Combination Therapy With Thalidomide Plus Dexamethasone for Newly Diagnosed Myeloma

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Purpose: Multiple myeloma is a malignancy of plasma cells and is characterized by increased marrow angiogenesis. Thalidomide, an agent with antiangiogenic properties, is effective in relapsed myeloma. We report the results of a study combining thalidomide and dexamethasone as initial therapy for myeloma.

Patients and Methods: Fifty patients with newly diagnosed myeloma were studied. Thalidomide was given at a dose of 200 mg/d orally. Dexamethasone was given at a dose of 40 mg/d orally on days 1 to 4, 9 to 12, and 17 to 20 (odd cycles) and 40 mg/d on days 1 to 4 (even cycles), repeated monthly.

Results: Of all 50 patients, a confirmed response was seen in 32 patients yielding a response rate of 64% (95% confidence interval, 49% to 77%). Thirty-one patients (62%) proceeded to stem-cell collection after four cycles of therapy including 26 who underwent stem-cell transplantation and

five who chose stem-cell cryopreservation. Major grade 3 or 4 toxicities were observed in 16 patients (32%), and the most frequent were deep vein thrombosis (six patients), constipation (four patients), rash (three patients), and dyspnea (two patients). Three deaths occurred during active therapy because of a pancreatitis, pulmonary embolism, and infection.

Conclusion: We conclude that the combination of thalidomide plus dexamethasone is a feasible and active regimen in the treatment of multiple myeloma. It merits further study as an oral alternative to infusional chemotherapy with vincristine, doxorubicin, and dexamethasone and other intravenous regimens currently used as pretransplantation induction therapy for myeloma.

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M ULTIPLE MYELOMA accounts for 10% of malignant hematologic neoplasms.[1,2] Recent evidence suggests that angiogenesis is increased in multiple myeloma and has prognostic value in this disease.[3-5] On the basis of the increased angiogenesis observed in myeloma, thalidomide has been studied as an antiangiogenic therapy. Although its mechanism of action in myeloma is unclear, several trials show that thalidomide is active in 25% to 35% of patients with relapsed, refractory myeloma.[6,7]

The current standard of care for patients with myeloma who are in good performance status is combination chemotherapy using non–alkylator-containing regimens such as vincristine, doxorubicin, and dexamethasone (VAD) for 4 to 6 months followed by high-dose therapy with autologous stem-cell transplantation. Such an approach has been shown to improve both response rates and survival.[8-10] The response rate with VAD is approximately 55% to 65%.[11] The goal of pretransplantation chemotherapy with VAD and similar regimens is to reduce tumor burden before stem-cell collection and transplantation.[12] VAD is preferred over regimens such as melphalan and prednisone and other alkylator-based regimens because it is less toxic to bone marrow stem cells, which is an important consideration for stem-cell transplant. However, VAD has significant toxicity and is cumbersome, requiring an indwelling central venous access for continuous infusion of chemotherapy that places the patient at risk for catheter-related infection, sepsis, and thrombosis.

Dexamethasone has significant single-agent activity in myeloma in both previously untreated and relapsed disease.[13,14] Recently, Weber et al[15] demonstrated a clinical benefit by the addition of dexamethasone to patients for whom thalidomide alone was unsuccessful. On the basis of these results and the ease of administration over infusional VAD and other intravenous regimens, we conducted a clinical trial of thalidomide and dexamethasone in newly diagnosed myeloma. Because autolo-

gous stem-cell transplantation has been shown in randomized, controlled trials to be superior to conventional dose chemotherapy, the aim of the study was not to determine time to progression or survival with this regimen. Rather, our goal was to determine whether the combination of thalidomide and dexamethasone would provide an orally administered, less toxic alternative to VAD (and other similar regimens) as pretransplantation induction therapy.

PATIENTS AND METHODS

Eligibility

Patients were eligible to enter onto the study if they had previously untreated symptomatic myeloma. Patients were required to have bone marrow plasma cells $\geq$ 10% and measurable disease defined as serum monoclonal (M) protein $\geq$ 20 g/L and/or urine M protein $\geq$ 400 mg/24 hours. Patients with hemoglobin less than 70 g/L, platelets less than 25×10^9/L, absolute neutrophil count less than $1,000 \times 10^6$/L, or Eastern Cooperative Oncology Group (ECOG) performance score of 4 were excluded. Pregnant or nursing women were not eligible. Women of child bearing potential who were unwilling to use a dual method of contraception and men who were unwilling to use a condom were not eligible for the study. All patients gave written informed consent before enrollment onto the study.

Approval of the study and consent form 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 System for Thalidomide Education and Prescribing Safety program. Women of childbearing age were required to have a pregnancy test performed every 2 weeks while on the study.

Treatment Schedule

Thalidomide was given orally at a dose of 200 mg/d for 2 weeks and then increased as tolerated by 200 mg/d every 2 weeks to a maximum dose of 800 mg/d. After the first seven patients were enrolled, thalidomide dose escalation was discontinued because of unexpected skin toxicity in two patients, consisting of toxic epidermal necrolysis in one patient and generalized erythroderma in one patient.[16] The dose of thalidomide was kept constant at 200 mg/d for all subsequent patients. The thalidomide dose was reduced to 50 to 100 mg/d if grade 2 or higher toxicity was encountered. Dexamethasone was given at a dose of 40 mg/d orally on days 1 to 4, 9 to 12, and 17 to 20 (odd cycles) and 40 mg/d days 1 to 4 (even cycles), repeated monthly. Patients were evaluated every 4 weeks for response. After four cycles of therapy, patients who were candidates for high-dose therapy were allowed to terminate study treatment to pursue stem-cell collection and transplantation.

Response and Toxicity Criteria

The primary end point of this trial was a confirmed response on two consecutive evaluations at least 4 weeks apart. The response and progression criteria used in this study are standard Mayo Clinic and ECOG criteria. Response was defined as a reduction of serum and urine M protein by at least 50% accompanied by a similar reduction of soft tissue plasmacytomas if present. If response was assessed solely based on urine M protein, a 90% or greater reduction was required. In addition, responses were categorized as a complete response if there was complete disappearance of M protein in the serum and urine by immunofixation and absence of M plasma cells in the bone marrow. Disease progression was defined as a 50% increase in the M protein over the lowest response level. Increase in the size of existing lytic bony lesions or soft tissue plasmacytomas or the appearance of new lytic bony lesions constituted progression. A repeat M protein evaluation was required to confirm progression based on serum or urine monoclonal protein increase. However, as is standard in other myeloma protocols, if progression in M protein was accompanied by any other unequivocal evidence of progression, a repeat measurement was not necessary. Disease that does not satisfy the criteria for response, complete response, or progression was categorized as stable disease. The National Cancer Institute common toxicity criteria (version 2) were used to grade adverse effects.

Statistical Analysis

This trial was originally designed to accrue 30 patients to assess the response rate and toxicity of thalidomide and dexamethasone in the setting of newly diagnosed multiple myeloma. On the basis of promising activity noted at interim analysis, 20 additional patients were accrued to better define toxicity and response rate.

Ninety-five percent confidence intervals (CIs) for the confirmed response probability were calculated using exact binomial 95% CIs. Toxicity incidence was estimated and summarized using frequency and descriptive techniques to assess any patterns. The Fisher's exact test was used to compare differences in nominal variables.

RESULTS

Patient characteristics are listed in Table 1. The median age was 61 years (range, 33 to 78 years). The median serum M protein level before therapy was 3.8 g/dL (range, 0.0 to 7.6 g/dL). The bone marrow plasma cell percentage before therapy ranged from 10% to 97% (median, 41%).

Among the first seven patients treated, two had grade 3 or 4 skin toxicity including one patient with toxic epidermal necrolysis.[16] One other patient had grade 2 exfoliation. Therefore, the protocol therapy was amended to stop the dose escalation of thalidomide and to keep the thalidomide dose constant at 200 mg for the subsequent 43 patients studied. Of the first seven patients,

Table 1. Patient Characteristics

Characteristic	All Patients	
	No.	%
Sex		
Male	31	62
Female	19	38
Immunoglobulin heavy chain type		
IgG	33	66
IgA	10	20
Biclonal IgG and IgA	1	2
Light-chain only (Bence Jones protein)	6	12
Beta 2-microglobulin > 2.7 μg/mL	31	62
Plasma cell labeling index $\geq$ 1%	18	36
Lactate dehydrogenase > 250 U/L	5	10
Bone marrow plasma cell % > 40%	26	52

one patient did not receive dose escalation beyond 200 mg. The remaining six patients received a maximum thalidomide dose of 400 mg. However, only two of these patients received this dose level for more than one cycle (one patient received 400 mg for six cycles and another for two cycles).

Response to Therapy

Thirty-two of the 50 patients (64%) had a response to therapy (95% CI, 49% to 77%). An additional 14 patients were categorized as stable disease and all had more than a 25% reduction in serum and urine M protein and can be considered as minor responses. If these minor responses are included, the overall response rate increases to 92%. The level of M protein reduction and bone marrow plasma cell reduction is listed in Table 2. When response was assessed by baseline M immunoglobulin (Ig) subtype, the confirmed response rates for IgG, IgA, and light-chain only were similar at 62%, 64%, and 60%, respectively. Four patients were taken off the study because of progressive disease after initial response.

Response to therapy was accompanied by hematologic recovery and improvement in symptoms. Forty-seven patients had anemia at baseline (grade 1 in 29 patients, grade 2 in 16 patients, and grade 3 in two patients). Of these, 38% (18 of 47) patients had an increase in hemoglobin by at least 20 g/L or higher,

Table 2. Extent of Monoclonal Protein and Bone Marrow Response

Response Level	No. of Patients	%
Level of monoclonal protein reduction from baseline*		
90% or greater	15	30
75%-90%	11	22
50%-75%	8	16
25%-50%	12	24
No response or progression	4	8
Level of bone marrow response from baseline†		
90% or greater	10	24
75%-90%	12	29
50%-75%	6	14
25%-50%	4	10
10%-25%	4	10
No response or progression	6	14

*Urine monoclonal protein level was used when serum monoclonal protein level was less than 1 g/dL; two patients who achieved > 50% reduction in monoclonal protein levels in this Table were not considered responders because they did not meet all criteria for response and were classified as stable disease.

†Of 42 patients in whom a repeat bone marrow biopsy was performed after protocol therapy.

Table 3. Major (grade 3 and 4) Toxicities

Type	No. of Patients	%
Treatment-related deaths	3	6
Thrombosis	6	12
Constipation	4	8
Rash	3	6
Dyspnea	2	4
Depression	1	2
Sedation	1	2
Arrhythmia	1	2
Rash	1	2
Edema	1	2
Inner ear	1	2
Neuropathy	1	2
Syncope	1	2

including both patients with grade 3 anemia and 11 of 16 patients with grade 2 anemia. One of the patients with improvement in anemia received erythropoietin support. Seven patients had baseline grade 1 or 2 leukopenia, which resolved with therapy in five patients. Eleven patients had baseline thrombocytopenia (grade 1 in nine patients, grade 2 in one patient, and grade 3 in one patient). Six of the nine patients with grade 1 thrombocytopenia had an increase in platelet count by at least 50×10^9/L after therapy.

Of the 50 patients treated, 31 proceeded to stem-cell collection after four cycles of therapy including 26 who underwent stem-cell transplantation and five who chose stem-cell cryopreservation and are back on thalidomide plus dexamethasone. No problems were encountered with stem-cell collection. The remaining 19 patients did not undergo stem-cell collection for varying reasons; this includes eight patients not considered to be transplant candidates because of age or patient refusal and were continued on thalidomide/dexamethasone therapy, four who proceeded to other therapy because of disease progression, four who pursued other therapy because of lack of adequate response or toxicity, and three patients who died while receiving therapy.

Toxicity

Therapy was generally well tolerated except for unexpected grade 3 or 4 skin toxicity in two of the first seven patients who had thalidomide dose escalation. There were three deaths that occurred during study treatment. One patient died with acute pancreatitis within 1 week of initiating therapy, which was attributed to either gallstones or dexamethasone therapy. One patient died within days of initiating therapy with a clinical diagnosis of pulmonary embolism, and one other patient died of infectious complications also in the first month of therapy. Grade 3 or higher nonhematologic toxicity was seen in 17 patients (34%), and the most frequent were venous thrombosis in six patients (12%), constipation in four patients (8%), rash in three patients (6%), and dyspnea in two patients (4%). Table 3 summarizes the grade 3 and 4 toxicities seen in the trial. The most common grade 1 and 2 toxicities were constipation (72%), neuropathy (58%), fatigue (50%), sedation (46%), rash (38%), tremor (30%), edema (28%), and elevated alkaline phosphatase (22%).

DISCUSSION

Thalidomide was first introduced in clinical practice as a sedative in the late 1950s and was subsequently withdrawn from the market in 1962 because of its severe teratogenicity. The mechanism of its teratogenicity is still unclear but may be related to its antiangiogenic properties or inhibition of tumor necrosis factor alpha (TNF α) production.[17] Free radical mediated oxidative damage to DNA has also been postulated as a mechanism for the teratogenic effects.[18] Despite its tragic past, thalidomide has re-entered clinical practice because of its immunomodulatory and antiangiogenic properties. It was found to be effective in the treatment of erythema nodosum leprosum in the mid-1960s.[19] In the last 10 years, thalidomide has been studied and found to be useful in the treatment of AIDS-related cachexia, aphthous ulcers in patients with Behçet's disease, and in the treatment of chronic graft versus host disease.

Clinical trials with thalidomide in myeloma were initiated because of its antiangiogenic properties and based on evidence indicating a role for increased angiogenesis in the pathogenesis and progression of myeloma.[3,20] Researchers at the University of Arkansas conducted a landmark trial investigating the activity of thalidomide in relapsed myeloma.[6] For most patients (90%) in this study, stem-cell transplantation had failed. Treatment consisted of thalidomide given at a dose of 200 mg/d orally for 2 weeks and then increased by 200 mg/d every 2 weeks up to a maximum daily dose of 800 mg/d depending on toxicity. They observed an overall response rate of 32% with a median time to response of 1 month. M protein responses were accompanied by improvements in anemia and disease-related symptoms. The median duration of response was not reached after 14.5 months of follow-up. Considering that for 90% of the patients transplantation had failed, these results were impressive. An update to this study on 169 patients confirmed these results, demonstrating a 2-year overall and event-free rates of 48% and 20%, respectively.[21] Several groups including ours have since confirmed the activity of thalidomide in relapsed, refractory myeloma.[7,22,23] A recent Mayo Clinic trial demonstrated a 38% response rate with the use of thalidomide in patients with previously untreated indolent or smoldering myeloma, indicating that thalidomide may have a role in early-stage disease as well.[24]

The present study enrolled patients with newly diagnosed active myeloma, and most patients had high-risk disease. Sixty percent of those studied had high β2M levels, and 36% had a high plasma cell labeling index, which are two known adverse prognostic factors in myeloma. Only patients with marked cytopenias (hemoglobin < 70 g/L, platelet count $< 25 \times 10^9$/L, or absolute neutrophil count $< 1,000 \times 10^6$/L) were excluded from this study. The restrictions on cytopenias were placed because of safety concerns and concern that thalidomide may cause neutropenia. Further, when the study was designed, the combination had not been tested in newly diagnosed myeloma, and these restrictions excluded only a small minority of patients with myeloma. The study demonstrates significant activity (64% partial response rate) for the combination of thalidomide and dexamethasone in these patients. In addition, both the original Arkansas study in relapsed myeloma[6] and the recent Mayo Clinic study in smoldering myeloma[24] used less stringent criteria for measuring response (> 25% reduction in serum and urine M protein) and observed response rates of 32% and 69%, respectively, with single-agent thalidomide. When this definition of response is used in the present study, the response rate with thalidomide plus dexamethasone increases to 92%. Thus, this combination merits further study as a simple oral alternative to

VAD as induction therapy in preparation for stem-cell transplantation. The toxicity seems lower, and the response rate is as good or better than that obtained using complex combination chemotherapy regimens.[11,12] None of the known prognostic markers in myeloma predicted response to therapy. More research is needed to determine which factors predict response to thalidomide therapy.

This trial allowed patients to go off the study at 4 months to pursue stem-cell collection and transplantation. We believe that the current standard of therapy for multiple myeloma includes autologous stem-cell transplantation after three to four cycles of induction therapy with VAD or dexamethasone or a similar regimen. Randomized trials have shown this approach to be superior to conventional chemotherapy in terms of overall survival.[25] In the United States, Medicare now covers autologous transplantation for newly diagnosed myeloma up to the age of 78. The effect of prolonged thalidomide therapy on the collection of stem cells is unknown. For these reasons, we felt it was unethical to deny patients the option of stem-cell collection and transplantation. Thus, the study did not attempt to answer the question of time to progression with thalidomide and dexamethasone therapy. The main goal of this study was to develop an alternative pretransplantation induction regimen for VAD that would be easier to use and possibly less toxic. However, a study comparing long-term thalidomide plus dexamethasone versus transplantation would be of interest in the future.

The appropriate dose of thalidomide in myeloma is still unknown and is the subject of much debate. This trial was the first to combine thalidomide with dexamethasone for newly diagnosed myeloma. At the time this trial was designed, shortly after reports of the efficacy of thalidomide in relapsed myeloma, 200 mg was felt to be the appropriate starting dose. During this study we learned that thalidomide doses more than 200 mg in combination with high-dose dexamethasone might be toxic. Doses less than 200 mg are being studied by other investigators in an attempt to minimize toxicity. In fact, grade 3 and 4 neuropathy, constipation, and fatigue were infrequently seen in this study probably as a result of the relatively short duration of therapy for most patients, as well as the lower dose of thalidomide compared with earlier studies in relapsed myeloma. Other studies have also found that toxicities are much lower with the 200 mg dose of thalidomide compared with higher doses.[6] However, there is no data at present on whether there is any accompanying loss of efficacy.

Most side effects can be managed by decreasing the dose of thalidomide to 50 to 100 mg/d. Because of our experience with skin toxicity at higher doses,[16] we do not recommend escalating the dose of thalidomide beyond 200 mg when combining with dexamethasone. The increased skin toxicity seen with this combination is felt to be the result of potentiation of thalidomide toxicity by dexamethasone, the mechanisms for which are unclear.[16] We also recommend that physicians exercise caution when combining thalidomide with other drugs known to cause skin toxicity, such as trimethoprim-sulfamethoxazole and allopurinol.

Twelve percent of patients had deep vein thrombosis (DVT) in this study. However, it is known that up to 10% to 20% of patients with newly diagnosed myeloma develop DVT in the first 6 months of therapy.[12] There is evidence that the combination of thalidomide with doxorubicin containing multiagent chemother-

apy may increase the incidence of DVT.[26,27] The incidence of DVT with single-agent thalidomide is less than 5%.[21] It is not clear if the risk of DVT with thalidomide therapy is increased in the absence of doxorubicin and other cytotoxic agents.

Most patients (52%) in this study will proceed to stem-cell collection and transplantation after four cycles of thalidomide and dexamethasone. In addition, some patients (10%) have elected to resume thalidomide and dexamethasone after stem-cell mobilization has been completed, opting to delay transplantation until disease progression. In this case, their stem cells are cryopreserved for future use. We currently mobilize stem cells after four cycles of therapy because the effects of prolonged thalidomide therapy on stem-cell yield is not known. Only eight patients not considered candidates for transplantation because of advanced age or poor performance status are continuing long-term thalidomide/dexamethasone therapy.

The high response rate seen suggests a synergy between thalidomide and dexamethasone. There are in vitro data that lend support to this hypothesis.[28] The mechanisms of the synergy are likely complex because both drugs have a wide variety of preclinical and clinical effects. One hypothesis is that dexamethasone has a preferentially greater effect on the myeloma cells directly, and thalidomide effects are indirect, mediated through its effect on the microenvironment. It is also hypothesized that thalidomide helps in overcoming dexamethasone-induced resistance by its effects on adhesion molecules, tumor cell growth, and survival.[28] In addition, both agents probably inhibit angiogenesis through different pathways.[29,30] Preliminary results from Weber et al[15] demonstrate responses with combined thalidomide and dexamethasone among patients with relapsed myeloma for whom previous treatment with the same agents given individually had failed. The increased toxicity seen in this trial at higher doses of thalidomide in the first seven patients also supports a potentiation of thalidomide effects by dexamethasone.

The mechanism of action of thalidomide in myeloma is unclear. Laboratory studies using the rabbit cornea micropocket assay have shown that thalidomide has potent antiangiogenic properties.[30,31] Animal studies show that it can decrease vascular density in granulation tissue.[32] In the Arkansas study, there were no statistically significant differences in posttreatment microvessel density change between responders and nonresponders.[6] However, these findings do not fully exclude an antiangiogenic mechanism. In addition to its antiangiogenic effects, thalidomide also has several immunomodulatory properties. It inhibits the production of TNFα by enhancing the degradation of TNFα mRNA.[33] Thalidomide stimulates cytotoxic T-cell proliferation and induces the secretion of interferon gamma and interleukin-2 by these cells.[34] It may also modulate the expression of several cell surface adhesion molecules.[35] Another potentially significant mechanism of action of thalidomide may be through inhibition of the transcription factor nuclear factor-kappaB.[36,37]

The response rate seen in this study is higher than historical data with dexamethasone alone (43%) or thalidomide alone (38%) for previously untreated myeloma. Nevertheless, the results of this trial do not establish that thalidomide plus dexamethasone has superior response rate to dexamethasone alone. The response criteria used in this trial differ from the response criteria used in clinical trials using single-agent dexamethasone and other induction regimens used before tandem transplantation at the University of Arkansas. We

believe that a randomized clinical trial comparing the two regimens is needed. Such a trial, led by ECOG, is now ongoing in the United States.

We conclude that the response rate to induction therapy with the combination of thalidomide plus dexamethasone is similar to that expected with VAD and dexamethasone. Further studies are needed to document the effect on long-term outcomes posttransplantation with this regimen. Another strategy that needs study is to initiate induction therapy with dexamethasone alone and add thalidomide to patients who fail to respond.

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