

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

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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)

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### Introduction

Although approximately 20% of patients with symptomatic deep-vein thrombosis (DVT) have a known malignant disease, only a few thrombotic episodes occur as the first manifestation of an occult neoplastic process.<sup>1</sup> This phenomenon is multifactorial, and several concomitant factors are necessary to trigger a thrombotic event.

Hypercoagulability has been observed in patients with dysproteinemias, and multiple myeloma (MM) has been associated with DVT in 10% of treated patients.<sup>2</sup> We previously showed that thalidomide is an active agent in patients with MM refractory to combination chemotherapy and autotransplantation.<sup>3</sup> In a study of 169 patients treated with thalidomide as a single agent, DVT occurred in 1%.<sup>4</sup> We here describe a significantly increased rate of DVT in patients with newly diagnosed MM who were randomly assigned to receive thalidomide and repeated cycles of combination chemotherapy as part of an ongoing phase III trial. Informed consent approved by the Institutional Review Board of the University of Arkansas for Medical Sciences was obtained from each patient.

### Study design

Patients with newly diagnosed MM (untreated or with one cycle of preceding chemotherapy) were randomly assigned in our Total Therapy II phase III study to receive combination chemotherapy with or without thalidomide at a dose of 400 mg daily. The treatment regimen consisted of an induction phase with 4 cycles of multiagent chemotherapy, with peripheral blood stem cell (PBSC) collection after the third cycle, followed

by 2 cycles of high-dose melphalan (200 mg/m<sup>2</sup> of body-surface area) with autologous PBSC rescue.

The induction phase included one cycle of vincristine (0.5 mg/day by continuous infusion [CI] on days 1-4), doxorubicin (10 mg/m<sup>2</sup> per day by CI on days 1-4), and dexamethasone (40 mg/day orally on days 1-4, 9-12, and 17-20; then one cycle of dexamethasone (40 mg orally on days 1-4), cyclophosphamide (400 mg/m<sup>2</sup> by CI on days 1-4), etoposide (40 mg/m<sup>2</sup> by CI on days 1-4), and cisplatin (15 mg/m<sup>2</sup> by CI on days 1-4) (DCEP); one cycle of cyclophosphamide (750 mg/m<sup>2</sup> by CI on days 1-4), doxorubicin (15 mg/m<sup>2</sup> by CI on days 1-4), and dexamethasone (40 mg orally on days 1-4); and another cycle of DCEP.

### Results and discussion

At the time of the analysis described here, 100 patients had completed at least one cycle of induction chemotherapy. The patients' median age was 56 years (range, 32 to 71 years), and 67% of them were men. Six patients had a previous history of DVT and were not receiving anticoagulation therapy at enrollment. The 2 study arms were comparable with respect to key baseline myeloma prognostic factors, including immunoglobulin subtype, cytogenetic findings, histopathological features, Durie-Salmon stage, bone marrow plasmacytosis, and levels of serum  $\beta_2$  microglobulin, C-reactive protein, lactic dehydrogenase, albumin, and paraprotein. A slightly higher proportion of patients in the thalidomide arm than in the nonthalidomide (control) arm had an IgA-subtype myeloma (34% versus 22%;  $P = .18$ ). Known risk factors for DVT, such as the presence of central venous catheters (CVCs), which all patients had in place at the time of their first cycle of chemotherapy; age; and performance status were not different in the 2 study groups.

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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 has 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 reinstated, 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,<sup>5</sup> 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.<sup>4</sup>

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.

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