

High Risk of Severe Bleeding in Aged Patients With Chronic Idiopathic Thrombocytopenic Purpura

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The purpose of this study was to estimate the incidence and to establish which factors were associated with an increased risk of hemorrhagic complications in an historic cohort of 117 consecutive and unselected patients with chronic idiopathic thrombocytopenic purpura (ITP). Sixty-eight patients (58%) underwent medical treatment and/or splenectomy and 33 (48% of treated) achieved a complete stable remission. At equivalent platelet count the incidence of major hemorrhagic complications was significantly higher in aged (> 60 years)

than in younger (<40 years) patients (10.4% v 0.4%/pt-y, relative risk = 28.9, $P < .01$). A previous hemorrhagic event was identified as another major risk factor for hemorrhage (relative risk = 27.5, $P < .0005$), while hypertension and underlying disorders had no influence. We conclude that age more than 60 years and a previous history of bleeding are major risk factors for severe hemorrhages in adults with ITP. © 1991 by The American Society of Hematology.

IDIOPATHIC thrombocytopenic purpura (ITP) is an immune-mediated disease in which platelets are destroyed by the reticuloendothelial system. The acute form, usually observed in children, is a self-limiting disorder, while the chronic form, generally occurring in young adults, persists for years. Hemorrhages are the only clinical manifestations and they may be mild, such as petechiae, easy bruising, epistaxis, and gingival bleeding, although severe complications such as hemoptysis, gastrointestinal (GI) and genitourinary tract bleeding are also observed and are generally associated with marked thrombocytopenia. Intrabuccal and retinal hemorrhages may have prognostic significance reflecting respectively imminent GI and cerebro-meningeal bleeding.¹ The most serious and life-threatening complications are intracranial hemorrhages, with mortality of 1% in acute ITP and about 5% in the chronic form.^{2,3} The first-choice therapy of chronic ITP includes steroids and splenectomy. However, steroids have failed to induce long-term complete remission in 80% to 90% of cases, and splenectomy is reported to be ineffective in 30% to 40% of patients.^{3,4} Several other treatments have been proposed for patients refractory to steroids and splenectomy but their efficacy is uncertain.³ Thus, a large number of patients with ITP continue to be at risk for hemorrhagic complications despite treatment. However, the extent of this risk is not known, because no data on the incidence of bleeding (ie, new cases/years estimated by follow-up studies) is available in the literature. In addition, there is no information on the part played by potential risk factors for bleeding, such as age, previous hemorrhagic events, hypertension, and underlying organic lesions. These data might be of clinical interest because they would serve to identify patients at higher risk for severe hemorrhagic complications. With this aim, we retrospectively examined our series of 117 consecutive adult patients with chronic ITP.

PATIENTS AND METHODS

Baseline features. The clinical records of 117 adults (> 16 years old at diagnosis) with ITP, admitted to our institution between January 1982 and December 1989, were reviewed. Diagnostic criteria for chronic ITP were⁵: platelet count less than $100 \times 10^9/L$ determined automatically, normal or increased number of megakaryocytes in the bone marrow, absence of palpable spleen and normal white blood cell (WBC) count and hemoglobin levels, exclusion of other mechanisms of thrombocytopenia, and thrombocytopenia present for more than 6 months.

Baseline coagulation studies were performed according to standard methods and were normal in all patients.

Patients taking drugs and/or following a diet to control hypertension, or with systolic blood pressure (BP) greater than 170 mm Hg and diastolic BP greater than 100 mm Hg were considered hypertensive. Patients with GI (peptic ulcer), pulmonary (bronchiectasis), or genitourinary disorders (nephrolithiasis and uterine leiomyoma), prone to bleeding, were recorded as having underlying lesions.

Follow-up. All patients were regularly followed at 2-month intervals and clinical events and platelet counts at the time were recorded.

We classified bleeding as major⁶ when it required hospital admission (nine patients) or was clinically overt with a fall in hemoglobin of at least 20 g/L (six patients) or both (three patients). Major hemorrhagic events included: intrabuccal hemorrhagic vesicles and diffuse ecchymosis (five cases), hemoptysis (two cases), GI (one case), or genitourinary tract bleeding (eight cases), and cerebral hemorrhage, diagnosed by computerized tomography (two cases). Ecchymosis, purpura, gum bleeding, and mild epistaxis were considered minor and were not included in the present analysis of risk factors.

Therapeutic program. Criteria for starting therapy were: the presence of hemorrhagic complications and/or thrombocytopenia lower than $30 \times 10^9/L$.

Sixty-eight out of 117 patients (58%) were treated as follows: prednisone was the first treatment in all patients, at a daily dosage of 1 to 2 mg/kg during the first 2 to 4 weeks; the maintenance dosage was 0.3 to 1 mg/kg daily or at intermittent intervals if the treatment was for more than 60 days. Only patients who received steroids for at least 30 days were evaluated. Splenectomy was performed in 33 patients who failed to reach a prolonged complete remission (PCR), as defined below, with corticosteroids. Danazol was given orally at a dosage of 200 mg three times a day for 2 months⁷ in 28 patients refractory to steroids and splenectomy or in those not eligible for surgery. During this treatment, other drugs, including prednisone, were discontinued. Other treatments included vincristine (six patients), administered intravenously at a dosage of 1 mg once a week for a minimum of three doses,⁸ and azathioprine (four patients), given orally at a daily dosage of 2

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mg/kg for at least 16 weeks, and were used in patients refractory to steroids, splenectomy, and danazol.⁹

Complete remission (CR) was considered more than $100 \times 10^9/L$ platelets. Partial remission (PR) was a platelet count more than $30 \times 10^9/L$. PCR and prolonged partial remission (PPR) were, respectively, a CR and a PR lasting more than 6 months after all treatment had been discontinued.

Data analysis. The event-free follow-up of each patient was defined as the person-time at risk (pt-y) of that individual. The sum of the individual pt-y represented the total pt-y (expressed as 100 persons per year). The person-time incidence was calculated by dividing the number of new hemorrhagic episodes (ie, incident events) by the total pt-y. The likelihood of hemorrhage in ITP patients exposed to risk factors (age, previous hemorrhagic events, hypertension, and underlying lesions) was calculated as odds ratio, ie, the ratio of the incidence in exposed versus unexposed patients.¹⁰ The standard chi-square test (with Yates correction) for association in a 2×2 table provided an approximate test of significance.^{11,12}

RESULTS

At diagnosis the mean age was 43 years (range 16 to 84 years) and the men/women ratio was 1:2.9 (M:W 30/87). The mean platelet count was $49 \times 10^9/L$ (range 5 to $100 \times 10^9/L$); hemoglobin concentration and WBC were in the normal range in all patients (mean and range, respectively, 134, 125 to 140 g/L and 6.5, 5.5 to $9.5 \times 10^9/L$). Eight patients presented a major bleeding at diagnosis (three intrabuccal hemorrhages and diffuse ecchymosis, two hemoptysis in patients with bronchiectasis, one macrohematuria in a patient with nephrolithiasis, and two vaginal bleeding). These events were not considered in the calculation of the incident rate. The median follow-up time was 36 months (range 6 to 84 months). There were five deaths: one patient aged 70 years died of cerebral hemorrhage and four (age 70 to 84 years) died of causes unrelated to thrombocytopenia (three patients died of cardiovascular disorders and one, not splenectomized, of acute pneumonia). No patient was lost to follow-up.

Forty-nine patients (42%), 16 men and 33 women, mean age 41 years (range 16 to 67 years) and mean platelet count $69 \times 10^9/L$ (range 31 to $100 \times 10^9/L$) were followed for a median of 30 months (range 6 to 76 months) and did not receive any treatment. No major hemorrhages occurred among these patients.

Sixty-eight patients (58%), 14 men and 54 women, with a mean age of 45 years (range 16 to 84 years), and a mean platelet count of $30 \times 10^9/L$ (range 5 to $100 \times 10^9/L$) (two-sample *t*-test $P < .01$) were followed for a median of 40 months (range 6 to 84 months) and underwent medical treatment or splenectomy. The therapeutic outcome is summarized in Table 1. Overall, 33 of 68 patients (48%) (4

elderly patients and 29 younger than 60 years) achieved a PCR (9 after prednisone, 21 after splenectomy, and 3 after danazol). The other 28 patients (41%) (16 elderly and 12 younger than 60 years) had a stable platelet count of more than $30 \times 10^9/L$. Complications of steroid treatment severe enough to reduce or stop treatment, such as gastritis, diabetes mellitus, psychosis, and infections were significantly more frequent in older than in younger patients: 14 of 21 patients versus 12 of 47 patients (corrected χ^2 according to Yates, 7.9, $P < .01$).

During follow-up 58 of the 68 treated patients (85%) remained free of bleeding complications or had minor hemorrhagic episodes, whereas 10 (15%) suffered major hemorrhagic events. Two patients had intrabuccal hemorrhage with diffuse ecchymosis, four (two with uterine leiomyoma) had vaginal bleeding. One patient with peptic ulcer had melena and another without any underlying lesions had macrohematuria. Two patients suffered cerebral hemorrhage, one of which was fatal. Six events were recurrences in patients who had already had hemorrhagic complications at diagnosis, while in the remaining four patients hemorrhagic episodes occurred only during follow-up.

The distribution of 18 major hemorrhagic episodes (8 at diagnosis and 10 during follow-up) according to platelet number at the time indicated that there were 14 complications (78%) when platelets were less than $20 \times 10^9/L$, four (22%) of the hemorrhagic episodes occurred with platelets between 20 and $30 \times 10^9/L$, and no severe hemorrhage was seen with more than $30 \times 10^9/L$ platelets.

In all patients the incidence of major bleeding was 3.2%/pt-y. However, the incidence was significantly higher in elderly than in younger patients (Table 2). A previous hemorrhagic event, recorded at diagnosis, also raised the risk of hemorrhagic complications, whereas hypertension and underlying lesions did not significantly influence it.

Because major hemorrhage was more likely with lower platelet count and also with older age, we further evaluated the relation between these two variables. Elderly (>60 years) and younger patients (<60 years) were compared for platelet number at diagnosis (43.5 ± 24.3 v 50.1 ± 29.2 platelets $\times 10^9/L$) and platelet number at the time of major hemorrhagic event (25.1 ± 4.0 v 22.2 ± 4.1 platelets $\times 10^9/L$). None of these parameters was significantly different between the two groups (two-sample *t*-test $P = .20$) showing that older age is a risk factor for hemorrhagic complications at equivalent platelet count.

DISCUSSION

The major finding of this study was that older age and previous hemorrhagic events significantly increase the risk of severe bleeding in adult patients with ITP. The high risk of bleeding in aged patients is remarkable because old ITP patients are rarely examined separately even in the largest series.^{13,14} Elderly patients had a greater risk for bleeding at equivalent platelet count, suggesting that advanced age is an independent risk factor for hemorrhagic complications. A similar observation has been made also in old patients receiving heparin therapy¹⁵ and long-term oral anti-coagulation.¹⁶

Table 1. Long-Term Response to Treatments in Adults With ITP

Age (y)	No. of Cases	PCR (%)	PPR (%)
≤ 60	45	29 (64)	12 (27)
> 60	23	4 (17)	16 (70)
Total	68	33 (48)	28 (41)

PCR = platelets $> 100 \times 10^9/L$ for > 6 months after withdrawal of therapy. PPR = platelets $> 30 \times 10^9/L$ for > 6 months after withdrawal of therapy.

Table 2. Subgroup Analysis of the Odds of Hemorrhage in 117 Patients With ITP

Category	No. of Patients	Total Person-Years of Observation	No. of Events	Person-Time Incidence Rates	Odds Ratio	P Value
Age (y)						
< 40	54	257	1	0.4	1.0*	—
40-60	32	177	2	1.1	2.8	NS
> 60	31	67	7	10.4	28.9	<.010
Previous hemorrhagic events						
No	111	468	4	0.8	1.0*	
Yes	6	33	6	18.2	27.5	<.0005
Hypertension						
No	99	432	8	1.8	1.0*	
Yes	18	69	2	2.9	1.6	NS
Overt coexistent organic lesion						
No	96	409	7	1.7	1.0*	
Yes	21	92	3	3.3	1.9	NS

Abbreviation: NS, not significant.

*Reference category.

Aged patients showed a lower proportion of PCR but an higher percentage of PPR (platelets $>30 \times 10^9/L$) after treatment of ITP. This result can be due to the fact that complications of steroid treatment severe enough to reduce or stop treatment were more frequent in elderly, and that splenectomy was rarely performed in patients more than 60 years old who stably had more than $30 \times 10^9/L$ platelets. Because severe bleeding episodes occurred only at platelet count less than $30 \times 10^9/L$ it is unlikely that the different response to therapy played a major role in bleeding of elderly patients.

It has recently been reported that elderly thrombocytopenic patients in whom steroids and splenectomy fail may actually have an asymptomatic myelodysplastic syndrome that becomes clinically and hematologically evident during follow-up.¹⁷ This possibility can be reasonably ruled out in our patients because the majority of them did achieve partial or complete long-lasting remission mostly after prednisone or splenectomy, which cannot be expected in

myelodysplastic syndromes, and none developed signs of a myelodysplastic syndrome during 12 to 72 months follow-up (median 24 months).

Another factor enhancing the risk of bleeding was the initial hemorrhagic complication observed at diagnosis. In this group the incidence rate of hemorrhage was 18.2%/pt-y against 0.8%/pt-y in the patients without bleeding at diagnosis. Other potential risk factors such as hypertension or underlying lesions did not influence the hemorrhage rate, although this cannot be firmly stated because of the relatively small number of exposed patients.

In conclusion, our analysis provides a formal estimate of the relative risk of bleeding in patients treated for chronic ITP, showing that aged patients constitute a high risk-group for severe bleeding.

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