

ORIGINAL ARTICLE

## Assessing lenalidomide for treating multiple myeloma, myelofibrosis and myelodysplastic syndrome

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### KEYWORDS

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### Abstract

**Objective:** Lenalidomide (LDM) is an immunomodulatory and anti-angiogenic drug which has been shown to be effective in several haematological disorders (multiple myeloma [MM], myeloid metaplasia with myelofibrosis [MF] and myelodysplastic syndrome [MDS]). The objective of this study is to evaluate the effectiveness and tolerability of LDM in our patients.

**Method:** Retrospective observational study which included patients at our hospital who were monitored by the haematology unit, diagnosed with MM, MF and MDS and candidates for LDM treatment. Treatment effectiveness was assessed after approximately 4 cycles of treatment.

**Results:** Between February 2007 and March 2008, 16 patients were listed as candidates for receiving treatment with LDM (50%female/ 50%male, with a mean age of 69.6 years); of these candidates, 3 never initiated treatment. Five of the six patients with MM treated at our hospital obtained some sort of response (83.3%). Of the 4 patients with MF, 2 (66.6%) experienced some sort of response to treatment. Of the 6 patients diagnosed with MDS, treatment was initiated in 3, and it had to be suspended in 2 cases due to different reasons. Treatment only had to be suspended in two of the 13 patients who began it (15.4%) due to adverse effects (AE).

**Conclusion:** LDM is well-tolerated and produces sustained clinical benefits, especially in MM and MF. More studies are needed for in-depth examination of treatment duration, new indications and the use of treatments combined with other drugs.

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**PALABRAS CLAVE**

Lenalidomida;  
Síndrome  
mielodisplásico;  
Mielofibrosis;  
Mieloma múltiple

## Evaluación de lenalidomida en el tratamiento del mieloma múltiple, la mielofibrosis y el síndrome mielodisplásico

**Resumen**

**Objetivo:** La lenalidomida (LDM) es un agente inmunomodulador y antiangiogénico que ha demostrado su eficacia en varios trastornos hematológicos (mieloma múltiple [MM], metaplasma mielóide con mielofibrosis [MF] y síndrome mielodisplásico [SMD]). El objetivo de este estudio fue evaluar la efectividad y la tolerabilidad de la LDM en nuestros pacientes.

**Método:** Estudio retrospectivo observacional que incluyó a los pacientes de nuestro hospital en seguimiento por la consulta de Hematología que fueron diagnosticados de MM, MF y SMD, y que eran candidatos a recibir tratamiento con LDM. La evaluación de la eficacia se realizó transcurridos aproximadamente 4 ciclos desde el inicio del tratamiento.

**Resultados:** Desde febrero de 2007 hasta marzo de 2008 fueron 16 los pacientes candidatos a recibir tratamiento con LDM (50% mujeres, 50% varones, con una edad media de 69,6 años), aunque 3 de ellos no llegaron a iniciarlo. De los 6 pacientes con MM tratados en nuestro hospital, 5 de ellos obtuvieron algún tipo de respuesta (83,3%). De los 4 pacientes con MF, 2 (66,6%) experimentaron algún tipo de respuesta al tratamiento. De los 6 pacientes diagnosticados de SMD, únicamente se inició el tratamiento en 3, y en 2 de ellos se tuvo que suspender por distintas causas. Destacamos que únicamente hubo que suspender el tratamiento en dos de los 13 pacientes que lo iniciaron (15,4%) por los efectos adversos.

**Conclusión:** La LDM consigue, con buena tolerancia, beneficio clínico mantenido sobre todo en el MM y la MF. Son necesarios más estudios que profundicen en la duración del tratamiento, en nuevas indicaciones y en el uso de tratamientos combinados con otros agentes.

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**Introduction**

Lenalidomide (LDM) is an immunomodulatory and antiangiogenic analogue of thalidomide, but has greater potency and is better tolerated. The most frequent adverse effects (AE) are neutropenia and thrombopenia, which tend to appear within the first eight weeks of treatment. Its efficacy has been demonstrated in various haematological disorders (multiple myeloma [MM], myeloid metaplasia with myelofibrosis [MF], and myelodysplastic syndrome [MDS]), and its use in various solid tumours, such as prostate cancer, melanoma, and glioma,<sup>1</sup> is currently being researched.

In principle, this medication was obtained for compassionate use in all of its indications, but has recently been approved in Spain for combined use with dexamethasone under special hospital diagnostic circumstances for the treatment of MM in patients that have received at least one previous treatment.

New studies are produced ever more frequently on the experience with MM patients treated with new drugs,<sup>2</sup> as well as new strategies for managing the AE without the need for reducing or suspending treatment.<sup>3</sup> However, few references exist for other pathologies, such as MF and MDS. For this reason, we consider it of interest to communicate our experience with patients with different pathologies, responses, and tolerances to treatment.

**Method**

We performed a retrospective observational study that included MM, MF and MDS patients at our hospital who were

monitored by the haematology unit and were considered as candidates for LDM treatment. We excluded patients that, even though they were diagnosed with these pathologies, were not proposed for receiving the treatment due to non-compliance with the inclusion criteria stipulated in the treatment protocols. Patient recruitment took place over 13 months (February 2007 to March 2008) and a total of 16 subjects took part in the study. The Haematology Department elaborated diagnostic and treatment protocols for the use of LDM, which were approved by the *Comisión de Farmacia y Terapéutica* (Pharmacy and Treatment Commission).

According to these protocols, the treatment consisted of 8 cycles (induction and consolidation phase) of 21 days taking 25 mg (MM) or 10 mg (MF and MDS) of LDM with one week of rest. The inclusion criteria for study patients were: 1) for MM, 2nd line of treatment in patients with neuropathy that could be worsened with bortezomib or thalidomide, or 3rd line in refractory patients or those with an early progression of the disease after receiving bortezomib or thalidomide; 2) for MF, treatment in patients with neuropathy that could be aggravated by applying thalidomide, or a 2nd line of treatment in patients refractory to thalidomide, and 3) for MDS, in patients with a 5q deletion and dependence on transfusions, patients refractory to spacing with erythropoietin (EPO), regardless of karyotype, or patients over 80 years of age with good performance status, dependence on transfusions, and poor prognosis.

Table 1 displays the characteristics of the patients included in the study, as well as the previously received treatments and the reasons for administering LDM.

Upon delivering the first dose of the medication in the Pharmacy Department, the pharmacist informed the patient

**Table 1** Characteristics of the candidate patients for lenalidomide treatment

Patient	Sex	Age	Diagnosis	Previous treatments	Justification of LDM treatment
1	F	68	MM	VBMCP/ VBAD, bortezomib	Progression, grade I neuropathy
2	F	44	MDS	Erythropoietin	No response to erythropoietin High transfusion requirements
3	M	79	MF	NA	No response to erythropoietin High transfusion requirements
4	M	85	MDS	Erythropoietin	Not indicated, not started
5	M	84	MDS	Erythropoietin	Not indicated, not started
6	M	85	MDS	Erythropoietin	Not indicated, not started. Acute kidney failure
7	F	68	MDS	Erythropoietin	No response to erythropoietin. High transfusion requirements
8	M	54	MM	VBMCP/ VBAD, thalidomide	Progression, grade II neuropathy
9	M	67	MF	Corticosteroids thalidomide, hydroxyurea	Progression, thalidomide intolerance
10	F	59	MM	VBMCP/ VBAD, bortezomib, adriamycin liposomal	Progression, grade II neuropathy
11	M	67	MF	Corticosteroids thalidomide, hydroxyurea	Progression, grade II neuropathy
12	M	70	MM	VBMCP/ VBAD	Progression, grade II neuropathy
13	F	69	MM	VBMCP/ VBAD, bortezomib	Progression
14	F	77	MF	Corticosteroids thalidomide	Progression
15	F	64	MM	VBMCP/ VBAD	Progression, grade I neuropathy
16	F	73	MDS	Erythropoietin	No response to erythropoietin. High transfusion requirements

F indicates female; LDM, lenalidomide; M, male; MDS, myelodysplastic syndrome; MF, myelofibrosis; MM, multiple myeloma; NA, no information available; VBMCP/ VBAD, vincristine, carmustine, melphalan, cyclophosphamide and prednisone/ vincristine, carmustine, doxorubicin and dexamethasone.

as to the characteristics of the drug, the form of administration, conservation, the AE, and special precautions to take given the potential teratogenous effects of the drug. In each of the monthly visits, the patient was interviewed on the tolerance and AE of the medication.

MM patients were considered to have responded to the treatment when paraprotein (PP) levels were reduced through immunofixation. In contrast, the absence of a response was defined as no reaction in this category or progression of the disease. In the case of MF and MDS, efficacy was measured in terms of haemoglobin levels, independence from or reduction in transfusion requirements, the need for support and/ or spacing with EPO, the tendency towards normality of leukocyte/ platelet levels, and splenomegaly.

In order to evaluate tolerance and safety of the treatment, we used leukocyte and platelet levels.

The data were obtained from the outpatient dispensing programme (Farmasyst<sup>®</sup>) and a review of the patient clinical histories.

## Results

During the study period (February 2007 to March 2008), 16 candidate patients were included for receiving LDM treatment. The proportion of males to females at the start of the treatment was 50% with a mean age of 69.9 years.

The evaluation of LDM treatment was performed after receiving the 4th cycle, at which point, according to protocol, the response to treatment must be assessed. If no response was observed, the treatment was abandoned. Table 2 describes the causes for which patients did not initiate treatment (4, 5, and 6) and the reasons for which already started treatment sessions were interrupted (7, 2, and 3). Five patients finished the 8 treatment cycles.<sup>1,8-11</sup> Table 3 summarises the evolution of patients treated with LDM.

### Patients with multiple myeloma treated with lenalidomide (Figure)

Of the 6 patients treated at our hospital, 5 of them responded to treatment (response rate of 83.3%). Of these, 2 patients (10 and 12; 40%) had a reduction in plasma PP levels of at least 50% and another patient (13) had a very significant clinical response (disappearance of costal plasmacytoma and a 36% reduction in LDH levels). Patient 1 was diagnosed with oligosecretory MM that manifested itself more in general symptoms than quantitative signs (PP levels), and so we could not evaluate the efficacy of treatment in terms of PP levels. In this instance, the improvement was mostly clinical and radiological, with diminished bone damage that resulted in reduced bone pain, which was the principal limitation before starting the patient's treatment.

**Table 2** Reason for not starting or discontinuing lenalidomide treatment

Patient	Diagnosis	Reason for exclusion/ suspension of treatment
4	MDS	Age>80 years (does not comply with protocol)
5	MDS	Age>80 years (does not comply with protocol)
6	MDS	Age>80 years (does not comply with protocol). Acute kidney failure
7	MDS 5q-	Did not finish 1st cycle due to acute lymphoblastic leukaemia
2	MDS	Due to neutropoenia, the dosage was reduced by 50% in the 4th cycle, and filgastrim was added, leading to a recuperation of leukocyte levels. Lastly, treatment was suspended for lack of positive results and poor tolerance
3	MF	Treatment was suspended in the 2nd cycle in spite of having reduced the dosage due to exanthema

MDS indicates myelodysplastic syndrome; MF, myelofibrosis.

**Table 3** Summary of the response and patient evolution of lenalidomide treatment

Patient	Diagnosis	Response/ evolution
1	Oligosecretory MM	Clinical evaluation of response to treatment. Two months after finishing LDM treatment, developed multiple cutaneous plasmacytomas and so reinitiation of treatment is considered
8	MM with 13q deletion	No response. Marker for poor prognosis
10	MM	Good response. One month after halting treatment, suffered an increase in PP, and so bortezomib treatment was started
12	MM	Good response
13	MM	No available data on PP levels. Other markers improved (36% reduction of LDH). Clinical and radiological improvement. Disappearance of massive costal plasmacytoma
15	MM	12% reduction in PP levels. Was receiving the 5th cycle when the study was published
3	MF	Treatment was suspended in the 2nd cycle due to exanthema
9	MF	40% reduction in splenomegaly and 26% reduction in leukocytes. Upon suspending treatment due to oedemas, leukocyte levels and spleen size increased, treatment was reinitiated
11	MF	Major reduction in splenomegaly, with progressive reduction in haematopoietic support therapy
14	MF	Receiving the 4th cycle with no improvement in blood parameters
7	MDS 5q-	Developed lymphoblastic leukaemia during the 1st cycle
2	MDS	Treatment was suspended after the 4th cycle due to lack of positive results and poor tolerance (developed neutropenia)
16	MDS	Developed erythema during the 2nd cycle, which was controlled with support treatment. Has started the 3rd cycle with a reduced dosage

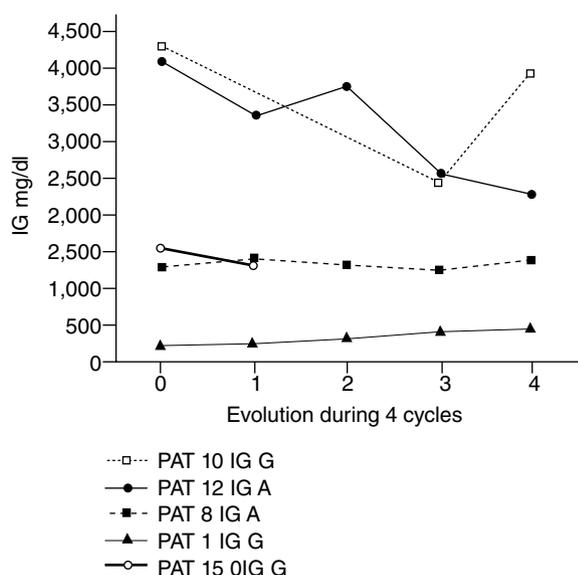
LDM indicates lenalidomide; MDS, myelodysplastic syndrome; MF, myelofibrosis; MM, multiple myeloma; PP, paraprotein.

Two months after finishing the LDM treatment, the patient developed multiple cutaneous plasmacytomas, which responded to 2 further cycles of LDM. One patient (15) had negative immunofixation after receiving the 5th treatment cycle. Patient 8 was the only patient diagnosed with MM and had a deletion of the 13q gene, a marker associated with a poor prognosis. This patient did not respond to treatment, although the disease did not progress either. Even so, continued treatment is being evaluated until the appearance of toxicity or disease progression. In one of the patients that

initially responded to treatment, other therapies (bortezomib) were required one month after finishing the LDM treatment due to signs of disease progression.

#### Patients with myelofibrosis treated with lenalidomide

Of the 4 patients that started LDM treatment, one had to have the treatment suspended due to erythema that was produced at the start of the 2nd cycle (patient 3). Two



**Figure** Response to lenalidomide in multiple myeloma patients with measurable paraprotein levels. IG indicates immunoglobulin; PAT, patient.

patients (9 and 11) had some type of response to treatment (66.6%). The splenomegaly that was produced in patient 9 was reduced by 40% after 5 cycles, and the leukocyte count dropped from 35,000 to 9,100/ $\mu$ l (26%) at the 4th cycle. The 8th cycle had to be delayed due to tibiomalleolar and conjunctival oedemas that did not respond to diuretics. During the time in which the LDM was suspended (approximately 2 months), the patient's leukocyte levels increased to 20,000/ $\mu$ l, and the size of the spleen also increased, requiring an 8th cycle. Patient 11 experienced an initially significant reduction in splenomegaly (demonstrated by physical and ultrasound exams), as well as a progressive reduction in haematopoietic support therapy. Treatment was continued, and the patient is about to start the 10th cycle. Patient 14 is currently receiving the 4th cycle, but no response has yet been noted, with blood parameters at the same levels as when LDM treatment was started, with further transfusions required along with EPO support and treatment with lenogastim.

#### Patients with myelodysplastic syndrome treated with lenalidomide

Only 3 patients with MDS started treatment with LDM. Patient 7 had a 5q deletion and did not make it to the end of the 1st cycle, due to a lymphoblastic leukaemia. From the start of treatment, patient 2 experienced a reduction in leukocytes (from 3600 to 1600/ $\mu$ l), which required reducing the LDM dose by 50%. In spite of this, and starting treatment with filgrastim (7 monthly doses of 300  $\mu$ g), neutropenia persisted after the 4th cycle (500 neutrophils/ $\mu$ l), for which treatment was suspended due to lack of efficacy and low tolerance.

Patient 16 is currently receiving the 2nd cycle of treatment. This patient developed a skin rash that was controlled with the corresponding medication

(corticosteroids and antihistamines). The 3rd cycle was started with the dosage reduced by 50%

#### Treatment tolerance

Of the 13 patients that started LDM treatment, the treatment was suspended in only 2 (15.4%) due to the AE caused. In the rest of the patients, the most frequent AE were: gastric complications, asthenia, moderate neutropenia, urinary infections, and self-limited skin reactions.

#### Discussion

MM is a malignant haematological disease characterised by the clonal proliferation of plasma cells in the bone marrow. The past decade has been characterised by major advancements in understanding the physiopathology of this disease, as well as in its treatments, which has translated into a significant improvement in patient survival. The disease is approached by treating the specific cause and/or the clinical manifestations (hyperkalaemia, musculoskeletal complications, anaemia, infections, and pain). To a great extent, the treatment is determined by the age and general state of the patient. Since 1998, three new active agents for MM have been identified (thalidomide, bortezomib, and LDM), whereas in earlier decades, alkylating agents were used (melphalan, carmustine, and cyclophosphamide) along with corticosteroids.<sup>4</sup> However, exposure to melphalan is associated with an increased risk of myelodysplasia and acute leukemia.<sup>5</sup> With conventional treatment, approximately 5% of patients have complete remission. Salvage therapy uses vincristine, doxorubicin, and dexamethasone, reaching response rates of 30% to 50%.<sup>6</sup> With the new agents, whether taken alone or in combination, the response rate and duration of positive results increases, leading to improved survival.

The effectiveness of LDM in refractory MM has been demonstrated in two parallel phase III clinical trials in which patients were randomised for LDM and DXM treatment or only DXM.<sup>7</sup> In both studies, the response rate (58% vs 22%) and duration of positive results (11 months vs 5 months) were greater in the LDM group. The AE required suspension of treatment in 20% of patients. These results led to other studies in which LDM was administered along with DXM as a primary therapy, producing response rates of 91% with minimal toxicity.<sup>8</sup> Our study produced similar results (83.3% of our patients had some type of response). We wish to point out that these results are not entirely comparable, since the evaluation of the response was somewhat premature (near the 4th cycle) with the goal of reducing unnecessary costs when the treatment was not effective.

MF is characterised by splenomegaly, immature erythrocytes, and granulocytes in peripheral blood. In addition to clonal proliferation, myeloid metaplasia is characterised by colonization of extramedullary sites, such as the spleen and liver. The majority of patients are over 60 years old when diagnosed, and 33% are asymptomatic. The median survival is 3.5-5.5 years, but patients under 55 years of age have a median survival of 11 years.<sup>9</sup> The main causes of death are progressive medullary failure, transformation

into acute leukaemia, infection, thrombohaemorrhagic episodes, heart failure, and portal hypertension.<sup>10</sup> In the case of asymptomatic patients, no treatment is required. In the rest, transfusions are required for treating anaemia, and erythropoietin, hydroxyurea, cladribine, thalidomide, LDM, and interferon are also administered. Favourable responses to thalidomide and LDM are produced in 20% to 60% of cases.<sup>11</sup> According to our experience, response rates were on the order of 66.6%. We believe that these data justify the need to carry out further studies in order to determine the role that LDM could play in this pathology, above all for acquiring data on improving survival.

Regarding the treatment of MDS with LDM, List et al<sup>12</sup> achieved a 55% cytogenetic response rate, and a complete haematological response in 29% of cases, the patients of this study having 5q- deletions. Furthermore, the need for transfusion was reduced in 76% of patients. The response was rapid (median of 4.6 weeks) and sustained.<sup>12</sup> These studies presumed that the FDA would approve LDM treatment of MDS with 5q- deletion (5q- syndrome),<sup>13</sup> since the impact of LDM in other patients is still unclear. However, our experience with MDS is limited, due to the reduced number of patients that started treatment and the AE that required suspending treatment in two of them. Patient 16 was recently included and it is still too early to evaluate this case.

In general, the AE were manageable and treatment had to be suspended in only 15.4% of patients, comparable to the 20% obtained in other studies.<sup>7</sup>

In conclusion, our experience has shown that LDM can produce clinical benefits, above all in MM and MF, with good tolerance. We believe that these are sufficient reasons for supporting the current optimism regarding the treatment of these pathologies. Indeed, survival has improved from 3 years in the decades of 1960-1990 to 5 years today. Some authors claim that with current regimens and the introduction and combination of new agents, survival could increase to over 7 years in the future.<sup>14,15</sup> We wish to point out that an important limitation of our study was, in addition to it being a retrospective study, we made premature evaluations (halfway through the treatment) for the sake of suspending those treatments that were ineffective as soon as possible, and we did not perform any long-term follow-up. In our opinion, the improvement in this group of patients amply justifies the economic costs associated with LDM, not taking into account that diminishing the need for transfusions, hospitalizations, and patient transfers also reduced costs. Also, given that this is a novel drug, few studies have researched its use, and those that have been published are very heterogeneous. We believe that, although a limit has been placed at 8 cycles in our hospital, and given that no studies exist that clarify the duration of treatment, the best option would be to continue treatment until disease progression or drug intolerance. In light of this, we believe that more studies are necessary that research the optimal

duration of treatment and new possible indications, prescriptions, and combined treatments.

## Conflict of interests

The authors affirm that they have no conflicts of interests.

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