Thalidomide and thrombosis in patients with multiple myeloma

Thalidomide has recently been employed as a single agent and in combination chemotherapy for experimental treatment of relapsed or refractory multiple myeloma and as a first line treatment. A new complication has emerged: a thalidomide-induced hypercoagulable state. We report on 5 patients who developed deep vein thrombosis of the lower limbs while on thalidomide and chemotherapy. The biological mechanism underlying this complication is unknown and appears to be worsened by the association with dexamethasone and/or chemotherapy.

The anti-angiogenic properties of thalidomide have been exploited in the experimental treatment of multiple myeloma (MM) as salvage therapy for relapsed or refractory disease[1] and, more recently, in combination with dexamethasone and chemotherapy as first and second line treatment.[2-4] An emerging problem is the occurrence of deep vein thrombosis (DVT)[5,6] in MM patients treated with thalidomide. In this report we describe five patients with relapsed or progressing MM who developed DVT while receiving thalidomide and chemotherapy.

We treated 18 patients with relapsed or refractory MM with thalidomide and chemotherapy. Thalidomide was given orally at a dose of 100 mg for 2 weeks, then increased to 200 mg. Five patients developed DVT: their hematologic data and treatment prior to thalidomide and chemotherapy are illustrated in Table 1. Except for patient #1, who had developed post-operative DVT two years previously, none had experienced thromboembolic events in the past. DVT occurred while still on the initial thalidomide dose. None of the patients was receiving hemopoietic growth factors. DVT was diagnosed by compression ultrasonography and treated with subcutaneous low molecular weight heparin and dicoumarin.[7] Anticoagulants were withheld after three months, except for patient #1 who continued for six months. In all DVT-patients thalidomide was left at the initial dose through the DVT episode, except for patient #1, in whom it was stopped because of severe gastrointestinal symptoms.

Published reports on thalidomide-associated DVT are rare and concern only patients treated for chronic inflammatory or autoimmune diseases[8] such as anti-phospholipid antibody syndrome or Behçet's syndrome, a patient population already at risk of thrombosis.[9] Thalidomide as a single agent was not associated with DVT.[1] By contrast, DVT was observed in combination with either dexamethasone alone or dexamethasone and chemotherapy.[5,6] At present, the incidence of thrombosis in thalidomide-treated MM patients is difficult to establish, but it does represent a problem for a proportion of patients. Our experience concerns relapsed or refractory patients during their second and third line of treatment: we observed an incidence of 27.8%, which is similar to the reported 27% and 28% in previously untreated patients.[5,6] In the latter reports the combination thalidomide-dexamethasone appears to be less thrombogenic than thalidomide-dexamethasone-chemotherapy.

Thalidomide may exert its thrombogenic effect along with other contributing factors. Individual risk factors related to inherited thrombophilic conditions might play a role in the occurrence of DVT. However, Zangari *et al.* found no correlation between positive tests for inherited thrombophilia and DVT in his patients. Thus, extended and expensive searches for inherited thrombophilic factors are inappropriate. Furthermore, low dose anticoagulant therapy does not protect against thrombosis;[6] full dosage anticoagulation may have to be implemented until non-thrombogenic analogs of thalidomide are available.

Thalidomide and some of its metabolites have been shown to modulate the expression of cell adhesion molecules.[10] Some unknown drug-cell interaction might cause local coagulation disturbances leading to thrombosis. In addition, chemotherapy and dexamethasone may exacerbate the thrombogenic properties of thalidomide through a cytolytic mechanism.

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Table 1. Some hematologic data of the patients treated with thalidomide and chemotherapy (THD-CT).

	Patient #1	*Patient #2*	*Patient #3*	*Patient #4*	*Patient #5*
Age/gender	71/M	56/M	75/M	70/M	79/M
Date of diagnosis	October 1999	December 1997	January 1998	May 1992	December 1999
Paraprotein	IgGγ	IgGκ	IgGκ	IgGκ	IgAκ
Treatment before THD-CT	VAD × 2 courses, February 2000	VAD × 7 courses, January 1998	MP × 6 courses, Jan 1998. VAD × 5 courses, Sep 1998	VAD × 2 courses, Oct 1992. MP × 6 courses, Dec 1997	Steroids and rHu-EPO
APBSCT	May 2000	November 1998 (1st) March 1999 (2nd)	March 1999	No	No
Relapse/progression	January 2001	October 2001	November 2000	October 2000	October 2000
THD-CT, started	DT-PACE, Jan 2001	DT-PACE, Feb 2001	THD-DV, Nov 2000	THD-DV, Oct 2001	THD-DV, Oct 2001
DVT: date and site	Mar 2001, before 4th course. R popliteal vein.	Apr 2001, before 3rd course. R and L popliteal veins. PE.	Mar 2001, before 5th course. L tibial vein.	Feb 2001, before 2nd course. L femoral and popliteal veins.	Apr 2001, before 3rd course. L popliteal vein.
Acquired risk factors	Previous DVT	None known	None known	None known	None known

APBSCT: autologous peripheral blood stem cell transplantation. CT: chemotherapy. DT-PACE: dexamethasone, thalidomide, cisplatinum, ara-C, cytoxan, etoposide. DV: dexamethasone, vinblastine. DVT: deep vein thrombosis. MP: melphalan and prednisone. PE: pulmonary embolism. rHu-EPO: erythropoietin. THD: thalidomide. VAD: vincristine, adriamycin, prednisone.

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References

1. Singhal S, Mehta J, Desikan R, et al. Antitumour activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999; 341:1565-71.
2. Palumbo A, Giaccone L, Bertola A, et al. Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma. Haematologica 2001; 86:399-403.
3. Hus M, Dmoszynska A, Soroka-Wojtaszko M, et al. Thalidomide treatment of resistant or relapsed multiple myeloma patients. The Polish Multiple Myeloma Study Group. Haematologica 2001; 86:404-8.
4. Tosi P, Ronconi S, Zamagni E, et al. Salvage therapy with thalidomide in multiple myeloma patients relapsing after autologous peripheral blood stem cell transplantation. Haematologica 2001; 68:409-13.
5. Osman K, Comenzo R, Rajkumar SV. Deep vein thrombosis and thalidomide therapy for multiple myeloma. N Engl J Med 2001; 344:1951-2.
6. Zangari M, Anaissie E, Barlogie B, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood 2001; 98:1614-5.
7. Lensing AW, Prandoni P, Prins MH, Bueller HR. Deep-vein thrombosis. Lancet 1999; 353:479-85.
8. Flageul B, Wallach D, Cavelier-Balloy B, Bachelez H, Carsuzaa F, Dubertret L. Thalidomide and thrombosis. Ann Dermatol Venerol 2000; 127:171-4.
9. Matei D, Brenner B, Marder VJ. Acquired thrombophilic syndromes. Blood Rev 2001;15:31-48.
10. Geitz H, Handt S, Zwingenberger K. Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. Immunopharmacol 1996, 31:213-21.