Thalidomide for Patients with Recurrent Lymphoma

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BACKGROUND. Thalidomide has significant clinical activity in patients with multiple myeloma. However, its activity against other lymphoid tumors is unknown. The authors reported their experience with thalidomide in patients with recurrent/refractory non-Hodgkin lymphoma and in patients with Hodgkin disease.

METHODS. Nineteen patients (median age, 62 years) who had undergone a median of 5 previous treatment regimens were treated with escalating doses of thalidomide (200–800 mg per day) until disease progression or prohibitive toxicity was observed. The authors measured serum levels of angiogenesis factors before and after treatment.

RESULTS. One patient (5%) with evidence of recurrent gastric mucosa—associated lymphoid tissue lymphoma achieved a complete response, and 3 patients (16%) achieved stable disease.

CONCLUSIONS. The current study suggests that thalidomide has limited single-agent activity in heavily pretreated patients with recurrent or refractory lymphoma. *Cancer* **2004;100:1186–9.** *© 2004 American Cancer Society.*

KEYWORDS: thalidomide, multiple myeloma, Hodgkin disease, non-Hodgkin disease, single-agent activity.

Thalidomide is an oral sedative with antiinflammatory, immunomodulatory, and antiangiogenic properties.[1] Several clinical trials have investigated the activity of thalidomide in solid and hematologic malignancies.[2–5] In patients with recurrent and refractory multiple myeloma, thalidomide has an overall response rate of 30%.[6] Because of this favorable response rate, thalidomide was recently combined with rituximab, achieving a high response rate in a small number of patients with recurrent mantle cell lymphoma.[7] However, the single-agent activity of thalidomide in patients with recurrent lymphoma remains unknown. We report our experience with thalidomide in patients with recurrent and refractory non-Hodgkin lymphoma (NHL) and Hodgkin disease (HD).

MATERIALS AND METHODS

Patients were eligible for thalidomide treatment if they had recurrent or refractory NHL or HD, a Karnofsky performance status of > 60, and were $>$ 16 years. Patients were excluded if there was evidence of central nervous system involvement with lymphoma, human immunodeficiency virus infection, had received antilymphoma therapy within 3 weeks, or required concurrent steroids. Patients of childbearing age were eligible provided that they were practicing adequate contraception. Negative results for serum pregnancy testing were required before study entry and monthly thereafter for all women of childbearing potential.

Thalidomide was administered orally at a starting dosage of 200 mg per day. The dosage was increased every 2 weeks up to a maxi-

TABLE 1
Patient Characteristics

Characteristic	No. of patients (%)
Median age in yrs (range)	62 (30–78)
Median no. of previous treatment regimens (range)	5 (2–7)
Histology	
Diffuse large cell	6 (32)
Follicular small cleaved	4 (21)
Small lymphocytic	3 (16)
Mucosa-associated lymphoid tissue	1 (5)
Mantle cell	3 (16)
Hodgkin disease	2 (11)
Pretreatment LDH	
Normal	14 (74)
High	5 (26)

LDH: lactate dehydrogenase.

mum of 800 mg per day. Treatment was continued with the maximum tolerated dose until disease progression or intolerable toxicity. Restaging studies were conducted after 8 weeks of treatment and every 3 months thereafter. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (Version 2.0). We evaluated toxic effects every 2 weeks during the dose escalation phase and then monthly. The primary objective was to assess the activity and safety profile of thalidomide. Secondary objectives were to analyze the effects of thalidomide on serum expressions of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor, tumor necrosis factor alpha, and interleukin 6 and to correlate the levels of these cytokines with clinical responses. We obtained specimens for measuring these angiogenic factors at the time of registration, every 2 weeks for 8 weeks, and every 3 months thereafter. Serum concentrations of cytokines were determined using enzyme-linked immunosorbent assays (Quantikine; R&D Systems, Minneapolis, MN).

RESULTS

Between August 2000 and October 2001, after obtaining informed consent from each patient and approval from the institutional review board, we registered 21 patients for the study. Two patients withdrew consent after registration, leaving 19 patients evaluable for treatment toxicity or response. Patients had a median age of 62 years (range, 30–78 years) and had received a median of 5 previous treatment regimens (range, 2–7 regimens). Seventeen patients had NHL, and two had HD (Table 1).

Treatment was discontinued during the first 2 weeks for 3 patients, due to either pancytopenia ($n = 1$) or rapidly progressing disease ($n = 2$). All other patients received ≥ 8 weeks of therapy with a median dosage of 400 mg of thalidomide. Treatment was reasonably well tolerated, with the most common side effects being of Grade I/II. Peripheral neuropathy was observed in 76% of the patients, fatigue in 52%, edema in 52%, and constipation in 41%. The thalidomide dose was escalated to the scheduled level of 800 mg per day in 7 patients (41%).

One male patient with recurrent mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach achieved a pathologic complete response 2 months after initiation of thalidomide. He previously experienced treatment failure after receiving cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), fludarabine, radiotherapy, and rituximab. Pretreatment endoscopy revealed patchy erythema of the gastric body with some mucosa cobblestoning. Multiple biopsies confirmed the diagnosis of recurrent MALT lymphoma. After 4 months of treatment, a follow-up endoscopy showed a scarred area at the site that was previously abnormal. Multiple biopsies were negative for evidence of disease. He received a reduced dose of thalidomide (100 mg per day) due to fatigue and lethargy and response was maintained at the lower dose. Treatment was continued for 9 months, at which time treatment was discontinued due to bradycardia. His disease remains in remission 19 months after his initial response was documented. Three patients had stable disease, two with large cell histology and one with small lymphocytic lymphoma (SLL). The first patient with transformed large B-cell lymphoma was a 65-year-old male who previously experienced treatment failure after CHOP-type chemotherapy and autologous bone marrow transplantation. Pretreatment radiographic studies revealed left paraaortic adenopathy and bulky left external iliac lymph node disease. This patient received thalidomide for 4 months, at which time treatment was discontinued due to progressive disease. The second patient with large B-cell lymphoma was a 56-year-old female who had experienced failure after 3 previous treatment regimens, including cisplatin-based and methotrexate-based regimens. At the time of study entry, she had enlarging multicompartment cervical adenopathy. Both patients had stable disease after 2 months of treatment. The patient with SLL was a 75-year-old male who previously experienced treatment failure after receiving fludarabine-based chemotherapy and rituximab. Before treatment, he had paraaortic and mesenteric adenopathy. Stable disease was maintained for > 9 months. Serum levels of angiogenic factors were determined before and after therapy in seven patients (Fig. 1). Treatment with thalid-

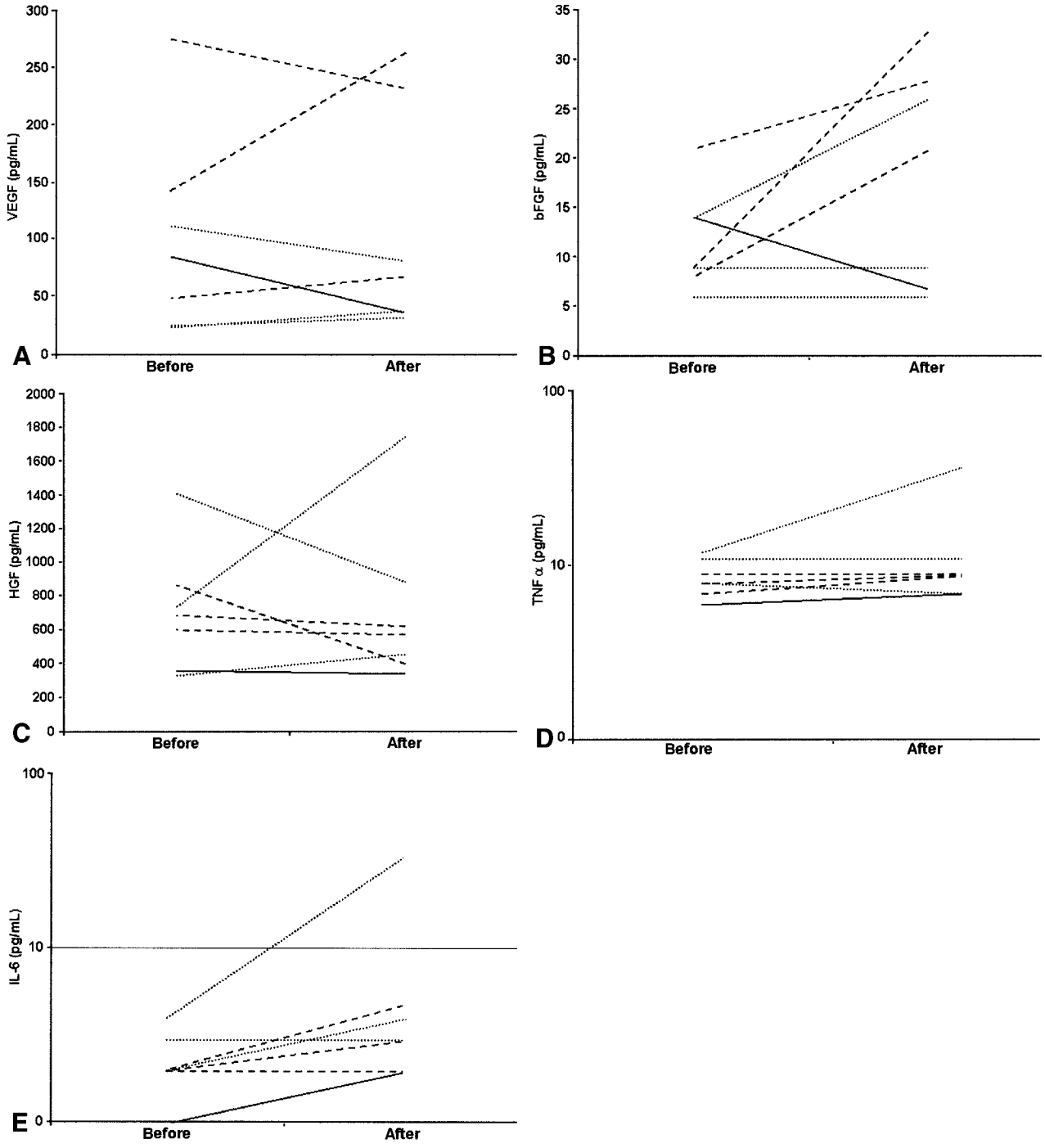

FIGURE 1. Serum levels of (A) vascular endothelial growth factor (VEGF), (B) basic fibroblast growth factor (bFGF), (C) hepatocyte growth factor (HGF), (D) tumor necrosis factor alpha (TNF-α), and (E) interleukin 6 (IL-6) before treatment with thalidomide and at the time of evaluation of response. In the one patient who achieved a complete response (solid line), levels of VEGF and bFGF decreased from 85 pg/mL and 14 pg/mL (pretreatment) to 36 pg/mL and 7 pg/mL, respectively. In patients with stable disease (dashed lines) and patients with progressive disease (dotted lines), serum levels of angiogenic factors were variably affected.

omide variably affected the level of these factors. However, in the one patient who achieved a complete response, serum levels of VEGF and b-FGF were significantly decreased.

DISCUSSION

The current results indicate that thalidomide used as a single agent has minimal activity in heavily pretreated patients with lymphoma. These findings differ strikingly from those of a recent study that treated patients with recurrent mantle cell lymphoma. In that study, the thalidomide dosage was escalated from 200 mg per day to 400 mg per day on Day 15. Rituximab was administered at 375 mg/m^2 weekly for 4 doses. The combination induced clinical responses in 10 of 11 patients (91%), including complete responses in 3 patients.[7] In our series, three patients with mantle cell lymphoma received thalidomide and no responses were observed. Although patient selection may account for this difference, other factors may also exist. Most antiangiogenesis agents such as thalidomide are cytostatic. Increased activity may be observed only when used in combination with other agents.[8] It is also possible that thalidomide enhanced rituximab activity by modulating the immune response. Alternatively, thalidomide may have made mantle cell lymphoma cells more sensitive to rituximab by modulating intracellular resistance pathways such as nuclear factor Kappa B (NF-kB). Our data certainly do not support the use of thalidomide as a single agent in patients with recurrent and refractory lymphoma. Although the findings presented by Drach et al.[7] are encouraging, the number of patients reported on is insufficient, and therefore, it is too early to conclude whether thalidomide-based therapy will be of clinical value for patients with recurrent lymphoma.

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