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


Introduction

Case reports have described the use of thalidomide for treatment of chronic graft-versus-host disease (cGVHD).1-4 and preclinical studies demonstrated activity in a rat model of cGVHD.5 In a subsequent phase II clinical trial, 8 (38%) of 21 patients with high-risk cGVHD improved after primary treatment with thalidomide.6 In the same study, improvement was also observed after treatment with thalidomide in 18 (78%) of 23 patients with cGVHD who had not responded previously to other treatment. In a confirmatory study, 16 (20%) of 80 patients with refractory cGVHD showed improvement after treatment with thalidomide.7

Study design

Fifty-two patients with clinical extensive cGVHD consented to participate. Twenty-six were assigned to receive thalidomide and 26 were assigned to receive placebo. One patient assigned to receive thalidomide withdrew from the study before beginning treatment and was excluded from further evaluation.

Prednisone was administered orally at a dose of 1.0 mg/kg per day for the first 2 weeks, followed by gradual reduction to 0.5 mg/kg every other day by week 22. Cyclosporine was administered orally at a dose of 12 mg/kg per day, if tolerated, and then gradually decreased after 22 weeks to 6 mg/kg per day. Alternatively, tacrolimus was administered orally at a dose of 0.12 mg/kg per day, if tolerated, and then gradually decreased after 22 weeks to 0.06 mg/kg per day.

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 studies6,7 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 results6,7 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.

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References

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