Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma

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We report the results of a phase 2 trial using lenalidomide plus dexamethasone (Rev/Dex) as initial therapy for myeloma. Thirty-four patients were enrolled. Lenalidomide was given orally 25 mg daily on days 1 to 21 of a 28-day cycle. Dexamethasone was given orally 40 mg daily on days 1 to 4, 9 to 12, and 17 to 20 of each cycle. Objective response was defined as a decrease in serum monoclonal protein level by 50% or greater and a decrease in urine M protein level by at least 90% or to a level less than 200 mg/24 hours, confirmed by 2 consecutive determinations at least 4 weeks apart. Thirty-one of 34 patients achieved an objective response, including 2 (6%) achieving complete response (CR) and 11 (32%) meeting criteria for both very good partial response and near complete response, resulting in an overall objective response rate of 91%. Of the 3 remaining patients not achieving an objective response, 2 had minor response (MR) and one had stable disease. Forty-seven percent of patients experienced grade III or higher nonhematologic toxicity, most commonly fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%), and rash (6%). Rev/Dex is a highly active regimen with manageable side effects in the treatment of newly diagnosed myeloma. (Blood. 2005;106:4050-4053)

Introduction

Multiple myeloma is a malignant plasma-cell proliferative disorder that accounts for over 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%, and median survival is approximately 3 years. Recently, autologous stem cell transplantation has been shown to be effective in the treatment of multiple myeloma in 2 randomized clinical trials.[4,5] Patients eligible for stem-cell transplantation should avoid alkylator-based induction therapy to enable an adequate and safe stem-cell harvest early in the disease course.

Vincristine, doxorubicin, and dexamethasone (VAD) was typically used as pretransplantation induction therapy for patients who were considered candidates for stem-cell transplantation.[2,6,7] However, VAD had several disadvantages, including the need for an intravenous indwelling catheter, which predisposes patients to catheter-related sepsis and thrombosis; most of the activity of VAD was from the high-dose dexamethasone component.[8] Recently the combination of thalidomide plus dexamethasone (Thal/Dex) has emerged as an alternative to VAD in newly diagnosed myeloma based on three phase 2 clinical trials and a case-control study.[9-12] Response rates with Thal/Dex range between 64% and 76%, which are comparable to or better than those obtained with VAD.[12,13] In a recent randomized trial conducted by the Eastern Cooperative Oncology Group (ECOG), the response rate with Thal/Dex was significantly higher compared with dexamethasone alone, 58% versus 42%, respectively ($P = .02$).[14] However, grade III or greater nonhematologic toxicities were significantly higher with Thal/Dex compared with dexamethasone alone, 68% versus 43%, respectively.

Lenalidomide (CC-5013) is an analog of thalidomide that has demonstrated significantly more potent preclinical activity compared with thalidomide.[15,16] It has also shown significant activity in relapsed and refractory myeloma alone and in combination with dexamethasone, with fewer nonhematologic side effects compared with thalidomide.[15,17,18] Responses were observed even in patients in whom thalidomide treatment had previously failed. Thus, lenalidomide (Rev)/Dex may be a safer and more effective alternative to Thal/Dex in newly diagnosed myeloma. The goal of this phase 2 clinical trial was to determine the response rate and toxicity of Rev/Dex in patients with previously untreated, newly diagnosed multiple myeloma.

Patients and methods

Eligibility

Informed consent was provided according to the Declaration of Helsinki. Patients were eligible to enter the study if they had previously untreated symptomatic multiple myeloma. Patients were required to have bone marrow plasma cells 10% or greater and measurable disease defined as

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An Inside *Blood* analysis of this article apears at the front of this issue.

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serum monoclonal protein level greater than 10 g/L, urine monoclonal protein level greater than or equal to 200 mg/24 hours, or measurable soft tissue plasmacytoma that had not been radiated. Patients also needed to have hemoglobin level greater than 80 g/L, platelet count greater than 100×10^9/L, absolute neutrophil count greater than 1.5×10^9/L, and creatinine level less than 221 μM (2.5 mg/dL). No systemic therapy for myeloma, with the exception of bisphosphonates, was permitted. Prior corticosteroid use for the treatment of myeloma was not permitted; prior corticosteroid use for the treatment of nonmalignant disorders was permitted but concurrent use was restricted to the equivalent of prednisone 10 mg or less per day. Prior localized radiation therapy for solitary plasmacytoma was permitted provided at least 4 weeks had passed from the date of last radiation therapy to the date of registration. Patients with smoldering multiple myeloma or monoclonal gammopathy of undetermined significance were excluded. Also excluded were patients with uncontrolled infection, another active malignancy, deep vein thrombosis (DVT) that had not been therapeutically anticoagulated, and ECOG performance score of 3 or 4. Pregnant or nursing women, as well as 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. Women of child-bearing age were required to have a pregnancy test done every 4 weeks if their periods were regular, and every 2 weeks if their periods were irregular. Patients were required to be at least 18 years of age. The study was approved by the Mayo Clinic Institutional Review Board in accordance with federal regulations and the Declaration of Helsinki.

Treatment schedule

Lenalidomide was given orally at a dose of 25 mg daily on days 1 to 21 of a 28-day cycle. Dexamethasone was given orally at a dose of 40 mg daily on days 1 to 4, 9 to 12, and 17 to 20 of each cycle. Patients also received an aspirin (80 mg or 325 mg per physician discretion) once daily as thrombosis prophylaxis. Each cycle was repeated every 4 weeks. Patients were allowed to go off treatment after 4 cycles of therapy to pursue stem-cell transplantation, but treatment beyond 4 cycles was permitted at physician's discretion. For patients continuing therapy beyond 4 months, the dose of dexamethasone was reduced to 40 mg on days 1 to 4 of each cycle.

Dose adjustments were permitted based on toxicity. Lenalidomide was to be permanently discontinued in the event of erythema multiforme/Stevens Johnson syndrome, desquamating/blistering rash of any grade, any rash of grade IV severity, grade IV neuropathy or hypersensitivity, and grade III or higher bradycardia or cardiac arrhythmia. Subjects experiencing other grade III or greater adverse events felt related to lenalidomide had the drug held until resolution of the adverse event and restarted at the next lower dose level. Except for isolated neutropenia, in which case the addition of granulocyte colony-stimulating factors (G-CSFs) were permitted instead of dose reduction, lenalidomide was progressively reduced for other related grade III or higher adverse events to dose levels of 15 mg, 10 mg, and 5 mg administered on days 1 to 21 of a 28-day cycle. When grade III or IV adverse events occurred prior to day 15 of a cycle and resolved to grade II or lower severity prior to day 21 of the cycle, lenalidomide was resumed at the next lower dose level until day 21, with the next cycle continuing at the reduced dose level. For grade III or IV adverse events occurring on or after day 15 of a given cycle, lenalidomide was held for the remainder of the cycle and reduced by one dose level beginning with the next cycle. Once the dose of lenalidomide was reduced for toxicity, no dose re-escalation was permitted. Dose reductions were permitted for dexamethasone-related toxicity by lowering the dose of dexamethasone progressively to 40 mg daily for 4 days every 2 weeks, 40 mg daily for 4 days every 4 weeks, and 20 mg daily for 4 days every 4 weeks. Patients unable to tolerate the lowest doses of lenalidomide or dexamethasone needed to stop therapy with that agent permanently.

Response and toxicity criteria

The primary end point of this trial was response rate estimated based on the best response to therapy for each patient during the course of treatment. The response criteria used were standard European Group for Blood and Bone

also defined. An objective (partial) response was defined as at least 50% reduction in the level of the serum monoclonal (M) protein and a reduction in 24-hour urinary M protein level of at least 90% or to less than 200 mg. In addition, there must be no increase in the number or size of lytic bone lesions or any other evidence of progressive disease by other parameters. In addition to criteria listed for partial response, complete response (CR) required complete disappearance of the monoclonal protein in the serum and urine by immunofixation studies and 5% or less plasma cells on bone marrow examination. Subclassification as VGPR required in addition to criteria for partial response, at least 90% reduction in serum M protein level, 24-hour urine M protein level 100 mg or less, and 5% or less plasma cells on bone marrow examination. Similarly, subclassification as nCR required all criteria for CR except that the monoclonal protein level in serum and urine was not present on electrophoresis but detectable on immunofixation alone. Patients achieving at least 25% reduction in serum M protein level and at least 50% to 89% reduction in urine M protein level were considered to have minor response (MR) but were not included in the calculation of the overall response rate. All response categories needed confirmation by 2 consecutive measurements at least 4 weeks apart, which is a modification from the Bladé criteria[19] in which responses are confirmed at least 6 weeks apart.

Disease progression required any one of the following criteria: (1) increase in serum M protein level 25% or higher above the lowest response level or a rise in level by more than 5 g/L; (2) increase in urine monoclonal protein level by 25% above the lowest remission value or increase in excretion by 200 mg/24 hours or greater; (3) increase in size of soft tissue plasmacytoma by more than 50% or appearance of a new plasmacytoma; (4) definite appearance of bone lesions or increase in the size of existing bone lesions by more than 50%; and (5) unexplained hypercalcemia greater than 2.875 mM (> 11.5 g/dL). For patients in CR, relapse included reappearance of monoclonal protein level by immunofixation or protein electrophoresis of the serum or urine or any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia).

The National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), version 3, was used to grade adverse events as well as to assign perceived attribution of these events to the study treatment regimen. By these criteria, toxicity was defined as an adverse event considered to be possibly, probably, or definitely related to treatment.

Statistical design and analysis

The primary end point of this trial was the proportion of confirmed responses (includes patients achieving CR, VGPR, or PR) as defined earlier. All patients meeting the eligibility criteria who had signed a consent form and had begun treatment were evaluated for response. Thirty evaluable patients with previously untreated symptomatic multiple myeloma were to be accrued. A one-stage design with an interim analysis was used to evaluate the confirmed response rate in 30 evaluable patients with previously untreated symptomatic multiple myeloma. Specifically, a true response rate of 45% in this patient population would be considered promising, versus the null hypothesis that the true response rate was at most 20%. Based on these assumptions, this treatment regimen was considered inactive if 9 or fewer confirmed responses were seen. If 10 or more confirmed responses would be considered sufficient evidence of promising activity then this treatment regimen may be recommended for further testing in subsequent studies. These decision criteria were based on a modification of a 2-stage Fleming design where accrual was not halted for the interim analysis. An interim analysis was done after the 13th patient was accrued, where if 2 or fewer responses were observed this would be considered early evidence that the treatment regimen was inactive and could terminate accrual. Using this design, we had 92% power at 0.06 level of significance to detect a response rate of at least 45% (versus the null hypothesis that the true response rate was at most 20%). In addition, we anticipated accruing additional patients to account for the possibility of ineligibility, cancellations, or major treatment violations. To include all evaluated patients in the confidence interval, an exact binomial confidence interval will be used for the response rate, assuming that the number of patients who respond to treatment is binomially distributed. The maximum

Results

Overall, 34 patients (median age, 64 years; range; 32-78 years) were registered to the study from March 2004 through October 2004 and all were evaluable for response and toxicity. Patient characteristics at study entry for these patients are presented in Table 1. All patients, including 4 with Durie-Salmon stage I myeloma, were symptomatic at study entry.

Response to therapy

Thirty-one (91%) of 34 patients (95% confidence interval, 79% to 98%) achieved an objective response to therapy. Of the 31 responders, 2 patients (6%) achieved a CR, 11 patients (32%) achieved a VGPR, and 18 patients achieved a PR as their best response to treatment (Table 2). All patients who met criteria for VGPR also met criteria for nCR. Of the 3 patients who did not achieve at least a partial response to treatment, 2 met criteria for MR and one had stable disease. Responses were rapid; the median time to response was one month.

Patients were allowed to proceed to stem-cell harvest after completing 4 cycles of therapy if they were willing and deemed eligible for such therapy. As of May 2005, 15 (44%) of the 34 patients have undergone a stem-cell harvest; 10 of these patients went off treatment to proceed with autologous stem cell transplantation and the remaining 5 have elected to stay on treatment and their stem cells have been cryopreserved for future use. Adequate stem cells ($> 3.0 \times 10^6$ CD34 cells/kg body weight) were obtained in all patients who underwent autologous stem cell transplantation (median CD34 cells 7.9×10^6/kg over 2 to 7 collections). Stem cells were mobilized with G-CSF 10 μg/kg in all but 2 patients who received cyclophosphamide 1500 mg/m^2 intravenously daily for 2 days in addition to G-CSF.

Besides the 10 patients who have gone off treatment for autologous stem cell transplantation, 2 patients ended treatment to seek alternative treatment and 1 patient died on treatment (details in "Toxicity and deaths").

Toxicity and deaths

Side effects were manageable. Major toxicities seen in this trial are listed in Table 3 and represent the most severe toxicity associated with the study treatment for each patient. Overall, 47% of patients experienced grade III or higher nonhematologic toxicity. The most common grade III or higher nonhematologic toxicities were fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%), and rash (6%). One patient died on study and this was attributed to infection unrelated to therapy; the patient had stopped all therapy for over a month before the fatal infection occurred. One patient developed a pulmonary embolism (grade IV toxicity) but recovered with therapy; no other patient developed DVT or pulmonary embolism.

Table 1. Characteristics of eligible patients

Characteristic	All patients, n = 34	
	No. of patients	Percent of patients
Sex, female	11	32
Durie-Salmon stage		
I	4	12
II	14	41
III	16	47
ISS stage		
I	14	41
II	16	47
III	4	12
Immunoglobulin heavy chain type		
IgG	16	47
IgA	11	32
Light chain only, Bence Jones protein	7	21
Anemia, hemoglobin level less than 110 g/L	14	41
Lytic bone lesions	19	59
Beta 2-microglobulin level greater than 2.7 mg/L	18	53

Table 2. Response to therapy

Response category	No. of patients, n = 34	Percent patients responding
Overall objective response, CR + VGPR/nCR + PR	31	91
CR	2	6
VGPR/nCR	11	32
PR	18	53
MR	2	6
No response	1	3

Discussion

In order to overcome the nonhematologic toxicities of thalidomide including its teratogenicity, several active analogs of thalidomide have been developed. Lenalidomide has demonstrated significantly more potent and promising preclinical activity than thalidomide

Table 3. Major hematologic and nonhematologic toxicities

Toxicity	Grade 1-2, % of patients	Grade 3-4, % of patients
Hematologic toxicity		
Anemia	6	6
Neutropenia	32	12
Leukopenia	15	9
Lymphopenia	15	6
Thrombocytopenia	27	0
Nonhematologic toxicity		
Fatigue	41	15
Muscle weakness	29	6
Pneumonitis	3	6
Skin rash	6	6
Anxiety	15	6
Agitation	15	3
Cardiac arrhythmia	3	3
Nausea	3	3
Hyperglycemia	3	3
Elevated AST level	0	3
Infection	0	3
Colonic perforation	0	3
Increased liver enzymes	0	3
Deep vein thrombosis/pulmonary embolism	0	3
Neuropathy	21	0
Constipation	15	0
Depression	15	0
Confusion	12	0
Dizziness	9	0
Dyspepsia	9	0
Elevated alkaline phosphatase level	6	0
Bilirubin level	6	0

and has entered clinical trials.[15,16] Two phase 1 trials of lenalidomide showed activity in heavily pretreated patients with relapsed refractory myeloma with myelosuppression as the major adverse event.[15,17] A subsequent multicenter randomized phase 2 study in relapsed and refractory myeloma[18] showed that 38% of patients responded with at least a 25% or greater reduction in paraprotein levels, establishing the activity of this drug. Approximately one third of the patients who did not respond to monotherapy developed responses when dexamethasone was added to the regimen. More recently, two large phase 3 trials have compared Rev/Dex to placebo plus dexamethasone in relapsed, refractory myeloma. Preliminary results from both trials show superior response rates and time to progression in favor of Rev/Dex.[20]

In this trial, we show a high response rate with oral Rev/Dex therapy in newly diagnosed myeloma. Ninety-one percent of patients responded to therapy, with 2 additional patients achieving MR. Although response confirmation was defined as being 4 weeks apart rather than 6 weeks, this would not affect the observed response rate since only one disease progression has occurred so far (10 months after the last patient was enrolled). The observed response rate compares favorably with those previously reported with Thal/Dex. More importantly, the rate of serious adverse effects seen in this trial was similar to that observed with dexamethasone alone in a recent randomized trial conducted by ECOG. Unlike, thalidomide side effects such as constipation and neuropathy were uncommon and sedation was not seen; no patient developed grade III or higher neuropathy. The similarity of the adverse event rate to that observed with dexamethasone alone suggests that high-dose corticosteroid therapy contributes greatly to most of the nonhematologic adverse events noted on this trial, especially fatigue, muscle weakness, hyperglycemia, agitation, and anxiety.

Lenalidomide has been noted to cause myelosuppression in earlier trials conducted in myelodysplastic syndrome and relapsed myeloma. However, myelosuppression was minimal in this trial, probably reflecting the better bone marrow reserve of patients with previously untreated disease. There was no adverse effect on stem-cell mobilization, indicating that this would be a useful pretransplantation conditioning regimen. The relatively low toxicity of this regimen lends itself as a major contender for primary therapy of myeloma, provided appropriate phase 3 trials can be conducted. Since the regimen is orally administered it is less cumbersome than complex intravenous regimens.

DVT was a toxicity about which we were particularly concerned and therefore initiated aspirin prophylaxis routinely in this study for all patients, based on the efficacy of aspirin in preventing Thal/Dex-associated DVT.[21] Although typically used to prevent arterial thromboembolism, aspirin has been found to be effective in prevention of venous thrombosis as well in certain settings such as the antiphospholipid antibody syndrome.[22] The incidence of DVT was low in this trial (3%), similar to that observed in the dexamethasone-alone arm of a recent randomized trial that compared Thal/Dex to dexamethasone alone.[14] On the other hand, two phase 3 trials in relapsed refractory myeloma using Rev/Dex conducted without routine aspirin (or other anticoagulant) prophylaxis noted an increased incidence of DVT (9%-15%).[20] Recently, accrual to a large phase 3 ECOG trial using Rev/Dex in newly diagnosed myeloma patients has been temporarily suspended because of an increased risk of DVT in the absence of mandatory thromboprophylaxis. Based on this, we recommend caution and routine prophylaxis with aspirin once daily for all patients treated with Rev/Dex.

We conclude that Rev/Dex is highly active in newly diagnosed multiple myeloma, inducing objective responses in over 90% of treated patients and complete or near complete responses in 38%. Both cooperative group randomized trials currently ongoing in the United States are testing Rev/Dex as initial therapy for myeloma. The Southwest Oncology Group trial compares Rev/Dex with dexamethasone alone as primary therapy. The ECOG trial on the other hand compares Rev/Dex as administered on the current trial to Rev/low-dose dexamethasone, in an attempt to further reduce toxicity while preserving the same response rate.

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