VOLUME 24 · NUMBER 3 · JANUARY 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Clinical Trial of Thalidomide Plus Dexamethasone Compared With Dexamethasone Alone in Newly Diagnosed Multiple Myeloma: A Clinical Trial Coordinated by the Eastern Cooperative Oncology Group

S. Vincent Rajkumar, Emily Blood, David Vesole, Rafael Fonseca, and Philip R. Greipp

From the Division of Hematology, Mayo Clinic, Rochester, MN; Eastern Cooperative Oncology Group Statistical Center, Dana-Farber Cancer Institute, Boston, MA; the Medical College of Wisconsin, Milwaukee, WI; and Mayo Clinic, Scottsdale, AZ.

Submitted June 8, 2005; accepted August 15, 2005.

Supported by the Eastern Cooperative Oncology Group (Robert L. Comis, MD, Chair) and supported in part by Public Health Service Grants No. CA23318, CA66636, CA21115, CA13650, and CA93842 from the National Cancer Institute, National Institutes of Health and the Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to S. Vincent Rajkumar, MD, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: rajks@mayo.edu.

0732-183X/06/2403-431/$20.00

DOI: 10.1200/JCO.2005.03.0221

ABSTRACT

Purpose
To determine if thalidomide plus dexamethasone yields superior response rates compared with dexamethasone alone as induction therapy for newly diagnosed multiple myeloma.

Patients and Methods
Patients were randomly assigned to receive thalidomide plus dexamethasone or dexamethasone alone. Patients in arm A received thalidomide 200 mg orally for 4 weeks; dexamethasone was administered at a dose of 40 mg orally on days 1 to 4, 9 to 12, and 17 to 20. Cycles were repeated every 4 weeks. Patients in arm B received dexamethasone alone at the same schedule as in arm A.

Results
Two hundred seven patients were enrolled: 103 were randomly assigned to thalidomide plus dexamethasone and 104 were randomly assigned to dexamethasone alone; eight patients were ineligible. The response rate with thalidomide plus dexamethasone was significantly higher than with dexamethasone alone (63% *v* 41%, respectively; $P = .0017$). The response rate allowing for use of serum monoclonal protein levels when a measurable urine monoclonal protein was unavailable at follow-up was 72% *v* 50%, respectively. The incidence rates of grade 3 or higher deep vein thrombosis (DVT), rash, bradycardia, neuropathy, and any grade 4 to 5 toxicity in the first 4 months were significantly higher with thalidomide plus dexamethasone compared with dexamethasone alone (45% *v* 21%, respectively; $P < .001$). DVT was more frequent in arm A than in arm B (17% *v* 3%); grade 3 or higher peripheral neuropathy was also more frequent (7% *v* 4%, respectively).

Conclusion
Thalidomide plus dexamethasone demonstrates significantly superior response rates in newly diagnosed myeloma compared with dexamethasone alone. However, this must be balanced against the greater toxicity seen with the combination.

J Clin Oncol 24:431-436. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Multiple myeloma is a malignant plasma-cell proliferative disorder that accounts for more than 11,000 deaths each year in the United States.[1,2] For many years, melphalan and prednisone had remained the standard therapy for this disease.[3] Response rates with this therapy are approximately 50%; median survival is approximately 3 years. Recently, autologous stem-cell transplantation has been shown to be effective in the treatment of multiple myeloma in randomized clinical trials.[4,5] Patients eligible for stem-cell transplantation typically avoid alkylator-based induction therapy to enable an adequate and safe stem-cell collection early in the disease course.

Vincristine, doxorubicin, and dexamethasone (VAD) has been used as pretransplantation induction therapy for patients who are considered candidates for stem-cell transplantation.[2,6,7] However, VAD has several disadvantages, including the need for an intravenous indwelling catheter, which predisposes patients to catheter-related sepsis and thrombosis. Moreover, the activity of VAD primarily is due to the high-dose dexamethasone component; vincristine and doxorubicin have minimal roles.[8] As a result, dexamethasone alone is a safer and better tolerated induction therapy for multiple myeloma, particularly in patients who will proceed to more definitive therapy with early autologous stem-cell transplantation.

Thalidomide has shown significant single-agent activity in relapsed refractory multiple myeloma.[9] In combination with dexamethasone, response rates increase to approximately 50% in relapsed refractory disease.[10] The combination of thalidomide plus dexamethasone (thal/dex) has also shown high activity in newly diagnosed myeloma in three phase II clinical trials.[11-13] Response rates range from 65% to 70%, which are comparable to those obtained with VAD. Thal/dex has the advantage of being an oral regimen without the neurotoxicity, cardiotoxicity, alopecia, and other complications related to infusional VAD.

The goal of this clinical trial was to compare the response rate and efficacy of thal/dex versus dexamethasone alone in newly diagnosed multiple myeloma.

PATIENTS AND METHODS

Eligibility

Patients were eligible to enter onto the study if they had previously untreated symptomatic multiple myeloma, bone marrow plasmacytosis ($\geq$ 10% plasma cells or sheets of plasma cells) or a biopsy-proven plasmacytoma, and measurable disease defined as serum monoclonal protein more than 1.0 g/dL and/or urine monoclonal protein $\geq$ 200 mg/24 h. Patients also needed to have hemoglobin more than 7 g/dL, platelet count more than 50,000 cells/μL, absolute neutrophil count more than 1,000 cells/μL, creatinine less than 3 mg/dL, bilirubin $\leq$ 1.5 mg/dL, and ALT and AST $\leq$ 2.5$\times$ the upper limit of normal. No prior systemic therapy, with the exception of bisphosphonates, was permitted. Prior systemic glucocorticoids were not permitted for any illness in the last 6 months. Prior palliative localized radiation therapy was permitted provided at least 4 weeks had passed from the date of last radiation therapy. Also excluded were patients with grade 2 or higher peripheral neuropathy, active infection, current or prior deep vein thrombosis, and Eastern Cooperative Oncology Group (ECOG) performance score of 3 or 4. 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. Patients with prior malignancy were eligible provided they had been treated with a curative intent and had been free of disease for the time period considered appropriate. The study was approved by the National Institutes of Health central institutional review board as well as by institutional review boards in the participating institutions. Patients were enrolled between June 2002 and April 2003.

Treatment Schedule

Patients in arm A received thalidomide 200 mg orally for 4 weeks. The dose of thalidomide was based on a previous phase II study using this combination in newly diagnosed myeloma.[11] Dexamethasone was administered at a dose of 40 mg orally on days 1 to 4, 9 to 12, and 17 to 20. Each cycle was repeated every 4 weeks. Patients in arm B received dexamethasone alone at the same schedule as in arm A. Dose adjustments were permitted for toxicity. Patients were expected to discontinue the study after four cycles of therapy, but treatment beyond four cycles was permitted at physician's discretion. All patients received monthly infusions of pamidronate or zoledronic acid as part of supportive care. Patients who developed DVT or pulmonary embolism were required to stop thalidomide therapy temporarily; patients were allowed to resume treatment with a 50% dose reduction after therapeutic anticoagulation was achieved.

Response and Toxicity Criteria

The primary end point of this trial was best response within four cycles of treatment (4 months from the start of treatment). Standard ECOG response criteria were used. An objective response was defined as a 50% or higher decrease in the serum and urine monoclonal protein levels from baseline. Patients with measurable disease only in the urine needed to have a greater than 90% reduction in 24-hour urine monoclonal protein excretion to be considered as having a response. All responses needed to be confirmed at least 2 weeks apart by two consecutive determinations. For objective response criteria to be met there must have been no new bone lesions, no increase in existing lytic lesions, no recurrence or persistence of hypercalcemia, no increase in any existing plasmacytomas, and no new plasmacytomas. For patients in whom serum monoclonal protein was not measured, the appropriate serum immunoglobulin levels were used. Similarly, urinary light-chain excretion measured by κ or λ light-chain assays was permitted when follow-up urine monoclonal protein level was not determined.

A complete response (CR) was defined as a complete disappearance of the monoclonal protein in the serum and urine by immunofixation studies and less than 3% plasma cells on bone marrow examination. In patients seeming to meet CR criteria except for the lack of repeat bone marrow examination, the presence of 3% to 6% plasma cells or clusters of plasma cells on bone marrow examination were considered to have near-complete response. Patients who met objective response criteria, but not the criteria for CR or near-complete response, were defined as having partial response (PR). Disease that does not satisfy the criteria for response, CR, or progression was classified as no response.

Disease progression required two of the following four criteria: increase in serum monoclonal protein 50% or higher above the lowest response level or an increase in level by more than 2g/dL; increase in urine monoclonal protein by 50% above the lowest remission value or increase in excretion by 2,000 mg/24 h or higher; increase in size of soft tissue plasmacytoma by more than 50%; and definite appearance of bone lesions or increase in the size of existing bone lesions by more than 50%. For patients meeting only the serum or the urine monoclonal protein criteria, hypercalcemia, anemia, increase in bone marrow plasma cell percentage by greater than 50%, or generalized bone pain also constituted progression. The National Cancer Institute Common Toxicity Criteria, version 2, was used to grade adverse effects.

Statistical Design and Analysis

The primary end points of this study were best response within 4 months/four cycles and toxicity within 4 months/four cycles. This study was designed to detect a 20% improvement in response rate in the thal/dex arm. It was assumed that the 4-month response rate would be 60% with dexamethasone and 80% with thal/dex. To provide 90% power while maintaining an overall one-sided .05 significance level, the design required enrolling 184 eligible patients (194 total, assuming a 5% ineligibility rate). This allowed for two interim analyses and one final analysis. The two interim analyses were scheduled to take place when response information was available on 61 and 123 patients, and the final analysis was planned when response information was available on 184 eligible patients. The nominal significance level for declaring a significant increase in response rate in the thal/dex arm at full planned information was .047. All toxicities were monitored. We planned to compare the two arms specifically for the proportion of patients with a rash, DVT, neuropathy, or bradycardia of grade 3 or higher, or a toxicity of any type of grade 4 or higher.

One-sided Fisher's exact tests were used to test for difference in response rate and specified toxicity rates between the arms. Two-sided Fisher's exact tests were used to compare other characteristics between the two arms. Two-sided Wilcoxon rank sum tests were used to compare continuous characteristics between the arms. The study crossed the boundaries for declaring a significant increase in response rate as well as increased toxicity in the thal/dex arm at a planned interim analysis.

RESULTS

Patient characteristics are listed on Table 1. Two hundred seven patients were registered onto the study. Eight patients were declared ineligible: no measurable disease at baseline (three patients); no baseline urine protein electrophoresis (one patient); no baseline urine protein electrophoresis and no baseline serum electrophoresis (one patient); no biopsy of plasmacytoma (one patient); no data sent (one patient); and bone marrow biopsy inadequate (one patient). Patients

Table 1. Characteristics of Eligible Patients

Characteristic	Thalidomide Plus Dexamethasone (n = 99)		Dexamethasone (n = 100)		*P*
	No.	%	No.	%	
Age, years					
Median	65		65		.86
Range	38-83		38-82		
Sex					.25
Male	50	51	59	59	
Female	49	49	40*	40	
International staging system (%)					.64
I/II	54	83	43	78	
III	11	17	12	22	
Missing	34		45		
ECOG Performance status					.27
0	42	42	38	38	
1	48	48	45	45	
2	9	9	17	17	
Serum monoclonal protein size, g/dL					.43
Median	3.7		3.3		
Range	0-9.0		0-11.2		
Type of M protein					
IgG	62	63	58	58	
IgA	21	21	22	22	
IgM	0	0	1	1	
Biclonal	0	0	1	1	
Light-chain only	16	16	17	17	
Missing	0		1		
Urine monoclonal protein size mg/24 h median (range), n					.16
Median	91.1		219.5		
Range	0-20,494		0-14,100		
Urine monoclonal protein size, mg/24 h					.24
≥ 200	31	41	35	51	
< 200	45	59	33	49	
Missing	23		32		
Serum creatinine, mg/dL					.33
> 2	3	3	7	7	
≤ 2	96	97	93	93	
Hemoglobin, g/dL					.54
< 10	32	32	28	28	
≥ 10	67	67	72	72	
Platelets, $\times 10^9$/L					.68
< 100	3	3	2	2	
≥ 100	96	97	98	98	
Serum calcium, mg/dL					.28
> 11	2	2	6	6	
≤ 11	96	97	93	93	
Missing	1		1		
Radiographic bone abnormalities					.14
Absent	20	20	30	30	
Present	79	80	69	70	
Missing	0		1		

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin.
*Information missing for one patient.

were well matched between the two arms, as listed on Table 1. One hundred seven patients (54%) had measurable levels of M protein in serum alone, 27 patients (14%) had measurable levels in urine alone, 55 patients (28%) had measurable levels in both serum and urine, and 10 patients (5%) had measurable levels in the serum and unknown levels in the urine at baseline.

Response to Therapy

On the basis of standard ECOG criteria, the best response within four cycles of therapy was significantly higher with thal/dex compared with dexamethasone alone; 62 of 99 patients (63%) versus 41 of 100 patients (41%), respectively ($P = .0017$). Eighteen patients (9%) had a measurable urine protein (> 200 mg/d) at

baseline that was unavailable for assessment at follow-up or had urine follow-up but not enough to confirm response; the median serum M protein in these patients was 4.5 g/dL (range, 2.1 to 9.0 g/dL). When response was assessed using serum monoclonal protein levels in these 18 patients in whom a measurable urine protein was unavailable at follow-up, the adjusted response rates were 72% with thal/dex versus 50% with dexamethasone alone. The 4-month responses occurred rapidly; the median time to response among ECOG criteria responders was 1.1 months in both arms (range, 0.7 to 4.1 months with thal/dex versus 0.7 to 2.9 months with dexamethasone alone).

Complete responses occurred in 4% of patients within four cycles of therapy with thal/dex, and in 0% of patients in the dexamethasone-alone arm. Disease progression within four cycles of therapy was noted in 2% of patients with thal/dex and 5% of patients with dexamethasone alone.

At present, information on whether a stem-cell harvest had been performed is known for 79% of patients. Of these patients, 37% have undergone a stem-cell harvest: 29 of 79 patients (37%) in the thal/dex arm, and 30 of 79 patients (38%) in the dexamethasone-alone arm. Stem-cell harvest was successful in 90% of patients in each arm.

Overall survival curves for the two arms are provided in Figure 1; however, because patients were allowed to discontinue protocol therapy, survival was not an end point for the study and the study was not powered to compare differences in survival between arms.

Toxicity and Deaths

The most common grade 1 to 2 nonhematologic toxicities were fatigue (67% with thal/dex and 51% with dexamethasone alone) and hyperglycemia (67% with thal/dex and 71% with dexamethasone alone). The frequency of major grade 3 or higher nonhematologic toxicities, including treatment-related deaths, that occurred during the course of the trial are listed on Table 2. Grade 3 to 4 neutropenia was seen in 9% of patients receiving thal/dex and in 6% of patients receiving dexamethasone alone.

Grade 3 or higher nonhematologic toxicities were seen with 67% of patients within four cycles with thal/dex and 43% with dexamethasone alone ($P < .001$, one sided). The rate of grade 3 or higher nonhematologic toxicities after excluding DVT was 62% *v* 43% in the two arms, respectively. The incidence of grade 3 (or higher) DVT, rash, sinus bradycardia, neuropathy, and toxicity of any type grade 4 or higher occurring within four cycles was monitored specifically for a planned comparison between the two arms. The incidence of these specifically monitored toxicities was 45% with thal/dex versus 21% with dexamethasone alone ($P < .001$; Table 3).

Table 2. Major Grade 3 or Higher Nonhematologic Toxicities

Toxicity	Treatment Arm: No. of Patients Receiving Thalidomide Plus Dexamethasone (n = 102)	Treatment Arm: No. of Patients Receiving Dexamethasone Alone (n = 102)
Treatment related deaths	5	4
Thrombosis/embolism	20	3
Hyperglycemia	15	15
Fatigue	15	10
Dyspnea	11	10
Hypocalcemia	8	3
Confusion	8	2
Constipation	8	1
Neuropathy-motor	7	4
Muscle weakness	6	9
Edema	6	2
Pneumonitis/pulmonary infiltrates	5	4
Hyponatremia	4	7
Hypotension	4	3
Dehydration	4	1
Neuropathy-sensory	4	1
Rash/desquamation	4	0
Nausea	4	0
Hypoxia	3	3
Depressed level of consciousness	3	2
Anorexia	3	1
Seizure	3	0
Syncope	3	0
Infection without neutropenia	2	5
Conduction abnormality	2	0
Insomnia	0	5
Hypertension	0	3
Anxiety/agitation	0	3

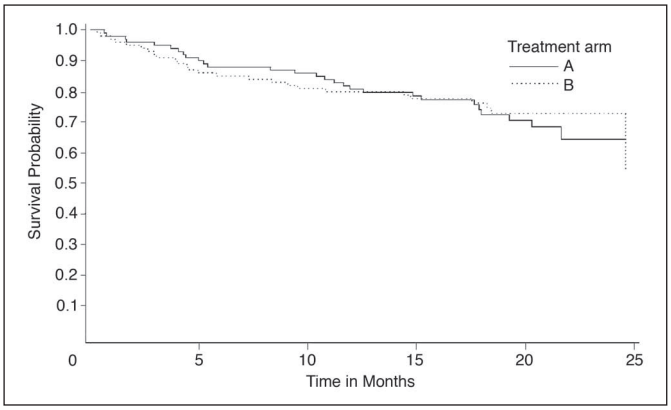

Fig 1. Overall survival estimates of patients enrolled onto the trial by the Kaplan-Meier method. (——) patients treated with thalidomide plus dexamethasone (arm A); (· · ·) patients treated with dexamethasone alone (arm B).

Table 3. Specifically Monitored Grade 3 or Higher Toxicities

Toxicity	Patients Receiving Thalidomide Plus Dexamethasone (n = 102): No.	Patients Receiving Thalidomide Plus Dexamethasone (n = 102): %	Patients Receiving Dexamethasone Alone (n = 102): No.	Patients Receiving Dexamethasone Alone (n = 102): %
Deep vein thrombosis (grade ≥ 3)	17	17	3	3
Skin rash (grade ≥ 3)	4	4	0	0
Sinus bradycardia (grade ≥ 3)	1	1	0	0
Peripheral neuropathy (grade ≥ 3)	7	7	4	4
Toxicity of any type (grade ≥ 4)	35	34	18	18
Total*	46	45	21	21

*Rows do not add to total as patients could have more than one of these toxicity types.

There were seven deaths in the thal/dex arm within four cycles compared with 11 deaths in the dexamethasone-alone arm. Among the seven deaths within 4 months of treatment start, in the thal/dex arm, four were determined to be a result of toxicity (three due to infections and one suicide) possibly, probably, or definitely related to treatment. Among the 11 deaths within 4 months of treatment start, in the dexamethasone arm, four were determined to be a result of toxicity (one each due to infection, respiratory failure, stroke, and GI bleeding) possibly, probably, or definitely related to treatment.

As expected, DVT occurred more frequently with thal/dex compared with dexamethasone alone (17% *v* 3%, respectively; $P < .001$, one sided). In the thal/dex arm, the incidence of DVT was not associated significantly with age; DVT occurred in 12% of patients younger than age 65 compared with 22% in those 65 and older ($P = .29$). There was also no significant association between incidence of DVT and response to therapy ($P = 1.0$). Forty-two percent of all incidences of DVT occurred within the first 2 months of therapy: nine of 23 (39%) patients with thal/dex and two of three (67%) patients with dexamethasone alone.

DISCUSSION

Thalidomide has been reintroduced into clinical practice as an anticancer drug.[10,14,15] In the first clinical trial conducted at the University of Arkansas, 25% of patients with advanced relapsed refractory multiple myeloma achieved a partial response to therapy.[9,16] Subsequently, numerous clinical trials have confirmed the single-agent activity of thalidomide.[17,18] Thalidomide alone produces a response rate of 25% to 35% in patients with relapsed refractory disease. Weber et al[19] made the interesting observation that patients who previously had experienced treatment failure after thalidomide and dexamethasone as single agents could respond again when the two drugs were combined. This led to several clinical trials with thal/dex in relapsed multiple myeloma.[20,21] Response rates with this combination are approximately 50% in the relapsed refractory setting.

Three phase II trials have been conducted with the thal/dex combination in newly diagnosed multiple myeloma. In the Mayo Clinic trial, 50 patients were treated and 64% responded to therapy.[11] Similar response rates were seen in the M.D. Anderson clinical trial and the Italian clinical trial, respectively.[12,13] As a result of these phase II trials, the use of thal/dex has increased significantly in standard practice. Recently, Cavo et al[22] reported a matched case-control study of 200 patients, which showed a significantly higher response rate with oral thal/dex therapy compared with intravenous VAD (76% *v* 52%, respectively).

This clinical trial shows that the addition of thalidomide to dexamethasone significantly increases the 4-month response rate. The response rates seen with thal/dex in this trial are similar to those obtained with complex intravenous regimens including VAD.[6] Thus, thal/dex appears to be an oral alternative to infusional, intravenous chemotherapy. However, the trial shows that thal/dex does increase the rate of the specifically monitored toxicities and grade 3 or higher nonhematologic toxicity in a significant manner. The occurrence of increased DVT with thal/dex therapy has been reported previously by us and others.[23-25] When the trial was designed and initiated, the benefit of routine prophylaxis was not well established. On the basis of the high rate of DVT seen in this trial, and recent results using thrombosis prophylaxis,[26] we recommend routine DVT prophylaxis be used in all patients starting therapy with thal/dex, with either a prophylactic dose of low molecular weight heparin (equivalent of enoxaparin 40 mg once daily), or full-dose anticoagulation with warfarin (targeting a therapeutic international normalized ratio of 2 to 3). In patients considered to have a high bleeding risk, aspirin (81 or 325 mg enteric-coated tablets) once daily can be used instead.

There does not seem to be any adverse effect of the addition of thalidomide on the ability to collect stem cells. On the basis of the results of this trial, thal/dex or dexamethasone alone would both be suitable induction regimens for the treatment of multiple myeloma.

The increased response rates with thal/dex need to be balanced against the increased toxicity. In our opinion, for patients in whom a delay of 1 to 2 months to assess response to dexamethasone alone is possible because of low tumor burden and minimal symptoms, therapy can be initiated with dexamethasone alone. If response is not observed within 1 to 2 months, thalidomide can be added to the regimen. Alternatively, thal/dex can be used from the outset with routine prophylactic anticoagulation after the risks and benefits are reviewed with the patient. For patients with more aggressive disease, including those with painful lytic lesions, impending spinal cord compression, or other symptomatic disease, thal/dex with prophylactic anticoagulation should be preferred over dexamethasone alone as initial therapy. Although the trial had no age restrictions, it should also be noted that patients with performance status of 3 to 4, serum creatinine ≥ 3 mg/dL, hemoglobin ≤ 7 g/dL, and those with active infections were excluded from the study, and the safety and efficacy of thal/dex in these patients cannot be determined from this trial.

One limitation of this trial was that overall survival comparisons were not possible because the trial was intended to study pretransplantation induction therapy. However, an ongoing multicenter study comparing these two regimens, in which stem-cell transplantation is reserved for relapsed disease, will shed light on these outcome measures.

Although thal/dex has emerged as an oral alternative to intravenous induction regimens for myeloma, more effective and safer regimens are needed. Recent studies show that lenalidomide, an analog of thalidomide, may be safer and more effective than thalidomide.[27] A combination trial with lenalidomide plus dexamethasone has already shown improved activity with lower toxicity in a phase II clinical trial.[28] Large phase III trials are ongoing in the United States headed by ECOG and the Southwest Oncology Group to investigate the role of lenalidomide plus dexamethasone in newly diagnosed multiple myeloma. Similarly, high activity has been observed with bortezomib-based induction in several phase II trials. Future randomized trials should compare these active induction regimens to determine the optimum initial therapy for multiple myeloma.

REFERENCES

1. Kyle RA, Rajkumar SV: Plasma cell disorders, in Goldman L, Ausiello D (eds): Cecil Textbook of Medicine (ed 22). Philadelphia, PA, WB Saunders, 2004

2. Kyle RA, Rajkumar SV: Multiple myeloma. N Engl J Med 351:1860-1873, 2004

3. Myeloma Trialists' Collaborative Group: Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: An overview of 6,633 patients from 27 randomized trials. J Clin Oncol 16:3832-3842, 1998

4. Attal M, Harousseau JL, Stoppa AM, et al: A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma: Intergroupe Francais du Myelome. N Engl J Med 335:91-97, 1996

5. Child JA, Morgan GJ, Davies FE, et al: High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 348: 1875-1883, 2003

6. Alexanian R, Barlogie B, Tucker S: VAD-based regimens as primary treatment for multiple myeloma. Am J Hematol 33:86-89, 1990

7. Sirohi B, Powles R: Multiple myeloma. Lancet 363:875-887, 2004

8. Alexanian R, Dimopoulos MA, Delasalle K, et al: Primary dexamethasone treatment of multiple myeloma. Blood 80:887-890, 1992

9. Singhal S, Mehta J, Desikan R, et al: Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 341:1565-1571, 1999

10. Dimopoulos MA, Anagnostopoulos A, Weber D: Treatment of plasma cell dyscrasias with thalidomide and its derivatives. J Clin Oncol 21:4444-4454, 2003

11. Rajkumar SV, Hayman S, Gertz MA, et al: Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. J Clin Oncol 20:4319-4323, 2002

12. Weber DM, Rankin K, Gavino M, et al: Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. J Clin Oncol 21:16-19, 2003

13. Cavo M, Zamagni E, Tosi P, et al: First-line therapy with thalidomide and dexamethasone in preparation for autologous stem cell transplantation for multiple myeloma. Haematologica 89:826-831, 2004

14. Kumar S, Witzig TE, Rajkumar SV: Thalidomide: Current role in the treatment of non-plasma cell malignancies. J Clin Oncol 22:2477-2488, 2004

15. Rajkumar SV, Kyle RA: Thalidomide in the treatment of plasma cell malignancies. J Clin Oncol 19:3593-3595, 2001

16. Barlogie B, Desikan R, Eddlemon P, et al: Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: Identification of prognostic factors in a phase 2 study of 169 patients. Blood 98:492-494, 2001

17. Kumar S, Gertz MA, Dispenzieri A, et al: Response rate, durability of response, and survival after thalidomide therapy for relapsed multiple myeloma. Mayo Clin Proc 78:34-39, 2003

18. Richardson P, Schlossman R, Jagannath S, et al: Thalidomide for patients with relapsed multiple myeloma after high-dose chemotherapy and stem cell transplantation: Results of an open-label multicenter phase 2 study of efficacy, toxicity, and biological activity. Mayo Clin Proc 79:875-882, 2004

19. Weber DM, Rankin K, Gavino M, et al: Thalidomide with dexamethasone for resistant multiple myeloma. Blood 96:167a, 2000 (abstr 719)

20. Anagnostopoulos A, Weber D, Rankin K, et al: Thalidomide and dexamethasone for resistant multiple myeloma. Br J Haematol 121:768-771, 2003

21. Palumbo A, Giaccone L, Bertola A, et al: Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma. Haematologica 86:399-403, 2001

22. Cavo M, Zamagni E, Tosi P, et al: Superiority of thalidomide and dexamethasone over vincristine-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. Blood 106:35-39, 2005

23. Osman K, Comenzo R, Rajkumar SV: Deep vein thrombosis and thalidomide therapy for multiple myeloma. N Engl J Med 344:1951-1952, 2001

24. Zangari M, Siegel E, Barlogie B, et al: Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: Implications for therapy. Blood 100:1168-1171, 2002

25. Zangari M, Anaissie E, Barlogie B, et al: Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood 98:1614-1615, 2001

26. Zangari M, Barlogie B, Thertulien R, et al: Thalidomide and deep vein thrombosis in multiple myeloma: Risk factors and effect on survival. Clin Lymphoma 4:32-35, 2003

27. Richardson PG, Schlossman RL, Weller E, et al: Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood 100:3063-3067, 2002

28. Rajkumar SV, Hayman SR, Lacy MQ, et al: Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood 10.1182/blood-2005-07-2817

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
S. Vincent Rajkumar					Celgene (A)			
Emily Blood			Celgene (A)					
David Vesole					Celgene (A)			Celgene (A)
Philip R. Greipp			Celgene (A)					

Dollar Amount Codes (A) < $10,000 (B) $10,000-99,999 (C) ≥ $100,000 (N/R) Not Required

Author Contributions

Conception and design: S. Vincent Rajkumar, Emily Blood, David Vesole, Rafael Fonseca, Philip R. Greipp
Financial support: S. Vincent Rajkumar, Philip R. Greipp
Administrative support: S. Vincent Rajkumar, Philip R. Greipp
Provision of study materials or patients: S. Vincent Rajkumar, David Vesole, Rafael Fonseca, Philip R. Greipp
Collection and assembly of data: S. Vincent Rajkumar, Emily Blood
Data analysis and interpretation: S. Vincent Rajkumar, Emily Blood, David Vesole, Philip R. Greipp
Manuscript writing: S. Vincent Rajkumar, Emily Blood, David Vesole, Rafael Fonseca, Philip R. Greipp
Final approval of manuscript: S. Vincent Rajkumar, Emily Blood, David Vesole, Rafael Fonseca, Philip R. Greipp