Prothrombotic coagulation abnormalities in patients with newly diagnosed multiple myeloma

Prothrombotic coagulation abnormalities were analyzed in patients with untreated multiple myeloma. Increases in factor VIII, in von Willebrand factor and a decrease in protein S were observed and these changes were strongly associated with disease stage. No difference in baseline coagulation parameters was found between patients with and without subsequent venous thromboembolism.

Haematologica 2007; 92: 279-280

Patients with multiple myeloma (MM) are at high risk for venous thromboembolism (VTE) with reported incidences of this complication being up to 30%, especially in patients receiving multi-agent chemotherapy and anti-angiogenic drugs.[1] Although the mechanism of VTE has not been fully elucidated, the first report on altered coagulation factors in MM dates back to 1976[2] and concerned an observed increase in factor VIII (FVIII). Elevated von Willebrand factor (vWF) levels were reported by Minnema *et al.*[3] and more recently a high incidence of acquired resistance to protein C has been described.[4] In order to elucidate the mechanism of VTE further, we performed this prospective study to evaluate baseline coagulation parameters in relation to disease stage[5] and development of clinical VTE in patients with untreated MM. The Medical Ethical Committee of the Erasmus University Medical Center approved the study and written informed consent was obtained from the participants. Basic descriptive statistics are provided and the results are presented as mean ± standard deviation. Differences between groups were tested using analysis of variance. Levels of prothrombotic variables in different International Staging System (ISS) were compared using ANOVA, which takes multiple testing into account (Bonferroni's correction with mean correlation=0.40). A p value below 0.013 is considered statistically significant.

One hundred and thirty-five consecutive patients with untreated MM admitted to the Department of Haematology of the Erasmus Medical Center, an academic tertiary referral hospital, who were eligible for intensified chemotherapy followed by high dose melphalan and autologous stem cell support were included in this study, as were 124 sex- and age-matched, healthy controls.

The results of the coagulation variables are presented in Table 1. The prevalence of factor V Leiden mutation and G20210A prothrombin gene variant was similar in the MM patients and in the control group. At baseline the incidence of lupus anti-coagulant (LAC) was 4% and that of anti-cardiolipin antibodies (ACA) 6% in the MM patients. These findings are in accordance with recently reported incidences.[4] Anti-phospholipid antibodies (APA) were re-tested after 3 months and had disappeared in all cases. We found no relationship with the presence of monoclonal IgG or IgA serum immunoglobulin, seen in the MM patients, which excludes the possibility that our findings are due to a cross-reactivity of the monoclonal IgG and the APA tests. Acquired activated protein C resistance was observed in only 2% of the patients, which is a lower incidence than the previously reported 9%.[4]

FVIII and vWF antigen levels and activity were significantly higher in MM patients than in the controls (Table 1). Furthermore, there was a significant correlation between disease stage according to ISS criteria and levels of FVIII and vWF, which were highest in stage III (Table 1). The correlation with disease stage according to the Durie and Salmon classification system was less clear. The pathogenetic mechanism of the increased levels of FVIII and vWF is unclear, but may be related to neovascularization in the bone marrow stroma.[6] We measured-protein S using an assay (Staclot® Protein S, Diagnostica Stago) that is known not to interfere with FVIII when levels are lower than 250%.[7] Protein S levels decreased significantly with increasing ISS stage. Lower protein S levels may increase the risk of thrombo-embolic complications in the more severe stages of MM, since protein S deficiency is known to be associated with VTE.

The levels of other prothrombotic coagulation factors, including antithrombin, fibrinogen and D-dimer, were similar in patients and control subjects, and did not differ

Table 1. Subjects' characteristics and coagulation variables.

	Controls	*Patients*	*p value*	*ISS*			*p value disease stage*
				Stage I	*Stage II*	*Stage III*	
Number	124	135		42 (31%)	75 (56%)	18 (13%)	
Age (years)	57 (11.6)	58 (8.4)					
Male gender (%)	53	58					
vWF Ag (U/mL)	1.17 (0.50)	1.92 (1.13)	0.0001*	1.69 (1.05)*	1.97 (1.10)	2.94 (1.16)*	0.008*
vWF CB (U/mL)	1.27 (0.70)*	1.84 (1.10)*	0.01*	1.73 (1.01)*	1.91 (0.97)	2.72 (1.36)*	0.008*
vWF Rco (U/mL)	1.06 (0.47)*	1.78 (1.08)*	0.0001*	1.60 (0.75)*	1.84 (1.10)	2.60 (1.33)*	0.002*
Factor VIII (U/mL)	1.13 (0.46)*	2.11 (1.15)*	0.001*	1.83 (0.80)*	2.34 (1.17)*	3.17 (1,35)*	0.001*
Protein C activity (U/mL)	0.7-1.4§	0.95 (0.27)		0.98 (0.28)	0.93 (0.29)	0.88 (0.18)	n.s.
Protein S activity (U/mL)	0.7-1.4§	0.72 (0.25)		0.82 (0.24)*	0.68 (0.20)*	0.59 (0.32)	0.01*
LAC		6 (4%)					
APC (ratio)		1,12 (0,20)					
ACA IgG		6 (6%)					
ACA IgM		0 (0%)					
FV Leiden, n (%)	4 (3%)	3 (2%)					
FII variant, n (%)	5 (4%)	5 (4%)					

**p value (ANOVA), # median (SD), ISS: International Staging System, §Laboratory reference; LAC: lupus anticoagulants; ACA: anticardiolipin antibodies; APC: activated protein C, # median.*

Table 2. Thrombo-embolic complications during therapy.

Patient	*ISS stage*	*Therapy at time of thrombosis*	*Thrombotic complication*
Female (62 years)	I	VAD	DVT & PE
Male (49 years)	II	VAD	DVT
Female (45 years)	I	HDM	CVC thrombosis
Male (42 years)	I	Radiotherapy*	DVT
Female (65 years)	II	VAD	PE
Male (56 years)	II	VAD	DVT
Female (58 years)	I	TAD	PE
Male (54 years)	II	TAD	DVT
Male (52 years)	I	TAD	PE
Female (48 years)	I	TAD	DVT
Female (46 years)	III	CAD	CVC thrombosis
Male (44 years)	I	TAD	PE
Male (58 years)	I	BAD	PE
Male (38 years)	II	BAD	DVT

*A: adriamycin; B: bortezomib; C: cyclophosphamide; D: dexamethasone; T: thalidomide; V: vincristine; HDM: high-dose melphalan; CVC: central venous catheter. *radiotherapy performed prior to induction chemotherapy. DVT: deep vein thrombosis.*

significantly between the ISS stages.

Thrombo-embolic complications were observed in 14 patients (10%) and occurred most frequently during induction chemotherapy (Table 2). Thromboprophylaxis, consisting of low dose molecular weight heparin, was given to the patients who received the thalidomide-based regimen. There was no correlation between ISS disease stage and the development of a VTE. Furthermore, the coagulation variables prior to chemotherapy did not differ significantly between the patients who did or did not develop VTE. However, the number of patients with VTE in our study is low and these issues should be addressed in larger cohorts.

In conclusion, our study indicates that not all prothrombotic markers (e.g. D-dimer) were abnormal in patients with newly diagnosed untreated MM. However, we observed increases in vWF and FVIII, and a decrease in protein S levels. These prothrombotic abnormalities result in a hypercoagulable state which might promote the development of thrombo-embolic complications. Furthermore, we observed a significant difference in relation to the severity of ISS disease stage. However, no single prothrombotic abnormality can be used to predict which patients will develop VTE.

Johannes J.A. Auwerda,° Pieter Sonneveld,* Monica P.M. de Maat,* Frank W.G. Leebeek**

**Department of Haematology, Erasmus University Medical Center, Rotterdam; °Department of Internal Medicine Ikazia Hospital, Rotterdam, the Netherlands*

Key words: newly diagnosed multiple myeloma, coagulation abnormalities, vWF, factor VIII, antiphospholipid antibodies, protein S.

Correspondence: Johannes J.A. Auwerda, MD, Erasmus MC, Dept of Hematology, 3000 CA Rotterdam, PO Box 2040, the Netherlands. Phone: international +31.10.4633740. Fax: international +31.10.4635814. E-mail: jja.auwerda@ikazia.nl

References

1. Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med 2006; 354:1021-30.
2. Gomperts ED, Shulman G, Lynch SR. Factor VIII and factor-VIII-related antigen in multiple myelomatosis and related conditions. Br J Haematol 1976;32:249-55.
3. Minnema MC, Fijnheer R, De Groot PG, Lokhorst HM. Extremely high levels of von Willebrand factor antigen and of procoagulant factor VIII found in multiple myeloma patients are associated with activity status but not with thalidomide treatment. J Thromb Haemost 2003;1:445-9.
4. Elice F, Fink L, Tricot G, Barlogie B, Zangari M. Acquired resistance to activated protein C (aAPCR) in multiple myeloma is a transitory abnormality associated with an increased risk of venous thromboembolism. Br J Haematol 2006;134:399-405.
5. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J, et al. International Staging System for multiple myeloma. J Clin Oncol 2005;23:3412-20.
6. Rajkumar SV, Leong T, Roche PC, Fonseca R, Dispenzieri A, Lacy MQ, et al. Prognostic value of bone marrow angiogenesis in multiple myeloma. Clin Cancer Res 2000; 6: 3111-6.
7. Wolf M, Boyer-Neumann C, Leroy-Matheron C, Martinoli JL, Contant G, Amiral J, et al. Functional assay of protein S in 70 patients with congenital and acquired disorders. Blood Coagul Fibrinolysis 1991;2:705-12.