Thalidomide and thrombosis in patients with multiple myeloma

Thalidomide has recently been employed as a single agent and in combination chemotherapy for experimental treatment of relapsed or refractory multiple myeloma and as a first line treatment. A new complication has emerged: a thalidomide-induced hypercoagulable state. We report on 5 patients who developed deep vein thrombosis of the lower limbs while on thalidomide and chemotherapy. The biological mechanism underlying this complication is unknown and appears to be worsened by the association with dexamethasone and/or chemotherapy.

The anti-angiogenic properties of thalidomide have been exploited in the experimental treatment of multiple myeloma (MM) as salvage therapy for relapsed or refractory disease and, more recently, in combination with dexamethasone and chemotherapy as first and second line treatment. An emerging problem is the occurrence of deep vein thrombosis (DVT) in MM patients treated with thalidomide. In this report we describe five patients with relapsed or progressing MM who treated with thalidomide and chemotherapy. We treated 18 patients with relapsed or refractory MM with thalidomide and chemotherapy. Thalidomide was given orally at a dose of 100 mg for 2 weeks, then increased to 200 mg. Five patients developed DVT; their hematologic data and treatment prior to thalidomide and chemotherapy are illustrated in Table 1. Except for patient #1, who had developed post-operative DVT two years previously, none had experienced thromboembolic events in the past. DVT occurred while still on the initial thalidomide dose. None of the patients was receiving hemopoietic growth factors. DVT was diagnosed by compression ultrasonography and treated with subcutaneous low molecular weight heparin and dicoumarin. Anticoagulants were withheld after the DVT episode, except for patient #1, in whom it was stopped because of severe gastrointestinal symptoms. Published reports on thalidomide-associated DVT are rare and concern only patients treated for chronic inflammatory or autoimmune diseases such as anti-phospholipid antibody syndrome or Behçet’s syndrome, a patient population already at risk of thrombosis.

Thalidomide as a single agent was not associated with DVT. By contrast, DVT was observed in combination with either dexamethasone alone or dexamethasone and chemotherapy. At present, the incidence of thrombosis in thalidomide-treated MM patients is difficult to establish, but it does represent a problem for a proportion of patients. Our experience concerns relapsed or refractory patients during their second and third line of treatment: we observed an incidence of 27.8%, which is similar to the reported 27% and 28% in previously untreated patients. In the latter reports the combination thalidomide-dexamethasone appears to be less thrombogenic than thalidomide-dexamethasone chemotherapy.

Thalidomide may exert its thrombogenic effect along with other contributing factors. Individual risk factors related to inherited thrombophilic conditions might play a role in the occurrence of DVT. However, Zangari et al., found no correlation between positive tests for inherited thrombophilia and DVT in his patients. Thus, extended and expensive searches for inherited thrombophilic factors are inappropriate. Furthermore, low dose anticoagulant therapy does not protect against thrombosis; full dosage anticoagulation may have to be implemented until non-thrombogenic analogs of thalidomide are available.

Thalidomide and some of its metabolites have been shown to modulate the expression of cell adhesion molecules. Some unknown drug-cell interaction might cause local coagulation disturbances leading to thrombosis. In addition, chemotherapy and dexamethasone may exacerbate the thrombogenic properties of thalidomide through a cytolytic mechanism.

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Key words: multiple myeloma, thalidomide, thrombosis.

Table 1. Some hematologic data of the patients treated with thalidomide and chemotherapy (THD-CT).

<table>
<thead>
<tr>
<th>Patient #1</th>
<th>Patient #2</th>
<th>Patient #3</th>
<th>Patient #4</th>
<th>Patient #5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/gender</td>
<td>71/M</td>
<td>56/M</td>
<td>75/M</td>
<td>70/M</td>
</tr>
<tr>
<td>Paraprotein</td>
<td>IgGκ</td>
<td>IgGκ</td>
<td>IgGκ</td>
<td>IgGκ</td>
</tr>
<tr>
<td>APLSCT</td>
<td>May 2000</td>
<td>November 1998 (1)</td>
<td>March 1999 (2)</td>
<td>March 1999</td>
</tr>
<tr>
<td>Acquired risk factors</td>
<td>Previous DVT</td>
<td>None known</td>
<td>None known</td>
<td>None known</td>
</tr>
</tbody>
</table>

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References