Continuous treatment with lenalidomide in multiple myeloma: a case report

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We present the case of a 72-year-old woman diagnosed with multiple myeloma (MM) in 1992 and treated with lenalidomide plus dexamethasone (LD) as third-line therapy. The patient achieved a complete remission (CR) after 6 cycles of LD treatment, was treated with LD for almost 4 years, and has now been in CR for 5 years. This case illustrates the potential of lenalidomide for continuous treatment in MM, with side effects controllable through tailored patient management including step-wise dose adaptations.

Keywords: Continuous treatment, lenalidomide, multiple myeloma

Introduction

The introduction of thalidomide, bortezomib, and lenalidomide has fundamentally changed the treatment of multiple myeloma (MM). In one epidemiological study, the survival after relapse of MM patients diagnosed between 1997 and 2006 and treated with at least one of these novel drugs was found to be twice as long as that of patients not having received one or more of these agents (23.9 *vs.* 11.8 months, $p < 0.001$) [1].

Treatment with conventional chemotherapy results in response rates of about 50%, with only few patients achieving complete remission (CR) [2] and with a median survival of around 33 months [3]. Newer treatment regimens induce higher response rates [4–9], a better quality of response, and long-term disease control with favourable tolerance [2, 10].

Lenalidomide (Revlimid®, Celgene, Summit, NJ) has a dual mode of action: it causes direct tumour cell death and it exerts important immunomodulatory effects, which likely contribute to maintaining remission [11, 12]. In patients with relapsed or refractory MM, lenalidomide in combination with dexamethasone has been found to significantly increase overall remission and CR rates, time to progression (TTP), duration of response, and overall survival (OS) compared to

single-agent dexamethasone [5, 8, 9]. In addition, lenalidomide is usually well tolerated, with initial myelosuppression as the clinically most relevant toxicity. Lenalidomide lacks cumulative toxicity [13], allowing for continuous treatment. In Europe, the drug was first approved in 2007.

We report on a 72-year-old patient diagnosed with MM in 1992 and treated with lenalidomide plus dexamethasone as third-line therapy. We consider this case of interest because of the rapid and complete response achieved with lenalidomide, the long treatment duration of almost 4 years, and the long duration of complete remission for the past 5 years.

Case report

The patient is a 72-year-old woman with IgG kappa MM first diagnosed in June 1992 at the age of 53 years. She presented with Salmon-Durie stage IIA. A fluorescence *in situ* hybridization (FISH) test performed in 2009 on stored bone marrow revealed no cytogenetic abnormalities. The patient was started on VMCP (vincristine, melphalan, prednisone, and cyclophosphamide) plus interferon- α and was treated for 12 cycles; thereafter, maintenance treatment with interferon- α was initiated and continued for a total of 11 years (Fig. 1).

In June 2004, the patient presented with progressive disease, mild lumbar pain and scoliotic changes and was enrolled into a randomized, placebo-controlled phase 3 study (MM-010, Celgene) [5] comparing lenalidomide-dexamethasone (LD) with placebo-dexamethasone therapy. Patients in the LD group were to receive lenalidomide at a dose of 25 mg orally on days 1–21 of each 28-day cycle, combined with 40 mg of oral dexamethasone on days 1–4, 9–12, and 17–20 for the first four cycles and on days 1–4 thereafter. Patients in the control group received dexamethasone as above and placebo instead of lenalidomide. In addition, monthly pamidronate at a dose of 90 mg was administered for 34 cycles. Response was evaluated according to the European Group for Blood and Marrow Transplantation (EBMT) criteria [14].

After 3 cycles of treatment, a greater than 50% reduction in M protein, corresponding to a partial remission (PR), was noted (Figs. 1 and 2), and this result was maintained over the next year. During this time, the dexamethasone dose was reduced twice (Fig. 2) because of side effects, particularly muscle weakness, impaired vision, constipation, bone pain,

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Fig. 1: Disease course based on M protein levels, 1992–2011

Fig. 2: M protein and lenalidomide-dexamethasone (LD) doses (study cycle -2 through end of reporting period)

oedema in the lower extremities, and loss of appetite. In cycle 8, a fracture of the first lumbar vertebral body was diagnosed.

Progressive disease was noted in cycle 17 (M protein 8.2 g/L), therefore the treatment code was broken, revealing that the patient had received dexamethasone only. Haemoglobin was 7 g/L, corresponding to a grade 3 toxicity for which she received 2 units of red cells. In this cycle, the dose of dexamethasone was reduced to 20 mg on days 1–4 of each cycle because of severe leg cramps and nausea. Both symptoms subsided after the dexamethasone dose reduction.

By cycle 18, the patient's M protein had increased to 9.1 g/L, and she was crossed over to lenalidomide 25 mg on days 1–21, with the dexamethasone dose unchanged. Apart

from intermittent herpetic skin affections, the first cycles of lenalidomide were well tolerated. Cycle 22 was delayed for 1 week because of neutropenia ($0.9 \times 10^9/L$) and leukopenia ($2.7 \times 10^9/L$), corresponding to CTC grade 3 toxicity. Bullous skin disease was recorded, but subsided within 1 week, after which lenalidomide was continued at 15 mg daily on days 1–21. At that time, the patient had already achieved a PR with a reduction of the M protein to 3 g/L. The lower lenalidomide dose was well tolerated, with the previously reported side effects no longer present. After 6 cycles of LD treatment, the patient was in CR, with negative immunofixation and less than 5% of plasma cells in the bone marrow biopsy. A skeletal survey showed partial bone healing with no new bone lesions.

LD treatment was delayed in cycles 6 and 8 (corresponding to a total of 24 and 26 cycles) because of CTC grade 3 neutropenia. This resulted in a further decrease of the lenalidomide dose to 10 mg and, one cycle later, to 5 mg. The previously noted symptoms, such as urinary urgency and severe diarrhoea alternating with constipation, normalized completely. Continuation of therapy over the next 18 months was well tolerated without any symptoms (ECOG status: 0) through the end of therapy.

The dexamethasone dose was reduced in cycle 35 of LD treatment (or a total of 53 cycles) to 12 mg on days 1–4 of each cycle because of symptoms related to corticosteroid therapy, such as impaired vision, hypertension and polyuria. In March 2010, treatment with lenalidomide-dexamethasone was discontinued at the patient's request, after a total of 45 cycles, with 39 cycles being in complete remission and total treatment duration with lenalidomide-dexamethasone of 3 years and 9 months. At the time of this report, she continues to be in complete remission and is doing well.

Discussion

The introduction of lenalidomide has significantly expanded the treatment options in patients with MM [5, 8, 9], both as initial and as rescue therapy. In relapsed and refractory myeloma, two pivotal phase 3 studies with LD [5, 8] were unblinded after a median follow-up of 17.5 months because a preplanned interim analysis had shown that LD is significantly superior to dexamethasone alone [9]. Subsequently, all patients were allowed to cross over to lenalidomide-based treatment. At a median follow-up of 48 months, a significant survival benefit was maintained (38 vs. 31.6 months, $p=0.045$), although almost half of the patients (47.6%) on dexamethasone-placebo had been switched to lenalidomide-dexamethasone after disease progression or study unblinding.

The patient in this report had initially responded to single-agent dexamethasone but developed progressive disease after 16 cycles and was crossed over to LD, which elicited a rapid PR after only 2 treatment cycles and a CR after an additional 3 cycles, with the CR now ongoing for more than 5 years. We believe this case to be of interest because of the long survival duration and because of the rapid and complete response obtained with lenalidomide-dexamethasone even after long-term pretreatment with dexamethasone-placebo. Overall, the patient was on lenalidomide therapy for a total of 3 years and 9 months.

A subgroup analysis [15] of the two pivotal phase III studies [5, 8] has shown that longer durations of treatment and maintenance of best response with LD are associated with prolonged overall survival. The side effects in our patient were manageable by step-wise dose reductions, with treatment throughout the last 37 cycles consisting of 5 mg lenalidomide daily in combination with low-dose dexamethasone. Another subgroup analysis [16] on the effects of lenalidomide dose adjustments on outcome found that patients in whom the full dose of 25 mg daily was reduced after 12 months had a significantly longer progression-free survival than patients in whom no dose reduction was performed, supporting the assumption that patients benefit from dose reductions later in the course of treatment because lower doses improve tolerability, thereby prolonging the overall duration of treatment

Tab. 1: Summary of adverse effects during lenalidomide therapy

Adverse effect	Induction grade	Maintenance grade
Neutropenia	3	1
Anaemia	2	1
Diarrhoea	2	1
Herpetic skin affections	2	
Neuropathy, sensory		2
Urinary urgency	2	
Constipation	1	
Bullous skin disease	1	1

and improving long-term outcome. Reducing the dose of dexamethasone after response to lenalidomide-based induction therapy has also been shown to improve the efficacy of LD in patients with relapsed or refractory MM [17].

Notably, the patient has now been in CR for 5 years. Obviously, she is a good-risk patient who has a good likelihood of maintaining her CR for many years or even forever. She achieved a PR after dexamethasone and a CR after subsequent lenalidomide-dexamethasone. This accords with previous reports [18] showing that the quality of the first response affects prognosis, with patients with a CR or a very good partial response (VGPR) initially having a significantly better TTP and OS than patients with PR. Of interest, the analysis [18] also found that 50% of patients who initially achieved a PR later had CR or VGPR with continued treatment, suggesting that, in the absence of disease progression or unacceptable toxicity, continuing treatment with LD provides added clinical benefits.

Lenalidomide is an ideal candidate for long-term continuous therapy in MM. It offers the convenience of oral administration, has anti-myeloma and immunomodulatory activity, provides long-term tumour suppression, and it is well tolerated even with long-term use. For example, in the two phases III studies with lenalidomide plus dexamethasone [5, 8], only few patients developed grade 2 (1.4%) or grade 3 (1.4%) peripheral neuropathy.

Dose-limiting or -delaying side effects are mainly haematological in nature and usually limited to the first 6 LD cycles. Other side effects usually are mild and easily manageable.

The probability of adverse events has been found to be higher in the first months of treatment and to decrease thereafter [19], and this was also seen in our patient (Table 1).

Throughout the second half of treatment, our patient's ECOG status improved to 0, allowing her to resume her previous working position.

Second primary malignancies (SPMs) are a published phenomenon in patients with MM [20–22] and have recently also been associated with lenalidomide maintenance treatment [23–25]. In the pivotal studies [5, 8] with lenalidomide-dexamethasone for relapsed myeloma however, the incidence of invasive SPMs was within the expected background rate for this population and similar across treatment arms [26]. No

SPM was detected in our patient treated with lenalidomide for almost 4 years.

In summary, taking into account the limitations of a single case, this report illustrates the potential of lenalidomide for long-term continuous treatment in MM, with side effects controllable through tailored patient management including step-wise dose adaptations.

Conflict of interest

The authors declare that there is no conflict of interest.

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