Original Article

Thalidomide in the Treatment of Relapsed Multiple Myeloma

S. Vincent Rajkumar, MD; Rafael Fonseca, MD; Angela Dispenzieri, MD; Martha Q. Lacy, MD; John A. Lust, MD, PhD; Thomas E. Witzig, MD; Robert A. Kyle, MD; Morie A. Gertz, MD; and Philip R. Greipp, MD

• *Objective*: To describe the efficacy of therapy with thalidomide, a drug that has antiangiogenic properties, in patients with relapsed multiple myeloma.

• *Patients and Methods*: We studied 16 patients (median age, 64 years) who received thalidomide for relapsed myeloma at the Mayo Clinic in Rochester, Minn, between November 1998 and August 1999. Treatment consisted of thalidomide given orally at a dose of 200 mg/d for 2 weeks, then increased by 200 mg/d every 2 weeks, up to a maximal dose of 800 mg/d.

• *Results*: The stage of myeloma at treatment was Durie-Salmon IIIA in 9 patients (56%) and IIIB in 7 (44%). The median time from myeloma diagnosis to initiation of thalidomide therapy was 32 months. In 4 patients (25%) prior stem cell transplantation had failed, and 14 (88%) had received 2 or more prior chemotherapeutic regimens before institution of thalidomide. All patients were evaluable for response. Four (25%) achieved a partial response to therapy, with a greater than 50% reduction in the serum or urine M protein level. Responses lasted 2, 4+, 8, and 10+ months. Major adverse effects included constipation, sedation, rash, and peripheral neuropathy.

• *Conclusion*: Thalidomide is an active agent in the treatment of patients with advanced myeloma.

Mayo Clin Proc. 2000;75:897-901

bFGF = basic fibroblast growth factor; IL = interleukin; PCLI = plasma cell labeling index; STEPS = System for Thalidomide Education and Prescribing Safety; VEGF = vascular endothelial growth factor

Multiple myeloma accounts for more than 11,000 deaths each year in the United States.[1] The median survival with conventional chemotherapy is about 3 years. Survival is improved with autologous stem cell transplantation in selected patients.[2-4] However, almost all patients eventually have a relapse, and therapy for relapse is disappointing. Typically, patients who have a relapse are treated with chemotherapeutic regimens such as VAD (vincristine, doxorubicin [Adriamycin], and dexamethasone), VBMCP (vincristine, bleomycin, melphalan, cyclophosphamide, prednisone), or dexamethasone. With such treatment, remissions are usually brief.

Angiogenesis, the formation of new blood vessels, normally occurs during embryonal growth and wound healing, as well as in the female genital system during the menstrual cycle. Angiogenesis is also important for the proliferation and metastases of most malignant neoplasms.[5] In the absence of angiogenesis, tumors cannot grow beyond 1 to 2 mm.[5] Increased angiogenesis has been found to be an adverse prognostic factor in several solid tumors.[6,7] Although many initial studies were done on solid tumors, angiogenesis seems important in hematologic malignancies as well.[8,9] There is evidence that increased bone marrow angiogenesis occurs in myeloma and is correlated with the plasma cell labeling index (PCLI) (a measure of plasma cell proliferative activity) and the stage of disease.[10]

Thalidomide, previously withdrawn from clinical use because of its severe teratogenicity, has been reintroduced because of its immunomodulating and antiangiogenic properties. The aim of this study was to analyze the effect of thalidomide in the treatment of patients with relapsed multiple myeloma.

PATIENTS AND METHODS

Patients and Data Collection

Our study population comprised 16 patients (median age, 64 years) who received thalidomide for relapsed myeloma at the Mayo Clinic in Rochester, Minn, between November 1998 and August 1999. Treatment consisted of thalidomide given orally at a dose of 200 mg/d for 2 weeks, then increased by 200 mg/d every 2 weeks, up to a maximal dose of 800 mg/d depending on toxicity.

From the Division of Hematology and Internal Medicine, Mayo Clinic, Rochester, Minn.

This study was supported in part by grants CA85818 and CA62242 from the National Cancer Institute, Bethesda, Md. Dr Rajkumar and Dr Fonseca are Leukemia and Lymphoma Society of America Translational Research Awardees. Dr Rajkumar is also supported by the Judith and George Goldman Foundation.

Address reprint requests and correspondence to S. Vincent Rajkumar, MD, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55905.

Table 1. **Patient Characteristics**

Characteristic	No. (%) of patients (N=16)
Sex	
Male	11 (69)
Female	5 (31)
Durie-Salmon stage	
IIIA	9 (56)
IIIB	7 (44)
No. of prior chemotherapeutic regimens	
≥2	14 (88)
≥4	4 (25)
Prior transplantation	4 (25)

All patients gave written informed consent on the System for Thalidomide Education and Prescribing Safety (STEPS) consent form before receiving treatment. Approval of the study by the Mayo Institutional Review Board was obtained in accordance with federal regulations and the Declaration of Helsinki. All physicians prescribing the drug and all study participants adhered to the requirements of the STEPS program.

Definition of Response

Complete response was defined as lack of detectable monoclonal (M) protein in the serum and urine by immunoelectrophoresis and immunofixation. Partial response was defined as reduction of M protein in the serum or urine by at least 50% accompanied by a similar reduction of soft tissue plasmacytomas if present. Disease progression was defined as a 50% increase in the M protein over the lowest remission level. An increase in the size of existing lytic bony lesions or soft tissue plasmacytomas or appearance of new lytic bony lesions constituted progression. Disease that did not satisfy the criteria for complete response, partial response, or progression was categorized as stable disease.

Statistical Analysis

Overall survival was calculated from the date of initiation of therapy to the date of death or date of last follow-up. Survival analysis was done by using the method described by Kaplan and Meier.[11]

RESULTS

Patient characteristics are summarized in Table 1. Among the 16 patients, the median age was 64 years (range, 48-85 years). The median serum M protein spike was 25 g/L, and the median time from myeloma diagnosis to initiation of thalidomide therapy was 32 months.

In 4 patients (25%), prior stem cell transplantation had failed, and 14 patients (88%) had received 2 or more previous chemotherapeutic regimens before thalidomide had been instituted, including 4 patients (25%) in whom 4 or more regimens had failed. Patients had progressive disease at the time of initiation of thalidomide therapy. No patient was in plateau phase at the time thalidomide therapy was initiated, and no patient was lost to follow-up.

Response and Survival

All patients were evaluable for response. No complete responses were observed. Four patients (25%) achieved a partial response to therapy. All responders had pronounced improvement in symptoms, associated with recovery of cytopenias. In 2 of these patients, response duration was 2 months and 8 months. The other 2 patients continue to respond, after 4 months and 10 months of follow-up. Six other patients had stable disease for a median duration of 5 months (range, 2-9 months), including 1 who had a minor response (48% reduction in M protein). Two of the patients with stable disease had improvements in hemoglobin concentration and platelet counts, but none had improvement in renal function.

The PCLI was high (>1%) in 3 of 4 patients who achieved a partial response, as well as in 5 of 12 nonresponders, indicating that drug effects were not restricted to the hypoproliferative category. Deletions of chromosome 13 were noted in 1 of 4 responders and in 5 of 12 nonresponders.

Nine patients have died, and the median survival after thalidomide therapy was 5 months (Figure 1, left); progression-free survival was 3 months (Figure 1, right). Cause of death was progressive myeloma in 8 patients and stroke in 1 patient. The median survival from the initial diagnosis of myeloma was 56 months.

Illustrative Case

A 69-year-old woman in whom 2 prior chemotherapeutic regimens and radiation therapy for myeloma had failed was referred for treatment. She had advanced disease, poor performance status, gingival bleeding, and extensive ecchymoses. Her hemoglobin concentration was 9.9 g/dL, and her leukocyte count was 14.8×10^9/L with 20% circulating plasma cells on the differential test. She had pronounced thrombocytopenia with a platelet count of 3×10^9/L. A bone marrow examination revealed greater than 90% involvement with myeloma, and the serum M protein level was 66 g/L (IgAκ). Within 2 months of initiation of thalidomide therapy, she had a dramatic response, with substantial improvement in symptoms and laboratory test results. Her hemoglobin concentration improved to 12.2 g/dL, leukocyte count was 3.6×10^9/L with no plasma cells on the differential test, and platelet count was 202×10^9/L. The serum M protein level decreased to

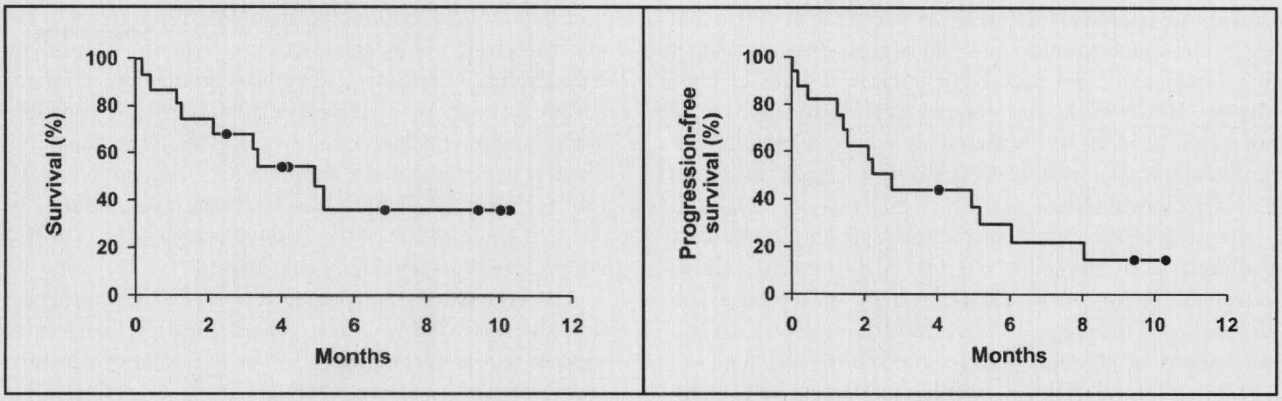

Figure 1. Kaplan-Meier estimation of (left) overall survival and (right) progression-free survival after thalidomide therapy for relapsed myeloma.

less than 10 g/L. She is still in remission after 4 months of follow-up.

Thalidomide Dosage and Toxicity

The median tolerated dose of thalidomide was 400 mg/d. For each patient, the dosage of thalidomide varied considerably, from 100 to 800 mg/d. The dose of thalidomide was reduced according to toxicity. If a grade 2 or higher toxicity (grade 3 or higher for sedation and constipation) occurred at a dosage of 400 mg/d or greater, the dose was withheld until toxicity subsided and then decreased to 200 mg/d. If such toxicity was seen with a dosage of 200 mg/d, the dose was withheld until toxicity subsided and then reinitiated at 50 to 100 mg/d. All responses occurred with doses ranging from 200 to 400 mg/d and could be sustained with doses as low as 100 mg/d. However, 2 of the responding patients required doses of up to 400 mg/d to sustain a response.

Major adverse effects included constipation (25%), excessive sedation (25%), fatigue (25%), and rash (19%). These toxicities were grade 1 to 2 (on a scale of 1 to 4), except in 2 patients who had grade 3 sedation and constipation. One patient each discontinued treatment because of peripheral neuropathy and cardiac arrhythmia (grade 3 toxicity).

DISCUSSION

Earlier we reported that angiogenesis is increased in myeloma and persists even after a complete response.[8] We also determined that angiogenesis is a powerful prognostic factor in newly diagnosed myeloma.[12] Data from Munshi et al[13] lend additional support to these findings.

Antiangiogenic therapy represents a novel and possibly less toxic approach to treat malignancies.[14] Researchers at the University of Arkansas recently reported on the activity of thalidomide in a group of heavily pretreated patients with myeloma.[15] In most of the patients in that study, stem cell transplantation had failed. Treatment consisted of thalidomide given orally at a dose of 200 mg/d for 2 weeks, then increased by 200 mg/d every 2 weeks, up to a maximal dose of 800 mg/d depending on toxicity. The overall response rate was 32%. The median time to response was 1 month. Eight patients (10%) had a greater than 90% reduction in paraprotein levels. Paraprotein responses were accompanied by improvements in anemia and other symptoms. Among the 48 patients who had repeated bone marrow analysis after thalidomide therapy, 81% had confirmation of paraprotein responses. The best predictor of a response was a PCLI lower than 0.2. The median duration of response had not been reached after 14.5 months of follow-up.

Our study demonstrates a 25% response rate with thalidomide in patients with relapsed myeloma. In addition, some patients had clinically meaningful stabilization of their disease, including 1 who achieved a 48% reduction in the monoclonal protein level but did not meet criteria for a partial response. Since almost all available therapy for relapse had failed in most of these patients, the responses observed are impressive. Thalidomide is also the first drug to demonstrate clinically important single-agent activity in relapsed refractory myeloma in more than 2 decades.

Based on the available evidence, thalidomide can be considered for patients with relapsed multiple myeloma after stem cell transplantation or conventional chemotherapy. Until ongoing studies are completed, thalidomide is not recommended as initial therapy for patients with newly diagnosed myeloma. The usual starting dose is 200 mg/d taken orally as a single dose at bedtime. In the absence of adverse effects, the dose is increased by 200 mg every 2 weeks, to a maximal dose of 800 mg/d. Most

patients are unable to tolerate doses greater than 400 to 600 mg/d. Preliminary data from Munshi et al[16] suggest that thalidomide can be effectively combined with chemotherapy. However, because of concerns of toxicity, we do not recommend the use of thalidomide in combination with dexamethasone or other chemotherapeutic agents except as part of a clinical trial.

Because of the risk of severe teratogenicity, the use of thalidomide in pregnant women is absolutely contraindicated. There are restrictions on the prescribing and dispensing of the drug. Both the prescribing physician and the dispensing pharmacy are required to register with the STEPS program. Women in the childbearing age group must undergo pregnancy testing before therapy can be instituted and every 2 to 4 weeks during treatment. They must abstain from sexual intercourse or use 2 highly effective contraceptive methods during treatment. Men must abstain from sexual intercourse or use a condom while receiving treatment even if they have undergone a successful vasectomy. All patients must continue these measures for at least 1 month after the last dose of the drug. Breastfeeding is contraindicated.

The most common adverse effects of thalidomide are sedation, fatigue, constipation, and rash. Most patients are unable to tolerate doses greater than 400 mg/d because of excessive sedation and fatigue. Laxatives have been prescribed prophylactically. Peripheral neuropathy can occur, usually with treatment durations of 6 months or longer.

The mechanism of action of thalidomide in myeloma is unknown. Laboratory studies using the rabbit cornea micropocket assay have shown that thalidomide has potent antiangiogenic properties, probably by blocking the action of potent angiogenic factors such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF).[17,18] Animal studies indicate that thalidomide treatment can decrease vascular density in granulation tissue.[19] In studies of murine Lewis lung tumors, thalidomide reduced the development of metastases and increased sensitivity to chemoradiotherapy.[20] Since angiogenesis is increased in myeloma, the efficacy of thalidomide may be related to its antiangiogenic properties. However, in the Arkansas study,[15] there were no statistically significant differences in bone marrow angiogenesis after thalidomide therapy, suggesting that other mechanisms may also be involved. The rapidity of response seen with thalidomide therapy also argues against antiangiogenesis as the sole mode of action. Thalidomide has potent immunomodulatory effects, which may be responsible for its activity in myeloma. It is a potent inhibitor of tumor necrosis factor α, enhancing the degradation of tumor necrosis factor α messenger RNA.[21] Thalidomide stimulates cytotoxic T-cell proliferation and induces the secretion of interferon γ and interleukin (IL) 2 by these cells.[22] Thalidomide also induces helper T cell type 2 cytokine production in human peripheral blood mononuclear cell cultures while concomitantly inhibiting helper T cell type 1 cytokine production.[23] Finally, it modulates the expression of cell surface adhesion molecules.[24] The responses seen in myeloma may be due to a combination of these immunologic effects of thalidomide with its antiangiogenic effects.

The association of angiogenesis with PCLI, its prognostic value, and the responses observed with thalidomide support a role for angiogenesis in the pathogenesis and progression of myeloma. There are also data that myeloma cells express VEGF and bFGF.[25,26] Stimulation of myeloma cell lines with IL-6 leads to an increase in VEGF secretion.[27] Moreover, stimulation of human microvascular endothelial cells and bone marrow stromal cells with VEGF induces an increase in IL-6 secretion in a dose-dependent manner.

We conclude that thalidomide is an active agent in the treatment of patients with advanced myeloma. A prospective trial to confirm these findings is ongoing at the Mayo Clinic in Rochester, Minn, and includes correlative studies to assess the effect of thalidomide on bone marrow angiogenesis, as well as the expression of VEGF, bFGF, and their receptors. We are also studying patients with newly diagnosed, untreated asymptomatic myeloma with single-agent thalidomide. Moreover, studies of chronic lymphocytic leukemia, myelodysplastic syndrome, and myelofibrosis are being developed.

REFERENCES

1. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. *CA Cancer J Clin.* 1999;49:8-31.
2. Barlogie B, Hall R, Zander A, Dicke K, Alexanian R. High-dose melphalan with autologous bone marrow transplantation for multiple myeloma. *Blood.* 1986;67:1298-1301.
3. Attal M, Harousseau J-L, Stoppa A-M, et al, Intergroupe Français du Myélome. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med.* 1996;335:91-97.
4. Barlogie B, Jagannath S, Desikan KR, et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. *Blood.* 1999;93:55-65.
5. Folkman J. Clinical applications of research on angiogenesis. *N Engl J Med.* 1995;333:1757-1763.
6. Fox SB. Tumour angiogenesis and prognosis. *Histopathology.* 1997;30:294-301.
7. Weidner N, Semple JP, Welch WR, Folkman J. Tumor angiogenesis and metastasis—correlation in invasive breast carcinoma. *N Engl J Med.* 1991;324:1-8.
8. Rajkumar SV, Fonseca R, Witzig TE, Gertz MA, Greipp PR. Bone marrow angiogenesis in patients achieving complete response after stem cell transplantation for multiple myeloma. *Leukemia.* 1999;13:469-472.
9. Perez-Atayde AR, Sallan SE, Tedrow U, Connors S, Allred E, Folkman J. Spectrum of tumor angiogenesis in the bone marrow of

children with acute lymphoblastic leukemia. *Am J Pathol.* 1997; 150:815-821.
10. Vacca A, Ribatti D, Roncali L, et al. Bone marrow angiogenesis and progression in multiple myeloma. *Br J Haematol.* 1994;87: 503-508.
11. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.
12. Rajkumar SV, Leong T, Fonseca R, et al. Bone marrow angiogenesis has prognostic value in multiple myeloma: an Eastern Cooperative Oncology Group study [abstract]. *Program Proc Am Soc Clin Oncol.* 1999;18:19a. Abstract 68.
13. Munshi N, Wilson CS, Penn J, et al. Angiogenesis in newly diagnosed multiple myeloma: poor prognosis with increased microvessel density (MVD) in bone marrow biopsies [abstract]. *Blood.* 1998;92(suppl 1):98a. Abstract 400.
14. O'Reilly MS, Boehm T, Shing Y, et al. Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. *Cell.* 1997;88:277-285.
15. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma [published correction appears in *N Engl J Med.* 2000;342:364]. *N Engl J Med.* 1999;341:1565-1571.
16. Munshi N, Desikan R, Zangari M, et al. Chemoangiotherapy with DT-PACE for previously treated multiple myeloma (MM) [abstract]. *Blood.* 1999;94(suppl 1):123a. Abstract 540.
17. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci U S A.* 1994;91: 4082-4085.
18. Kenyon BM, Browne F, D'Amato RJ. Effects of thalidomide and related metabolites in a mouse corneal model of neovascularization. *Exp Eye Res.* 1997;64:971-978.
19. Or R, Feferman R, Shoshan S. Thalidomide reduces vascular density in granulation tissue of subcutaneously implanted polyvinyl alcohol sponges in guinea pigs. *Exp Hematol.* 1998;26:217-221.
20. Minchinton AI, Fryer KH, Wendt KR, Clow KA, Hayes MM. The effect of thalidomide on experimental tumors and metastases. *Anticancer Drugs.* 1996;7:339-343.
21. Moreira AL, Sampaio EP, Zmuidzinas A, Frindt P, Smith KA, Kaplan G. Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. *J Exp Med.* 1993;177:1675-1680.
22. Haslett PA, Corral LG, Albert M, Kaplan G. Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8+ subset. *J Exp Med.* 1998;187:1885-1892.
23. McHugh SM, Rifkin IR, Deighton J, et al. The immunosuppressive drug thalidomide induces T helper cell type 2 (Th2) and concomitantly inhibits Th1 cytokine production in mitogen- and antigen-stimulated human peripheral blood mononuclear cell cultures. *Clin Exp Immunol.* 1995;99:160-167.
24. Geitz H, Handt S, Zwingenberger K. Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. *Immunopharmacology.* 1996;31:213-221.
25. Bellamy WT, Richter L, Frutiger Y, Grogan TM. Expression of vascular endothelial growth factor and its receptors in hematopoietic malignancies. *Cancer Res.* 1999;59:728-733.
26. Rajkumar SV, Yoon SY, Li CY, et al. Angiogenesis in myeloma: expression of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) and their receptors by neoplastic plasma cells [abstract]. *Blood.* 1999;94(suppl 1):303b. Abstract 4581.
27. Dankbar B, Padró T, Mesters RM, et al. VEGF is expressed by myeloma cells and stimulates IL-6 secretion by microvascular endothelial and marrow stromal cells [abstract]. *Blood.* 1998; 92(suppl 1):681a. Abstract 2807.