Thalidomide for treatment of patients with chronic graft-versus-host disease


In a randomized, placebo-controlled, double-blind trial, thalidomide or placebo together with glucocorticoids and either cyclosporine or tacrolimus was administered as initial therapy for clinical extensive chronic graft-versus-host disease (cGVHD). All patients had thrombocytopenia or cGVHD that evolved directly from acute GVHD as an indicator of a poor prognosis. The study drug (thalidomide or placebo) was administered initially at a dose of 200 mg orally per day, followed by a gradual increase to 800 mg/d if side effects were tolerable. Treatment with the study drug was discontinued before resolution of cGVHD in 23 (92%) of the 25 patients who received thalidomide and in 17 (65%) of the 26 patients who received placebo (P = .02). Neutropenia and neurologic symptoms were the most frequent reasons for early discontinuation of treatment with thalidomide. The duration of treatment with thalidomide was too short to assess its efficacy in controlling cGVHD. (Blood. 2000;96:3995-3996)

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Results and discussion

The maximum administered dose of the study drug was significantly lower for patients who received thalidomide as compared to those who received placebo ($P = .005$) (Table 1). Only 4 (16%) of 25 patients were able to tolerate thalidomide at the prescribed daily target dose, whereas 14 (54%) of 26 patients were able to tolerate placebo at the prescribed daily target dose. Thirteen patients (52%) in the thalidomide group and 2 (8%) in the placebo group received only 25% of the prescribed daily target dose. Neutropenia occurred in 64% of the patients treated with thalidomide and in 23% of those who received placebo ($P = .003$). Numbness occurred in 48% of the patients treated with thalidomide and in 23% of those who received placebo ($P = .08$). After treatment with thalidomide, 17 patients reported sedation, and 10 had constipation. After treatment with placebo, 5 patients reported sedation, and 2 had constipation ($P = .001$ and .009, respectively).

The median duration of treatment with thalidomide was 53 days (range, 1-411) compared to 245 days (range, 9-654) for placebo (Figure 1). Administration of study drug was discontinued before resolution of cGVHD in 23 (92%) of the patients assigned to receive thalidomide and in 17 (65%) of those assigned to receive placebo ($P = .02$). Treatment with study drug was discontinued before resolution of cGVHD because of neutropenia in 14 patients who received thalidomide and in 4 patients who received placebo ($P = .002$). Treatment with study drug was discontinued because of neurologic symptoms in 11 patients who received thalidomide and in 3 patients who received placebo ($P = .01$). We suspect that patients who enrolled in previously published studies required considerable encouragement and support to sustain compliance with a regimen of thalidomide at doses of 200 mg or greater per day.

The cumulative incidence of secondary therapy for cGVHD is projected to reach 28% at 4 years for patients treated with thalidomide and 47% for those who received placebo ($P = .35$). The cumulative incidence of discontinuation of all immunosuppressive medications after resolution of cGVHD is projected to reach 39% at 4 years for patients who received thalidomide and 23% for those who received placebo ($P = .12$). These trends support previous results suggesting that thalidomide might have limited efficacy for treatment of cGVHD. At 3 years after enrollment in the study, the product limit estimate of survival was 49% for patients treated with thalidomide and 47% for those who received placebo ($P = .87$). The most frequent causes of death were infection, cGVHD, and recurrent malignancy.

The duration of treatment with thalidomide in our study was quite short. Treatment with thalidomide might promote the development of tolerance, thereby explaining how such a limited intervention might improve the longer-term prospects of resolving cGVHD during continued immunosuppressive treatment. Our results suggest that a regimen of 100 mg/d might be well tolerated, especially if given as a single dose at night. With this regimen, it would be possible to determine whether administration of thalidomide for 9 to 12 months has any benefit for patients with cGVHD.

Acknowledgments

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References


Table 1. Maximum dose of study drug, according to treatment arm

<table>
<thead>
<tr>
<th>Percent of prescribed dose</th>
<th>Thalidomide no. (%)</th>
<th>Placebo no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>13 (52)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>50</td>
<td>4 (16)</td>
<td>9 (35)</td>
</tr>
<tr>
<td>75</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>100</td>
<td>7 (28)</td>
<td>14 (54)</td>
</tr>
</tbody>
</table>

The maximum administered daily dose at any time after randomization was calculated as a percentage of the prescribed daily target dose. Three of the 7 patients who reached 100% of the prescribed target dose of thalidomide later had to reduce the dose because of toxicity. None of the 14 patients who reached 100% of the prescribed target dose of placebo had toxicity that led to reduction of the dose. The $P$ value for trend was .005.

Figure 1. Duration of treatment. The time to discontinuation of study drug was shorter for patients who received thalidomide than for those who received placebo. One patient who received thalidomide and 5 patients who received placebo continued treatment with study drug until the onset of their terminal illness. These patients were categorized as not having discontinued treatment with the study drug before death.
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