

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Anticoagulation Regimens for Thalidomide and Lenalidomide

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H&O What coagulation-related toxicities have been found to be associated with thalidomide and lenalidomide?

MZ In the Total Therapy II trial, in which patients with newly diagnosed multiple myeloma were randomized to receive thalidomide (Thalomid, Celgene) plus chemotherapy or chemotherapy alone, patients who received thalidomide had an increased risk of deep vein thrombosis (DVT) up to 35%. This side effect had not been previously observed when thalidomide was used as monotherapy.

H&O What contributing factors were identified as being related to the occurrence of DVT?

MZ One contributing factor that seemed to be important in the development of DVT was the association of thalidomide and the doxorubicin-containing regimen used at the time. Also, it was observed that newly diagnosed patients developed DVT more frequently than did previously treated patients. Patients developed thrombotic episodes during the first 3–4 cycles of treatment, with the incidence reaching a plateau thereafter.

H&O What is the mechanism of action of thalidomide-associated DVT?

MZ No clear mechanism of action has been identified; this phenomenon is multifactorial. The most common coagulation abnormality observed in myeloma patients is the presence of APC resistance not associated to factor V Leiden. Such abnormalities have been identified in other cancers as well.

H&O Has lenalidomide been found to cause DVT?

MZ In the phase I/II studies of lenalidomide (Revlimid, Celgene), DVT was not a major problem. Single-agent lenalidomide does not appear to be associated with increased risk of DVT, but when combined with dexamethasone, the incidence of thromboembolism increases, particularly among newly diagnosed patients.

H&O How were patients who experienced DVT treated?

MZ Once it was realized that patients treated with chemotherapy and thalidomide in the Total Therapy II study were developing a higher incidence of DVT, we began administering prophylactic therapy with low-dose coumadin first and then low molecular weight heparin (LMWH). This approach significantly reduced the incidence of thrombosis among patients receiving thalidomide plus chemotherapy. Other groups have used different prophylactic anticoagulation therapies. Full anticoagulation with coumadin and aspirin also has been reported to have some benefit.

H&O Why are thalidomide and lenalidomide associated with DVT?

MZ It is not clear why these agents are associated with DVT. No specific drug-related coagulation abnormalities have been described. We and others have studied levels of protein C, protein S, fibrinogen, and other factors before and after treatment with thalidomide, and only a slight, if any, change was observed. In vitro studies have suggested the possible toxicity of this agent to the endothelium, but still we do not see clinical evidence.

H&O Which patients are likely to experience a thromboembolic effect?

MZ The characteristics of patients who are more likely to experience a thromboembolic effect are newly diagnosed patients who are immobile or who have a previous history of clots treated with combinations of thalidomide or lenalidomide and steroids/chemotherapy.

H&O Are patients who need to be treated for DVT able to continue their immunomodulatory therapy?

MZ This question has not yet been answered. Multiple reports have shown that the risk of recurrent DVT is increased in cancer patients. In light of this finding, we conducted a retrospective study in newly diagnosed patients who were previously treated for DVT. Our analysis did not show an increased risk of recurrence among those patients who resumed thalidomide therapy while undergoing anticoagulation therapy. This finding suggests that patients can resume treatment during full anticoagulation without additional risk of thrombosis.

H&O Are other possible approaches for managing this side effect being explored?

MZ At this time, new classes of anticoagulants are available but no studies have been focused on cancer patients. An important consideration is whether or not the patient is newly diagnosed. These patients tend to have a more thrombotic propensity, and prophylactic anticoagulation for the first few months of treatment is highly recommended.

H&O Has the optimal anticoagulation regimen for these patients been defined?

MZ Ours and other groups' experience support the use of LMWH for patients receiving thalidomide and chemotherapy. LMWH can be administered until the patient becomes severely thrombocytopenic (platelet count <30,000/ μ L) and then resumed when the platelet count increases over 50,000/ μ L. There are no prospective data supporting this approach, but this is our practice.

H&O Are there any cautions regarding the use of anticoagulants in these patients?

MZ The main concern with anticoagulation therapy is always the risk of bleeding. This risk appears to increase

when platelet counts fall, but the exact level of this decrease has not been determined. In a large European study in which patients were treated with thalidomide, vincristine, and doxorubicin, LMWH was administered throughout induction therapy regardless of the platelet count. No serious bleeding problems were observed in this study.

H&O Does the occurrence of DVT have an effect on the survival of patients being treated with thalidomide or lenalidomide?

MZ In the myeloma arena the answer is no. Recently, we have reviewed the experience of the Total Therapy II study and found that there was no difference in survival between patients who experienced a thrombotic episode and those who did not. Thus, the occurrence of DVT does not appear to be an adverse prognostic factor.

It is important to remember that the development of DVT in these patients is a multifactorial phenomenon. There are host-related factors, such as activated protein C resistance, and also treatment-related factors. The occurrence of DVT in the setting of treatment of multiple myeloma patients with thalidomide/lenalidomide with chemotherapy/steroids is not due to just one specific drug but rather to the combined effect of the various factors.

Suggested Reading

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