To the editor:

**Marburg I polymorphism of factor VII–activating protease and risk of venous thromboembolism**

The factor VII–activating protease (FSAP), a newly discovered serine-protease present in human plasma, has 2 main functions in hemostasis: it is a potent activator of prourokinase1 and accelerates coagulation by activating factor VII, independently of tissue factor.2 The FSAP Marburg I polymorphism (1601G>A) was recently evaluated as a candidate risk factor for venous thromboembolism (VTE), since it impairs the capacity of FSAP to activate prourokinase while preserving its capacity to activate factor VII.3

Hoppe et al4 first reported the Marburg I polymorphism to be associated with an increased risk of VTE,2 but these data were not confirmed by Van Minkelen et al.5 Since such different findings were possibly related to the different selection of the control group (formed by blood donors in the former study and by unselected healthy subjects in the latter), Hoppe et al6 reviewed their data using a different control group of non–blood donors and confirmed the association between the Marburg I polymorphism and VTE only for patients with idiopathic events (ie, those occurring in the absence of triggering factors [OR = 2.7; 95% CI, 1.2-6.1]).4

To further investigate the role of the Marburg I polymorphism as a risk factor for VTE, we carried out a large case control study of 418 patients (161 men and 257 women) who had a first, objectively confirmed VTE and were referred to our Thrombosis Center for a thrombophilia screening, and 422 healthy controls (173 men and 249 women) who were partners or friends of the whole population of thrombosis patients seen at the center. The Marburg I polymorphism was evaluated by amplification refractory mutation system (primers and conditions available on request). The median age at VTE for patients and at blood sampling for controls was 39 years (range, 14-76 years) and 42 years (range, 16-84 years), respectively. We confirmed a statistically significant association between VTE and such established risk factors as factor V Leiden, prothrombin 20210G>A, antithrombin, protein C and protein S deficiencies, hyperhomocysteinemia, and oral contraceptive use (data not shown).

Table 1 shows the prevalence of the Marburg I polymorphism, which was very similar in patients and controls, either considering all VTEs (5.3% vs 5.2%; OR = 1.0; 95% CI, 0.51-1.9) or only the 190 idiopathic events (4.4% vs 5.2%; OR = 1.1; 95% CI, 0.5-2.7). All carriers of FSAP Marburg I were heterozygous for the variant.

In conclusion, the present study ruled out a strong association between the FSAP 1601G>A polymorphism (Marburg I) and unselected or idiopathic VTE. Whether the Marburg I polymorphism determines a weak effect on thrombotic risk could be observed only in very large study populations, and remains to be determined.

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**References**


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To the editor:

**Experience with bortezomib for the treatment of patients with relapsed classical Hodgkin lymphoma**

The proteasome inhibitor bortezomib has been successfully used to treat patients with multiple myeloma and non-Hodgkin lymphoma.1,3 We have recently reported that bortezomib can induce cell cycle arrest and apoptosis in a variety of Hodgkin lymphoma (HL)-derived cell lines in vitro.4 Furthermore, bortezomib potentiated the activity of chemotherapy and agonistic antibodies to the TRAIL death receptors.5 Based on these preclinical data, we initiated a pilot study of bortezomib in patients with relapsed and refractory classical HL.

Patients were enrolled in the study if they had relapsed classical HL with a bidimensionally measurable disease, had received a minimum of 2 prior treatment regimens (including stem cell transplantation), and had adequate pretreatment bone marrow, hepatic, and renal functions. Patients were excluded if they had a history of human immunodeficiency virus infection or central nervous system involvement with HL. Patients were treated with 1.3 mg/m² bortezomib intravenously on days 1, 4, 8, and 11 of...
21-day cycles. Treatment was delayed if the platelet count on the first day of each cycle was less than 30 × 10⁹/L (30 000/µL). After 3 cycles of bortezomib, patients were evaluated for treatment response. If there was no evidence of disease progression, patients were allowed to receive a maximum of 6 cycles.

Fourteen patients were enrolled in the study (Table 1). All patients were heavily pretreated and were refractory to their last therapy. Patients received a median number of 4 prior treatment regimens, and 13 (93%) patients were previously treated with autologous stem cell transplantation. The median pretreatment platelet count was 126 × 10⁹/L (126 000/µL) (range, 66 × 10⁹/L-339 × 10⁹/L [66 000-339 000/µL]). All patients received at least one cycle of bortezomib (range, 1-6 cycles) and were evaluable for treatment toxicity and response. Treatment was well tolerated, with the majority of toxic effects of grades 1 and 2. Two patients had grade 3 dyspnea, and one patient had grade 3 neutropenic fever. Thrombocytopenia was the most common hematologic toxicity, which frequently caused delays in therapy. Nadir platelet counts below 30 × 10⁹/L (30 000/µL) were observed in 29% of the patients during the first cycle and in 67% during the third cycle. Nadir absolute neutrophil counts below 1.0 × 10⁹/L (1000/µL) were observed in 10% of the patients during cycle 1 and in 17% during cycle 3. One patient had a partial remission and 2 had minor responses. The patient who achieved a partial response was a 39-year-old woman who had received 9 prior treatment regimens, including stem cell transplantation (Table 1). She was also receiving concomitant low-dose prednisone for pain management. She had an extensive pulmonary, splenic, and nodal disease and had a dramatic response within 8 weeks of therapy, but her disease progressed shortly after discontinuation of bortezomib therapy.

Our data demonstrate that in these heavily pretreated patients with treatment refractory relapsed classical HL, bortezomib has minimal single-agent activity. Future studies should evaluate bortezomib in less heavily pretreated patients, preferably whose disease responded to their last treatment modality. Furthermore, bortezomib-based combination therapy should also be investigated in patients with relapsed classical HL to determine whether bortezomib may potentiate the activity of chemotherapy in vivo.

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References


To the editor:

Long-term engraftment and clonal dominance of donor-derived del(20q) hematopoietic cells after allogeneic stem cell transplantation

In 1997, a 50-year-old woman who was retrospectively diagnosed with early asymptomatic myelodysplastic syndrome (MDS) served as a hematopoietic cell donor for her HLA-identical sister who had chemotherapy-refractory angioimmunoblastic T-cell lymphoma. The preparative transplant regimen consisted of high-dose cyclophosphamide and fractionated total body irradiation; cyclosporine and methotrexate were given for graft-versus-host disease prophylaxis. The MDS of the donor was classified as refractory anemia...
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