 50% of the subjects. Petechias are observed in the subconjunctivae, buccal mucosa, soft palate and skin. Ecchymoses are usually observed on the anterior part of the lower extremities and on bone prominences (costae, scapula, shoulders, legs and pubic area). In addition to this type of hemorrhages, epistaxis, gingival bleeding, gastrointestinal system bleeding and hematuria may be observed especially in the beginning of the disease (1). Severe menorrhagia, retinal hemorrhage, middle ear hemorrhage which may lead to hearing deficit and central nervous sytem hemorrhage which is one of the most frightening complications may also occur. Hematoma and hemarthrosis are observed rarely. They may develop after intramuscular injection or severe trauma.

The classification which evaluates the severity of bleeding based only signs and symptoms without considering the thrombocyte count is used more frequently in the childhood (19):

A. There are no symptoms or mild symptoms are present: Very few petechiae or ecchymoses are present. There is no mucosal bleeding. Daily life is not affected markedly. 57% of the newly diagnosed patients are in this group.

B. Moderate degree: More severe skin and mucosal lesions, epistaxis and menorrhagia are present.

C. Severe: Hemorrhage periods which requires transfusion or hospitalization (retinal, intracranial bleeding, menorrhagia, epistaxis, melena) are present. The quality of life is affected severely. Transfusion may be needed.

Physical examination usually does not reveal any pathology except for hemorrhage findings. Paleness is not present unless severe bleeding occurs. The spleen is palpable in less than 10% of the subjects and is associated with viral infection (1). The presence of splenomegaly should suggest the possibility of leukemia, SLE, infectious mononucleosis or hypersplenism. No lymphadenopathy is found unless a triggering factor like viral disease is present.

The frequency of intracranial bleeding is 0,1-0,5% in immune (idiopathic) thrombocytopenic purpura. Thrombocyte count is below 10000/mm^3 in 73% of patients with intracranial bleeding, between 10000 and 20000/mm^3 in 25% and above 20000/mm^3 in 2%. The period between the time of diagnosis of immune (idiopathic) thrombocytopenic purpura and the time of intracranial bleeding is approximately 27 weeks (51% of the subjects in the first 4 weeks, 49% between 4 weeks and 9 years). Approximately 50% of the patients with intracranial bleeding have other risc factors [cranial trauma (29%), use of acetyl salycylic acid (5%), arteriovenous malformation (17%)]. The most significant clue in these patients is the presence of mucocutenous (wet¬-purpura) bleeding (49%). 77% of bleedings are intracranial hemorrhages (87% supratentorial) and 23% are subdural hemorrhages (1,21,22).

Laboratory findings

In complete blood count, thrombocyte count is always below 150000/mm^3 (<100000/mm^3 according to the last guideline) and frequently <20000/mm^3 in patients with diffuse findings of bleeding. MPV is increased. Anemia in relation with the amount of blood loss may be present.

Thrombocytopenia found in complete blood count should be supported by peripheral smear prepared from the fingertip. Pseudothrombocyteopenia and other hematologic causes should be excluded. In addition to thrombocyte morphology and cluster formation erythrocyte and leukocyte morphology should also be evaluated (1,23).

Bone marrow examination: This is recommended only if an abnormality other than thrombocytopenia in complete blood count/peripheral smear or systemic findings (bone pain, unexplained splenomeglay) are present in a newly diagnosed patient. It should also be considered in patients who have a very low response or no response to primary care treatments (8) (Table 2, 3).

On examination of bone marrow aspiration, megacariocytes are increased and frequently unmatured, there is no budding, erythroid and myeloid cells are normal, increased eosinophyles may be observed rarely and erythroid hyperplasia is found if

Table 2. Classification of the severity of bleeding

Severity of bleeding	Bleeding
Mild	Petechiae, <5cm ecchymosis Epistaxis whic stops by compression
Moderate	Uncountable petechiae, >5cm ecchymosis Epistaxis lasting more than 20 minutes Intermittent bleeding in the gingiva, throat, GIS, Reduction in Hb below 2 g as a result of hematuria,hypermenorrhea etc
Severe	Epistaxis which requires cautery or tamp Reduction in Hb >2 g as a result of bleeding in GIS, gingiva etc., suspicious organ bleedings
Life-threatening bleeding	Intracranial bleedings or bleeding causing hypotension and requiring >10ml/kg intravenous fluid and blood transfusion

Table 3. Recommendations about BMA in ASH 2011 guideline (8)

- Bone marrow aspiration (BMA) examination is not required in children and adults with typical ITP findings (1B).
- Bone marrow aspiration examination is not definitely required in patients who do not respond to IVIG treatment (1B).
- Bone marrow aspiration examination is not definitely required before steroid treatment or splenectomy (2C).

marked blood loss is present. If it is a typical ITP case, there is no need to perform bone marrow aspiration. However, the necessity of performing bone marrow aspiration before steroid treatment is still contradictory. Nevertheless, in most centers, bone marrow aspiration is performed if steroid treatment is to be started. Patients with acute leukemia very rarely present with thrombocytopenia alone (<0.1%) (1). However, bone marrow aspiration should be definetely performed, if atypical findings are present or if there is no response to treatment. The definite need for bone marrow aspiration before starting treatment to prevent masking of other diagnoses by steroid treatment was stated in 1996 guideline. In the 2011 guideline of the American Hematology Journal, it is stated that bone marrow aspiration is not needed before corticosteroid treatment is started or splenectomy is performed (proof level 2C), when there is no response to IVIG treatment (proof level 1B), if history, clinical findings and laboratory findings support the diagnosis of ITP. We still perform bone marrow aspiration in Cerrahpaşa Medical Faculty before starting corticosteroid treatment. We belive that one should be careful when making a diagnosis of ITP in countries (including Turkey) where consanguineous marriages are common, complete blood count is not performed regularly and therefore previos values of the patients are not known. Thus, we have many patients in whom we made diagnoses including depot disease, hemaphagocytosis, myelodysplastic syndrome and megaloblastic anemia in this way. Again, among our patients who were followed up with a diagnosis of ITP, there are patients who were diagnosed as Bernard-Soulier, vWF disease and portal hypertension by only deepening the history.

In the coagulation profile, bleeding time is usually long, prothrombin time (PT), activated thromboplastin time (APTT) and fibrinogen level are normal.

If clinically required, antinuclear antibody (ANA) and anti-ds-DNA, blood group, direct Coombs test, liver function tests, BUN and creatinine, Epstein-Barr virus, CMV, HIV and parvovirus tests should be ordered. Causes of secondary thrombocytopenia including Fanconi aplastic anemia, myelodysplastic syndrome, Evans syndrome, hypersplenism, microangiopathic hemolytic anemia, diffuse intravascular coagulation, vonWillebrand disease type 2B and drug-induced thrombocytopenia should be excluded.

Drug-related ITP is found more frequently in adults, but drugs should be interrogated in every pediatric ITP case (24). In clinical practice, we confront thrombocytopenia most commonly in use of anticonvulsants. In the literature, cases with use of antiinflammatory drugs, acsiximab, acetaminophen and bevacizumab have been reported (24).

The relation with immune (idiopathic) thrombocytopenic purpura and H.pylori was shown in adults (25). Studies performed in recent years about childhood ITP elucidated this subject. There are studies indicating that elimination of H.pylori especially in chronic ITP cases increased thrombocyte count (26,27). However, there are investigators who do not agree with this (28). In 20% of children with chronic ITP, H.pylori was found and elimination of infection by treatment increased the thrombocyte count to normal values in 39% of the cases (27).

Additionally, this guideline includes the following recommendations:

- Antinuclear antibody test is not needed to be performed in children and adolescents with a suspicious diagnosis of ITP (2C).
- In persistent or chronic ITP, it is not recommended to order H.pylori test (1B).
- The first MMR vaccine should be administered at the planned time in children with a history of immune (idiopathic) thrombocytopenic purpura who have not received MMR vaccine before(1B).
- When the time of the second dose comes in children with MMR vaccine-related or non-MMR vaccine related ITP, antibody levels should be checked. If immunity is adequate (90-95% of the children), the vaccine should not be administered. If immunity is inadequate, MMR vaccine should be readministered at the recommended time (1B).

Treatment of acute childhood ITP

The treatment of acute ITP aims to increase the thrombocytopenia which causes or may cause clinical findings to a level which will not lead to bleeding and to keep the thrombocytopenia as short as possible rather than targeting the cause. Therefore, the aim is to obtain a thrombocyte level which will provide adequate hemostasis rather than achieve a normal thrombocyte count (1,23). During the thrombocytopenic period, the patient should avoid sportive activities and use of antiaggregant drugs including aspirin and intramuscular injections. The information that immune (idiopathic) thrombocytopenic purpura is a benign disease and improves in most patients without problems and sequelas should be shared with the family and the child. Since most patients can be followed up at home, information related to the physician to be contacted in case of bleeding should be given. The family should be informed about what should be done in cases of severe bleeding. Since immune (idiopathic) thrombocytopenic purpura can last for weeks-months, the child should not fall behind at school or daily activities. Patients without severe bleeding can be followed up as outpatients initially with weekly intervals and then with longer intervals. In patients with skin eruptions alone, there is no need to perform complete blood count at frequent intervals. However, close follow-up is appropriate for the first 7-10 days in

Table 4. Points which have changed in recent years in ITP (53)

- In most children with ITP the thrombocyte count is <20 000/mm^3 and the clinical picture is limited with cutaneous bleedings.
- Most children improve in a very short time spontaneously without treatment
- Treatment is not needed in cases with mild bleeding
- Patients who are found to have thrombocytopenia can be followed up for a while without performing bone marrow aspiration
- In persistent thrombocytopenia, investigation and treatment is needed.
- Currently, the lower limit of thrombocytopenia is accepted to be 100 000/mm^3
- The rate of treated subjects has decreased from 69% to 16%.

patients with a thrombocyte count <20000. In patients who maintain very low thrombocyte counts, but no bleeding is found, a decision of treatment can be made together with the patient and the family, if the quality of life is affected (not being able to participate in sportive activities, etc.). Treatment of immune (idiopathic) thrombocytopenic purpura can increase the thrombocyte count much more rapidly compared to follow-up without treatment (Proof level 1B) (Table 4).

Treatments of immune (idiopathic) thrombocytopenic purpura usullay do not cure the underlying pathology and do not guarantee for complete remission. In addition, they have side effects. Therefore, currently the best treatment in ITP is "wait and see" treatment (29). Treatment options should be considered in patients with bleeding.

Clinical data indicate that there is no treatment to prevent intracranial or life-threatening severe bleedings, yet. In addition, severe bleeding attacks can be found during follow-up even though the patient was treated adequately at the time of diagnosis. In the follow-up, scoring and classification of bleeding is based on the experience of the physician. The countries in North Europe suggested a scoring system by showing that problematic bleedings occured more frequently in patients with a thrombocytopenia lasting more than 3 months and with a thrombocyte count of <20000/mm^3: this scoring system was based on 6 clinical findings including sudden onset (5), age<10 years (3), presence of previous infection (2), thrombocyte count < 5 x 10(9)/l, wet purpura (1) and male gender (1). High scores determine low risk (30). In immune (idiopathic) thrombocytopenic purpura, the most frightening finding is intracranial bleeding (ICB) which leads to administration of treatment (1,23), because morbidity with a rate of up to 50% is reported in children with ITP in addition to mortality. This means that a child who has had ITP which is considered to be a benign disease will live the rest of his/her life with neurological sequela. While Rosthoj et al. (31) found no ICB and severe bleeding in 500 children who were followed up for 6 months after the diagnosis, Kuhne et al. (32) reported 3 cases of ICB (0.17%) in the follow-up of 2540 children. In these 3 cases of ICB, thrombocyte count was <20 000/ mm^3 at the time of diagnosis and two of them received treatment. Donato et al. (33) found ICB in 3 of 1683 patients (0.2%). All these clinical data do not give a clue about the lower limit of treatment and treatment type. Thus, drug selection and the decision of treatment are left to the physician.

If immune (idiopathic) thrombocytopenic purpura is not manifested by severe clinical findings or has a course showing mild bleeding findings (ecchymosis and petechia), the patient can be followed up with close observation independent of the thrombocyte count. As a matter of fact, one of the best studies on this subject was performed in our country. Duru et al. (34) followed up 26 children with a thrombocyte count of <20 000/mm^3 10 of whom (38%) had mucosal bleeding without treatment for 5-32 months and administered treatment during the follow-up period in only two children who had epistaxis initially (34). In a similar study, Fujisawa (35) divided the patients who had no wet purpura and whose thrombocyte count was between 10000 and 29000 into two groups and found no difference between the two groups one of which was followed up without treatment and the other one was followed up by giving oral steroid for 21 days. Neunert (36) emphasized that severe bleeding was found in only 3 of the subjects who had no severe bleeding during the first 28 days, although the thrombocyte count was <20 000/mm^3 at the time of diagnosis in 505 of 863 patients with newly diagnosed ITP and none had ICB. Interestingly, no relation was found between administration of treatment initially and severe bleeding. As in adults, the subject of which pediatric age group needs treatment is controversial (for example, 2-3 year-old naughty boys who stop at nothing). Under normal conditions, 75-80% of the children are expected to enter remission in 6 months. However, Kuhne (32) reported that the disease become chronic with a rate of 23% between 3 months and 12 months, with a rate of 28% between 12 months and 10 years and with a rate of >47% above the age of 10 years. Kalyoncu et al. (37) found no difference between age groups in terms of becoming chronic, treatment response and clinical findings in their study

In acute ITP, treatment options include corticosteroids, IVIG and anti-D IgG and thrombocyte suspension in conditions where bleeding can not be stopped or in case of urgent surgical intervention (1,23,38,39-44). In recent years, interferon, monoclonal antibodies (rituksimab) and helycobacter treatment have also been tried (38). None of these treatments have been shown to prevent bleeding or prevent chronicity.

In Cerrahpaşa Medical Faculty, we generally follow up patients with ITP, but make a decision of treatment, when the thrombocyte count is <20000, wet purpura or bleeding is present. We prefer IVIG in young infants and 30 mg/kg steroid treatment for 3 days at other ages after performing BMA. In chronic ITP cases, we determine the method of treatment for bleeding independent of the thrombocyte count.

Primary treatment

1. When a decision of treatment is made, it is recommended to use a single dose of IVIG (0,8-1 g/kg) or short-term corticosteroids (proof level 1B).

2. IVIG should be preferred, if the thrombocyte count is desired to be increased rapidly (proof level 1B).

3. Anti-D is not recommended as the first-line treatment in conditions in which autohemolysis is present or bleeding-related anemia develops (proof level 1C).

4. Anti-D can be used as the first-line treatment as a single dose in patients in whom splenectomy can not be performed and who have a blood type of Rh+ (proof level 2B).

In cases who do not respond to treatment second-line treatment options are used.

1. Rituksimab can be tried, when there is no response to first-line treatments (IVIG, anti-D, conventional dose steroid) and if there is continuing risk of bleeding (proof level 2C).

2. As in cases of chronic ITP, rituksimab can be tried as an alternative for splenectomy or in cases in whom no response is obtained with splenectomy (proof level 2C).

3. When there is no response to first-line treatments and bleeding is continuing, high dose dexamethasone can be tried (proof level 2C).

4. High dose dexamethasone can be tried as an alternative to splenectomy or in cases who do not respond to splenectomy (proof level 2C).

When there is no repsonse to first-line and second-line treatments, splenectomy may be a treatment option (proof level 1B).

Splenectomy should not be performed before the 12th month after the diagnosis, if there is no life-threathening condition (prof level 2C). Splenectomy should not be performed before one year, because there is still a chance for spontaneous remission during this period. 80% of the patients respond to splenectomy. The response is permanent and additional treatment is not needed at least for 5 years (1,23,38,45). Partial or transient response is present in patients without complete response (45). 14% of the patients do not respond and the response may be lost in time in 20% of the patients with response (45). Open or laparoscopic splenectomy can be performed (46). Complications of splenectomy include bleeding, infection and thrombosis. The mortality rate is reported to be 1% in open surgery and 0.2% in laparoscopic surgery. To predict the response to splenectomy thrombocyte destruction in the spleen can be shown by using indium-labeled autologous thrombocytes (23). Accesory spleen which is the most significant cause of recurrence after splenectomy should definetely be investigated. Vaccines for H.influenza, pneumococcus and meningococcus should be administered at least 4 weeks before splenectomy or 2 weeks after splenectomy. After splenectomy vaccines for pneumococcus and meningococcus should be repeated every 5 years. Vaccination may not be adequate in patients who have received rituximab in the last 6 months. In these patients, vaccination should be repeated, when B cells are improved. After splenectomy thromboembolism should be prevented with acetyl saslicylic acid, when thrombocyte count is >800-1000 000/mm^3. In patients with splenectomy, prophylactic penicillin is recommended in the first 2 years, since development of sepsis is observed frequently in the first 2 years. However, the patient should warn his/her physician in potentail conditions with fever and should be educated in terms of infection.

Corticosteroids

1) Standard-dose prednisolone: 1-2 mg/kg/day (maximum 60 mg/day) for 2 weeks. Afterwards, the dose is tapered (should not last longer than a total of 3 weeks).

2) High dose methylprednisolone (HDMP):

a. 7,5 mg/kg, 4 days

b. 15 mg/kg, 4 days

c. 30 mg/kg/da or 500 mg/m^2, maximum dose 1 g/day, 3 days

d. 30 mg/kg/day, 3 days and 20 mg/kg, 4 days. A total of 7 days.

It can be used in patients with severe bleeding risk and with a thrombocyte count of 20000 mm^3 and lower.

Steroids act by decreasing phagocytosis and vascular permeability in addition to preventing antibody production and antibody-antigene binding. However, they have many side effects. Steroids may cause hypertension, hyperglycemia, hirsutism (with long-term use), striae on the skin, increase in appetite, psychosis and gastric complaints. In recent years, short-term treatment options are preferred with a higher rate to avoid side effects: there are studies indicating that administration of 16-24 mg/m^2 dexamethasone for 4 days or 4 mg/kg/day oral prednisolone for 4 days every 28 days is effective. We generally prefer a dose of 30 mg/kg for 3 days in newly diagnosed ITP. On examination of treatment response with complete blood count daily, >100000/mm^3 is considered to be a good response.

Intravenous Immunglobulin

It is thought that intravenous immunglobulin has various mechanisms of action. Intravenous immunglobulin decreases phagocytic activity in the reticuloendothelial system by inhibiting Fc receptors. The dose is given as 2 g/kg divided into 2 or 5 days. In recent years, it was proved that the same response was obtained with a single dose of 0.8 mg/kg. There are even studies conducted with 0.25-0.5 mg/kg (1,23).

Intravenous immunglobulin increases thrombocytes rapidly and the response lasts for 2-4 weeks.

Complications related to intravenous immunglobulin are observed rarely. Allergy, fever and shivering may occur. Headache, common cold-like clinic and a picture of aseptic meningitidis with vomiting and photophobia may develop (47). In children with IgA deficiency, IVIG may lead to anaphylactic reactions. It should be kept in mind that intravenous immunglobulin is a blood product and has a very high cost.

Anti-D treatment

It can only be used in Rh positive ITP patients. It was shown to increase thrombocytes with success in 80% of the patients. The effect lasts for 1-5 weeks. Its side effect is development of anemia as a result of dectruction of erythrocytes. It is a cheaper treatment compared to IVIG. The recommended dose is 50-75 ug/kg by intravenous infusion. Generally, a reduciton of 0.5-1 g/dl is observed in hemoglobin. However, high success rates in acute ITP have been reported with a dose of 75 ug/kg (48).

Rituximab

This is the second treatment method which can provide a cure other than splenectomy in immune (idiopathic) thrombocytopenic purpura. 60% of the patients respond. 40% of these maintain their response at the end of the first year. The rate of response decreases to 30% at the end of the second year. In 15-20% of the patients who respond initially, the response is maintained for 5 years or more. The response may occur between 1-2nd weeks and 6-8th weeks. If relaps occurs in the patients, response can be obtained again with the second administration. Dose: 375 mg/m^2 weekly, a total of 4 doses. The most severe side effects include progressive multifocal leucoencephalopathy, serum sickness and anaphylactic reactions. New data about long-term side effects are being obtained. Rituximab should not be used in patients with active hepatitis B. The risk of long-term B cell deficiency and low immunoglobulinemia (acquired hypogammaglobulinemia) should not be ignored (1,23,49). In an analysis evaluating 313 ITP patients who used rituximab, a significant advers event was reported in 19 patients (life-threatening complication in 10 patients, death in 9 patients). The mortality rate was reported to be 2.9%. It should be kept in mind that this rate is higher than the rate found with splenectomy (50).

TPO-receptor agonists

Traditional ITP treatment policies functioned to decrease increased thrombocyte destruction. However, cell culture studies performed in recent years showed that the increase in TPO levels were not so high in these patients in contrast to what is expected. Thus, the option of achieving adequate thrombocyte count by increasing production was added to treatment policies. Romiplostim and Eltrombopag increase the production of thrombocytes by activating TPO receptor. Romiplostim is used at a dose of 1-10 µg/kg weekly as subcutaneous injection. The response develops in 1-4 weeks. The response is maintaned as long as the drug is continued. Eltrombopag is used orally at doses of 25, 50, 75 mg/day. The effect starts after 2 weeks. Both drugs have similar effects in patients in whom splenectomy was performed and splenectomy was not performed. With these drugs side effects including headache, fatigue, epistaxis and arthralgia which can be easily overcomed are observed in 20% of the patients. However, the most important adverse effects of TPO receptor agonists include decrease in thrombocytes by 10% compared to the baseline value with discontinuation of the drug (rebound thrombocytopenia), increase in reticuline fibers in the bone marrow and thrombotic complications. Hepatic dysfunction may be observed in 13% of the patients who use eltrombopag. Safety data related to long-term use of these drugs are not adequate yet (51). Data about use in children are very limited (52).

In addition to these commonly used drugs the following drugs are used rarely:

Azathioprine: 50-150 mg/g

Danazole: 10-15 mg/kg/day (200 mg, 2-4 times a day)

Dapson: 75-100 mg/day (causes hemolysis in G6PD deficiency)

Mycophenolate mophetil: 250-1000 mg/day 2x1, 1-3 weeks

Cyclophosphamide: 1-2 mg/kg/day orally or 0.3-1 g/m^2 every 2-4 weeks 1-3 doses

Cyclosporine A: can be used as 2.5-3 mg/kg/day

Supportive treatments

Supportive treatments which increase quality of life by decreasing bleeding findings in patients with immune (idiopathic) thrombocytopenic purpura should definetely be used. Local and systemic use of antifibrinolytics (tranexamic acid) is beneficial in controlling bleeding in terms of supportive treatment. It should not be used in renal bleedings and kidney-related bleedings.

Other treatments

Various treatments have been tried in children whose thrombocytopenia and bleeding continue. However, most of these studies have been conducted in small patient groups. The drugs used have generally been tried by imitating adult studies. The use of cytotoxic drugs in treatment of ITP in children is controversial. In refractory patients and in patients with bleeding findings, combined chemotherapies (cyclophosphamide, prednosone, vincristin, azatioprine or etoposide), Campath-1H (immunsuppressive effect, may cause life-threatening infections) and hematopoetic stem cell transplantation have been reported to be used in case of irresponsiveness to multiple drugs. However, these treatments are considerably toxic, expensive and side effects in long-term are not known. In childhood, such anticancer drugs are not frequently preferred in benign diseases including ITP.

It was shown that colchicine, vitamin C, IFN-alfa, protein A immunadsorption column, plasmapheresis, recombinant FVIIa use is not beneficial in patients with ITP.

Transfusion of thrombocyte suspension

Life-threatening bleeding is the first rationale for transfusion of thrombocyte suspension (1). Transfusion administered at

normal doses may be inadequate in conditions where destruction of thrombocytes is excessive including ITP. Especially in intracranial bleeding, administration of continious IVIG combined with thrombocyte suspension for 8 hours every half an hour is recommended. With this treatment bleeding usually stops. Sometimes rFVIIa is given to control bleeding.

In addition, antifibrinolytic agents (tranexamic acid) which will delay dissolving of clots may be used.

References

1. Bussel J. Disorders of platelets. In: Lanzkowsky P (ed). Manual of pediatric hematology and oncology. 5th edt. San Diego: Elsevier Academic Press, 2011: 321-77.
2. Pamuk GE, Pamuk ÖN, Başlar Z, et al. Overview of 321 patients with idiopathic thrombocytopenic purpura. Retrospective analysis of the clinical features and response to therapy. Ann Hematol 2002; 81: 436-40.
3. Roganovic J, Letica-Crepulja M. Idiopathic thrombocytopenic purpura: A 15 year natural history study at the Children's Hospital Rijeka, Croatia. Pediatr Blood and Cancer 2006; 47: 662-4.
4. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009; 113: 2386-93.
5. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010; 115: 168-86.
6. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. British Committee for Standarts in Haematology General Haematology Task Force. Br J Haematol 2003; 120: 574-96.
7. Bussel J. Therapeutic approaches to secondary immune thrombocytopenic purpura. Semin Hematol 2009; 46: 44-58.
8. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011; 117: 4190-207.
9. Beardsley DS. ITP in the 21st century. Hematology Am Soc Hematol Educ Program 2006: 402-7.
10. Kurata Y, Fujimura K, Kuwana M, Tomiyama Y, Murata M. Epidemiology of primary immune thrombocytopenia in children and adults in Japan: a population-based study and literature review. Int J Hematol 2011; 93: 329-35.
11. Shirahata A, Fujisawa K, Ishii E, et al. A nationwide survey of newly diagnosed childhood idiopathic thrombocytopenic purpura in Japan. J Pediatr Hematol Oncol 2009; 31: 27-32.
12. Yıldız İ, Özdemir G, Soylu S, ve ark. Çocukluk çağında immün trombositopenik purpura: 32 yıllık deneyim sonuçları. Türk Hematoloji Derneği kongresi 2011, Ankara, sözlü bildiri: 0074, SO18: 49.
13. Blanchette M, Freedman J. The history of idiopathic thrombocytopenic purpura (ITP). Transfus Sci 1998; 19: 231-6.
14. Bansal D, Bhamare TA, Trehan A, Ahluwalia J, Varma N, Marwaha RK. Outcome of chronic idiopathic thrombocytopenic purpura in children. Pediatr Blood Cancer 2010; 54: 403-7.
15. Gernsheimer TB. The pathophysiology of ITP revisited: ineffective thrombopoiesis and the emerging role of thrombopoietin receptor agonists in the management of chronic immune thrombocytopenic purpura. Hematology Am Soc Hematol Educ Program 2008: 219-26.
16. Hsieh YL, Lin LH. Thrombocytopenic purpura following vaccination in early childhood: experience of a medical center in the past 2 decades. J Chin Med Assoc 2010; 73: 634-7.
17. Walter AO, Larry KP. Immunizaiton practices: Vaccines reccomended in special circumstances. Nelson textbook of pediatrics. 19th edition; 165: 891.
18. American Academy of Pediatrics. Immunization in special clinical circumstances. In: Pickering LK, Baker CJ, Long SS, McMillan J, (eds). Red Book: 2006 report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village IL: American Academy of Pediatrics, 2006.
19. Del Vecchio GC, De Santis A, Giordano P, et al. Management of acute childhood idiopathic thrombocytopenic purpura according to AIEOP consensus guidelines: assessment of Italian experience. Acta Haematol 2008; 119: 1-7.
20. Elalfy M, Elbarbary N, Khaddah N, et al. Intracranial hemorrhage in acute and chronic childhood immune thrombocytopenic purpura over a ten-year period: an Egyptian multicenter study. Acta Haematol 2010;123: 59-63.
21. Choudhary DR, Naithani R, Mahapatra M, Kumar R, Mishra P, Saxena R. Intracranial hemorrhage in childhood immune thrombocytopenic purpura. Pediatr Blood Cancer 2009; 52: 529-31.
22. Koçak U, Aral YZ, Kaya Z, Oztürk G, Gürsel T. Evaluation of clinical characteristics, diagnosis and management in childhood immune thrombocytopenic purpura: a single center's experience. Turk J Pediatr 2007; 49: 250-5.
23. Cuker A, Cines DB. Immune thrombocytopenia. Hematology Am Soc Hematol Educ Program 2010: 377-84.
24. Moulis G, Sommet A, Sailler L, et al The French Association of Regional Pharmacovigilance Centers.Drug-induced immune thrombocytopenia: a descriptive survey in the French PharmacoVigilance database. Platelets 2011. [Epub ahead of print].
25. Franchini M, Plebani M, Montagnana M, Veneri D, Lippi G. Pathogenesis, laboratory, and clinical characteristics of Helicobacter pylori-associated immune thrombocytopenic purpura. Adv Clin Chem 2010; 52: 131-44.
26. Jaing TH, Yang CP, Hung IJ, Chiu CH, Chang KW. Efficacy of Helicobacter pylori eradication on platelet recovery in children with chronic idiopathic thrombocytopenic purpura. Acta Paediatr 2003; 92: 1153-7.
27. Russo G, Miraglia V, Branciforte F, et al. AIEOP-ITP study group. Effect of eradication of Helicobacter pylori in children with chronic immune thrombocytopenia: a prospective, controlled, multicenter study. Pediatr Blood Cancer 2011; 56: 273-8.
28. Treepongkaruna S, Sirachainan N, Kanjanapongkul S, et al. Absence of platelet recovery following Helicobacter pylori eradication in childhood chronic idiopathic thrombocytopenic purpura: a multi-center randomized controlled trial. Pediatr Blood Cancer 2009; 53: 72-7.
29. Bekker E, Rosthøj S. Successful implementation of a watchful waiting strategy for children with immune thrombocytopenia. Dan Med Bull 2011; 58: A4252.
30. Edslev PW, Rosthøj S, Treutiger I, et al. A clinical score predicting a brief and uneventful course of newly diagnosed idiopathic thrombocytopenic purpura in children. Br J Haematol 2007; 138: 513-6.
31. Rosthøj S, Hedlund-Treutiger I, Rajantie J, et al. Duration and morbidity of newly diagnosed idiopathic thrombocytopenic purpura in children: A prospective Nordic study of an unselected cohort. J Pediatr 2003; 143: 302-7.
32. Kühne T, Buchanan GR, Zimmerman S, et al. A prospective comparative study of 2540 infants and children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) from the Intercontinental Childhood ITP Study Group. J Pediatr 2003; 143: 605-8.
33. Donato H, Picón A, Martinez M, et al. Demographic data, natural history, and prognostic factors of idiopathic thrombocytopenic purpura in children: a multicentered study from Argentina. Pediatr Blood Cancer 2009; 52: 491-6.
34. Duru F, Fisgin T, Yarali N, Kara A. Clinical course of children with immune thrombocytopenic purpura treated with intravenous immunoglobulin G or megadose methylprednisolone or observed without therapy. Pediatr Hematol Oncol 2002; 19: 219-25.
35. Fujisawa K, Iyori H, Ohkawa H, et al. A prospective, randomized trial of conventional, dose-accelerated corticosteroids and intravenous immunoglobulin in children with newly diagnosed idiopathic thrombocytopenic purpura. Int J Hematol 2000; 72: 376-83.
36. Neunert CE, Buchanan GR, Imbach P, et al. Severe hemorrhage in children with newly diagnosed immune thrombocytopenic purpura Blood 2008; 112: 4003-8.
37. Kalyoncu D, Yildirmak Y, Cetinkaya F. Comparison of idiopathic thrombocytopenic purpura in children between 3 months and 2 years versus 2-5 years. Pediatr Blood Cancer 2009; 52: 656-8.

38. Pels SG. Current therapies in primary immune thrombocytopenia. Semin Thromb Hemost 2011; 37: 621-30.
39. Blanchette V, Imbach P, Andrew M, et al. Randomised trial of intravenous immunoglobulin G, intravenous anti-D, and oral prednisone in childhood acute immune thrombocytopenic purpura. Lancet 1994; 344: 703-7.
40. Tarantino MD, Madden RM, Fennewald DL, Patel CC, Bertolone SJ. Treatment of childhood acute immune thrombocytopenic purpura with anti-D immune globulin or pooled immune globulin. J Pediatr 1999;134: 21-6.
41. Newman GC, Novoa MV, Fodero EM, Lesser ML, Woloski BMR, Bussel JB. A dose of 75 µg/kg/d of i.v. anti-D increases the platelet count more rapidly and for a longer period of time than 50 µg/kg/d in adults with immune thrombocytopenic purpura. Br J Haematol 2001; 112: 1076-8.
42. Kumar M, Vik TA, Johnson CS, Southwood ME, Croop JM. Treatment, outcome, and cost of care in children with idiopathic thrombocytopenic purpura. Am J Hematol 2005: 78: 181-7.
43. Albayrak D, Işlek I, Kalaycí AG, Gürses N. Acute idiopathic thrombocytopenic purpura: A comparative study of very high oral doses of methylprednisolone and intravenously administered immune globulin. J Pediatr 1994; 125: 1004-7.
44. Ozsoylu S, SaylTR, Ozturk G. Oral megadose menthylprednisolone versus intravenous immunoglobulin for acute childhood idiopathic thrombocytopenic purpura. Pediatr Hematol Oncol 1993; 10: 317-21.
45. Türk hematoloji derneği İTP el kitapçığı.
46. Wu Z, Zhou J, Pankaj P, Peng B. Laparoscopic splenectomy for immune thrombocytopenia (ITP) patients with platelet counts lower than 1 × 109/L. Int J Hematol 2011. [Epub ahead of print].
47. Kattamis AC, Shankar S, Cohen AR. Neurologic complications of treatment of childhood immune thrombocytopenic purpura with intravenously administered immunoglobulin G. J Pediatr 1997; 130: 281-3.
48. Despotovic JM, Lambert MP, Herman JH, et al. RhIG for the treatment of immune thrombocytopenia: consensus and controversy. Transfusion 2011. doi: 10.1111/j.1537-2995.2011.03384.x. [Epub ahead of print].
49. Brah S, Chiche L, Fanciullino R, et al. Efficacy of rituximab in immune thrombocytopenic purpura: a retrospective survey. Ann Hematol 2011. [Epub ahead of print].
50. Arnold DM, Dentali F, Crowther MA, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med 2007; 146(1): 25-33.
51. Khellaf M, Michel M, Quittet P, et al. Romiplostim safety and efficacy for immune thrombocytopenia in clinical practice: 2-year results of 72 adults in a romiplostim compassionate-use program. Blood 2011; 118: 4338-45.
52. Bredlau AL, Semple JW, Segel GB. Management of immune thrombocytopenic purpura in children: potential role of novel agents. Paediatr Drugs 2011; 13: 213-23.
53. Grainger JD, Rees JL, Reeves M, et al. Changing trends in the UK management of childhood ITP. Arch Dis Child 2011. Doi: 10.1106 /adc 2010 184234.