References


To the editor

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 al1 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 vinristine 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 achieve 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 tolerated). Baidas et al2 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 al3 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.

Fa-Chyi Lee

Correspondence: Division of Hematology/Oncology, Dept of Internal Medicine, University of New Mexico, Albuquerque, NM

References


Table 1. Clinical course and dosing adjustment

<table>
<thead>
<tr>
<th>Date</th>
<th>M-protein g/dL</th>
<th>Thalidomide mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/13/1999</td>
<td>5.2</td>
<td>400</td>
</tr>
<tr>
<td>1/5/2001</td>
<td>2.72</td>
<td>300</td>
</tr>
<tr>
<td>3/30/2001</td>
<td>3.07</td>
<td>NT</td>
</tr>
<tr>
<td>5/10/2001</td>
<td>3.45</td>
<td>Starting 100</td>
</tr>
<tr>
<td>6/11/2001</td>
<td>2.79</td>
<td>100</td>
</tr>
<tr>
<td>7/9/2001</td>
<td>2.47</td>
<td>100</td>
</tr>
<tr>
<td>9/10/2001</td>
<td>1.93</td>
<td>100</td>
</tr>
<tr>
<td>10/31/2001</td>
<td>1.89</td>
<td>100</td>
</tr>
<tr>
<td>1/2/2002</td>
<td>1.78</td>
<td>100</td>
</tr>
</tbody>
</table>

NT indicates no treatment.
Response:

Thalidomide and thromboembolism

Drach and colleagues report that thalidomide in combination with a variety of cytotoxic drugs is associated with the increased risk of deep-vein thrombosis (DVT) in malignant disorders. The development of thrombosis in cancer patients is multifactorial, and the role of these different factors in the thromboembolic events of patients treated with thalidomide is difficult to dissect. The incidence of DVT in myeloma patients treated with multagent chemotherapy without thalidomide is approximately 10%. When thalidomide was introduced as a single agent for refractory myeloma, no significant increase in thromboembolic events was noted. Because of its minimal myelosuppressive effect and its activity in chemotherapy–refractory myeloma, the drug was combined with chemotherapy; in that setting an increased incidence of DVT was observed which could not be explained by other known prothrombogenic factors. The highest incidence was observed when thalidomide was given with vincristine, adriamycin, dexamethasone (VAD) or other regimens containing anthracyclines. We have treated more than 70 patients with multiple cycles of cytoxan, dexamethasone, etoposide, platinum (CDEP) plus thalidomide, and the observed incidence of DVT has been below 15%. Many factors can contribute to the development of thromboembolism in cancer patients, including age, performance status, presence of a central-vein catheter, history of previous DVT, recent surgery, hereditary hypercoagulable states, and as recently reported by our group, non–Factor V Leiden activated protein C resistance. All of these factors need to be taken into consideration before reaching any conclusion. Drach and colleagues report frequent thromboembolic episodes in mantle cell lymphoma patients treated with cyclophosphamide, vincristine, and prednisone (CHOP), thalidomide, and rituximab. Rituximab as a single agent has also been associated with DVT in non–Hodgkin lymphoma patients. Therefore, the contribution of thalidomide to the development of DVT is not clear. Moreover, this regimen is a combination of thalidomide with an anthracycline and a corticosteroid. These findings therefore do not support the conclusions reached by Drach and colleagues that thalidomide is the main offender in the development of DVT in malignancies.

Maurizio Zangari
Correspondence: University of Arkansas for Medical Sciences, Myeloma Institute for Research and Therapy, Slot 776, Little Rock, AR 72205; e-mail: zangari maurizio@uams.edu

References


To the editor:

In situ localization of tissue factor in human thrombi

Exposure of tissue factor (TF) present in the vascular wall to blood is considered to initiate arterial thrombus formation. Moreover, antibody-mediated inhibition of TF function has been shown to prevent thrombus growth in human ex vivo perfusion experiments. TF-bearing monocytes and neutrophils were identified in human ex vivo–formed thrombi and in circulating blood. Based on in vitro perfusion experiments and flow cytometry, it was also reported that TF-positive microparticles originating from monocytes and possibly polymorphonuclear (PMN) leukocytes are transferred to platelets within the thrombus; thereby, TF-positive platelets trigger and propagate thrombosis. But the cell types that are associated with TF in thrombi remain unclear and could be related to the particular experimental conditions used by the investigators.

In order to circumvent the ex vivo and in vitro test systems, we have further characterized in situ TF in human arterial and venous thrombi obtained from patients undergoing thrombectomy. Informed consent was obtained from all patients. TF

Figure 1. TF activity in human thrombi. Procoagulant activity was measured in a 2-stage clotting assay. Human thrombi obtained from thrombectomy were homogenized, preincubated with FVIIa and FX for 3 minutes in presence or absence of the murine monoclonal anti-human TF antibody (HTF1-7B8). Then, human plasma containing a phospholipid mix (PC/PS = 70/30) was added and the clotting assay started by addition of Ca²⁺. The amount of TF was calculated from a standard curve obtained using relipidated full-length TF.
Second response to lower-dose thalidomide in a patient with multiple myeloma

Fa-Chyi Lee