Assessment of a therapeutic strategy for adults with severe autoimmune thrombocytopenic purpura based on a bleeding score rather than platelet count

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Background and Objectives. The optimal treatment for patients with autoimmune thrombocytopenic purpura (AITP) and a platelet count ≤20×10⁹/L is intravenous immunoglobulin (IVIg) but this treatment is expensive and steroids are a good alternative in less severe cases. Since the occurrence of life-threatening hemorrhage in adult AITP is a rare event, the aim of our study was to validate a therapeutic strategy based on a bleeding score for the short-term management of adults with AITP and a platelet count ≤20×10⁹/L.

Design and Methods. We developed a method to quantify hemorrhage in adults with AITP. Bleeding severity was graded on a numerical scale based on physical examination. When the bleeding score was ≤8, the patients were treated with steroids alone. For scores >8, patients received IVIg (1 to 2 g/kg) in combination with oral steroids. A good response was defined as the lowering of the initial bleeding score within 2 days after treatment initiation regardless of the platelet count.

Results. We applied this strategy for the management of 60 consecutive adults (mean age 48±23 years) with AITP and a platelet count ≤20×10⁹/L (mean platelet count 6±5×10⁹/L). Based on this strategy, IVIg was required in only 50% of the patients and no life-threatening bleeding occurred in patients treated with steroids alone.

Interpretations and Conclusions. A therapeutic strategy based on a bleeding score rather than the platelet count appears to be relevant and safe and is a good IVIg-sparing strategy.

Key words: autoimmune thrombocytopenic purpura, bleeding score, therapeutic strategy.

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Patients with severe autoimmune thrombocytopenic purpura (AITP) are at risk of life-threatening bleeding and require a treatment with rapid, reliable, and sustained effects.[1,2] We have previously shown in a randomized study that intravenous immunoglobulin (IVIg) is more frequently and rapidly effective than steroids in adults with severe AITP,[3] but steroids are still a good alternative.[4] However IVIg is expensive, meaning that only patients with the severest forms of AITP should receive IVIg.[1] Patients with mild bleeding could probably be treated with steroids alone, even if their platelet count is very low. The aim of our study was to validate a therapeutic strategy based on a bleeding score for the short-term management of adults with AITP and a platelet count ≤20×10⁹/L.

Design and Methods

All consecutive patients (aged 16 years old and above) diagnosed with AITP according to standard criteria[2,5] admitted to our department over a three-year period with a platelet count ≤20×10⁹/L were included. Patients with chronic AITP and stable low platelet count without hemorrhagic manifestations and admitted for other reasons were not included.

Bleeding score

The severity of bleeding manifestations at onset was assessed using a previously described clinical scoring system[3] with minor modifications (Table 1). The total bleeding score was calculated by adding the scores for each item. As elderly patients appear to have an higher risk of severe bleeding,[6,7] the bleeding score was increased by two points for patients over 65 years old and by five points for those over 75 years old.

Therapeutic strategy

Patients with a bleeding score >8 at the time of admission were treated with IVIg at a dose of 1g/kg body weight (bw)/day for one or two days in combination with oral prednisone (1 mg/kg bw) for 3 consecutive

Table 1. The bleeding score.

Age*	
Age over 65 years	2
Age over 75 years	5
Cutaneous bleeding*	
Localized petechial purpura (legs)	1
Localized ecchymotic purpura	2
Two locations of petechial purpura (e.g. legs + chest)	2
Generalized petechial purpura	3
Generalized ecchymotic purpura	4
Mucosal bleeding	
Unilateral epistaxis	2
Bilateral epistaxis	3
Hemorrhagic oral bullae, spontaneous gingival bleeding or both	5
Gastrointestinal bleeding*	
Gastrointestinal hemorrhage without anemia	4
Gastrointestinal hemorrhage with acute anemia (> 2g Hb decrease in 24h) and/or shock	15
Urinary bleeding*	
Macroscopic hematuria without anemia	4
Macroscopic hematuria with acute anemia	10
Genitourinary tract bleeding*	
Major meno/metrorrhagia without anemia	4
Major meno/metrorrhagia with acute anemia	10
Central nervous system bleeding	
Central nervous system bleeding and/or life-threatening hemorrhage	15

**For these items, only the highest value was taken into account.*

weeks. Patients with a bleeding score ≤8 received oral prednisone (1 mg/kg bw) for 3 weeks or one to three pulses of intravenous high dose methylprednisolone (HDMP) (15 mg/kg bw) followed by oral prednisone for 3 weeks (Figure 1). Treatment failure was defined as no platelet count increase and stability or worsening of the initial bleeding score on day 2 after admission. In the case of treatment failure, patients received the treatment they had not received initially (i.e. IVIg or HDMP). Therapeutic success was defined as a lowering of the initial bleeding score within the first 48 hours after treatment initiation, even if the platelet count remained low. The initial bleeding score could be lowered either by the disappearance of extra cutaneous bleeding symptoms (i.e mucosal, gastrointestinal, urinary, central nervous system or genital bleeding) when present initially, or by the improvement of initial cutaneous bleeding manifestations (i.e. from generalized to localized purpura) for patients with the less severe disease. The response to treatment in those patients with a score of 0 at the time of admission was defined by the non-occurrence of any bleeding symptoms after treatment initiation and during the following 3 weeks (duration of the initial steroid therapy) regardless of the platelet count. Finally, IVIg was also used as first-line treatment in cases of contraindication to steroids (e.g. uncontrolled diabetes mellitus or high blood pressure) or when the patient was known to be unresponsive to steroids.

Statistical analysis

Results are expressed as the mean±1 standard deviation or as percentages. Student's t test was used to compare data from patients who received steroids and those who received IVIg. Correlations between variables were assessed using Spearman's correlation coefficient. p values of <0.05 were considered to be statistically significant.

Results

Patients' characteristics

Sixty consecutive patients (36 females, 24 males; mean age 48±23 years, range 16-91 years) were included. Fifty-five (92%) were newly diagnosed with AITP and five had chronic AITP. Three of these five patients were known to be unresponsive to steroids. The mean platelet count at inclusion was $6\pm5\times10^9$/L (range 1-20). Forty-nine patients (82%) had a platelet count $<10\times10^9$/L.

Bleeding score

The mean bleeding score at inclusion was 7±5.5 (range, 0 to 33). Forty-four patients (73%) had a bleeding score ≤8. There was a moderate negative correlation between platelet count and bleeding score ($r = -0.40$; $p<0.01$).

Response to therapy

Six of the 44 patients with a bleeding score ≤8 received IVIg alone as the first-line treatment because of a contraindication to steroids (n=4) or known refractoriness to steroid therapy (n=2). A good response was observed in all these patients. Twenty-nine of the 38 remaining patients (76%) initially treated with steroids responded to the treatment. Overall, 39/60 patients received steroids alone as a first-line therapy: 22/39 (56%) at a conventional-dose of 1 mg/kg bw/day whereas 17/39 (44%) received pulses of intravenous HDMP. Nine of these 39 patients (24%) failed to respond to steroids, 3 in the subgroup treated with oral steroids and 6 among those receiving HDMP. All the 9 non-responders subsequently responded to IVIg and no major bleeding event due to the therapeutic delay was observed. Lastly, 9 of the 29 patients with a bleeding score ≤ 8 treated with steroids were treated as outpatients (Figure 2).

Fifteen of the 16 patients with a bleeding score >8 received IVIg and steroids. One patient with chronic AITP and a bleeding score of 12 was treated with

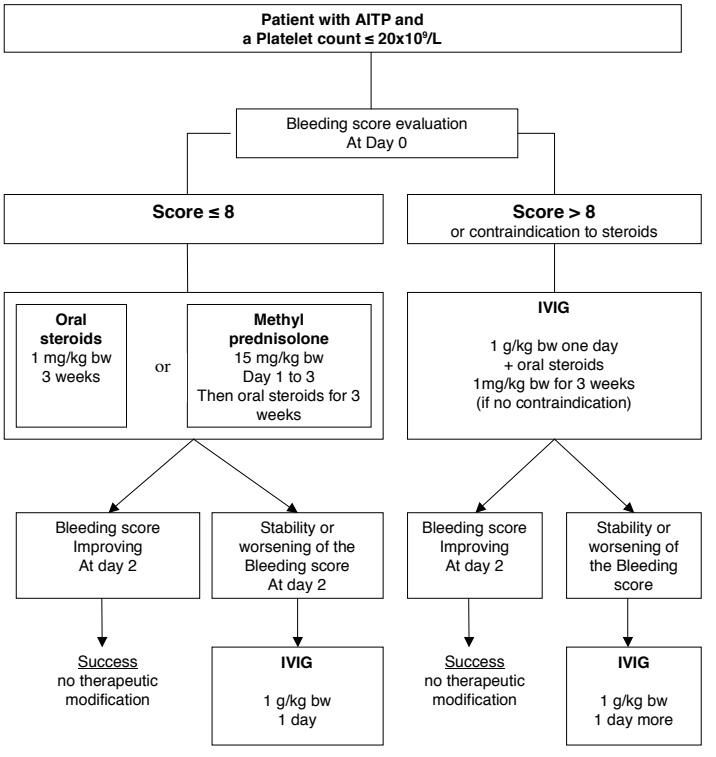

Figure 1. Therapeutic strategy for the management of AITP patients with platelet count ≤ 20×10⁹/L.

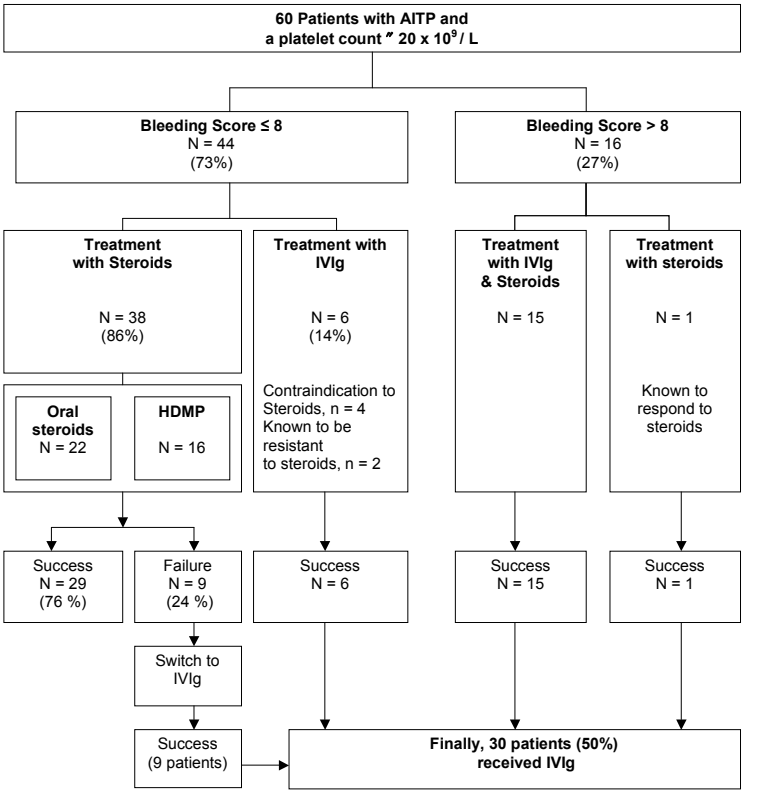

Figure 2. Results of the treatment according to the bleeding score.

HDMP, since he was known to respond rapidly to steroids. A response was observed in all 16 patients and no switch was required. The patients treated with steroids stayed in hospital a significantly shorter time than did the IVIg group (3.4±5.6 versus 8.7±8.8 days; p=0.02). The length of stay in hospital was similar for the patients who initially failed to respond to steroids and those treated with IVIg (5±2.4 vs 8.7±8.8 days; p=0.08). Finally, no death or life-threatening bleeding episodes were observed during the study.

Discussion

Corticosteroids and IVIg are the first-line treatments for adults with AITP and a low platelet count[1-5] (i.e. <20×10^9/L). There is, however, currently no general agreement as regards to which therapy should be used and particularly which patients must be treated with IVIg. Platelet count is currently used to assess the severity of the disease but some patients have no or very few bleeding symptoms despite marked thrombocytopenia.[8] We therefore developed a bleeding score based on clinical findings to determine which therapeutic strategy should be used for adult AITP patients with a platelet count ≤20×10^9/L. We focused our therapeutic strategy on steroids and IVIg since we and others have previously shown that these treatments are highly effective for obtaining a rapid increase in platelet count.[1-5] Other treatments, such as splenectomy,[9] immunosuppressive drugs or anti-CD20[10] antibody are mainly indicated for the management of chronic AITP. Anti-D is not currently available in France. We did not include platelet transfusions in our therapeutic strategy because they are required only for very rare life-threatening complications such as central nervous system hemorrhage.

Most of our patients had a platelet count below 10×10^9/L (82%), but a low bleeding score (≤8) documented in 73% of patients allowed us to use steroids as first-line treatment. A response was observed in 75% of these patients and no severe bleeding was observed during follow-up among the patients initially treated with steroids, including those who were subsequently switched to IVIg. Our bleeding scoring strategy allowed us to avoid the use of IVIg, which is much more expensive than steroids, in up to 50% of patients with a platelet count ≤20×10^9/L. Furthermore, the patients treated with steroids spent a significantly shorter time in hospital than did the IVIg group and 20% of the patients with a bleeding score under 8 were treated as outpatients.

We arbitrarily selected a bleeding score of 8 as the cut-off point above which to use IVIg. This cut-off implied the presence of relatively severe mucocutaneous hemorrhage or milder hemorrhage in the elderly. This cut-off value was deliberately chosen to be relatively low primarily for safety reasons since this was an open prospective study. The 5 points added to the score of patients aged 75 and above may seem an overestimation but this choice was based on our experience and on data in the literature[11,12] suggesting that the risk of life-threatening hemorrhage is higher in the elderly.

Using this cut-off value of 8, no serious bleeding events were observed in the patients with an initial score ≤8 who received steroids alone. Moreover, one patient with a bleeding score of 12 who was known to respond rapidly to steroids was successfully treated by steroids alone. Assessing the safety of using a higher cut-off value (i.e bleeding score >10 or even 12) for the use of IVIg would now definitely be helpful in future studies. In conclusion, a therapeutic strategy based on a bleeding score rather than on the platelet count appears to be relevant and safe. This strategy is currently used in our department for the management of patients newly diagnosed with AITP who have a platelet count ≤20×10^9/L and now needs further validation through prospective multicenter studies including a higher number of patients.

MK, MM: directly involved in the writing of the manuscript as well as the management of the majority of the patients included in this study; BG, PB: provided a major contribution to the design of the bleeding score and the therapeutic strategy; AS: former head of the department contributed to the inclusion of about one third of the patients evaluated in this study. The authors declare that they have no potential conflicts of interest.

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