Retrospective Analysis of Patients with Idiopathic Thrombocytopenic Purpura from Eastern Anatolia

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Key Words

Idiopathic thrombocytopenic purpura · Corticosteroid · Splenectomy

Abstract

Objective: We evaluated the clinical features and the effects of various treatment modalities on the clinical course in patients diagnosed with idiopathic thrombocytopenic purpura (ITP). **Materials and Methods:** Retrospective investigation of the medical records of 168 patients at our center between 1994 and 2005 was done. **Results:** Of the 168 patients, 115 (68.4%) were women and 53 (31.6%) men. At initial diagnosis, the median age of the patients was 33 years (range: 15–91) and 139 (82.7%) had signs of bleeding. Follow-up was complete in 130 patients and the median follow-up was 27 months (range: 3–132). Initial treatment with either standard or high-dose steroid as first-line therapy was begun in 123 (73.2%) of the 168 patients. Complete remission (CR) was achieved in 56% of the patients. Sixty-one (61) patients who were followed up regularly received second-line therapies. CR was achieved in 45.8% of the patients who received steroids as second-line therapy. Within a median follow-up of 7 months, 27.2% of these patients relapsed. Splenectomy was performed in 26 patients and CR was obtained in 72% of the 25 patients regularly followed up. CR obtained by splenectomy was significantly higher than that obtained by steroids ($p < 0.001$). The 10-year disease-free survivals in

patients who used steroids and who underwent splenectomy were 15 and 61.6%, respectively. **Conclusion:** Steroid therapy is effective both in the initial and relapse periods. Splenectomy is the treatment of choice for those ITP patients refractory to steroid therapy and younger than 40 years of age.

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Introduction

Idiopathic thrombocytopenic purpura (ITP) is a common cause of thrombocytopenia in both children and adults, with a combined prevalence of 1–13 per 100,000 persons [1]. This autoimmune disease is characterized by persistent thrombocytopenia (peripheral blood platelet count $<150 \times 10^9/l$) due to autoantibody binding to platelet antigen(s) causing their premature destruction by the reticuloendothelial system, in particular the spleen [2]. Although bone marrow megakaryocytes are often increased, relative marrow failure may play a role in some patients [3]. ITP is diagnosed by excluding other causes of thrombocytopenia. Although ITP can be seen at any age, it reaches a peak between the ages of 30 and 40 and is threefold more common in women [4]. Children are usually affected by the acute form, which most often resolves spontaneously or after a short course of steroids, whereas chronic ITP frequently occurs in young female

adults and may persist for years [5]. Associated with the decreased thrombocyte counts, the symptoms in ITP patients vary from spontaneous or trauma-related petechiae to severe intracranial bleeding [6, 8].

Steroid therapy remains the first-line treatment, and patients who are refractory to steroids are referred for splenectomy. However, relapses occur in 19–38% of cases after splenectomy and management of these patients is often difficult [6, 7]. About 20–30% of ITP patients are refractory to treatment with corticosteroids, other immunosuppressive drugs, or splenectomy [8]. In this retrospective study, we evaluated the initial clinical features, the response to therapy, and the clinical course in patients who were diagnosed with ITP at our center in a 10-year period.

Patients and Methods

In this study, the medical records of 168 patients diagnosed with ITP at Turgut Ozal Medical Center between 1994 and 2004 were retrospectively reviewed. All of the patients had chronic ITP, which was defined as a platelet count $<150,000/\text{mm}^3$ that had been present for at least 3 months with no clinical or laboratory findings that could account for it.

In addition to a detailed physical examination and history – including drug history – the diagnostic studies included a full blood count, evaluation of the stained peripheral blood smear, biochemical profile, routine tests of hemostasis, serological tests for infectious causes, and antinuclear antibody (ANA) for collagen vascular diseases. As testing for the presence of antithrombocyte antibody was not obligatory, it was not routinely determined in each patient. Patients who were diagnosed with thrombocytopenia – associated with drugs or diseases such as antiphospholipid syndrome or lymphoma were not included in the study. In 68 of 168 patients hepatitis B and C and in 72 patients HIV tests were carried out. Viral serology was negative in all patients included in the study. Thyroid function tests were also carried out in 112 cases.

Treatment at initial diagnosis was administered to patients with a platelet count $<50,000/\text{mm}^3$ or to those with significant signs of bleeding. Patients who required treatment received standard dose steroid therapy. These patients were given prednisone 1 mg/kg per day p.o. for 2–4 weeks. When a normal platelet number was reached, steroids were then tapered off within several weeks. Patients who were given high-dose steroids received pulsed methylprednisolone 30 mg/kg/day p.o. for 7 days. The dosage was tapered down after 7 days and continued at 1 mg/kg/day for 30 days. The patients having uncontrolled diabetes mellitus, hypertension, active gastroduodenal ulcer and bleeding, heart insufficiency and cardiac arrhythmia were not given high-dose steroid treatment. Intravenous immunoglobulin was used at a dose of 0.4 g/kg/day. Intravenous immunoglobulin was administered to patients before splenectomy in order to increase the thrombocyte counts temporarily. In patients unresponsive to first-line therapies or in those in whom a sustained response could not be

obtained, other treatment modalities were given. Oral steroids were generally the preferred agents in patients who relapsed. In patients refractory to steroids, those who became steroid-dependent in order to stay in remission, or those who relapsed, splenectomy was usually chosen as the second- or third-line therapy. Some patients also received cyclophosphamide (1–1.5 g/m² i.v. once a month for 3 months), danazol (600 mg/day p.o. for 3 months), azathioprine (150 mg/day p.o. for 3 months), cyclosporine (2.5 mg/kg/day $\times$ 2 p.o. for 6 weeks), anti-D (75 $\mu\text{g/kg}$ for 3 days), or mycophenolate mofetil (2 g/day p.o. for 3 months). Criteria of response to treatment were defined as follows: complete remission (CR), platelet count $\geq 150 \times 10^9/\text{l}$ lasting ≥ 4 weeks; partial response (PR), platelet count $\geq 50 \times 10^9/\text{l}$ but $<150 \times 10^9/\text{l}$ lasting ≥ 4 weeks; no response, platelet count $<50 \times 10^9/\text{l}$ after 6 weeks of therapy.

Of 168 ITP patients, 130 (77.3%) were followed up at regular intervals from the time of initial diagnosis until the end of the study. When evaluating the clinical features, we analyzed data from all 168 ITP patients; however, when considering the treatment outcomes and estimating the disease-free survivals, we evaluated only 130 patients who were followed up regularly.

The chi-square test was used to evaluate the statistical differences. Disease-free survival was calculated from the date of the final platelet recovery to the time of treatment failure or last follow-up, and survival estimations were made by the Kaplan-Meier method.

Results

Of 168 patients who were diagnosed with ITP within 11 years, 115 (68.4%) were females and 53 (31.6%) males. The median age at the time of initial diagnosis was 34 years (range: 15–91). The presenting features of the patients at the time of initial diagnosis are given in table 1. Leukopenia ($<4 \times 10^9/\text{l}$) was present in 4.5% and anemia ($<12 \text{ g/dl}$) in 23.2% of the patients. Anemia was significantly more frequent in females (28.1%) than in males (10.3%, $p < 0.01$). There was no statistical significance between males and females according to age, platelet and leukocyte count and mean corpuscular volume (MCV).

At the time of initial diagnosis, signs and symptoms of bleeding were present in 139 (82.7%) patients. Signs of bleeding were seen in 88% of the patients with a platelet count $<50,000/\text{mm}^3$ and in 24% of the patients with a platelet count $>50,000/\text{mm}^3$ ($p < 0.001$). The different types of bleeding are shown in table 1.

Tests of ANA and anti-double-stranded DNA in order to diagnose systemic lupus erythematosus (SLE) and other collagen tissue diseases could not be done routinely; therefore no patients were diagnosed with SLE. During the follow-up of the patients, 2 of them were found to have myelodysplastic syndrome, 1 aplastic anemia, 1 acquired amegakaryocytic thrombocytopenic purpura, 1 anti-

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

	Female (n = 115, 68.4%)	Male (n = 53, 31.6%)	Total (n = 168, 100%)
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	12.1 ± 2.2	13.9 ± 1.3	12.6 ± 2.3
Leukocytes, $10^9/l$	11.3 ± 21.5	9.2 ± 4.6	10.7 ± 18.1
MCV, fl	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%)

Mean $\pm$ SD are given for hemoglobin, leukocytes and MCV.

Table 2. First-line treatment modalities and responses to therapy in ITP patients followed up regularly

	Patients	No response	PR	CR
Standard-dose steroids	98	14 (14.2%)	33 (33.6%)	51 (52.2%)
High-dose steroids	25	3 (12%)	4 (16%)	18 (72%)
Total	123	17 (14%)	37 (30%)	69 (56%)

phospholipid syndrome, 1 gray platelet syndrome, 2 Brucella infections, 1 Salmonella infection. One (0.5%) patient had hemolytic anemia in addition to ITP.

The median follow-up of 168 patients was 4 months (range: 1–132). The follow-up for 54 (32.1%) patients was <6 months, and for 24 (14.2%) patients it was ≥ 5 years. Thirty-eight (22.6%) patients were lost to follow-up. The median follow-up of 130 patients was 27 months (range: 3–132). When all ITP patients were considered, there was an indication for treatment in 123 (73.2%).

First-Line Treatment

The first-line treatment modalities were as follows: standard-dose steroids: 113 patients; high-dose steroids: 32 patients. Sixteen patients received immunoglobulin treatment in addition to steroid therapy. Intravenous immunoglobulin without steroid therapy was not administered. Twenty-five (14.8%) patients were not given any therapy. Sixteen of them were lost to follow-up within the 1st year of diagnosis. The remaining 9 patients had a follow-up of at least 1 year and the platelet count continued to be above $50,000/mm^3$. Five of them were treated later because of bleeding. Of the 130 patients, 123 who were followed up regularly received therapy at initial diagnosis. The treatment modalities and the responses to therapy of these 123 patients are shown in table 2. Platelet

counts were elevated earlier in patients who received high-dose steroid than in those who received standard-dose steroid (3 days vs. 7 days). CR ratios were statistically significant in high-dose steroid vs. standard-dose steroid in first-line therapy ($p < 0.05$).

In ITP patients followed up until the end of the study, CR was obtained in 69 (56%) who used corticosteroids as the first-line therapy (table 2). Thirty-three (51.5%) of these patients relapsed during a median follow-up of 16 months (range: 3–108). During a median follow-up duration of 5 months (range: 3–72), no recurrence occurred in the remaining 31 (48.5%) patients.

Second-Line Treatment

Sixty-one of the regularly followed up patients received second-line therapies. They were either unresponsive to first-line therapies or relapsed after remission, or some of them in PR were admitted to hospital because of bleeding or interventional procedures. The various modalities of treatment and the outcome of patients are shown in table 3. CR was achieved in 11 (45.8%) patients who received corticosteroids as second-line therapy (table 3). Three (27.2%) of these patients relapsed during the median follow-up of 7 months (range: 3–48). Within a median follow-up of 6 months (range: 2–42), no relapse occurred in the other 8 patients. The percentage of CR

Table 3. Second-line treatment modalities and responses to these therapies in ITP patients followed up until the end of the study

	Patients	No response	PR	CR
Standard-dose steroids	16	4 (25%)	4 (25%)	8 (50%)
High-dose steroids	8	3 (37.5%)	2 (25%)	3 (37.5%)
Splenectomy	25	5 (20%)	2 (8%)	18 (72%)
Cyclophosphamide	3	1 (33.4%)	2 (66.6%)	–
Azathioprine	4	2 (50%)	2 (50%)	–
Cyclosporine	1	–	1 (100%)	–
Mycophenolate mofetil	2	–	2 (100%)	–
Anti-D	2	1 (50%)	1 (50%)	–
Total	61	16 (26.2%)	16 (26.2%)	29 (47.6%)

obtained with corticosteroids as initial therapy was slightly higher than the percentage of CR with the same agent in reinduction therapy; however, this was not significant (56 vs. 45.8%, $p > 0.05$). CR ratios were similar in standard dose steroid treatment for both first-line and second-line therapy although CR ratios were significantly lower in patients who received high-dose steroid in second-line therapy ($p = <0.05$).

Splenectomy

Splenectomy was undertaken in 26 (15.4%) patients. The median period of time from diagnosis until splenectomy was 5 months (range: 1–108). One of the splenectomized patients was lost to follow-up. Of the remaining 25 patients followed up regularly, CR was obtained in 18 (72%), PR in 2 (8%), and no response was obtained in 5 (20%) patients.

Three (16.6%) of the patients who had CR after splenectomy relapsed later, and the median follow-up time was 44 months (range: 8–132). The other 15 patients did not relapse until the end of the data collection (median follow-up time: 35 months, range: 5–74).

At the end of the 1st week, the highest platelet count was found to be $907 \times 10^9/l$. During the 1st week, 2 responsive patients suffered unexplained sudden platelet decreases, with persistence in 1 patient. He consequently suffered an intra-abdominal hemorrhage and died 3 months later. The other patient's platelet count recovered after 1 week.

Remission was obtained in 17 of 18 patients below the age of 40 and in 3 of 7 patients above the age of 40. The difference was statistically significant ($p = 0.05$).

Other Immunosuppressive Drugs

Combination therapy of azathioprine, cyclophosphamide, cyclosporine, danazol, mycophenolate mofetil, and anti-D was administered to 5 patients who were refrac-

tory to splenectomy and to the 3 patients who relapsed after splenectomy. There was no CR for any of these drugs (table 3). Danazol was given to 16 patients who were refractory to splenectomy. Four of 5 were responsive (2 complete, 2 partial), while 1 was totally refractory to medication. Three patients had relapsed, 1 was in CR. The 2 others survived with thrombocytopenia.

Disease-Free Survival

The evaluation of the Kaplan-Meier curves showed that the durations of CR obtained by splenectomy and corticosteroids were significantly different ($p < 0.0001$). The 5- and 10-year disease-free survivals in patients administered steroids were 41 and 15%, respectively; however, in patients who underwent splenectomy these ratios were 88.5 and 61.6%, respectively. The disease-free survival rates according to Kaplan-Meier curves in patients who had CR after splenectomy and steroid (first- and second-line) therapy are shown figure 1.

Adverse Effects

Steroid treatment was well tolerated by all patients in regular follow-up. No patient reported side effects that were severe enough to necessitate the discontinuation of treatment. Transient adverse effects were seen in 46 (35.3%) patients. Side effects included mild glucose increase: $n = 11$; increased appetite: $n = 6$; insomnia: $n = 4$; weight gain: $n = 7$; arterial hypertension: $n = 2$; weakness: $n = 16$; acne: $n = 12$; moon face: $n = 7$; symptoms of gastritis: $n = 6$; nausea: $n = 4$; psychosis: $n = 1$; myalgia: $n = 1$; skin stria: $n = 2$; gastrointestinal system bleeding: $n = 4$, and deep vein thrombosis: $n = 1$. We did not observe severe or mild adverse effects with other immunosuppressives. One patient died due to intra-abdominal bleeding 3 months after splenectomy. No other bleeding complications in the splenectomy group were noted.

Fig. 1. Kaplan-Meier curves of disease-free survival duration for patients who had CR after either splenectomy or steroid (first- and second-line) therapy.

Discussion

In the adult population, ITP is more frequent in females than in males (71.3%) [9], similar to our series. Patients diagnosed with ITP are mostly younger than 40 years of age and peak age is around 30 years [4, 6]. The median age of our patients was 33 years. Purpura, epistaxis, and gingival bleeding are frequently seen in ITP patients. Bleeding from the genitourinary or gastrointestinal tract is less common. The severity of bleeding correlated with the decreased number of platelets [10]. Signs of bleeding were seen in 88% of our patients with a platelet count $<50,000/\text{mm}^3$ and in 24% of the patients with a platelet count $>50,000/\text{mm}^3$ ($p < 0.001$). Major bleeding can influence the outcome of these patients. Intracranial hemorrhage, which is the most important cause of death, is reported to occur in about 5% of cases [11]. At the same thrombocyte values, the complication of bleeding is more severe in older patients compared to younger ones [12]. There were signs of bleeding in 82.7% of our patients. Intracranial hemorrhage and persistent bleeding after surgery did not occur.

According to the results at presentation, anemia was detected in 23.2% of our patients. It was significantly more frequent in females (28.1%) than in males (10.3%) ($p < 0.01$). These results are similar to the ones reported by Pamuk et al. [9]. They can be explained by the increase

in anemia due to the increase in menstrual bleeding facilitated by thrombocytopenia, which is a physiological phenomenon in young females.

ITP, which has no pathognomonic features, is diagnosed by excluding other causes of thrombocytopenia [4]. In our cases, causes of secondary thrombocytopenia were excluded. Although they were misdiagnosed initially as ITP, diagnoses of 9 patients were later corrected to other diseases such as myelodysplastic syndrome, aplastic anemia, antiphospholipid syndrome, amegakaryocytic thrombocytopenia, Brucella and Salmonella infections, and these cases were omitted from follow-up.

Due to the difficulties in ruling out other causes for thrombocytopenia, medication must always be considered as possibly causal. Quinine/quinidine and heparin can be regarded as drugs which can cause thrombocytopenia in nonhospitalized and hospitalized patients, respectively. Cases with sulfonamides, sulfonylureas, dipyridamole and salicylate have also been reported [13]. In our study 1 patient taking NSAID presented with thrombocytopenia, without being included in the series. Remission was observed during follow-up off drug. Except for this patient, there was no case of drug-induced thrombocytopenia in our series.

According to Leung et al. [14] 40.2% of their ITP patients were ANA-positive and 3.9% of these developed SLE. Moreover the relapse-free survival periods of ANA-negative patients after splenectomy were significantly longer compared to those of ANA-positive ones [14]. Since ANA analysis could not be done routinely in our center we did not have the opportunity to confirm these data.

Since the thrombocyte counts were higher than $30 \times 10^9/\text{l}$ and there were no signs of bleeding, no treatment was given in 41.8% of the patients in the series of Cortelazzo et al. [15]. In our study 14.8% (25/168) of the patients were evaluated as persistent ITP and given no treatment either because the thrombocyte counts were higher than $50 \times 10^9/\text{l}$ or no bleeding symptoms were detected. No major bleeding occurred in any of these cases at presentation, but in 5 cases due to later bleeding, treatment was initiated. During follow-up spontaneous remission was not seen in any of the patients mentioned above.

The treatment in chronic ITP is palliative and there is no curative treatment. The aim of the treatment in chronic ITP is preventive rather than normalizing the platelet counts. Even though treatment is given, in 30 or 40% of the patients thrombocytopenia persists. In patients with serious thrombocytopenia, prednisone is the initial standard therapy [4]. In chronic ITP the CR ratio is reported

to be 53% when the standard dosage of steroids is used as first-line treatment [9]. In our study this ratio was 56%, which was in keeping with this data. Many studies report that ITP treatment with high-dose steroids at the early stages is as effective as intravenous immunoglobulin therapy and it increases the thrombocyte counts earlier when compared with standard steroid treatment. In addition it has been reported that the CR ratios are higher when high-dose steroids are used instead of standard-dose steroids [16, 17]. In our study we also confirmed that the increase in platelet counts is earlier with high-dose steroid treatment when compared with classic standard-dose steroid therapy (median 3 days). CR ratio in patients receiving high-dose steroids as first-line treatment was significantly higher compared to patients receiving standard-dose therapy, which is in agreement with the results in the literature ($p < 0.05$).

It has been reported that the CR ratio in females receiving steroid treatment is higher than that in males [18, 19], however, in our study there was no significant difference between the two sexes ($p > 0.05$).

It has also been reported that in most patients in CR receiving steroid therapy, relapse occurs when the steroid dose is reduced [20, 21]. In our study, relapses occurred within a median duration of 20 months in 51.5% of the patients in CR receiving steroids. When we administered steroids as second-line treatment, we obtained nearly similar CR rates to when they were given as first-line treatment (45.8 vs. 56%). As a result we confirm that the use of steroids either as first- or second-line therapy is effective.

Response to intravenous immunoglobulin therapy is temporary, so that the thrombocyte count returns to its initial values after 3–4 weeks following treatment [22]. We used intravenous immunoglobulin with steroids only in cases where the thrombocyte counts had to be increased quickly such as before splenectomy. Taking into consideration the high cost of intravenous immunoglobulin, it is apparent that it is not suitable as first-line therapy except in some special circumstances.

In relapsed patients after splenectomy the CR + PR ratios were reported to be 59 and 72% for azathioprine and cyclosporine, respectively, by Vianelli et al. [11], whereas it was 100% each for cyclophosphamide and azathioprine in the series of Kumar et al. [23]. Even though we had fewer patients compared to the studies mentioned above, we had an average of 66% CR + PR ratio with immunosuppressive treatments. Despite our limited data, we conclude that these drugs can be useful in ITP cases [23].

It has been reported that anti-D is effective in two thirds of Rh-positive patients and it may be used in pa-

tients who did not undergo splenectomy or did not receive excessive steroids [24]. In the 2 patients in our study who received anti-D, CR was not obtained. More cost-effective studies should be carried out.

Steroids and other immunosuppressive drugs are used after splenectomy in patients with no response or those who relapsed. Remission was obtained in 5 of 7 of our patients using this therapy. While it may increase the risk of infection, this treatment proved to be appropriate. In some studies, postsplenectomy antibiotic prophylaxis was given [25]. No clear benefit has yet been demonstrated. Thus, no antibiotic prophylaxis was prescribed for our patients.

Splenectomy has the potential to provide long-term control of disease in adults with ITP who have failed to respond to steroid therapy or who cannot be weaned off corticosteroids. The procedure is associated with low mortality, and nearly two thirds of the patients undergoing splenectomy for ITP can be expected to have long-term control of their disease [23, 26]. After an initially successful splenectomy, relapse might occur in 10% of the patients within the 1st year, but relapses might be as late as 5 years [8]. The 10-year disease-free survivals in patients who used steroids and who underwent splenectomy were, respectively, 13 and 58% ($p < 0.001$) [9]. In our series splenectomy was undertaken in steroid-refractory or relapsing ITP; still, CR was reached in 72% of the cases. The disease-free survival without relapse was significantly longer in splenectomized patients than in those who used steroids ($p < 0.001$). The median time for relapse, which occurred in 3 of our splenectomized patients, was 44 months. This was much longer when compared with the group treated with steroids (16 months).

In recent meta-analyses evaluating the response to splenectomy, it has been claimed that splenectomy results are better below the age of 40 and this is an independent prognostic factor [27, 28]. In our study, age was found to be an important factor. The median age for responsive patients was 28 years and for unresponsive patients 47 years.

Conclusion

Our data show that steroid therapy is effective both in the initial and relapse periods. Splenectomy is the first treatment of choice for those ITP patients who are refractory to steroid therapy and younger than 40 years of age.

References

- 1 The American Society of Hematology ITP Practice Guideline Panel: Diagnosis and treatment of idiopathic thrombocytopenic purpura: recommendations of the American Society of Hematology. *Ann Intern Med* 1997;126:319–326.
- 2 Woods VL Jr, Kurata Y, Montgomery RR, Tani P, Mason D, Oh EH, McMillan R: Auto-antibodies against platelet glycoprotein Ib and IIb/IIIa complex in patients with chronic immune thrombocytopenic purpura. *Blood* 1984;64:156–160.
- 3 Ballem PJ, Segal GM, Stratton JR, Gernsheimer T, Adamson JW, Slichter SJ: Mechanism of thrombocytopenia in chronic autoimmune thrombocytopenic purpura: evidence of both impaired platelet production and increased platelet clearance. *J Clin Invest* 1987;80:33–40.
- 4 George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, Blanchette VS, Busnel JB, Cines DB, Kelton JG, Lichtin AE, McMillan R, Okerbloom JA, Regan DH, Warrior I: Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 1996;88:3–40.
- 5 Frederiksen H, Schmidt K: The incidence of idiopathic thrombocytopenic purpura in adults increases with age. *Blood* 1999;94:909–913.
- 6 Stasi R, Stipa E, Masi M, Cecconi M, Scimo MT, Oliva F, Sciarra A, Perrotti AP, Adomo G, Amadori S, Papa G: Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. *Am J Med* 1995;98:436–442.
- 7 Mazzucconi MG, Arista MC, Peraino M, Chistolini A, Felici C, Francavilla V, Macale E, Conti L, Gandolfo GM: Long-term follow-up of autoimmune thrombocytopenic purpura (ATP) patients submitted to splenectomy. *Eur J Haematol* 1999;62:219–222.
- 8 Karpatkin S: Autoimmune (idiopathic) thrombocytopenic purpura. *Lancet* 1997;349:1531–1536.
- 9 Pamuk GE, Pamuk ON, Baslar Z, Ongoren S, Soysal T, Ferhanoglu B, Aydin Y, Ulku B, Aktuglu G, Akman N: Overview of 321 patients with idiopathic thrombocytopenic purpura: retrospective analysis of the clinical features and response to therapy. *Ann Hematol* 2002;81:436–440.
- 10 Portielje JE, Westendorp RG, Kluin-Nelemans HC, Brand A: Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. *Blood* 2001;97:2549–2554.
- 11 Vianelli N, Valdre L, Fiacchini M, de Vivo A, Gugliotta L, Catani L, Lemoli RM, Poli M, Tura S: Long-term follow-up of idiopathic thrombocytopenic purpura in 310 patients. *Haematologica* 2001;86:504–509.
- 12 Guthrie TH Jr, Brannan DP, Prisant LM: Idiopathic thrombocytopenic purpura in the older adult patient. *Am J Med Sci* 1988;296:17–21.
- 13 Kaufman DW, Kelly JP, Johannes CB, Sandler A, Harmon D, Stolley PD, Shapiro S: Acute thrombocytopenic purpura in relation to the use of drugs. *Blood* 1993;82:2714–2718.
- 14 Leung AY, Chim CS, Kwong YL, Lie AK, Au WY, Liang R: Clinicopathologic and prognostic features of chronic idiopathic thrombocytopenic purpura in adult Chinese patients: an analysis of 220 cases. *Ann Hematol* 2001;80:384–386.
- 15 Cortelazzo S, Finazzi G, Buelli M, Molteni A, Viero P, Barbui T: High risk of severe bleeding in aged patients with chronic idiopathic thrombocytopenic purpura. *Blood* 1991;77:31–33.
- 16 Altintop L, Albayrak D: Oral high-dose methylprednisolone and intravenous immunoglobulin treatments in adult chronic idiopathic thrombocytopenic purpura. *Am J Hematol* 1997;56:191–192.
- 17 Alpdogan O, Budak-Alpdogan T, Ratip S, Firatli-Tuglular T, Tanriverdi S, Karti S, Bayik M, Akoglu T: Efficacy of high-dose methylprednisolone as first-line therapy in adult patients with idiopathic thrombocytopenic purpura. *Br J Haematol* 1998;103:1061–1063.
- 18 Den Ottolander GJ, Gratama JW, de Koning J, Brand A: Long-term follow-up study of 168 patients with immune thrombocytopenia: implications for therapy. *Scand J Hematol* 1984;32:101–110.
- 19 Shashaty GG, Rath CE: Idiopathic thrombocytopenic purpura in the elderly. *Am J Med Sci* 1978;276:263–267.
- 20 George JN, el-Harake MA, Raskob GE: Chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 1994;331:1207–1211.
- 21 Andersen JC: Response of resistant idiopathic thrombocytopenic purpura to pulsed high-dose dexamethasone therapy. *N Engl J Med* 1994;330:1560–1564.
- 22 Godeau B, Lesage S, Divine M, Wirquin V, Farcet JP, Bierling P: Treatment of adult chronic autoimmune thrombocytopenic purpura with repeated high-dose intravenous immunoglobulin. *Blood* 1993;82:1415–1421.
- 23 Kumar S, Diehn FE, Gertz MA, Tefferi A: Splenectomy for immune thrombocytopenic purpura: long-term results and treatment of postsplenectomy relapses. *Ann Hematol* 2002;81:312–319.
- 24 Cooper N, Woloski BM, Fodero EM, Novoa M, Leber M, Beer JH, Bussel JB: Does treatment with intermittent infusions of intravenous anti-D allow a proportion of adults with recently diagnosed immune thrombocytopenic purpura to avoid splenectomy? *Blood* 2002;99:1922–1927.
- 25 Makris M, Greaves M, Winfield DA, Preston EE, Lilleyman JS: Long-term management after splenectomy: lifelong penicillin unproved in trials. *BMJ* 1994;308:131–132.
- 26 Ismet A, Irfan K, Emin K, Ali EM, Ramazan U, Mustafa B, Onur O: Splenectomy results in patients with idiopathic thrombocytopenic purpura: 10 years of experience in Turgut Ozal Medical Center. *Clin Lab Haematol* 2004;26:211–214.
- 27 Andres E, Zimmer J, Noel E, Kattenbach G, Koumariannou A, Maloisel F: Idiopathic thrombocytopenic purpura: a retrospective analysis in 139 patients of influence of age on the response to corticosteroids, splenectomy and danazol. *Drugs Aging* 2003;20:841–846.
- 28 Fabris F, Tassan T, Ramon R, Carraro G, Randi ML, Luzzatto G, Moschino P, Girolami A: Age as the major predictive factor of long-term response to splenectomy in immune thrombocytopenic purpura. *Br J Haematol* 2001;112:637–640.