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Research Article

Efficacy of dose-reduced lenalidomide in patients with refractory or recurrent multiple myeloma

Effizienz von niedrig-dosiertem Lenalidomid bei Patienten mit refraktärem oder rezidiviertem Multiplen Myelom

Katharina Schwamborn[1]
Marcus Gorschlüter[1]
Axel Glasmacher[1]
Ingo G. H. Schmidt-Wolf[1]
German Refractory Myeloma Study Group

1 Department of Internal Medicine III, Center for Integrated Oncology (CIO), Universitätsklinikum Bonn, Germany

Abstract

Purpose: Introduction of lenalidomide has expanded the therapeutic options for refractory and recurrent multiple myeloma (MM) patients. However, the application of the approved doses may be difficult in some patients due to adverse effects.
Experimental design: Therefore, we evaluated the efficacy and safety of lenalidomide in 10 patients with relapsed and refractory MM who received a reduced dose due to leukopenia (4), polyneuropathy (1), muscle cramps (1), thrombocytopenia (1), renal insufficiency (1), at the request of patient (1), as continuous therapy (1), either from the beginning (2) or during treatment (8). They received lenalidomide at a mean (median) daily dose of 14 (15) mg/d once a day (days 1–21 every 28 days) in combination with dexamethasone at a mean (median) dose of 17.6 (28) mg per day (4–40 mg) on days 1–4, 9–12 and 17–20.
Results: Mean (median) duration of treatment with lenalidomide was 15.1 (15) months. Partial response or better was reported in seven and minimal response or better was reported in eight patients. Mean (median) values for time-to-progression (TTP) and for progression-free survival (PFS) were 8.7 (4) months. Mean overall survival (OS) has not been reached, all patients are still alive.
Conclusion: In conclusion, dose-reduced lenalidomide is an effective and well tolerated treatment for patients with recurrent or refractory MM who cannot tolerate full doses.

Keywords: myeloma, lenalidomide, dexamethasone, lymphoma, treatment

Zusammenfassung

Hintergrund: Die Einführung von Lenalidomid hat die therapeutischen Möglichkeiten für Patienten mit refraktärem oder rezidiviertem Multiplen Myelom (MM) erweitert. Allerdings ist die Anwendung der zugelassenen Dosierung bei einigen Patienten aufgrund unerwünschter Wirkungen schwierig.
Experimentelles Design: Deshalb haben wir die Wirksamkeit und Sicherheit von Lenalidomid bei 10 Patienten mit rezidiviertem und refraktärem MM ausgewertet, die eine reduzierte Dosis erhielten wegen Leukopenie (4), Polyneuropathie (1), Muskelkrämpfen (1), Thrombozytopenie (1), Niereninsuffizienz (1), auf Wunsch des Patienten (1), als Dauertherapie (1), entweder von Anfang an (2) oder während der Behandlung (8). Sie erhielten Lenalidomid mit einer mittleren (medianen) Tagesdosis von 14 (15) mg/d. einmal pro Tag (Tag 1–21 alle 28 Tage) in Kombination mit Dexamethason in einer mittleren (medianen) Dosis von 17,6 (28) mg pro Tag (4–40 mg) an den Tagen 1–4, 9–12 und 17–20.
Ergebnisse: Die mittlere (mediane) Dauer der Behandlung mit Lenalidomid betrug 15,1 (15) Monate. Partielles Ansprechen oder besser wurde in sieben, minimales Ansprechen oder besser wurde bei acht Patienten berichtet. Mittel-/(Median)werte für das Fortschreiten der Erkrankung

(time to progression; TTP) und für das progressionsfreie Überleben lagen bei 8,7 (4) Monaten. Die mittlere Überlebenszeit wurde nicht erreicht: Alle Patienten leben noch.
Fazit: Zusammenfassend ist Lenalidomid eine wirksame und gut verträgliche Behandlung auch für Patienten mit rezidiviertem oder refraktärem MM, die die volle Dosierung nicht tolerieren können.

Schlüsselwörter: Myelom, Lenalidomid, Dexamethason, Lymphom, Behandlung

Introduction

The immunomodulatory agent lenalidomide (CC-5013) is a potent thalidomide analog with a different toxicity profile from the parent molecule. It induces apoptosis of myeloma cells; overcomes cytokine and bone marrow stromal cell-mediated drug resistance; has antiangiogenic effects; enhances dexamethasone cytotoxicity; and stimulates host anti-myeloma T-cell and natural killer (NK)-cell immunity [1]. Frequent toxicities of lenalidomide are neutropenia, deep vein thrombosis (including pulmonary embolism), thrombocytopenia, anemia, pneumonia, atrial fibrillation, fatigue, and diarrhea [2].
The aim of our study was to evaluate the efficacy of treatment of patients with relapsed and refractory multiple myelomas who could not be treated with the usual dose of lenalidomide (25 mg per day, for 21 days in a 28 day cycle). We administered lenalidomide in reduced doses depending on the severity of contraindication.

Patients and methods

Patients

This was a clinical trial in patients with relapsed and refractory multiple myeloma. In retrospect we investigated patients between June 2007 and December 2009 who were treated at the University Hospital in Bonn, Germany. Ten patients with refractory or recurrent myeloma were registered. The performance of the study was in consensus with the Declaration of Helsinki of 2000. The Ethics Review Committee approved the protocol, patients' information and the declaration of consent.

Patient eligibility criteria

We observed patients with relapsed and refractory multiple myeloma who, for various reasons (see below), could not be treated with the usual dose of lenalidomide during the whole duration of treatment. Two patients started with a reduced dose, eight patients required a dose reduction during the therapy. They all were aged ≥18 years and had received at least two prior treatment regimens.

Treatment

On days 1 to 21 of a cycle of 28 days lenalidomide was administered once a day at doses between 5 and 25 mg. When the adverse events were limitative the dose was reduced, when they were regressive the dose was partially augmented again. Lenalidomide was given in combination with dexamethasone which was administered at a mean (median) dose of 17.6 (28) mg per day on days 1–4, 9–12 and 17–20. The dose of dexamethason was also adapted to the tolerance.

Assessment of study outcomes

The response was evaluated every two to six weeks (in one patient with the non-secretory MM after 3 month). The primary efficacy endpoint was achievement of at least a partial response (complete response [CR] + partial response [PR]). Secondary end points included assessment of overall response rate (ORR, defined as CR + PR + minimal response [MR]), progression-free survival (PFS), time-to-progression (TTP), overall survival (OS), CR, PR, MR, stable disease (SD), progressive disease (PD), duration of response safety and the mean given dose.
Investigator evaluated response was assessed according to the International Myeloma Working Group uniform response criteria for multiple myeloma [3]. ORR was calculated as CR + PR + MR as recommended by the American Society of Hematology/US Food and Drug Administration Workshop on Clinical Endpoints in Multiple Myeloma [4]. Duration of response was measured from the time of best response to progression of disease, for patients without disease progression the duration of response was measured from the time of best response to the time of data collection. TTP is estimated as the time from the start of lenalidomide treatment to disease progression, with death due to causes other than progression. PFS was assessed from start of the treatment to disease progression or death (regardless of cause of death). OS is defined as the time from the start of lenalidomide to death due to any cause. Mean dose was calculated as the midpoint of the mean doses of every single patient.
Adverse events were graded according to Common Terminology Criteria for Adverse Events (Version 4.0). The adverse event which was responsible for dose reduction was accentuated.

Statistical analysis

Due to the small collective of patients the probability of a response in each category was not estimated but the absolute numbers were reported. For OS and PFS the Kaplan-Meier procedure was used to characterize the survival function. The developing of the specific immunoglobulins and of the mean dose was demonstrated in a line graph that includes the representation of standard error.

To evaluate the impact of prognostic factors on response to a lower dose of lenalidomide crosstabulators were constructed using age (≤65 years, >65 years), gender, prior stem cell therapy, prior anti multiple myeloma regimens, prior radiotherapy, prior thalidomide treatment, mean dose of lenalidomide and mean duration of treatment.

Results

Patient characteristics

Baseline demographic and disease-related characteristics of patients are shown in Table 1. The mean (median) time from diagnosis was 4.8 (4.8) years (range 0.5–8.6). All patients received at least two treatment regimens, while five patients had at least three prior treatment regimens. Seven patients had received a prior autologous stem cell transplantation. Overall, seven patients had received prior treatment with thalidomide, eight with idarubicin, seven with melphalan and four with bortezomib. All 10 patients received a reduced dose of lenalidomide due to the following causes: Leukopenia (4), polyneuropathy (1), muscle cramps (1), thrombocytopenia (1), renal insufficiency (1), at the request of patient (1) or as continuous therapy (1). Two of them started with a reduced dose, eight of them achieved a dose reduction during the therapy (Table 2). The mean (median) daily dose of lenalidomide was 14 (15) mg (range 5–21.5 mg), Figure 1 shows the development of dose reduction. The mean (median) time to first dose reduction was 4.8 (3.5) months and the mean (median) duration of treatment was 15.1 (15) months (Table 1). All patients were investigated with regard to efficacy and toxicity.

Efficacy

The primary end point of CR + PR was achieved in seven patients, including one patient with CR and six patients with PR. One patient had a MR giving an ORR (CR + PR + MR) of eight patients. The treatment of one patient was stopped after two months due to a clinical progression.

Mean (median) time to first response after treatment with lenalidomide was 41.1 (30) days. The mean (median) duration of response for patients who experienced a CR, PR or MR was 9.1 (4.5) months. The development of specific immunoglobulins is shown in Figure 2.

Table 1: Patient characteristics (n=10)

Mean/median age (range), years	64.7/64.5 (57–74)
Sex, n	
Male	8
Female	2
Mean/median time from first pathologic diagnosis (range), years	4.8/4.8 (0.5–8.6)
Mean/median no. of prior treatment regimens including SCT (range)	3.5/3.5 (2–5)
No. of prior autologous SCT, n	
0	3
1	7
>1	0
No. of prior anti-multiple myeloma treatment regimes, not including SCT, n	
1	0
2	5
3	3
>3	2
Prior therapies, n	
Radiotherapy	3
Thalidomide	7
Dexamethasone	10
Bortezomib	4
Melphalan	7
Anthracyclines	10
Vincristin	4
Mean/median daily dose (mg)	14/15
Mean/median time to first dose reduction (months)	4.8/3.5

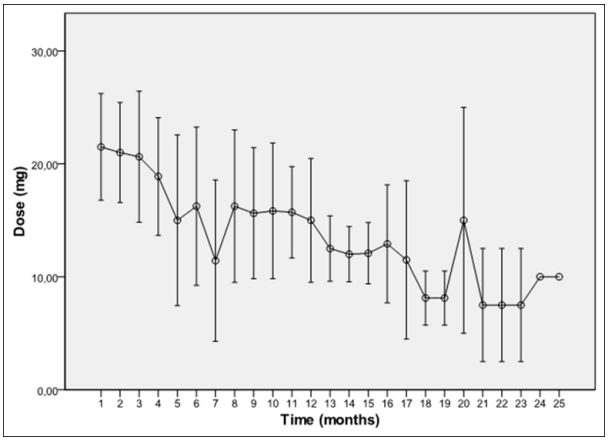

Figure 1: Mean dose of lenalidomide

Response results were analyzed according to pretreatment: ≤ two versus ≥ three prior anti-MM treatment regimens and of patients with prior treatment of thalidomide or bortezomib (Table 3).

Differentiating according to the mean daily dose there is one patient with a mean daily dose ≤5 mg. He achieved a MR. Two of four patients who received doses between 15 and 20 mg had a PD. Those who achieved a PR received doses between 5 and 25 mg (Table 4). The patient with CR had a mean dose of 17.5 mg (Table 2). At the time of best response the two patients with PD received

Table 2: Doses, best response and duration of treatment of the individual patients

Patient	Beginning dose (mg)	Cycles to dose reduction	Reason for dose reduction	Number of cycles	Mean/ median daily dose (mg)	Dose at best response (mg)	Best response
001	25	1	muscle cramps	9	10.6/10	25	PR
002	25	10	leukopenia	17	21.5/25	25	PR
003	25	9	request of patient	16	17.5/25	25	CR
004	25	2	polyneuropathy	10	15.5/15	25	PD
005	10	0	renal insufficiency	3	16.7/15	10	PD
006	25	9	leukopenia	20	18.8/17.5	25	PR
007	25	2	thrombocytopenia	10	15/15	15	PR
008	25	6	continuous therapy	25	10/10	25	PR
009	25	6	leukopenia	15	10/10	25	PR
010	5	0	leukopenia	8	5/5	5	MR

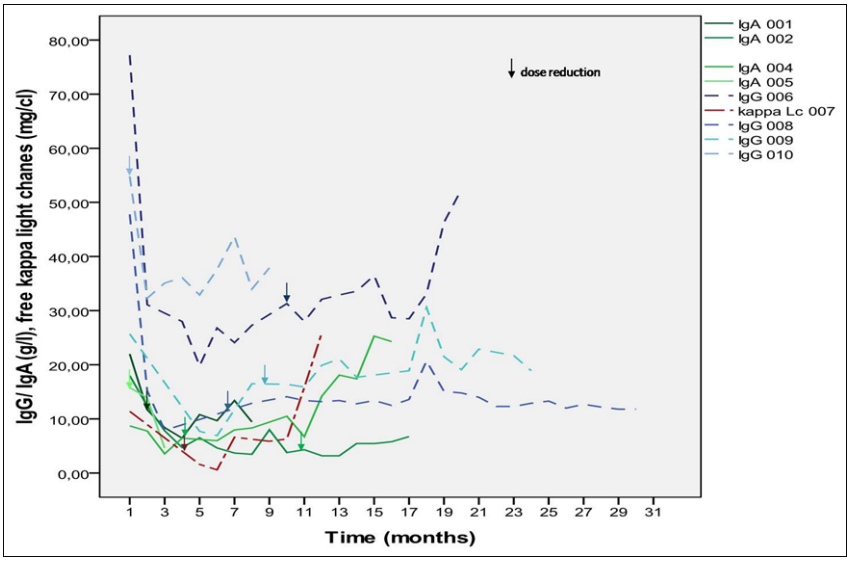

Figure 2: Development of specific immunoglobulins (IgG, IgA, free kappa light chains) for every patient excluded one patient with a non-secretory multiple myeloma. Lc, light chain.

Table 3: Response rates to lenalidomide therapy. Response criteria according to International Myeloma Working Group.

Response, n	Lenalidomide (N=10)	Patients with ≤2 prior treatment regimes (N=2)	Patients with ≥3 prior treatment regimes (N=8)	Patients with prior thalidomide treatment (N=7)	Patients with prior bortezomib treatment (N=4)
Complete response (CR)	1	1	0	0	1
Partial response (PR)	6	1	5	4	2
Minimal response (MR)	1	0	1	1	1
Stable disease	0	0	0	0	0
Progressive disease	2	0	2	2	0
Not evaluable/ known	0	0	0	0	0
CR + PR	7	2	5	4	3
CR + PR + MR	8	2	6	5	4

Table 4: Clinical response within subgroups

	Response, n			
	CR	PR	MR	PD
Total group (N=10)	1	6	1	2
Age, years ≤65 (n=5)	1	2	0	2
>65 (n=5)	0	4	1	0
Sex Male (n=8)	1	5	0	2
Female (n=2)	0	1	1	0
No. of prior autologous SCT				
0 (n=3)	1	1	1	0
1 (n=7)	0	5	0	2
No. of prior anti-multiple myeloma treatment regimes				
2 (n=2)	1	1	0	0
3 (n=3)	0	2	0	1
>3 (n=5)	0	3	1	1
Prior radiotherapy				
Yes (n=3)	0	3	0	0
No (n=7)	1	3	1	2
Mean/median duration of treatment, days	697/697	560/540	210/210	246/246
Mean daily dose				
≤5 (n=1)	0	0	1	0
]5–10] (n=2)	0	2	0	0
]10–15] (n=2)	1	1	0	0
]15–20] (n=4)	0	2	0	2
]20–25] (n=1)	0	1	0	0
Mean/median time to first dose reduction, months	13/13	5.5/6.5	0/0	1/1

Table 5: Progression-free survival and time-to-progression

Mean/median values, months (range)	Overall (N=10)	CR + PR (N=7)	CR + PR + MR (N=8)
Progression free survival[+]	8.7/4 (1–29)	11.1/4 (4–29)	10.5/5 (4–29)
Time-to-progression[*]	8.7/4 (1–29)	11.1/4 (4–29)	10.5/5 (4–29)

[+]Up to the time of data collection all patients were still alive.
*Three patients did not have a progression yet.

10 respectively 25 mg of lenalidomide, the one with MR 5 mg, the one with CR 25 mg. Those patients who achieved a PR received in time of best response in five cases 25 mg and in one case 15 mg (Table 2).

Mean (median) TTP and mean (median) PFS were 8.7 (4) months (Table 5, Figure 3). For those patients who achieved CR, PR or MR mean (median) TTP and mean (median) PFS were 10.5 (5) months. All patients we registered were still alive at the time of data collection (OS, Figure 4).

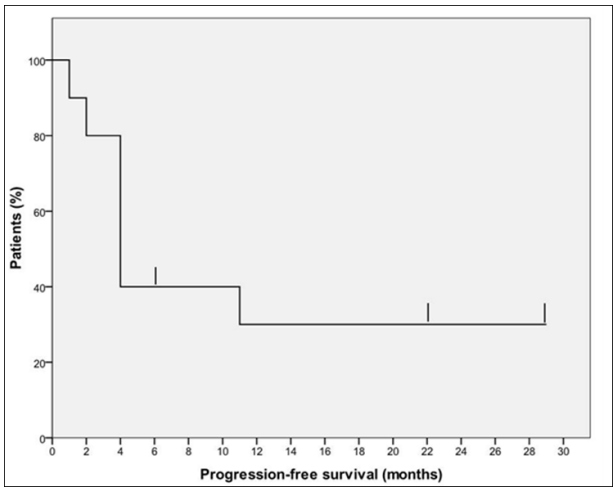

Figure 3: Kaplan-Meier plot of progression-free survival

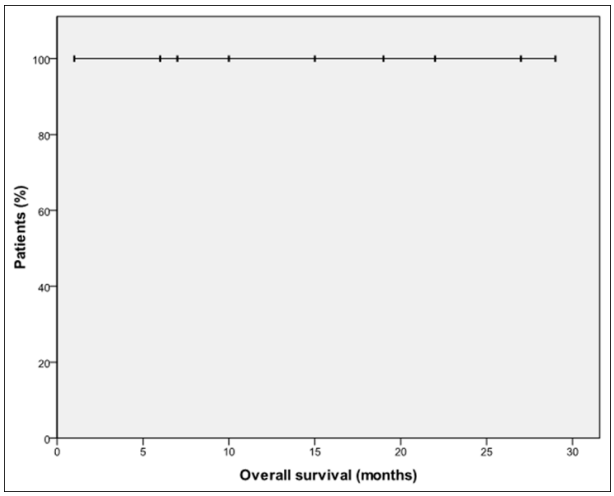

Figure 4: Kaplan-Meier plot of overall survival

Toxicity

Details of treatment-related hematological toxicities are shown in Table 6. Toxicity was distinguished between hematological and non-hematological toxicity. In hematological toxicities neutropenia was reported in eight patients (grades III+IV for three patients), thrombocytopenia in 7 patients (grades III+IV for three patients) and anemia in ten patients (grades III+IV for two patients). In two cases the application of granulocyte-colony stimulating factor was necessary, three patients obtained red blood cell transfusions. After dose reduction of lenalidomide the anemia, thrombocytopenia and leukopenia were stable or even regressive.

Table 6: Hematologic adverse events

Hematologic adverse event, n	All grades	Grade 3	Grade 4
Anemia	10	1	1
Leukopenia	8	3	0
Thrombocytopenia	7	3	0

In non-hematological toxicities the most frequently reported adverse events were backpain (5), polyneuropathy (3), muscle cramps (2), obstipation, pruritus. Polyneuropathy was preexistant in all cases at the beginning of therapy with lenalidomide due to a prior treatment with thalidomide, bortezomib or vincristine. In one patient polyneuropathy worsened during therapy and necessitated a dose reduction. This patient had previously received thalidomide for 10 months (with significant peripheral and central neuropathy), then bortezomib for 15 months (with painful neuropathy) and then lenalidomide for 16 months (with paresthesia).

Reasons for change of lenalidomide dose

As shown in Table 7 the most common reason for dose reduction of lenalidomide was leukopenia (4 patients). One patient needed a dose reduction due to muscle cramps, one patient due to polyneuropathy. Thrombocytopenia led to a dose reduction in one case as well as renal insufficiency. One patient required the dose reduction, another one got a planned dose reduction for continuous therapy.

Table 7: Reasons for dose reduction

Reason for dose reduction, n	
Leukopenia	4
Polyneuropathy	1
Muscle cramps	1
Request of patient	1
Thrombocytopenia	1
Renal insufficiency	1
Planned reduction for continuous therapy	1

Discussion

Patients with recurrent or refractory myeloma have a poor prognosis. Lenalidomide is an effective therapy for patients with relapsed and refractory multiple myeloma. We evaluated that it is also effective even if a dose reduction is necessary. It allows the treatment of selected patients who otherwise would be excluded from a treatment with lenalidomide.

Given that the dose reductions were effected at different moments the relation between response rates and mean dose is limited. There were three patients whose dose had been reduced before the first response. Five patients were treated with a reduced dose initiated after first response was achieved (three of them did not have a progression yet). Two patients, who had progressed, received lenalidomide leading to a stable disease. After obtaining stable disease the dose of lenalidomide was reduced leading to a continuation of stable disease.

Overall response rates were in almost all subgroups 60%, independent of number or character of prior treatment regimens. The mean daily dose of all patients who achieved a response (at least MR) was 13.5 mg.

The overall mean (median) PFS value for all patients treated with reduced dose of lenalidomide was 8.7 (4) months; for those who achieved at least PR it was 11.1 (4) months. The patient with a MR did not have a progression yet after six months of therapy. After duration of treatment between 1 and 29 months (mean (median) value of 15.9 (15) months) all patients were still alive.

In newly diagnosed multiple myeloma one-year PFS and overall response rates were superior with lenalidomide plus dexamethasone as compared to dexamethasone alone (78% vs. 52%, *P*=.002; 78% vs. 48%, *P*<.001) [5]. In addition, lenalidomide plus low-dose dexamethasone is associated with better short-term OS and with lower toxicity than lenalidomide plus high-dose dexamethasone in patients with newly diagnosed myeloma [6]. Another study suggests the superiority of lenalidomide/dexa-

methasone compared with thalidomide/dexamethasone in terms of response rates, survival, and toxicity [7]. There was also found a median TTP of 22.3 and 27.4 months and a median PFS of 19.1 and 26.7 months [6], [7].
A combined therapy of dexamethasone and lenalidomide (in a dose of 25 mg) for relapsed multiple myeloma produced an overall response of 60.2–61%, a median OS of 29.6 to 38 months and a median TTP of 11.1 to 13.4 months [8], [9], [10].
These results in a small patient sample indicate that in selected patients' therapy with a reduced dose of lenalidomide can be a safe and effective alternative for selected patients who may not tolerate full doses.
The most frequently reason for dose reduction was leukopenia (four patients). The myelosuppression was controllable with dose reduction or granulocyte-colony stimulating factor (necessary in two cases).
In conclusion, dose reduction of lenalidomide was feasible and seemed to be effective in relapsed or refractory myeloma patients who cannot tolerate normal doses. Certainly it cannot be recommended generally to give a lower dose of lenalidomide, but in selected cases it can be a possibility to treat patients who otherwise would be excluded from treatment with lenalidomide.

Notes

Competing interests

A.G. is affiliated with Celgene (product: lenalidomide).

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Corresponding author:
Ingo G. H. Schmidt-Wolf
Department of Internal Medicine III, Center for Integrated Oncology (CIO), University Hospital Bonn, Sigmund-Freud-Str. 25, 53105 Bonn, Germany, Tel.: +49-228-287-15507 Fax: +49-228-287-15849
Ingo.Schmidt-Wolf@ukb.uni-bonn.de

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