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Thalidomide as initial therapy for early-stage myeloma

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Patients with early-stage myeloma are typically observed without therapy until symptomatic disease occurs. However, they are at high risk of progression to symptomatic myeloma, with a median time to progression of approximately 1–2 years. We report the final results of a phase II trial of thalidomide as initial therapy for early-stage multiple myeloma in an attempt to delay progression to symptomatic disease. In total, 31 patients with smoldering or indolent multiple myeloma were studied at the Mayo Clinic. Two patients were deemed ineligible because they were found to have received prior therapy for myeloma, and were excluded from analyses except for toxicity. Thalidomide was initiated at a starting dose of 200 mg/day. Patients were followed-up monthly for the first 6 months and every 3 months thereafter. Of the 29 eligible patients, 10 (34%) had a partial response to therapy with at least 50% or greater reduction in serum and urine monoclonal (M) protein. When minor responses (25–49% decrease in M protein) were included, the response rate was 66%. Three patients had progressive disease while on therapy. Kaplan–Meier estimates of progression-free survival are 80% at 1 year and 63% at 2 years. Major grade 3–4 toxicities included two patients with somnolence and one patient each with neuropathy, deep-vein thrombosis, hearing loss, weakness, sinus bradycardia, and edema. Thalidomide has significant activity in early-stage myeloma and has the potential to delay progression to symptomatic disease. This approach must be further tested in randomized trials.
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Introduction

Multiple myeloma is a plasma cell proliferative disorder that accounts for 10% of all malignant hematologic neoplasms. In 2002, approximately 14 600 new patients with multiple myeloma will be diagnosed in the United States, and over 10 800 patients will die of the disease.[1] Multiple myeloma is not curable and given the leukemogenic potential of alkylating agents the current standard of care is to delay therapy until symptomatic disease occurs.[2–7] However, with this strategy, the median survival is only about 3–4 years.[8,9] With the advent of effective noncytotoxic biologic agents, the time is right to challenge this paradigm of myeloma therapy. Our earlier studies show that angiogenesis is a striking characteristic of multiple myeloma and has prognostic value in the disease.[10–12] Based on the increased angiogenesis seen in myeloma, thalidomide has been studied over the last few years in patients with advanced disease.[13,14] In these studies, thalidomide has shown significant activity with response rates of about 25–35% in patients with relapsed or refractory disease.

Our hypothesis is that early therapy with thalidomide can be effective in delaying progression from asymptomatic to symptomatic multiple myeloma. Therefore, we conducted a phase II trial to determine the response rate and time to progression with thalidomide therapy in patients with smoldering and indolent (asymptomatic; early stage) multiple myeloma.

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Materials and methods

Eligibility

Patients were eligible to enter the study if they had previously untreated smoldering multiple myeloma or indolent multiple myeloma using standard Mayo Clinic Criteria.[15] Patients were required to have bone marrow (BM) plasma cells $\geq$10% and measurable disease defined as serum monoclonal (M) protein $\geq$ 2gm/dl and/or urine M protein $\geq$400 mg/24 h. Pregnant or nursing women, women of child bearing potential who were unwilling to employ 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 prior to enrollment to 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 done every 2 weeks while on study.

Treatment schedule

Thalidomide was given orally at a dose of 200 mg/day for 2 weeks, and then increased as tolerated by 200 mg/day every 2 weeks to a maximum dose of 800 mg/day. Patients were evaluated every 4 weeks for response. The dose of thalidomide was decreased to as low as 50 mg per day, as needed, to minimize toxicity. Treatment was continued until disease progression or serious toxicity, except for patients achieving less than a minor response to therapy in whom therapy was stopped at 1 year.

Response and toxicity criteria

The primary end point of this trial was confirmed response on two consecutive evaluations at least 4 weeks apart. Response was defined as reduction of serum and urine M protein by at least 50%, accompanied by a similar reduction of soft-tissue plasmacytomas if present. In addition, responses were categorized as a complete response (CR) if there was complete disappearance of M protein in the serum and urine by immunofixation and absence of M plasma cells in the BM. 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 appearance of new lytic bony lesions constituted progression.

Disease that did not satisfy the criteria for partial response, CR or progression was categorized as stable disease. Overall survival was measured from the date of study entry to the date of death or last follow-up. Progression-free survival was measured from study entry to disease progression or death, whichever occurred earlier. The National Cancer Institute Common toxicity criteria (Version 2) were used to grade adverse effects.

Statistical analysis

Confidence intervals (95%) for the confirmed response probability were calculated assuming that the response incidence was binomially distributed. Fisher's exact test was used to compare differences in nominal variables. For continuous variables, the Wilcoxon rank-sum test was used for unpaired comparisons and the Wilcoxon signed-rank test was used for paired comparisons. The minimum and maximum doses of thalidomide that patients received were evaluated using descriptive statistics. The Kaplan–Meier method was used to estimate progression-free survival and overall survival. For all analyses, any result of $P<0.05$ was considered to be statistically significant.

Toxicity incidence was estimated and summarized using the frequency and descriptive techniques. The National Cancer Institute Common Toxicity Criteria (CTC), version 2, were used to grade nonhematologic adverse effects, and the perceived attribution of these events to the study treatment was also recorded. Any adverse events deemed at least possibly related to treatment were classified as toxicities by the NCI CTC definitions. Hematologic adverse events were graded by the CTC at any given evaluation only if the corresponding counts had decreased from baseline. Graded decreases in hemoglobin and platelets were considered to be unlikely related to treatment given the nature of MM. Any graded decreases in ANC were considered to be possibly related to treatment. In addition, any adverse events associated with WBC, creatinine or alkaline phosphatase were graded in a similar manner.

Results

Patient characteristics

In all, 31 patients were entered in the study between April 1999 and March 2002. The trial is closed to further accrual. Two patients were found ineligible because of prior therapy for myeloma, and were excluded from the efficacy analysis.

Table 1 lists the patient characteristics. The median age was 61 years (range, 40–74). The median serum M protein prior to therapy was 3.1 g/dl (range, 0.3–5.2). A total of 10 patients (34%) had indolent multiple myeloma based on the presence of lytic lesions (seven patients) and/or hemoglobin less than 11 gm/dl (six patients). The remaining 19 patients (66%) had smoldering multiple myeloma.

Response

Of the 29 eligible patients, 10 (34%; 95% CI 18–54%) had a partial response to therapy with at least 50% or greater reduction in serum and urine M protein. In addition, nine other patients had a minor response (25–49% decrease in M protein). When minor responses are included, the overall response rate increases to 66% (95% CI 46–82%). The remaining 10 patients had stable disease. All responses in M protein levels were accompanied by improvements in BM plasma cell percentages. The median time to partial response was 5 months (range 2–9 months).

Table 1 Patient characteristics

Characteristic	*All Patients*	
	No.	*%*
Total number of eligible patients	29	
Sex		
Male	16	55
Female	13	45
Smoldering/indolent myeloma		
Smoldering myeloma	19	66
Indolent myeloma	10	34
Immunoglobulin heavy-chain type		
IgG	24	83
IgA	3	10
Light chain only (Bence-Jones protein)	2	7
Anemia (hemoglobin <11 g/dl)	6	21
Lytic bone lesions	7	24
Beta 2-microglobulin >2.7 mg/l	13	45
Plasma cell labeling index $\geq 1\%$	3	10
Bone marrow plasma cell % $\geq 40\%$	8	28

When response was assessed according to the stage of disease, the partial response rates in patients with smoldering multiple myeloma and indolent multiple myeloma were 37 and 30%, respectively. The corresponding overall response rates (minor and partial responses) were 63 and 70%, respectively.

The maximum dose of thalidomide achieved by the responding (partial and minor) patients ranged from 200 to 800 mg (median 400 mg). However, all patients had at least one dose reduction because of adverse effects. The final maintenance dose ranged from 50 to 300 mg (median 200 mg).

Survival analysis

At the time of this analysis, two patients (7%) had died. Eight patients (28%) had progressed, with only three progressions occurring during therapy. The median time to progression and median response duration have not been reached after a median follow-up of over 2 years. On Kaplan–Meier analyses, the progression-free survival rate was 80% at 1 year and 63% at 2 years, respectively (Figure 1a). The Kaplan–Meier estimate of overall survival at 2 years was 96% (Figure 1b).

Toxicity

Toxicity assessments are based on all 31 enrolled patients. Table 2 summarizes the most common toxicities seen in this trial. Although most patients experienced grade 1–2 adverse events, they were generally amenable to appropriate dose reductions and therapy was generally well tolerated.

Discussion

Asymptomatic (smoldering and indolent) multiple myeloma accounts for probably less than 15% of all cases with newly diagnosed multiple myeloma.[3,4] Although some patients can

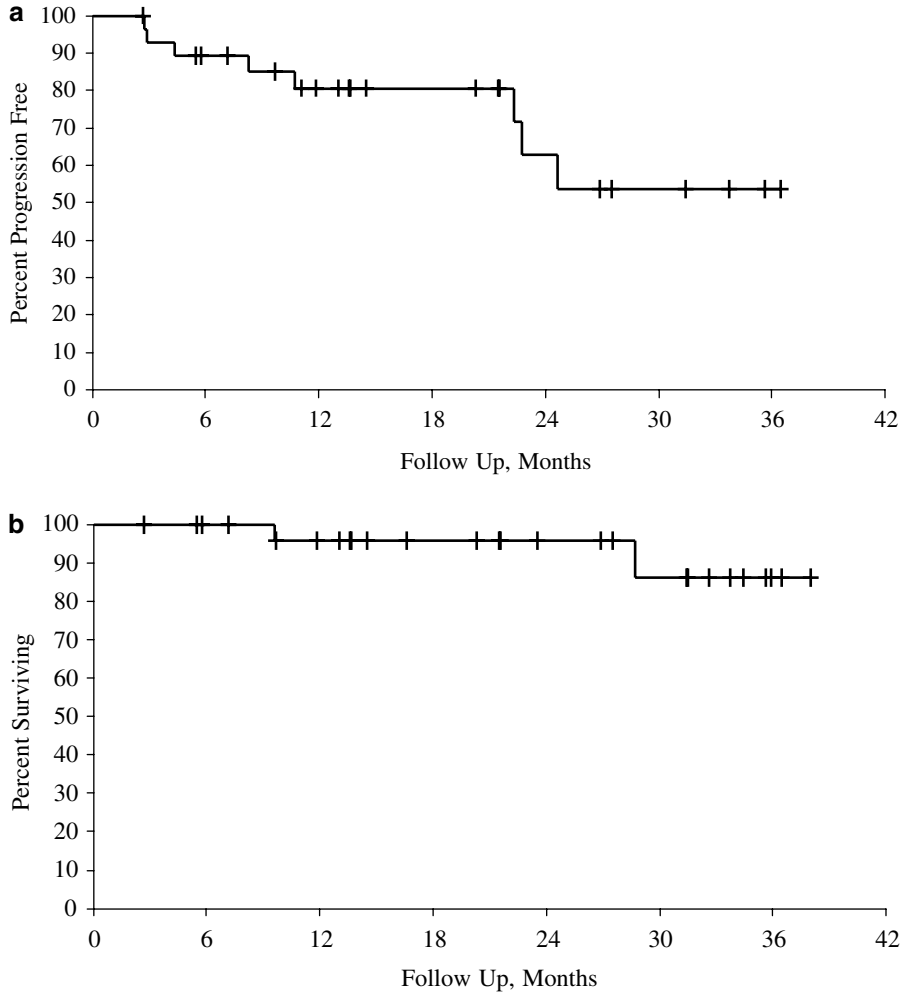

Fig. 1 Kaplan–Meier estimation of (a) progression-free survival and (b) overall survival of patients treated with thalidomide for early-stage myeloma.

Table 2 Toxicity profile

Toxicity	*Number of patients*	*%*
Skin rash		
Grade 1–2	17	55
Sedation		
Grade 1–2	23	74
Grade 3	2	6
Grade 1–2 constipation	27	87
Peripheral neuropathy		
Grade 1–2	27	87
Grade 3–4	1	3
Fatigue/weakness		
Grade 1–2	20	65
Grade 3	1	3
Sinus bradycardia		
Grade 1–2	7	23
Grade 3–4	1	3
Edema		
Grade 1–2	5	16
Grade 3	1	3
Grade 1–2 tremor	11	35
Grade 1–2 ataxia	5	16
Grade 3 hearing loss	1	3
Deep-vein thrombosis	1	3

remain free of progression for a number of years,[2] most progress eventually to symptomatic disease.[4]

The median time to progression to symptomatic disease is approximately 1–2 years.[4,16] Adverse prognostic factors for progression include an increase in the number or proliferative rate of circulating plasma cells by immunofluorescent assays, elevated BM plasma cell labeling index, serum M protein level more than 3.0 g/dl, immunoglobulin IgA subtype, urinary M protein excretion more than 50 mg/day and abnormal findings on magnetic resonance imaging of the spine are at higher risk for earlier progression to myeloma.[16–18,4,19]

The current standard of care for asymptomatic myeloma is close follow-up once every few months without any drug therapy. Hjorth *et al*[20] randomly assigned 50 patients with asymptomatic stage I myeloma to observation *vs* melphalan/prednisone chemotherapy.[21] No differences were observed in overall survival between the two groups. Grignani *et al*[21] reported similar survival time with immediate or deferred therapy in a series of 44 patients with asymptomatic myeloma.[21] Besides the results of these two trials, the recommendation for observation until progression is also based on the toxicity of therapy and the fact that some patients may not progress for months to years without any therapy.[2] However, there are several compelling reasons to challenge this paradigm at this

point. Firstly, the median time to progression of patients with asymptomatic myeloma is less than 2 years even in patients who have no bone lesions.[16] The presence of small bone lesions (as in some patients in this study) on skeletal survey or magnetic resonance imaging further increases this risk of progression to symptomatic myeloma.[18,19] Secondly, novel biologic agents such as thalidomide have the potential to delay significantly progression to active disease.[15] Thirdly, there is interest among patients and physicians to find ways in which the inevitable progression to multiple myeloma can be delayed so that patients can lead a productive life prior to needing autologous stem cell transplantation. Finally, there is mechanistic rationale that progression from asymptomatic to symptomatic myeloma may involve an angiogenic switch and it is reasonable to consider the antiangiogenic properties of thalidomide in this setting.[12]

In this study, we show that therapy with thalidomide has significant activity in early-stage disease, confirming the results of our earlier interim analysis.[15] Objective responses using standard ECOG criteria were seen in 34% of patients. The primary goal in early-stage myeloma is to delay or prevent progressive disease and we recognize that minor responses (25–49% reduction in M protein) are therefore meaningful. A total of 66% percent of patients enrolled on the study achieved this goal. The 2-year progression-free survival of 63% is impressive considering that approximately one-third of patients in this study had lytic lesions or significant anemia at baseline, and would qualify as multiple myeloma requiring stem cell transplantation in most other centers. Disease progression occurred only in 10% of patients while on therapy. In a series of 57 similar patients with untreated smoldering multiple myeloma defined using the same criteria as in this study,[15] the median time to progression was 22.5 months, and the 2-year progression-free survival was 47% (unpublished data).[16] Although these data put our results with thalidomide in perspective, we believe a randomized trial is needed to confirm these findings.

The dosage of thalidomide used in this trial is probably much higher than what would be required for the treatment of early-stage myeloma. These dosages were traditionally being used when the drug was first studied for myeloma.[13] During the course of the study, we aggressively dose reduced thalidomide to the dose that patients could tolerate and yet maintain response. We found that several patients were able to decrease the dose down to 50–100 mg/day of thalidomide and still maintain their response. We recommend doses of 200 mg or less for future studies in early-stage myeloma. With this strategy, we believe that the toxicities of thalidomide can be greatly reduced.

There have been questions about the effect of prolonged thalidomide therapy on stem cell collection. Since autologous transplantation is a proven method for the treatment of symptomatic myeloma, we feel that it is important not to use a therapy (such as alkylating agents) that can adversely impact stem cell collection. Based on the studies so far, it appears that short durations of thalidomide therapy do not have any significant effect on stem cell mobilization or transplantation.[22] In fact, thalidomide in combination with dexamethasone is an effective alternative to VAD therapy for induction prior to transplantation for symptomatic myeloma.[23] However, since we do not have data on stem cell mobilization with prolonged years (>1–2) of therapy with thalidomide, we would recommend that patients in future studies interrupt therapy for stem cell harvest at approximately 6–12 months.

The mechanism of action of thalidomide in myeloma is unclear. Rabbit cornea micropocket assay and other animal model studies demonstrate that it has potent antiangiogenic properties.[24–26] The Arkansas study did not find statistically significant differences in post-treatment MVD change between responders and nonresponders.[13] However, these findings do fully exclude an antiangiogenic mechanism since existing vessels may not regress and moreover, MVD is only a measure of intervascular distance and is not expected to decrease following antiangiogenic therapy.[27] The longer time to response (median, 5 months) seen in this study is less than what we and others find in relapsed myeloma (median, 1–2 months) (Rajkumar, unpublished observation).[28] This may be explained by the lower degree of BM angiogenesis in early-stage myeloma compared to relapsed disease.[12] In addition to its antiangiogenic effects, other possible mechanisms of action include inhibition of TNFα,[29] stimulation of cytotoxic T cells[30] and modulation of adhesion molecules.[31] Parman et al demonstrated that thalidomide-induced birth defects in rabbits can be abolished by pretreatment with the free radical spin trapping agent alpha-phenyl-*N*-*t*-butylnitrone, suggesting free radical-meditated DNA damage as a mechanism of action.[32]

Although it is tempting to recommend thalidomide as initial therapy for early-stage myeloma based on the results of this study, we caution that the study is not randomized. Further this study clearly shows that the therapy is not without adverse effects. In fact, the importance of this study is to highlight the fact that grade 1–2 adverse effects like sensory neuropathy, fatigue, constipation and sedation are seen in nearly all patients. Patients and physicians who are using this approach need to be cautious and recognize the investigational nature of this approach, its limitations and consequences. We do not recommend thalidomide for asymptomatic myeloma outside the setting of an approved clinical trial until randomized studies can be conducted. We are currently planning such a trial, the results of which will shed light on the role of thalidomide as initial therapy for early-stage myeloma.

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