

Long-term Results of Response to Therapy, Time to Progression, and Survival With Lenalidomide Plus Dexamethasone in Newly Diagnosed Myeloma

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OBJECTIVE: To determine the long-term effects of a combined regimen of lenalidomide and dexamethasone (Rev-Dex) on time to progression, progression-free survival, and overall survival (OS) in patients with multiple myeloma.

PATIENTS AND METHODS: From March 2004 through October 2004, 34 patients were registered for the study. They were treated with 25 mg/d of lenalidomide on days 1 through 21 of a 28-day cycle and 40 mg/d of dexamethasone on days 1 through 4, 9 through 12, and 17 through 20 of each cycle. After 4 cycles of therapy, patients were allowed to discontinue treatment to pursue autologous stem cell transplant (SCT). Treatment beyond 4 cycles was permitted at the physician's discretion.

RESULTS: Thirteen patients proceeded to SCT after initial therapy and were censored at that time point for purposes of calculation of response. Thirty-one patients achieved an objective response, defined as a partial response or better (91%; 95% confidence interval, 79%-98%), with a complete response plus very good partial response rate of 56%. The complete response plus very good partial response among the 21 patients who received Rev-Dex without SCT was 67%. The 2-year progression-free survival rates for patients proceeding to SCT and patients remaining on Rev-Dex were 83% and 59%, respectively; the OS rates were 92% and 90% at 2 years and 92% and 85% at 3 years, respectively. The 3-year OS rate for the whole cohort was 88%.

CONCLUSION: The Rev-Dex regimen is highly active in the treatment of newly diagnosed multiple myeloma. Responses are durable with a low progression rate at 2 years. Randomized trials that incorporate quality-of-life measures are needed to determine if this and other combination regimens are better used early in therapy or should be reserved for later interventions.

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CI = confidence interval; CR = complete response; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte colony-stimulating factor; OS = overall survival; PFS = progression-free survival; PR = partial response; Rev-Dex = lenalidomide and dexamethasone; SCT = stem cell transplant; Thal-Dex = thalidomide plus dexamethasone; TTP = time to progression; VGPR = very good partial response

Multiple myeloma remains incurable, notwithstanding recent advances in treatment options. Autologous stem cell transplant (SCT) has been shown to be superior to conventional dose chemotherapy in 2 randomized trials.^{1,2} The standard therapy before SCT was once vincristine, doxorubicin, and dexamethasone.³⁻⁵ Despite lack of a randomized phase 3 trial, the combination of thalidomide plus dexamethasone (Thal-Dex) is replacing vincristine, doxo-

rubicin, and dexamethasone in newly diagnosed myeloma based on efficacy, ease of administration, and low toxicity reported in phase 2 clinical trials⁶⁻⁸ and a case control study.⁹ In a recent randomized trial conducted by the Eastern Cooperative Oncology Group (ECOG), the response rate with Thal-Dex (63%) was significantly higher than with dexamethasone alone (41%) ($P=.0017$).¹⁰

Lenalidomide (CC-5013) belongs to a class of thalidomide analogues that are termed *immunomodulatory drugs*. The safety profile of lenalidomide differs from that of thalidomide in preclinical¹¹ and clinical studies.^{12,13} Data from clinical trials in patients with relapsed myeloma suggest that lenalidomide is less likely to cause peripheral neuropathy, constipation, and sedation than thalidomide¹³⁻¹⁵ but is more myelosuppressive. The incidence of thromboembolism is similar for the 2 regimens.^{16,17} We hypothesized that lenalidomide and dexamethasone (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 newly diagnosed multiple myeloma. We previously reported the remarkably high response rate (91%) seen in this trial with Rev-Dex as frontline therapy for myeloma.¹⁸ However, that report reflected responses seen primarily in the first 4 to 6 months of therapy, and data on long-term end points such as time to progression (TTP), progression-free survival (PFS), and overall survival (OS) were not available. We now present the first data on durability of response, TTP, PFS, and OS with the use of Rev-Dex as initial therapy for myeloma. Our analysis also includes new data regarding the depth and durability of responses with this regimen.

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PATIENTS AND METHODS

ELIGIBILITY

Patients who were aged at least 18 years and had previously untreated symptomatic multiple myeloma were eligible to enroll in the study, provided that they met the following conditions. Patients were required to have bone marrow plasma of 10% or greater and measurable disease, as defined by M protein greater than 10 g/L, urine light chain excretion greater than or equal to 200 mg/d, or measurable soft tissue plasmacytoma that had not been radiated. Patients also needed to have hemoglobin levels greater than 8 g/dL, platelet counts greater than $100 \times 10^9/L$, absolute neutrophil counts greater than $1.5 \times 10^9/L$, and creatinine levels less than 2.5 mg/dL (to convert to $\mu\text{mol/L}$, multiply by 76.25). No systemic therapy or prior corticosteroid treatment for myeloma was permitted. Prior localized radiation therapy for solitary plasmacytoma was allowed, provided that it occurred at least 4 weeks before 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 that had not been therapeutically anticoagulated, and an ECOG performance score of 3 or 4. Men who were unwilling to use a condom, pregnant or nursing women, and women of child-bearing age who refused to use a dual method of contraception were excluded from the study. Overall, 34 patients were registered to the study from March 2004 through October 2004, all of whom were evaluated for response and toxicity. The study was approved by the Mayo Foundation Institutional Review Board in accordance with federal regulations and the Declaration of Helsinki.

TREATMENT SCHEDULE

On days 1 through 21 of a 28-day cycle, patients received 25 mg/d of lenalidomide orally. On days 1 through 4, 9 through 12, and 17 through 20 of each cycle, 40 mg/d of dexamethasone was given orally. Patients also received an aspirin (81 mg or 324 mg, at the discretion of the physician) once daily as thrombosis prophylaxis. Antibiotic and antiviral prophylaxis was not mandated but left to physician discretion. Patients were allowed to discontinue treatment after 4 cycles of therapy to pursue SCT, but treatment beyond 4 cycles was permitted at the physician's discretion. Patients who continued therapy beyond 4 months received 40 mg/d of dexamethasone only on days 1 through 4 only of each cycle.

Dose adjustments were permitted based on toxicity. Lenalidomide was permanently discontinued in the event of erythema multiforme/Stevens-Johnson syndrome,

desquamating/blistering rash of any grade, any rash of grade 4 severity, grade 4 neuropathy or hypersensitivity, and grade 3 or higher bradycardia or cardiac arrhythmia. If patients experienced other grade 3 or higher adverse events that were thought to be related to lenalidomide, the drug was withheld until resolution of the adverse event and then restarted at the next lower dose level. Lenalidomide was progressively reduced for other related grade 3 or higher adverse events to dose levels of 15 mg, 10 mg, and 5 mg administered on days 1 through 21 of a 28-day cycle, except for isolated cases of neutropenia, in which the addition of granulocyte colony-stimulating factor (G-CSF) was permitted instead of dose reduction. When grade 3 or 4 adverse events occurred before day 15 of a cycle and resolved to a severity of grade 2 or lower before 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 3 or 4 adverse events that occurred on or after day 15 of a given cycle, lenalidomide was withheld for the remainder of the cycle and reduced by 1 dose level beginning with the next cycle. Once the dose of lenalidomide was reduced for toxicity, no dose reescalation was allowed. The following progressive dose reduction was permitted for dexamethasone-related toxicity: 40 mg/d for 4 days every 2 weeks, then 40 mg/d for 4 days every 4 weeks, and finally 20 mg/d for 4 days every 4 weeks. Therapy with lenalidomide or dexamethasone was discontinued permanently in patients who were unable to tolerate the lowest doses of these agents.

RESPONSE AND TOXICITY CRITERIA

The primary end point of this trial was the response rate, estimated on the basis of the best response to therapy for each patient during the course of treatment. The response criteria used were standard European Group for Blood and Marrow Transplant¹⁹ (ie, Bladé criteria). An objective (partial or better) response was defined as a 50% or greater reduction in the level of the serum M protein and/or a reduction in 24-hour urinary light chain excretion by 90% or greater or to less than 200 mg. No increase in the number or size of lytic bone lesions or any other evidence of progressive disease by other parameters was allowed. To be judged a complete response (CR), the partial response (PR) criteria had to be met, no serum or urine M proteins could be detected by immunofixation studies, and 5% or fewer plasma cells were observed on bone marrow examination. Patients were classified as having a very good partial response (VGPR) based on the International Myeloma Working Group response criteria.²⁰ In addition to criteria for PR, VGPR required that serum and urine M proteins be detectable only on immunofixation but not on electrophoresis, a 90% or greater reduction in serum M

TABLE 1. Patient Characteristics*†

Characteristic	All patients (N=34)	No transplant (n=21)	Transplant (n=13)	P value (transplant vs no transplant)
Sex, female	11 (32)	3 (14)	8 (62)	.01‡
Anemia (hemoglobin <11 g/dL)	15 (44)	9 (43)	6 (46)	.85
Lytic bone lesions	19 (56)	11 (52)	8 (62)	.60
β ₂ -Microglobulin >2.7 mg/L	19 (56)	11 (52)	8 (62)	.60
Lactate dehydrogenase (≥250 U/L)	4 (12)	3 (14)	1 (8)	>.99‡
ISS stage 3	4 (12)	3 (14)	1 (8)	>.99‡
BM plasma cell labeling index ≥1%§	14 (41)	9 (43)	5 (38)	.85

*BM = bone marrow; ISS =International Staging System.

†Data are given as number (percentage) unless indicated otherwise.

‡Exact P value.

§Only 32 of the 34 patients had a BM plasma cell labeling index done at baseline.

proteins, and a 24-hour urine M protein level of 100 mg/d or less. All response categories had to be confirmed by 2 consecutive measurements at least 4 weeks apart; this was a modification of the Bladé criteria that require responses to be confirmed at least 6 weeks apart.²⁰

Disease progression required any 1 of the following criteria: (1) increase in serum M protein by 25% or more above the lowest response level and an increase in absolute level by more than 5g/L, (2) increase in urine M protein by 25% above the lowest remission value and an absolute increase in excretion by 200 mg/d or greater, (3) increase in the 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 11.5 mg/dL (8.9-10.1 mg/dL) (to convert to mmol/L, multiply by 0.25). For patients with CR, relapse included reappearance of M protein on 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 Terminology Criteria for Adverse Events, 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 possibly, probably, or definitely related to treatment.

STATISTICAL ANALYSES

The primary end point of this trial was the proportion of confirmed responses (patients who achieved CR, VGPR or PR), as defined earlier. All patients who met the eligibility criteria, signed a consent form, and had begun treatment were evaluated for response. Our goal was to assess responses in 30 patients with previously untreated symptomatic multiple myeloma; more than 30 patients were accrued to account for the possibility of ineligibility, cancellations, or major treatment violations. A modified 2-stage Fleming

design, in which accrual was not halted for interim analysis, was used to evaluate the confirmed response rate. In this population, a true response rate of 45% would be considered promising vs the 20% true response rate arrived at by the null hypothesis. On the basis of these assumptions, 9 or fewer confirmed responses meant that the treatment regimen was inactive, 10 or more that it was promising and recommended for further testing. Interim analysis was performed after the 13th patient was accrued; if 2 or fewer responses were observed, the treatment regimen was considered inactive on the basis of this early evidence and accrual was terminated. This study design was powered at 92% ($P=.06$) for the detection of a response rate of at least 45%. To include all evaluated patients in the confidence interval (CI), an exact binomial CI was used for the response rate, assuming that the number of patients who responded to treatment was binomially distributed. The maximum grade for each type of adverse event along with perceived causality was recorded and reported for each patient.

RESULTS

Patient characteristics at study entry are presented in Table 1. All patients, including 4 with Durie-Salmon stage I myeloma, were symptomatic at study entry. Patients who discontinued therapy to proceed to SCT (n=13) received a median of 4 cycles of therapy (range, 4-13 cycles), whereas those who continued treatment with Rev-Dex (n=21) received a median of 19 cycles of therapy (range, 2-30 cycles). Median follow-up was 36 months.

RESPONSE TO THERAPY

Thirty-one of 34 patients (91%; 95% CI, 79%-98%) achieved an objective response to therapy. Six patients (18%) achieved a CR, 13 patients (38%) a VGPR, and 12 patients (35%) a PR as their best response to treatment (Table 2), with a CR + VGPR rate of 56%. Of the 3 patients

TABLE 2. Long-term Results of Lenalidomide-Dexamethasone Therapy*†

	Entire cohort (N=34)	No transplant group (n=21)
Objective response (CR or VGPR or PR)	31 (91)	18 (86)
CR	6 (18)	5 (24)
VGPR	13 (38)	9 (43)
PR	12 (35)	4 (19)

*CR = complete response; PR = partial response; VGPR = very good partial response.
 † Data are given as number (percentage).

who did not achieve at least a PR to treatment, 2 had at least a 25% reduction in M protein levels, and 1 had stable disease. Responses were rapid; the median time to response was 1 month.

As described previously, patients were allowed to proceed to stem cell harvest after completing 4 cycles of therapy if they were willing to undergo and were deemed eligible for such therapy. As of December 2006, 15 of the 34 patients (44%) had undergone a stem cell harvest, 13 of whom discontinued treatment to proceed with early autologous SCT within 1 year of diagnosis (transplant group). Adequate stem cells ($>3.0 \times 10^6$ CD34 cells/kg of body weight) were obtained in all patients who underwent autologous SCT; the median CD34 cell count was 7.9×10^6 /kg body weight over 2 to 7 collections. Stem cells were mobilized with 10 µg/kg of G-CSF in all but 2 patients who received a daily dose of 1500 mg/m² of cyclophosphamide for 2 days in addition to G-CSF. Both patients initially responded to Rev-Dex; however, their levels of M protein and circulating monoclonal plasma cells later increased.

Among the 21 patients who continued to receive Rev-Dex as primary therapy (the no transplant group), the depth of remission improved over time. Complete response was achieved by 5 patients (24%), VGPR by 9 patients (43%), and PR by 4 patients (19%) as their best response to treatment. The CR plus VGPR rate was 67%.

To assess whether transplant was offered only to patients with less-than-optimal responses, we examined re-

TABLE 3. Responses to Lenalidomide-Dexamethasone Therapy at Time of Stem Cell Transplant Decision (Month 4)*†

	No transplant (n=21)	Transplant (n=13)
CR or VGPR or PR	18 (86)	13 (100)
CR	1 (5)	1 (8)
VGPR	9 (43)	4 (31)
PR	8 (38)	8 (62)
NR	3 (14)	0 (0)

*CR = complete response; PR = partial response; NR = no response; VGPR = very good partial response.
 † Data are given as number (percentage).

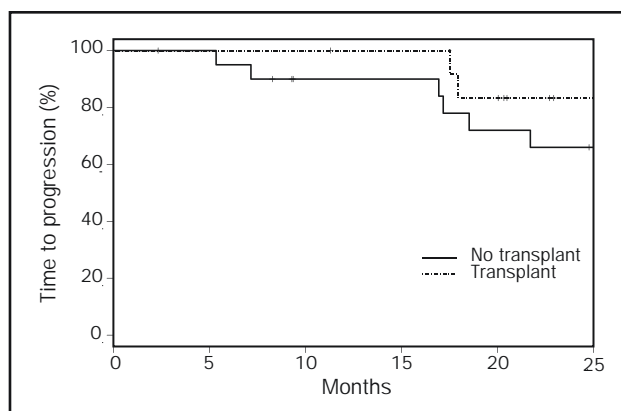


FIGURE 1. Time to progression of patients who proceeded to early stem cell transplant and those who did not.

sponse rates at month 4, which, in our experience, was when most patients decided whether to discontinue treatment to pursue SCT or to continue with Rev-Dex therapy. Baseline characteristics of the transplant vs no transplant group are summarized in Table 1. The overall response rate was 90% among the no transplant group and 100% among the transplant group. The details regarding depth of response at the 4-month time point are listed in Table 3.

TOXICITY AND DEATHS

Major toxicities seen in this trial were described in detail in our previous publication.¹⁸ Overall, 55% of patients experienced grade 3 or higher nonhematologic toxicity at some point during therapy, most commonly fatigue (21%), neutropenia (21%), anxiety (6%), pneumonitis (6%), muscle weakness (6%), and rash (6%). One patient developed a pulmonary embolism (grade 4 toxicity) but recovered with therapy; no other patient developed deep vein thrombosis or pulmonary embolism. Two patients died during the study, both from infection, possibly related to therapy. The 4-month mortality rate was 5.9% (95% CI, 0.7%-20.0%).

TIME TO PROGRESSION, PROGRESSION-FREE SURVIVAL, AND OVERALL SURVIVAL

The median TTP was 32.4 months for the no transplant group; median TTP has not been reached for the transplant group. The 2-year TTP rates were 71% for the entire cohort, including 66% in the no transplant group and 83% in the transplant group (Figure 1). The 2-year PFS rates for the no transplant group and the transplant group were 59% and 83%, respectively (Figure 2). The median PFS was 29 months for the no transplant group and has not yet been reached for the transplant group. The 2-year OS rates for the no transplant vs transplant group were 90% and 92%, respectively; the corresponding 3-year rates were 85% and 92%, respectively (Figure 3). The 3-year OS for the whole cohort was 88%.

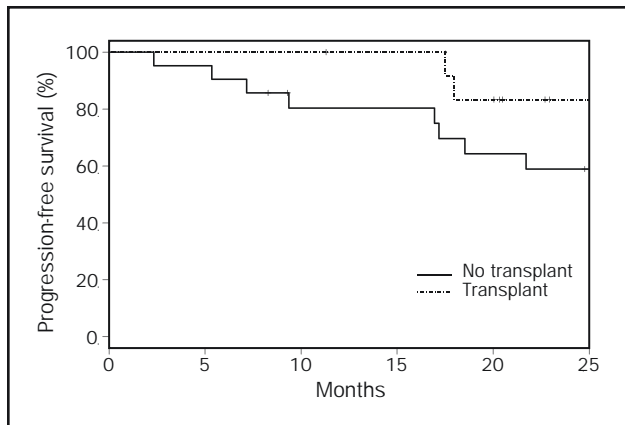


FIGURE 2. Progression-free survival of patients who proceeded to early stem cell transplant and those who did not.

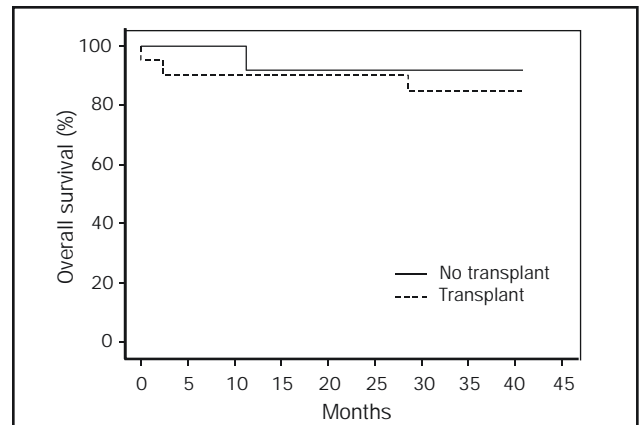


FIGURE 3. Overall survival of patients who proceeded to early stem cell transplant and those who did not.

DISCUSSION

We previously reported a remarkably high response rate (91%) with oral Rev-Dex therapy in newly diagnosed myeloma.¹⁸ The observed response rate compares favorably to those previously reported with Thal-Dex. With extended follow-up we now provide evidence of the depth and durability of these responses. The CR plus VGPR rate for the entire cohort was 44% at 4 months but improved over time to 56% for the entire cohort and 67% for those who continued to receive Rev-Dex as primary therapy.

We also show that responses are durable and that the OS rate at 2 years is excellent. The TTP and PFS of patients who proceeded to transplant vs those who received Rev-Dex as primary therapy should not be compared because this was not a randomized trial. The no transplant group includes patients (n=2) who died early before a decision on SCT could be made. The study is also potentially biased by the choice of one approach over the other. The estimated median TTP of 32.4 months in the no transplant group is comparable to that reported in the Intergroupe Français Du Myélome single vs double transplant trial in which all patients were younger than 60 years (vs the median age of 64 years in our trial).²¹

With the advent of new drugs and new drug combinations, response rates that exceed 80% are being seen with increasing frequency in patients with newly diagnosed myeloma. As an induction regimen, bortezomib has shown response rates of approximately 40% as a single agent.²² Significantly higher response rates (approximately 70%-90%) have been observed with bortezomib plus dexamethasone²³; bortezomib, thalidomide, dexamethasone²⁴; and other bortezomib-based combinations.²⁵ In one study,²³ the CR plus VGPR rate was approximately 25% to 30% with bortezomib plus dexamethasone. Future

studies are needed to compare Rev-Dex to bortezomib-based regimens.

Treatment with Rev-Dex was well tolerated in this trial, in contrast to results reported elsewhere with thalidomide. Adverse effects such as constipation and neuropathy were uncommon, and sedation was not seen; no patient developed grade 3 or higher neuropathy. Concerns regarding the toxicity of dexamethasone led ECOG to complete a large phase 3 trial that compared lenalidomide with standard high-dose pulse dexamethasone to lenalidomide with low-dose weekly dexamethasone. Preliminary results show that toxicity rates are significantly higher with Rev-standard-dose Dex compared to Rev-low-dose Dex. Early mortality rates (ie, first 4 months) were 5% and 0.5%, respectively.²⁶ Despite the use of high-dose dexamethasone, the incidence of thromboembolism in this series was only 3%. We attribute this low rate to prophylaxis with aspirin and minimal use of erythropoietins in these patients.

CONCLUSION

We showed that Rev-Dex is highly active in the treatment of newly diagnosed multiple myeloma and that responses were durable, with a low progression rate at 2 years. The development of new active agents for multiple myeloma has resulted in many such combination regimens. The high response rates observed with these regimens have raised questions about whether we should still be offering autologous SCT to patients as initial therapy. High response rates are not the only factor determining the desirability of using SCT. All new regimens have unique toxicities, and quality-of-life measures should be included in all future randomized trials. The challenge now is to build on this progress and find new, more active, and less toxic agents and combi-

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