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ORIGINAL ARTICLE

Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM)

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Patients with multiple myeloma progressing on current therapies have limited treatment options. Pomalidomide (CC4047), an immunomodulatory drug, has significant activity in relapsed myeloma and previous studies suggest activity in lenalidomide refractory disease. To better define its efficacy in this group, we treated a cohort of lenalidomide refractory patients. Pomalidomide was given orally (2 mg) daily, continuously in 28-day cycles along with dexamethasone (40 mg) given weekly. Responses were assessed by the International Myeloma Working Group Criteria. Thirty-four patients were enrolled. The best response was very good partial response in 3 (9%), partial response (PR) in 8 (23%), best responses (MR) in 5 (15%), stable disease in 12 (35%) and progressive disease in 6 (18%), for an overall response rate of 47%. Of the 14 patients that were considered high risk, 8 (57%) had responses including 4 PR and 4 MR. The median time to response was 2 months and response duration was 9.1 months, respectively. The median overall survival was 13.9 months. Toxicity was primarily hematologic, with grade 3 or 4 toxicity seen in 18 patients (53%) consisting of anemia (12%), thrombocytopenia (9%) and neutropenia (26%). The combination of pomalidomide and dexamethasone (Pom/dex) is highly active and well tolerated in patients with lenalidomide-refractory myeloma.
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Introduction

The introduction of immunomodulatory drugs (IMiDs) including thalidomide and lenalidomide has been a major advance in the treatment of multiple myeloma (MM). As the introduction of novel agents into clinical practice, median survival in MM has improved by 50%. Pomalidomide (CC4047) is a new IMiD with high *in vitro* potency. Phase I trials established pomalidomide as well tolerated in doses ranging from 1 to 5 mg/day.[1,2]

IMiDs are hypothesized to act through multiple mechanisms. Although interest was initially focused on their anti-angiogenic effects,[3] current hypotheses suggest their antineoplastic effects are mediated by blocking signaling through nuclear factor-kappa B (NFκB)[4] and induction of apoptosis through the caspase-8/death receptor pathway.[5] In addition, IMiDs have potent immunomodulatory properties including downregulation of inflammatory cytokines,[6–8] augmentation of anti-myeloma natural killer cell activity[9,10]and stimulation of cytotoxic T-cells.[11,12]

We previously reported our results using pomalidomide and low dose dexamethasone (Pom/dex) for patients with relapsed MM. We found overall response rate (partial response (PR) or better) of 63, and 82% of patients had at least a 25% drop in their measurable parameter by 12 weeks. Importantly, we observed responses in some patients who were refractory to lenalidomide, suggesting non-cross resistance between pomalidomide and the other IMiDs. In order to better define this, we treated a cohort of patients, all of whom were lenalidomide refractory, with Pom/dex. Results are reported here.

Patients and methods

Eligibility

Patients were eligible to enter on the study if they had previously treated, symptomatic, histologically confirmed MM. Patients must be refractory to lenalidomide therapy. For this purpose, lenalidomide refractory was defined as relapsing on or within 60 days of stopping lenalidomide. Patients were required to have measurable disease defined by one of the following: serum monoclonal protein >10 g/l, serum immunoglobulin free light chain (FLC) >10 mg per 100 ml and an abnormal FLC ratio, urine light chain excretion $\geqslant$ to 200 mg/24 h, measurable soft tissue plasmacytoma that had not been radiated, or $>30\%$ plasma cells in bone marrow. Patients also needed platelet count $>75\times10^9$/l, absolute neutrophil count $>1.0\times10^9$/l and creatinine <221 μmol/l (2.5 mg per 100 ml). All previous cancer therapy, including chemotherapy and investigational agent must have been discontinued $\geqslant$2 weeks before study registration. Patients with uncontrolled infection, another active malignancy, deep vein thrombosis that had not been therapeutically anticoagulated, Eastern Cooperative Oncology Group performance score of 3 or 4, grade 3 or 4 peripheral neuropathy, pregnant or nursing women, 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 excluded. The study was approved by the Mayo Clinic Institutional Review Board in accordance with federal regulations and the Declaration of Helsinki. This trial is registered at http://ClinicalTrials.gov, number NCT00558896.

Treatment schedule

Pomalidomide was given orally at a dose of 2 mg daily on days 1–28 of a 28-day cycle. Dexamethasone was given orally at a dose of 40 mg daily on days 1, 8, 15 and 22 of each

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cycle. Patients also received aspirin 325 mg once daily for thromboprophylaxis. Patients were allowed to substitute full dose anticoagulation with either low molecular weight heparin or warfarin at physician discretion. Granulocyte colony stimulating factor was not allowed to avoid dose reductions but could be used if a patient developed neutropenic fever.

Dose adjustments were permitted based on toxicity as described below. Pomalidomide was to be permanently discontinued in the event of a grade 4 rash, neuropathy or hypersensitivity, and grade 3 or higher bradycardia or cardiac arrhythmia. Pomalidomide was progressively reduced for other related grade 3 or higher adverse events to dose levels of 2 mg for 21 days each 28-day cycle. Subsequent dose reductions were done in 0.5 mg increments for 21 days each 28-day cycle. When grade 3 or 4 adverse events occurred before day 15 of a cycle and resolved to grade 2 or lower before day 28 of the cycle, pomalidomide was resumed at the next lower dose level, with the next cycle continuing at the reduced dose level. For grade 3 or 4 adverse events occurring on or after day 15 of a given cycle, pomalidomide was held for the remainder of the cycle and reduced by one dose level beginning with the next cycle. Dose reductions were permitted for dexamethasone-related toxicity, by lowering the dose of dexamethasone progressively to 20, 12, 8 and 4 mg once weekly. Patients unable to tolerate the lowest doses of pomalidomide or dexamethasone needed to stop therapy with that agent permanently. In absence of grade 3 or higher side effects, the daily dose of pomalidomide could be increased at physician discretion to 4 mg in patients who have not achieved a 25% reduction in serum or urine monoclonal protein levels after two cycles of therapy or who have previously responded and have rising serum or urine monoclonal protein levels, Among patients who had a previous dose reduction, escalation was allowed as long as there was no current grade 3 or 4 toxicity.

Response and toxicity criteria

Responses were assessed according to published criteria of the International Myeloma Working Group.[13,14] A PR was defined as $\geqslant$50% reduction in the level of the serum monoclonal (M) protein and/or a reduction in 24-h urinary light chain excretion $\geqslant$90% or to $<$200 mg. If on study, the bone marrow was only measurable parameter, $\geqslant$50% reduction in bone marrow plasma cells was required in place of M-protein, provided baseline percentage was $\geqslant$30%. In addition to the above criteria, if a plasmacytoma present was at baseline, $\geqslant$50% reduction in the size of soft tissue plasmacytomas was also required.

Complete response (CR) required complete disappearance of the monoclonal protein in the serum and urine by immunofixation studies and $<$5% plasma cells on bone marrow examination. Stringent CR required CR as defined above plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence. A very good partial response (VGPR) required, in addition to criteria for PR, serum and urine M-protein detectable only on immunofixation but not on electrophoresis or $\geqslant$90% reduction in serum M-protein and 24 h urine M-protein $<$100 mg/24 h. In patients in whom the only measurable disease was by serum FLC levels, CR required a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients was defined as a $>$90% decrease in the difference between involved and uninvolved FLC levels. All response categories (CR, stringent CR, VGPR and PR) require two consecutive assessments made at any time before the institution of any new therapy.

Disease progression required any one of the following criteria: (1) increase in serum monoclonal protein 25% or higher above the lowest response level and an absolute increase by more than 5 g/l, (2) increase in urine monoclonal protein by 25% above the lowest remission value and an absolute increase in excretion by 200 mg/24 h 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% or 5) unexplained hypercalcemia $>$2.875 mmol/l ($>$11.5 gm per 100 ml).

The National Cancer Institute Common Terminology 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.

We were interested in specifically looking at responses among high-risk patients. High risk was defined, according published criteria[13] as cytogenetic studies (hypodiploidy or karyotypic deletion of chromosome 13), fluorescent *in situ* hybridization (presence of translocations t(4;14) or t(14;16) or deletion 17p), or plasma cell labeling index$\geqslant$3%.

Statistical design and analysis

The primary end point was the proportion of confirmed responses (CR, VGPR or PR). This single-stage phase II trial was chosen based on the binomial distribution to test that the true confirmed response rate was at most 5% versus the alternative that it was at least 20%, with a type I error rate of 7% and power of 91%. The regimen would be declared ineffective if a maximum of 3 confirmed responses were observed in the first 32 evaluable patients. Secondary end points included overall survival, progression-free survival (PFS), duration of response and adverse event profile.

All analyses are based on an intent to treat principle. Exact binomial confidence intervals are constructed for the primary endpoint of confirmed response. The distributions of (1) overall survival time (time from study entry to death) (2), PFS time (time from study entry to earlier of disease progression or death) and (3) duration of response (time from first documentation of response until disease progression or death), are estimated using the method of Kaplan–Meier. Simple descriptive statistics are used to summarize the adverse events profile and baseline characteristics.

Results

Patient population

Overall, 34 patients were accrued to the study from November 2008 to April 2009. All patients were evaluable. Patient characteristics at study entry are presented in Table 1. The median age was 62 years (range: 39–77). The median number of previous regimens was four. In all 28, 37 and 35% of patients had 1, 2 and 3 previous regimens, respectively. Previous autologous stem cell transplant was administered in 68% of patients, including one who had both an autologous and an allogeneic stem cell transplant. All patients had previous lenalidomide therapy; 19 (58%) patients had previous thalidomide and 20 (59%) patients had previous bortezomib. Baseline peripheral neuropathy was present in 20 patients (59%). The median time from diagnosis to enrollment on study was 62 months. Fourteen (41%) were classified as high risk using standard criteria Table 2.[15]

Follow-up

The median number of cycles administered was five (range 1–14). Eight patients continued to receive treatment. The major

Table 1 Patient characteristics

	*Total (*N = *34)*
Age, years median (range)	61.5 (39.0–77.0)
Gender	
Female	11 (32%)
Male	23 (68%)
ECOG performance score	
0	15 (44%)
1	14 (41%)
2	5 (15%)
Months from diagnosis to on study, median (range)	62.1 (8.4–179.2)
mSMART risk	
High	14 (41%)
Standard	20 (59%)
Cytogenetics result	
Normal	15 (52%)
Abnormal	13 (45%)
Not available	6 (17%)
Deletion 13	1 (3%)
FISH	
Normal	3 (9%)
Abnormal	19 (60%)
Insufficient PC	1 (3%)
Not available	11 (33%)
FISH results	
3q−	12 (63%)
17p−	6 (32%)
t(4;14)	1 (5%)
Durie Salmon stage at diagnosis	
Stage I	1 (4%)
Stage II	7 (32%)
Stage III	14 (64%)
ISS stage for diagnosis	
Stage I	8 (47%)
Stage II	6 (35%)
Stage III	3 (18%)
Number of previous chemotherapies	
1	2 (6%)
2	8 (23%)
3	7 (20%)
4	4 (12%)
5	4 (12%)
6	3 (9%)
7+	6 (18%)
Previous thalidomide, yes	19 (58%)
Previous bortezomib, yes	20 (59%)
Previous transplant, yes	23 (68%)
Autologous	23
ALLO	1
Previous radiation therapy, yes	18 (53%)

Abbreviations: ALLO, allogeneic bone marrow transplant; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescent *in situ* hybridization; ISS, International Staging Sytem; mSMART, Mayo Stratification for Myeloma And Risk-adapted Therapy.

cause for stopping study drug was disease progression (23 patients). Three patients withdrew because of physician or patient discretion. Seven patients had died, all due to disease progression. The median follow-up on alive patients was 8.3 months (range: 0.6–14) (Table 3).

Table 2 High-risk patients

	*Total (*N = *34)*
mSMART risk	
High	14 (41%)
Standard	20 (59%)
Cytogenetics result	
Deletion 13	1
FISH	
17p−	6
t(4;14)	1
Bone marrow labeling index, high (>3%)	7

Abbreviations: FISH, fluorescent *in situ* hybridization; mSMART, Mayo Stratification for Myeloma And Risk-adapted Therapy.

Table 3 Follow-up

	*Total (*N = *34)*
Progression status	
No Progression	11 (32%)
Progression	23 (68%)
Follow-up status	
Alive	27 (79%)
Dead	7 (21%)
Months of follow-up (alive patients), median (range)	8.3 (0.6–14)
No. of cycles administered (per patient), median (range)	5.0 (1.0–14.0)
Reason for ending treatment	
Disease progression	23 (89%)
Alternate treatment	2 (8%)
Adverse event	1 (4%)

Efficacy

Eleven (34%; 95% CI: 19–53) of the first 32 patients met the protocol-defined criteria for confirmed response defined as ⩾PR at two consecutive assessments, thus passing the threshold for success. Best responses (⩾MR) consisted of VGPR in 3 (9%), PR in 8 (23%) and MR in 5 (15%) for an overall response rate of 47%. Twelve (35%) patients had best response of stable disease. The median time to response was 2 months (range: 0.7–3.9). Of the 14 patients that were considered high risk, 8 (57%) had responses including 4 PR and 4 MR. Eight (42%) of the 19 patients had previous thalidomide had a response and 9 (45%) of the 20 patients who had previous bortezomib had a response. Eight patients increased the dose of pomalidomide from 2 to 4 mg/day. Among these eight, only one patient improved from stable disease to PR.

The median duration of response on 11 responding patients (⩾PR) was 9.1 months (95% CI: 6.5–NA). The median PFS was 4.8 months (95% CI: 2.7–10.1). PFS was not significantly different in the patients with high-risk disease compared with those with standard risk disease ($P = 0.47$; Figure 1). The median overall survival time 13.9 months (95% CI: NA). Patient outcomes are summarized in Table 4.

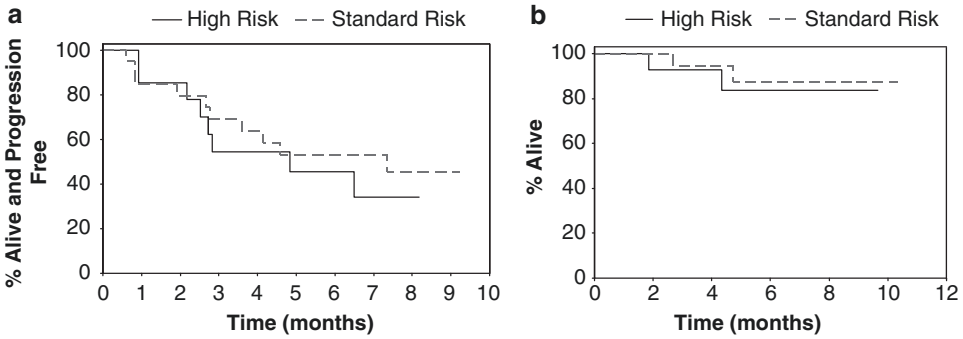

Figure 1 Progression-free (**a**) and overall (**b**) survival in standard and high-risk patients.

Table 4 Patient outcomes

Confirmed response rate[a,b]	32% (95% CI: 19–53)
Confirmed response rate[a]	32% (95% CI: 17–51)
No. of responders[a]	11
VGPR	2
PR	9
MR	4
Best response	
VGPR	3 (9%)
PR	8 (23%)
MR	5 (15%)
SD	12 (35%)
PD	6 (18%)
Median time to response[a]	2.0 mo (range: 0.7–3.9)
Duration of response[a,c]	9.1 mo (95% CI: 6.5–NA)
Overall survival[c]	13.9 mo (95% CI: NA)
Progression free survival[c]	4.8 mo (95% CI: 2.7–10.1)

Abbreviations: CI, confidence interval; mo, month; NA, not attained; VGPR, very good partial response; PR, partial response; MR, best response; SD, stable disease; PD, progressive disease.
[a]Does not include MR per study design.
[b]Study design uses the first 32 patients.
[c]Kaplan–Meier method.

Adverse events

Toxicity was defined as an adverse event considered possibly, probably or definitely related to treatment. Treatment was well tolerated. No grade 5 events were reported. Toxicity consisted primarily of myelosuppression. Grade 3 or 4 hematologic toxicity occurred in 13 patients (38%) and consisted of anemia (12%), thrombocytopenia (9%) and neutropenia (29%). The most common grade 3/4 non-hematologic toxicity was fatigue (9%). Other grade 3/4 non-hematologic toxicities seen in $<5\%$ of patients included: non-infectious pneumonitis (1 patient), edema, pneumonia, skin disorder (folliculitis) and hyperglycemia. Nine patients (26%) experienced neuropathy during treatment (six grade 1, three grade 2). Six of the nine patients had neuropathy at baseline, of whom three had a worsening of neuropathy grade during treatment. Patients received aspirin 325 mg once daily for thromboprophylaxis. Patients were allowed to substitute full dose anticoagulation with either low molecular weight heparin or warfarin at physician discretion. Venous thromboembolism prophylaxis was given in 204 of 209 cycles administered and consisted of aspirin (150 cycles) and warfarin (54 cycles). There were no thromboembolic events. Toxicities are outlined in Table 5.

Discussion

As the introduction of novel agents into routine clinical use, median survival in MM has doubled. However, none of the new agents are curative and a patient with MM can expect to receive most or all of the active agents during his or her lifetime. Almost invariably patients eventually develop disease refractory to thalidomide, lenalidomide, bortezomib and alkylating agents posing a major challenge to physicians. In this setting, the remarkable activity of Pom/dex seen in this trial in a cohort of patients refractory to lenalidomide is significant. Moreover, the durability of response (median, 9 months) is clinically meaningful in this group with limited alternative treatment options. These results suggest that pomalidomide is either more potent than lenalidomide, or has significant non cross-resistance making the drug a potentially valuable addition to the limited number of active agents available for the treatment of relapsed refractory myeloma.

In addition to being lenalidomide-refractory, the patients enrolled in this trial were heavily pre-treated with 70% having had three or more previous regimens. Our study results are supported by preliminary results reported by Richardson and colleagues[16] in the MM-002 trial. Patients in MM-002 trial were heavily pre-treated with a median of seven previous therapies; all had received previous lenalidomide and bortezomib. Minor response or better was seen in 52%, results similar to what we observed in our study. In all studies so far, the main toxicity is hematologic, and overall the regimen is well tolerated with a low incidence of non-hematologic side effects

We previously reported that Pom/dex has activity in patients with high-risk disease. We build on that observation in the current report. In both trials, response rates and duration of response with Pom/dex are not different between standard-risk and high-risk patients. Although follow-up is short, PFS in the present study is similar regardless of the presence or absence of high-risk features. Therefore, Pom/dex may be able to overcome the adverse prognostic impact of high-risk molecular and kinetic markers that lead to disease particularly resistant to treatment at the time of relapse. However, longer follow-up and randomized trials will be needed to validate this observation.

Our trial does not answer the question of whether dexamethasone is a necessary component for the regimen. A phase I trial including 24 patients used single agent pomalidomide and found 54% of patients experienced a PR or better including four patients (17%) with CR.[1] However, the trials are not directly comparable. The patients treated by Schey and colleagues were less heavily pre-treated, and were enrolled before lenalidomide and bortezomib were available. An ongoing randomized phase

Table 5 Maximum severity of toxicities[a] ($N=34$)

Body system	*Toxicity*[b]	*Gr.1*	*Gr.2*	*Gr.3*	*Gr.4*	*Total*	*Total severe*[c]
Hematology	Anemia	15	9	4	0	28	4
	Lymphocyte count Decreased	0	3	0	0	3	0
	Neutrophil count decreased	5	7	6	4	22	10
	Platelet count decreased	8	4	3	0	15	3
	Leukopenia	9	5	7	1	22	8
Infection/febrile neutropenia	Infection-No ANC	0	1	0	0	1	0
	Upper airway infection	0	1	0	0	1	0
	Bladder infection	0	1	0	0	1	0
	Pneumonia Gr 0–2 ANC	0	0	1	0	1	1
	Respiratory tract infection	0	2	0	0	2	0
	Skin infection	0	1	0	0	1	0
Lymphatics	Edema limbs	0	2	0	0	2	0
Metabolic/laboratory	Hyperglycemia	0	3	0	1	4	1
Musculoskeletal	Musculoskeletal	0	1	0	0	1	0
	Muscle weakness lower limb	0	1	0	0	1	0
Neurology	Agitation	0	2	0	0	2	0
	Anxiety	0	1	0	0	1	0
	Confusion	0	1	0	0	1	0
	Neuro	0	1	0	0	1	0
	Peripheral sensory neuropathy	6	3	0	0	9	0
	Tremor	0	1	0	0	1	0
Pain	Myalgia	0	1	0	0	1	0
Pulmonary	Dyspnea	0	1	0	0	1	0
	Pneumonitis	0	0	1	0	1	1
Cardiovascular	Edema	0	0	1	0	1	1
Constitutional symptoms	Fatigue	8	9	3	0	20	3
Dermatology/skin	Dermatology	0	0	1	0	1	1
Gastrointestinal	Anorexia	5	1	0	0	6	0
	Constipation	0	1	0	0	1	0
	Diarrhea	4	0	0	0	4	0
	Gastritis	0	1	0	0	1	0
	Nausea	2	2	0	0	4	0
	Oral Cav Ms Ce	0	1	0	0	1	0

Abbreviation: Gr, grade.
[a]Possibly, probably or definitely related.
[b]Common Terminology Criteria for Adverse Events version 3.0.
[c]Severe is grades 3, 4 and 5.

II trial comparing pomalidomide alone versus pomalidomide plus dexamethasone will provide an answer to this question.

The optimal dose of pomalidomide is also unclear. The Phase I portion of the MM-002 trial concluded the maximum tolerated dose is 4 mg daily administered on days 1–21 of a 28-day schedule. In our studies we have employed continuous daily dosing. In the present study, we allowed patients to escalate from 2 to 4 mg daily if there was a suboptimal response. Among the eight who escalated, one patient saw improvement (stable disease to confirmed partial response). It is not clear whether response rates would be better with a starting dose of 4 mg daily, rather than waiting to escalate to the 4 mg dose once the cells were already resistant. We are now accruing patients to follow-up studies in which patients with relapsed/refractory myeloma are treated with a starting dose of 4 mg per day administered continuously.

We conclude that the combination of Pom/dex is highly active and well tolerated in the treatment of lenalidomide-refractory MM. Toxicity in this trial was mild, and consisted primarily of neutropenia. Although waiting for the data to mature for the survival endpoints, we plan to further investigate the effect of Pom/dex in phase II trials for patients refractory to both lenalidomide and bortezomib (dual-refractory disease). Data from this phase II study also justifies further exploration of pomalidomide in combination with other novel agents.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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