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Multiple Myeloma

Recombinant human erythropoietin and the risk of thrombosis in patients receiving thalidomide for multiple myeloma

Among 199 patients treated with thalidomide for multiple myeloma, four thromboses occurred in 49 cases during erythropoietin therapy (prevalence 8.1%; annual rate 7.25%), and another 14 events occurred in patients not on erythropoietin (9.3%; 7.56%). Thus, erythropoietin would seem not to increase the risk of thrombosis of myeloma patients receiving thalidomide.

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Since 1999, thalidomide has been increasingly used in patients with multiple myeloma (MM).<sup>1</sup> In relapsed/resistant MM, thalidomide alone is effective in approximately 30% of patients, and in up to 60-70% of cases when used in combination with dexamethasone or chemotherapy regimens.<sup>2</sup> Among the various side effects of thalidomide treatment, venous thrombosis has been frequently reported in MM patients.<sup>3,4</sup> When thalidomide is used alone, the prevalence of thrombosis does not exceed 5% in many studies. This figure increases to 10-15% when the drug is used with dexametha-

Table 1. Details of 18 thromboses during thalidomide treatment of 199 patients with MM.

Prevalence,%	9.0
Incidence rate,% patient-year	7.49
Time to event, months	
Median (range)	3.7 (1.0-18.6)
Thalidomide dosage at the time of event, mg/day	
Median (range)	100 (50-300)
Hemoglobin level at the time of event, g/dL	
Median (range)	12 (8.8-15)
Type of event	
Deep vein thrombosis	15
Intestinal ischemia	2
Myocardial infarction	1

Table 2. Thrombosis during thalidomide treatment: relationship with steroids, rHuEpo, and chemotherapy administration to 199 patients with MM.

Concomitant treatment*	Patients with thrombosis		OR 95% CI**	Annual Incidence Rate <sup>‡</sup> % patients
	Yes n = 18	No n = 181		
Steroids <sup>§</sup>			2.71 0.86-8.56	
Yes, n = 116	14	102		7.28
No, n = 83	4	79		8.32
rHuEpo			0.86 0.27-2.76	
Yes, n = 49	4	45		7.78
No, n = 150	14	136		7.41
Chemotherapy <sup>°</sup>			1.00 0.12-8.34	
Yes, n = 11	1	10		4.37
No, n = 188	17	171		7.82

\*For each treatment, we considered only the thrombotic events occurring while patients were effectively receiving the drug; <sup>§</sup>prednisone or dexamethasone; <sup>°</sup>chemotherapy was melphalan/prednisone in 10 patients, and vincristine/adriamycin/dexamethasone in one patient; \*\*Odds ratio with 95% confidence intervals was calculated by means of contingency tables; <sup>‡</sup>Rates were calculated taking into account the effective time spent on each treatment.

son, and to about 30% when the thalidomide is combined with chemotherapy. Thalidomide is believed to cause thrombosis through activating endothelium injured by prior exposure to drugs, such as doxorubicin.<sup>5</sup> Among the drugs used in the supportive care of MM, recombinant human erythropoietin (rHuEpo) has a definite role in the treatment of anemia.

An increased rate of thrombosis has been reported in recipients of rHuEPO,<sup>6</sup> and this has been related to the ability of rHuEpo to trigger signaling pathways in endothelial cells, thus increasing their thrombogenicity.<sup>7</sup> Therefore, the combined use of thalidomide and rHuEpo may increase a patients' risk of thrombosis, as suggested by the results of a phase II trial in patients with myelodysplasia.<sup>8</sup> The study was prematurely discontinued, since three out of seven patients experienced deep vein thrombosis or fatal pulmonary embolism. On these premises, we retrospectively analyzed a large group of MM patients receiving thalidomide, to evaluate whether the concomitant administration of rHuEpo increased their risk of thrombosis.

One hundred and ninety-nine patients with MM were treated with thalidomide (Thalomid, Grunenthal, and Myrin, Lipomed) for at least one month at our three Institutions. There were 109 males and 90 females, aged 38-89 years (median, 66) at the beginning of thalidomide treatment. One hundred and forty-nine patients (75%) received thalidomide for relapsed/resistant MM, 36 as maintenance (18%), and the remaining 13 (7%) as first line therapy, alone or in combination with chemotherapy. The median duration of thalidomide treatment was 6.5 months (range, 1-45) and the median overall survival was 12 months. By the time of this analysis, 95 patients had died. Thrombotic events were objectively documented in all cases.

Eighteen patients experienced non-fatal thrombotic complications (Table 1). All thromboses but one occurred in refractory/resistant patients after a median time of 3.7 months from initiation of thalidomide treatment. As a consequence, six patients definitely stopped thalidomide, and three others resumed the drug after adequate treatment with warfarin (aimed at a target PT INR of 2.0-3.0 for three months). Overall, these findings are in line with those reported by other investigators.<sup>4</sup>

Analysis according to the concomitant treatments showed that neither rHuEpo, nor steroids and chemotherapy increased the prevalence, odds ratio, or annual incidence rate of thrombosis (Table 2). Our data are at variance with those recorded in myelodysplastic patients treated with a combination of thalidomide and rHuEpo.<sup>8</sup> The source and dosage of thalidomide cannot explain this difference. Steurer *et al.*<sup>8</sup> used dose-adjusted darbepoietin- $\alpha$ , once weekly, whereas our patients received various commercially available blends of rHuEpo, 10,000 units thrice weekly, or according to their degree of anemia. Although the risk of thrombosis of darbepoietin- $\alpha$  has been reported to be identical to that of rHuEpo in patients with lung cancer,<sup>9</sup> this may not necessarily be the case in other diseases. The correlation between hemoglobin level and risk of thrombosis is well acknowledged. One may, therefore, wonder whether the low prevalence of thrombosis observed in our MM patients receiving both thalidomide and rHuEpo depended on a poor response to rHuEpo. This does not seem likely, as three out of the four patients who developed thrombosis during rHuEpo therapy had hemoglobin levels > 11 g/dL at the time of the event.

Analysis according to the type of thrombosis showed that most events were venous, as expected. However, we also observed three arterial thromboses, none in patients taking rHuEpo. Cavenagh *et al.*<sup>10</sup> reported an excess of cerebral stroke in elderly MM patients treated with thalidomide. These observations underscore the possibility that thalidomide also increases the risk of arterial thrombosis. Seven other thrombotic episodes (six cases of superficial thrombophlebitis, and one transient cerebral ischemic attack) were not included in the present analysis, because they were diagnosed on clinical grounds only. Only two patients were receiving rHuEpo at

the time of these episodes.

In conclusion, our findings seem not to support the hypothesis that rHuEpo increases the thrombogenicity of thalidomide in patients with relapsed/refractory or *de novo* MM.

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## Platelets

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### Reduced plasma membrane Ca<sup>2+</sup>-ATPase function in platelets from patients with non-insulin-dependent diabetes mellitus

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We clearly show that plasma membrane Ca<sup>2+</sup> ATPase (PMCA) activity is lower in platelets from patients with non-insulin-dependent diabetes mellitus (NIDDM) than in those from healthy controls. The lower activity is likely due to reduced PMCA expression and increased tyrosine phosphorylation. These findings provide an explanation for the cellular ionic defects occurring in insulin resistant conditions.

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