Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy

Maurizio Zangari, Elias Anaissie, Bart Barlogie, Ashraf Badros, Raman Desikan, A. Viju Gopal, Christopher Morris, Amir Toor, Eric Siegel, Louis Fink, and Guido Tricot

The occurrence of deep-vein thrombosis (DVT) in patients with newly diagnosed multiple myeloma, who were randomly assigned to receive identical induction chemotherapy with or without thalidomide, are reported in this study. The 2 study arms were comparable with respect to key myeloma prognostic factors and known risk factors for DVT. One hundred patients received induction chemotherapy including 4 cycles of continuous infusion of combinations of dexamethasone, vincristine, doxorubicin, cyclophosphamide, etoposide, and cisplatin, and each patient completed at least one induction cycle. DVT developed in 14 of 50 patients (28%) randomly assigned to receive thalidomide but in only 2 of 50 patients (4%) not given the agent (P = .002). All episodes of DVT occurred during the first 3 cycles of induction. Administration of thalidomide was resumed safely in 75% of patients receiving anticoagulation therapy. Thus, thalidomide given in combination with multiagent chemotherapy and dexamethasone is associated with a significantly increased risk of DVT, which appears to be safely treated with anticoagulation and does not necessarily warrant discontinuation of thalidomide. (Blood. 2001;98:1614-1615)

© 2001 by The American Society of Hematology

From the Central Arkansas Veterans Healthcare System and the University of Arkansas for Medical Sciences, Little Rock, AR.


Supported in part by a grant from the National Cancer Institute (CA 55819) to M.Z., E.A., B.B., A.B., R.D., C.M., A.T., E.S., and G.T. and a grant provided by Dr. J. Zeldis, Celgene, to L.F.

Reprints: Maurizio Zangari, 4301 West Markham, Slot 776, Little Rock, AR 72205; e-mail: zangarimaurizio@uams.edu.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 U.S.C. section 1734.

© 2001 by The American Society of Hematology
Baseline serologic and plasma risk factors for thrombosis, including protein C and S activity antiphospholipid antibodies and activated protein C resistance (analysis obtained for 20 patients, 13 of whom were taking thalidomide), were not significantly different in the 2 study arms. However, the patients receiving thalidomide had less antithrombin III activity (0.90 versus 1.04; \(P = .18\)) and a lower fibrinogen level (2.8 versus 3.6 g/L; \(P = .11\)) but a higher proportion of von Willebrand factor antigen (2.55 versus 1.12; \(P = .09\)). One patient taking thalidomide was found to be heterozygous for factor V Leiden but had not had any thrombotic complications. None of the patients tested had prothrombin gene abnormalities (G20210A).

Patients were evaluated regularly by medical staff members and underwent additional studies if signs or symptoms suggestive of DVT were observed. Patients with such manifestations were assessed with use of Doppler ultrasonography followed by venography, if indicated. DVT developed in 14 of 50 patients (28%) receiving thalidomide but in only 2 of 50 patients (4%) in the nonthalidomide arm \((P = .002)\). All episodes of DVT occurred during the first 3 cycles of induction: 7 during cycle 1, 3 during cycle 2, and 6 during cycle 3. Although the response rate in each treatment arm had not been disclosed at the time this report was prepared, within the thalidomide arm, the time from start of treatment to 50% reduction in paraprotein was computed for evaluable patients and compared in the patients with and without DVT in that arm. No significant difference was observed \((P = .7)\).

All patients received 400 mg of oral thalidomide daily, except for one, who received 300 mg daily. The median time from start of thalidomide therapy to diagnosis of DVT was 42.5 days (range, 7 to 93 days). Thrombosis developed at the site of the CVC in 4 patients (3 in the thalidomide arm and 1 in the control arm) and at distant sites in 12 patients (11 receiving thalidomide and 1 control). DVT not related to a CVC developed in 12 patients, 5 of whom were affected bilaterally. In all 5 patients, calf veins were involved. Seven patients had unilateral occlusion, which was limited to deep veins below the knee in 2 patients.

In most patients (75%), administration of thalidomide was resumed safely after appropriate anticoagulation therapy was initiated. The most extensive thrombosis involved femoral-popliteal and calf veins in both legs. Anticoagulation therapy consisted of low-molecular-weight heparin followed by warfarin, with the target being the international normalized ratio of 2.5 to 3. This therapy was continued as long as it was clinically indicated and the patient was receiving thalidomide. At the time of analysis, no patient had clinical evidence of progression of DVT. One episode of pulmonary embolism was observed in one patient taking thalidomide. The embolism responded to appropriate therapy, and thalidomide administration was subsequently re instituted, without further complications.

Our data show that thalidomide given in combination with chemotherapy including dexamethasone is associated with an increased risk of DVT, the progression of which can be controlled by full anticoagulation. In support of our findings is a report by Flageul et al, who described occurrence of thrombotic events shortly after low-dose (50-100 mg/day) thalidomide therapy was begun in 5 patients with lupus erythematosus. All 5 patients were known to have hypercoagulability related to either antiphospholipid antibodies or recent trauma. An increased rate of DVT was not observed in patients with relapsed MM who were treated with thalidomide as a single agent.

In conclusion, close monitoring for DVT should be done in patients with MM who are receiving thalidomide concomitantly with glucocorticosteroids and cytotoxic agents. Studies aimed at preventing DVT in patients with myeloma and other patients with hypercoagulability receiving thalidomide are needed. Our preliminary experience suggests that administration of thalidomide can be resumed safely after successful anticoagulation therapy. Prophylactic anticoagulation should be strongly considered in patients receiving thalidomide in combination with chemotherapy. Occurrence of DVT is not an absolute contraindication to continuing thalidomide treatment.

References
Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy

Maurizio Zangari, Elias Anaissie, Bart Barlogie, Ashraf Badros, Raman Desikan, A. Viju Gopal, Christopher Morris, Amir Toor, Eric Siegel, Louis Fink and Guido Tricot