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Long-term follow-up of idiopathic thrombocytopenic purpura in 310 patients

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Background and Objectives. Idiopathic thrombocytopenic purpura (ITP) induces thrombocytopenia by means of an autoimmune mechanism. Despite the available therapies a subset of patients develop chronic refractory severe thrombocytopenia (i.e. a platelet count consistently lower than 20 to 30×10^9/L), and life-threatening bleeding can occasionally occur. It has been suggested that the risk of major bleeding is higher in elderly patients and in patients with bleeding at diagnosis. However, since clear data on the influence of clinical and/or laboratory parameters on outcome are lacking, some patients may be receiving unnecessary treatment.

Design and Methods. We made a retrospective analysis of a series of 310 patients with chronic ITP (108 males and 202 females), with a median age at diagnosis of 40 years (range 8-87 years). The median follow-up time was 121 months, (range 7-434 months). Therapy was most often started in the presence of hemorrhagic complications and/or a platelet count $<30\times10^9$/L either at diagnosis or during follow-up.

Results. Our findings confirmed that patients who were symptomatic at diagnosis were more likely to have bleeding during their follow-up. Moreover, all the patients who suffered major bleeding during their follow-up had median platelet counts of $10x10^9$/L (range 1-20) at that time. Only one patient, aged 43 years, died of hemorrhage following prolonged severe thrombocytopenia. Age >60 years was not associated with any significant differences in incidence of bleeding at diagnosis or during follow-up.

Interpretation and Conclusions. We conclude that prospective studies are required to evaluate whether it may be reasonable to treat only symptomatic patients, independently of age.

Key words: idiopathic thrombocytopenic purpura (ITP), major bleeding, severe symptomatic thrombocytopenia, elderly patients

Idiopathic thrombocytopenic purpura (ITP) is a potentially life-threatening condition characterised by thrombocytopenia of varying degrees of severity and mediated by an autoimmune mechanism in which platelets are destroyed by the reticuloendothelial system. 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[1,2] and may persist for years. However, recent data record both a significant increase of the incidence rate with age and the disappearance of the sex difference in the older patients.[3] The diagnosis of ITP is made by exclusion.[2,4] About 20-30% of ITP patients are refractory to treatment with corticosteroids or other immunosuppressive drugs, or splenectomy.[5] Hemorrhages are the only clinical manifestation of chronic adult ITP, and their severity is determined by the degree of thrombocytopenia. Major bleeding can influence the outcome of these patients. Intracranial hemorrhage (ICH), which is the most important cause of death, is reported to occur in about 5% of cases.[6] In a review of the literature Schattner estimated that the mortality rate among patients with refractory ITP may be as high as 16%.[7] No conclusive data exist regarding the ability of clinical or laboratory parameters at presentation to predict the risk of major bleeding. While some studies have suggested that long-term refractory ITP carries an increased risk of major bleeding in adults,[7] others have indicated age over 60 years and a previous history of bleeding as major risk factors.[8,9] However, a recent study failed to find any increase in the risk of bleeding in elderly patients.[3]The uncertainty surrounding prognosis makes it difficult to establish optimal levels of treatment for individual patients. A subset of patients with severe thrombocytopenia who are refractory to the most common forms of therapy do

not seem to develop major bleeding.[7]

To shed further light on this issue, we examined clinical and laboratory parameters at diagnosis potentially capable of affecting the risk of major bleeding and/or mortality in a retrospecive analysis of a large cohort of adult patients with chronic ITP with a long mean follow-up.

Design and Methods

Patients

We reviewed the 310 consecutive adult patients with chronic ITP diagnosed between January 1963 and December 1997 and subsequently treated and/or monitored at the "Seràgnoli" Institute of Hematology and Medical Oncology, Bologna, Italy. As can be seen from Table 1, the series included 108 males (35%) and 202 (65%) females (M/F ratio = 0.53). Their median age at diagnosis was 40 years (range 8-87 years). Sixty-seven patients were defined as being elderly (>60 years), with a mean age of 70 years. Among the 243 patients aged ≤ 60 years at diagnosis, 153 were aged < 40 years. There was no significant difference in the M/F ratio among any of the age groups. In 18 cases the diagnosis of ITP was initially made when the patient was a child (< 16 years of age). The median follow-up time was 121 months (range 7 to 434 months); 15 patients were lost to follow-up. Diagnostic criteria for ITP[2,4] included the presence of isolated thrombocytopenia with a platelet count $<150\times10^9$/L for at least 6 months when all other causes of thrombocytopenia had been systematically excluded. A bone marrow aspirate with either normal or increased megakaryocyte count was available for most patients, including the majority of those over 60 years of age. Follow-up allowed confirmation of the diagnosis, especially in cases with a borderline platelet count at the onset of the thrombocytopenia. One patient with a platelet count of 147×10^9/L at initial observation developed a rapid decrease of this platelet count, with the emergence of parameters compatible with ITP. Coagulation study abnormalities were never present. Antiplatelet autoantibodies were evaluated in 138 patients. In 254 patients, myelodysplasia was excluded by bone marrow aspirate (n=242) and/or biopsy (n=34). In the remaining 56 (mainly elderly) patients, myelodysplasia was excluded on the basis of the presence of isolated thrombocytopenia for more than 6 months. Megakaryocytes (MKs), which were evaluated on bone marrow aspirates[10] and/or biopsy, were classified as normal, increased or reduced in number. All patients were followed at intervals varying from 7 days to 12 months, depending on their clinical course, and platelet counts were taken in the presence of minor or major bleeding. Bleeding was classified as major[11] when it required hospital admission or was clinically overt with a fall in hemoglobin of at least 2g/dL or both. Intracranial hemorrhage (ICH) was confirmed by computerized tomography. Bleeding was considered to be minor in the presence of purpura, ecchymoses, gum bleeding or mild epistaxis.

Table 1. Patients characteristics.

No. of patients	310					
Females	202 (65%)					
Males	108 (35%)					
Male/female ratio	0.53					
Age at diagnosis (years); median (range) (67 patients with age >60 years)	40 (8-87)					
Patients	No.	%	median age	range	median plts*	range
asymptomatic	148	48	39.5	8-86	42.5	1-138
minor bleeding	137	44	43.0	6-87	20.0	1-147
major bleeding	25	8	29.0	9-23	10.0	2-47
Follow-up (months), median (range)	121 (7-434)					
2 patients with follow-up < 12 months						
153 patients with follow-up >120 months						
15 patients were lost to follow-up						

**platelet count ($\times10^9$/L)*

Table 2. Types of medical treatment and response.

Drug	*No. evaluable patients*	*CR (%)*	*PR (%)*	*CR+PR (%)*	*NR (%)*
Steroids	200	48 (24%)	87 (43%)	135 (67%)	65 (33%)
HD Ig*	31	4 (13%)	20 (64%)	24 (77%)	7 (23%)
Azathioprine	60	5 (8%)	25 (42%)	30 (50%)	30 (50%)
Danazol	9	1 (11%)	3 (33%)	4 (44%)	5 (56%)
CY°	7	1 (14%)	/	1 (14%)	6 (86%)
IFN#	5	1 (20%)	2 (40%)	3 (60%)	2 (40%)
Ascorbic acid	8	/	4 (50%)	4 (50%)	4 (50%)

**High dose immunoglobulins; °cyclophosphamide; #interferon-α-2b.*

Treatment and response

Medical treatment (and/or splenectomy) was most often started in the presence of hemorrhagic complications and/or in the presence of a platelet count $<30\times10^9$/L either at diagnosis or during follow-up. As regards medical treatment options, Table 2 reports the numbers of completed therapeutic schedules: 1) steroids administered as first therapy at a daily dosage of 1 mg/kg for one month prior to progressive tapering over a further 6 weeks; 2) intravenous γ-globulins administered in selected cases at a daily dosage of 400 mg i.v./kg for 5 consecutive days; 3)

azathioprine given orally at a daily dosage of 150 mg for at least two months; 4) danazol given orally at a dosage of 200 mg three times a day for at least two months; 5) cyclophosphamide employed i.v. at a dosage of 1,000-1,200 mg/m^2 administered in 5 days; 6) ascorbic acid given orally at a single daily dosage of 2 g for at least 8 weeks and 7) interferon α-2b administered at a dose of 3 MU s.c. three times a week for 5 weeks. Some patients received more than one type of treatment.

Complete remission (CR) was considered to have occurred when a platelet count of $\geq 150\times10^9$/L was achieved; partial remission (PR) a platelet count of 50-149$\times10^9$/L or an increase >30$\times10^9$/L with respect to the baseline value. No response (NR) was a platelet count < 50$\times10^9$/L or an increase < 30$\times10^9$/L with respect to the baseline value.

Data analysis

One-way analysis of variance and the Kruskal-Wallis test on ranks was performed when appropriate. The chi-squared test was used to evaluate differences between proportions. Logistic regression methods were used to evaluate the prognostic importance of various covariates with respect to the likelihood of bleeding at diagnosis or the likelihood of hemorrhage during follow-up. All statistical tests were two-sided. SPSS Statistical Software was used for the statistical tests.

Results

The median platelet count at diagnosis was 27$\times10^9$/L (range 1-147$\times10^9$/L). No differences were found with respect to sex or age >60 years (median platelet count at diagnosis was 26.5$\times10^9$/L (range 1-147) for females v.s 26$\times10^9$/L (range 1-131) for males, and 26$\times10^9$/L (range 2-147) in patients aged >60 years vs. 27$\times10^9$/L (range 1-138) in those $\leq$60 years). Platelet count at diagnosis was <50$\times10^9$/L in 230 (74%) patients, <30$\times10^9$/L in 178 (57%), and <10$\times10^9$/L in 54 (17%). Antiplatelet autoantibodies were detected in 68 (49%) of the 138 patients evaluated. Among the 242 patients in whom bone marrow aspirates were performed, MKs were elevated in 205 (85%) cases and normal in the remaining 37 (15%). Of the 34 patients who had a bone marrow biopsy, MKs were elevated in 17 (50%) cases, normal in 14 (41%) cases and reduced in 3 (9%) cases. In one patient MKs were slightly dysplastic. As can be seen from Table 1, 148 (48%) patients were asymptomatic, 137 (44%) had minor bleeding and 25 (8%) had major bleeding. Median platelet counts were 42.5$\times10^9$/L (range 1-138) in asymptomatic patients, 20$\times10^9$/L (range 1-147) in those with minor bleeding and 10$\times10^9$/L (range 2-47) in those with major bleeding (p<0.05 for each comparison, Kruskal-Wallis multiple comparison test). At multivariate analysis (including age, sex, antiplatelet autoantibodies and platelet count at diagnosis), only platelet count at diagnosis turned out to be predictive of hemorrhage (p= 0.00001, χ^2= 25). No significant difference could be found in the frequency of major or minor bleeding in patients aged >60 years with respect to those aged <60 years or <40 years.

Table 3. Results of medical treatment in 33 ITP patients after splenectomy (mean no. of treatment = 3; range 1-6).

Drug	*No. evaluable pts*	*CR (%)*	*PR (%)*	*CR+PR (%)*	*NR (%)*
Steroids	2	4 (18%)	11 (50%)	15 (68%)	7 (32%)
HD Ig*	14	3 (21%)	4 (29%)	7 (50%)	7 (50%)
Azathioprine	22	6 (27%)	7 (32%)	13 (59%)	9 (41%)
Danazol	7	1 (14%)	2 (28%)	3 (42%)	4 (58%)
CY°	7	1 (14%)	4 (58%)	5 (72%)	2 (28%)
IFN#	4	/	/	/	4 (100%)
Ascorbic acid	8	/	2 (25%)	2 (25%)	6 (75%)

**High dose immunoglobulins; °cyclophosphamide; #interferon-α.*

Figure 1 summarizes the treatment options adopted at diagnosis and during follow-up. The 200 patients who received medical treatment at diagnosis had a median age of 39.5 years (range 8-86 years) and a median platelet count of 19.5$\times10^9$/L (range 1-91$\times10^9$/L). The 107 patients who received no treatment at diagnosis had a median age of 43 year (range 8-87 years) and a median platelet count of 50x10^9/L (range 27-147$\times10^9$/L). Table 2 summarizes the outcome of the various forms of medical treatment. Steroids, which were the most frequent choice (80%) of first line therapy, produced a response (CR+PR) in 67% of cases. During follow-up, 26 patients remained in CR without any further therapy for a median of 51 months (range 6-169); five of these patients were aged <16 years at diagnosis. Furthermore, 125 patients who received only medical treatment maintained a response (most often PR) with low-dose steroids or other lines of therapy. None of the 50 patients who had never received any type of therapy spontaneously achieved CR. Among the 109 patients who underwent splenectomy, 102 had previously received one or two lines of medical therapy. Among the 37 patients who were refractory to splenectomy or relapsed afterwards, 33 subsequently received medical treatment (Table 3).

During follow-up, major bleeding occurred in 9 out of 310 (3%) patients (at the time of diagnosis, 2 had presented with major bleeding, 1 had minor wet bleeding, 4 had minor dry bleeding, and 2 were

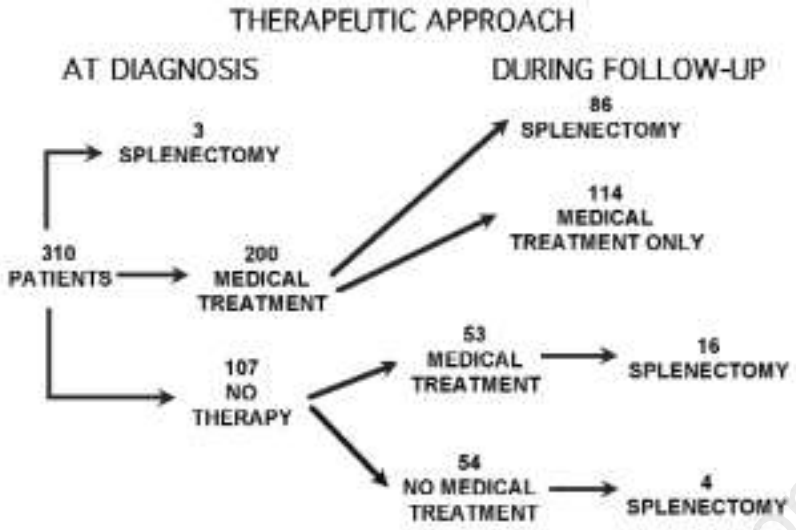

Figure 1. Treatment options employed at diagnosis and during follow-up in a cohort of Italian patients with chronic ITP (median follow-up 121 months, range 7-434).

asymptomatic). Among these 9 patients, the median platelet count at the time of bleeding was 10×10^9/L (range 1-20 $\times10^9$/L). Only 2 of these 9 patients were aged >60 years at the time of major bleeding. Bleeding was fatal in only one case (a 43-year old woman died from ICH after a follow-up of 22 years; she had presented with major bleeding at diagnosis). Minor bleeding was observed in 72 patients. No significant differences in terms of incidence of major or minor bleeding during follow-up were found with respect the patient's age (>60 years vs. ≤60 years, or >60 years vs. <40 years, n.s.). Patients who presented minor or major bleeding at diagnosis more frequently experienced bleeding during follow-up: logistic regression yielded a β=0.725 (χ^2=7.3, p=0.007) with a relative risk equal to 2.065. At last follow-up, 34 patients had a platelet count ≤ 30×10^9/L: of these, 19 (56%) were off therapy, whereas 15 (44%) were receiving maintenance treatment.

Discussion

Life-threatening hemorrhage is the most serious complication of ITP, and largely accounts for the relatively low, but by no means negligible, mortality rate which has been cited to be around 4-5% among adults.[1,6] In a sizable subset of patients, severe thrombocytopenia persists in spite of treatment with the main medical options and splenectomy. Such cases create a decisional dilemma for hematologists. Although further treatments, including experimental protocols,[12-15] may sometimes be useful, their real effectiveness and cost/benefit ratio requires assessment. Use of autologous bone marrow transplantation has been proposed, but at present it has been performed in too few cases to allow any firm conclusions to be drawn regarding its effectiveness,[16,17] and the risk of transplant-related mortality must also be considered. It has been reported that elderly patients seem to have a higher risk of major bleeding,[8,9] possibly implying the need for a more intensive therapeutic approach in this group. However, other authors found no increase in the incidence of major bleeding among elderly patients.[3] Moreover, it should be borne in mind that long-term treatments, especially in older patients, can induce toxicity or side effects affecting the quality of life.

In our retrospective analysis of 310 consecutive ITP patients, we were unable to find any significant difference in terms of the incidence of bleeding in general, and of life-threatening hemorrhage, in particular in elderly patients (i.e. >60 years vs. ≤ 60 years or < 40 years). However, it should be noted that the mortality rate from hemorrhage in our series (represented by a single case) was very much lower than the frequently reported figure of 4-5%. In other respects, the findings in our cohort of patients were in line

with those of other groups, for instance, as regards the influence of platelet count on the risk of hemorrhage.[6,18,19] In particular, 72% of the patients who presented with a platelet count $\leq 20 \times 10^9$/L had bleeding at diagnosis (as compared with 40% with a platelet count $>20\times10^9$/L; $\chi^2=30.4$; $p=0.000$). Moreover, bleeding at diagnosis seemed to significantly increase (2.1-fold higher probability) the risk of further hemorrhage during follow-up. The only death from hemorrhage was observed in a young woman (43 years) who had ICH after very prolonged and severe symptomatic refractory thrombocytopenia, while the other eight patients who experienced non-fatal major bleeding during follow-up all had very severe thrombocytopenia (median 10×10^9/L, range 1-20×10^9/L).

The low rates of major bleeding and mortality recorded by us pose the question as to whether less intensive forms of treatment could be justified for asymptomatic patients, including elderly ones, with severe refractory thrombocytopenia. It could, in fact, be hypothesized that younger patients with severe symptomatic refractory ITP and an expectancy of long exposure to marked thrombocytopenia have a higher eventual risk of hemorrhage-related mortality and morbidity. We think that for such patients it might be reasonable to adopt more aggressive curative or ameliorative forms of treatment, and possibly, in selected cases, experimental protocols using antibodies against CD20 or the CD40-ligand[12,14,15] or autologous bone marrow transplantation.[16,17]

In conclusion, the data from our series of patients do not seem to provide support for the concept that elderly patients carry a significantly higher risk of serious bleeding. We think that prospective studies are required to evaluate whether it may be reasonable to treat only symptomatic patients, independently of age. To this end, a multicenter study is currently being planned by the GIMEMA study group (*Gruppo Italiano per lo Studio delle Malattie Ematologiche dell'Adulto*).

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NV: conception, design, analysis and data interpretation, drafting and article revision; LV: collection of clinical data, analysis and data interpretation, drafting and article revision; MF: statistical analysis and data interpretation; AdV: statistical analysis and data interpretation; LG, LC, RML: data interpretation and article revision; MP: collection of clinical data and data interpretation; ST: data interpretation, article revision and final approval. We are grateful to Professor Franco Mandelli for valuable advice. We thank Robin M.T. Cooke for editing.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlappimg with previous papers.

Manuscript processing

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Potential implications for clinical practice

If treatment of chronic ITP can be limited only to symptomatic patients, irrespective of age, such a conservative strategy would provide savings in both human and economic terms. Patients would not have to bear the inconvenience, discomfort and possible side effects of treatment that it is not strictly necessary.

References

1. Williams WJ. Hematology. 5th ed. New New York: Mc Graw Hill: 1995.
2. Berchtold P, McMillan R. Therapy of chronic idiopathic thrombocytopenic purpura in adults. Blood 1989; 74:2309-17.
3. Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. Blood 1999; 94:909-13.
4. McMillan R. Chronic idiophatic thrombocytopenic purpura. N Engl J Med 1981; 304:1135-47.
5. Karpatkin S. Autoimmune (idiopathic) thrombocytopenic purpura. Lancet 1997; 349:1531-6.
6. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996; 88:3-40.
7. Schattner E, Bussel J. Mortality in immune thrombocytopenic purpura: report of seven cases and consideration of prognostic indicators. Am J Hematol 1994; 46:120-6.
8. 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; 77:31-3.
9. Guthrie TH Jr, Brannan DP, Prisant LM. Idiopathic thrombocytopenic purpura in the older adult patient. Am J Med Sci 1988; 296:17-21.
10. Vianelli N, Catani L, Gugliotta L, et al. Recombinant α-interferon 2b in the treatment of HIV-related thrombocytopenia. AIDS 1993; 7:823-7.
11. Gmur J, Burger J, Schanz U, Fehr J, Schaffner A. Safety of stringent prophylactic platelet transfusion policy for patients with acute leukaemia. Lancet 1991; 338:1223-6.
12. Bussel J, Wissert M, Oates B, Scaramucci J, Nadeau K, Adelman B. Humanized monoclonal anti-CD40 ligand antibody (hu5c8) rescue therapy of 15 adults with severe

chronic refractory ITP. Blood 1999; 94 (Suppl 1):646a.
13. Yang R, Han ZC. Pathogenesis and management of chronic idiopathic thrombocytopenic purpura: an update. Int J Hematol 2000; 71:18-24.
14. Mow BM, Hook CC. Rituximab for the treatment of refractory thrombocytopenic purpura. Case report. Blood 1999; 94 (Suppl 1):82b.
15. Perotta AL, Abuel C. Update of response to rituximab of chronic relapsing ITP. Blood 1999; 94 (Suppl 1):82b.
16. Skoda RC, Tichelli A, Tyndall A, Hoffmann T, Gillessen S, Gratwohl A. Autologous peripheral blood stem cell transplantation in a patient with chronic autoimmune thrombocytopenia. Br J Haematol 1997; 99:56-7.
17. Lim SH, Kell J, al-Sabah A, Bashi W, Bailey-Wood R. Peripheral blood stem-cell transplantation for refractory autoimmune thrombocytopenic purpura. Lancet 1997; 349:475.
18. Lawrence JB, Yomtovian RA, Dillman C, et al. Reliability of automated platelet counts: comparison with manual method and utility for prediction of clinical bleeding. Am J Hematol 1995; 48:244-50.
19. Imbach P, Kuhne T. Immune thrombocytopenic purpura ITP. Vox Sang 1998; 74(Suppl 2):309-14.