ideal candidates for TIPS implantation since they display normal liver synthetic function with little perinterventional risk.

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References


To the editor:

Thromboembolic events during treatment with thalidomide

Thalidomide has been shown to be an active agent in multiple myeloma (MM), particularly in patients with advanced and chemotherapy-refractory disease.\(^1\)\(^2\) Due to its activity as a single agent, thalidomide is now being evaluated in combination therapy regimens, either with dexamethasone or polychemotherapy. Recently, Zangari et al reported now being evaluated in combination therapy regimens, either with dexamethasone 40 mg orally, cyclophosphamide 300 mg/m\(^2\), which thalidomide is combined with DCEP polychemotherapy phase 2 trial in advanced and chemotherapy refractory MM, in receiving thalidomide plus chemotherapy. We have performed a

is not only restricted to patients with MM receiving thalidomide.

We have initiated a phase 2 trial in patients with mantle cell lymphoma who relapsed after or did not respond to standard chemotherapy (cyclophosphamide, vincristine, and prednisone [CHOP]). Treatment consists of 4 weekly infusions with the anti-CD20 monoclonal antibody rituximab (375 mg/m\(^2\)), which is concomitantly administered with thalidomide (starting dose 200 mg/d, with a dose escalation to 400 mg/d) followed by thalidomide maintenance. Two of 10 patients entered thus far on this protocol experienced a thrombotic event: in one patient, deep-vein thrombosis occurred just one week after the final infusion of rituximab; in the second patient, pulmonary embolism was diagnosed during a routine follow-up examination at week 20 when a thoracic computer tomography scan revealed thrombotic material in the pulmonary artery of the right lower lobe. This patient did not have any clinical sign or symptom of pulmonary embolism. The thrombotic events were not related to presence of a central venous catheter. During the study period, 8 patients with relapsed mantle cell lymphoma were treated with rituximab alone, but in none of these patients was venous thromboembolism observed.

In all patients reported here, occurrence of the thrombotic event was not associated with disease progression, and thalidomide could be safely readministered after appropriate anticoagulation therapy. We believe it is important to consider deep-vein thrombosis as an adverse event that may occur late in a treatment program combining thalidomide with other antineoplastic agents. Thromboembolic events associated with thalidomide do not appear to be specific for MM, which should be taken into account when thalidomide is administered to patients with other malignant disorders, in particular solid tumors, who already have a substantially increased risk of deep-vein thrombosis.

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Second response to lower-dose thalidomide in a patient with multiple myeloma

It is with great interest that I read the report of Barlogie et al.1 on the use of thalidomide in patients with refractory multiple myeloma. It was concluded that there is a dose-response effect with a higher response rate and a longer survival duration observed in patients receiving more than a 42 g cumulative dose of thalidomide in 3 months. That would be an average of close to 500 mg per day of thalidomide taken by those high-risk patients. Here I present a case that indicates the dose-response effect may not be present in every case.

The patient is a 66-year-old male who was diagnosed with multiple myeloma (MM) in April 1998 when he presented with shortness of breath (SOB) and fatigue. His disease progressed fairly rapidly after initial melphalan plus prednisone (MP) and then vincristine plus doxorubicin plus dexamethasone (VAD). He then transferred his care to the University of New Mexico Cancer Center in December 1999. Initial paraprotein level was 5.2 g/dL, and a thalidomide regimen was started at 400 mg per day. The dose was decreased to 300 mg per day in the second month because of intolerable somnolence, confusion, and sedation. While maintaining this dosage, the paraprotein level dropped to a low point of 2.72 g/dL by January 2001. By March 2001, the paraprotein level increased to 3.07 g/dL. For the 15 months he had been given thalidomide, he continued to have side effects of mental confusion, mild sedation, and difficulty in concentration. Because of the persistent side effects and the rising paraprotein level, he requested to end the thalidomide regimen. By May 2001, the paraprotein level had increased to 3.47 g/dL without thalidomide while the patient was feeling much better without the previously mentioned central nervous system (CNS) toxicities. On further discussion, he agreed to try thalidomide again but only at a much lower dose of 100 mg per day. A progressive drop of his paraprotein level was observed for 8 consecutive months as shown in Table 1. Overall CNS toxicity is also at a much lesser degree for the patient at this low daily dose.

Dose escalation in elderly patients may be especially difficult as CNS toxicity could be severe even at a fairly low dose, no more than 200 mg per day. One 73-year-old male treated in the University of New Mexico Cancer Center started a thalidomide regimen at 200 mg per day in July 2000. The dose was decreased to 50 mg per day in less than one month secondary to side effects that included dizziness, confusion, and neuropathy. Even at 50 mg per day, he acknowledged that he skipped doses from time to time if he felt that he could not concentrate on his artwork. He is now into 11 months of treatment with a stable paraprotein level.

It is correctly mentioned by Barlogie et al. that how thalidomide achieves its anti-MM cells effect is unclear. It truly is a new and exciting treatment for MM that is quite different from all other chemotherapy agents at our disposal. As such, the use of thalidomide may also be different from how we traditionally dose other chemotherapy agents (eg, dose escalation to reach the maximum tolerance). Baidas et al.2 reported their phase 2 evaluation of thalidomide, 200 mg versus 800 mg per day, in patients with metastatic breast cancer. On the 800 mg arm, all patients had progressive disease before 8 weeks staging. On the other hand, there were 2 patients on the 200 mg arm with stable disease at the 8 week mark. Hideshima et al.3 reported their study of how thalidomide overcomes drug resistance of human multiple myeloma cells to conventional therapy. The dose range among the 17 responding patients is 100 to 800 mg per day. Two patients were later taking only 50 mg per day and showed continued response.

In summary, since the initial publication showing thalidomide is a good treatment option for patients with multiple myeloma, starting at 200 to 400 mg per day with a target dose of 600 or even 800 mg per day has become a common practice.4 However, for some patients, dose de-escalation may be necessary.

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References

Table 1. Clinical course and dosing adjustment

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<th>Date</th>
<th>M-protein g/dL</th>
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NT indicates no treatment.

References
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