Tailored to patient 7 to 10 day lenalidomide desensitization protocol

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Lenalidomide (LEN) is an oral immunomodulatory drug, a synthetic derivative of thalidomide used in combination with dexamethasone to treat patients with multiple myeloma (MM) [1]. LEN acts inducing apoptosis of tumour cells and stimulating the host immune response through the activation of cytotoxic T-lymphocytes and Natural Killer-cells [2,3]. Cutaneous side effects are a known complication of LEN treatment, with a prevalence ranging from 6% to 43% [4].

Non-immediate drug hypersensitivity reactions (DHRs) are believed to be mediated by T cells. The most common clinical presentations are maculopapular eruptions and delayed urticaria. When no alternative agent exists and the use of the culprit drug is mandatory, drug desensitization becomes the sole choice of management [5]. However, there is little experience with delayed DHR involving chemotherapeutic agents [6].

Previously, lengthy LEN desensitization (DS) protocols have been proposed between 16 days and 7 months in length. There is scarce evidence, and those protocols described are long, complicated and, sometimes, clinically inapplicable [7,8,9]. Our group previously reported one case of DS to LEN with a shorter and effective protocol [1].

We present a retrospective observational study of clinical practice at La Paz University Hospital in Madrid (Spain). We included patients from 2018 to 2022, with multiple myeloma and treatment

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with LEN in 21 days cycles, which presented non-immediate DHRs and underwent a desensitization protocol.

We included 7 patients, 4 were women. The median age was 68 years old, ranging from 56 to 80 years. Treatment dosage was 10 mg daily in four patients and 25 mg in three of them. Cycles were prescribed for 21 days and 7 days of resting between cycles.

All patients presented mild non-immediate skin reactions during treatment with LEN, 3 of them associated eosinophilia, and 1 of these presented mild elevation of transaminases. The median time to develop cutaneous symptoms was 8 days, between cycles 1 and 10. In 4 patients the skin lesions took more than 15 days to resolve. Lymphocyte transformation test (LTT) was performed in 2 patients, with a positive result.

Based on allopurinol DS protocols for non-immediate reactions [10], we designed a 7-day protocol to reach the dose of 10 mg and a 10-day protocol for 25 mg (Table 1). The starting dose was 0.1 mg in a dilution of 1/100 of the target 10 mg and escalating the dose gradually. Of the 7 patients, 4 presented adverse reactions during the DS. All reactions were mild such as erythema and intense itching. The symptoms were developed during the 1st cycle of DS with the doses of 5 mg (in 1 patient) and 7.5 mg (in 3 patients). We prescribed antihistamines for these reactions, and sometimes, topical corticosteroids, and the last tolerated dose was maintained before increasing to the next after symptoms resolution.

Once tolerated the target dose, the tailored modified protocol was maintained in the following cycles. All patients tolerated their target dose. Since severe itching is a common adverse event of

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lenalidomide after the first cases, we premedicated every patient with antihistamines, and no further reactions occurred.

All patients tolerated their target dose (4 patients a target dose of 10 mg and 3 patients a target dose of 25 mg). Severe itching is a common adverse event of this drug. For this reason after the first cases we premedicate every patient with antihistamines. One patient has been receiving the treatment continuously with no resting. Therefore, she received only one DS cycle. She is currently taking 10 mg per day. The rest of the patients receive LEN in cycles of 21 days and 1 week of resting. Of these 6 patients, 2 are currently undergoing desensitization (one of them has done 14 DS cycles and the other one 22), 2 died during treatment (for reasons unrelated to DS), and 2 discontinued due to gastrointestinal toxicity. None of the patients stopped DS due to desensitization failure.

Those 2 patients who undergo DS at present go once a month to the day hospital. They receive the first dose under surveillance, and the rest are taken by the patient at home. They receive concomitantly ebastine 20 mg.

There is very little experience and described protocols for desensitization to LEN [7,8,9,11]. One case series in Japan described 5 patients, with a successful desensitization protocol. All of them tolerated the target dose with no adverse reactions in any of them. The protocol started with a dose of 2.5 mg given one day a week, and then slowly increased the dose every cycle, reaching the full dose of 10 mg in approximately 4 months and 25 mg in 7 months [8]. In Turkey, Semra Demir et al. performed a 16-day desensitization protocol in LEN non-immediate hypersensitivity reactions, in a case series of 10 patients. The protocol was performed with an initial dose of 1/100 of the targeted dose, giving 2 different doses each day, at 9:00 am and 3:00 pm [11].

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We have created a simple, fast, and tailored to the patient desensitization protocol, which can be easily performed on MM patients and has shown to be safe and effective since we communicated the first desensitization case in 2020 [1].

DS appears to be a safe option in patients with this type of reaction and who need to continue treatment. It can produce adverse reactions, but these are often mild. Adverse reactions can be reduced by adapting the protocol, according to the required dose and the patient's response. In this way, tolerance to LEN can be achieved, allowing the patient to continue treatment, which has a significant impact on quality of life and prognosis.

The allergological study is challenging because of the short time available to perform the skin tests, the concomitant corticoids treatment, and the lack of validation of skin tests for delayed reactions with this drug [6]. Using LTT can be useful as an *in vitro* diagnostic tool [1], to demonstrate the underlying mechanism.

In conclusion, to the best of our knowledge, this is the simplest, shortest but also effective LEN desensitization protocol, that allows restart treatment sooner reaching a therapeutic dose faster, and with very low risks and positively impacting their quality of life and prognosis. The DS protocol we used is tailored to each patient because it can be lengthened or shortened depending on their tolerance.

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Presentation At Conferences

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Conflict of interests

The authors have no relevant affiliations or financial involvement with any organization with the subject matter or materials discussed in the manuscript.

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Table. Lenalidomide desensitization protocol for target doses of 10 and 25 mg.

Target dose 10 mg			Target dose 25 mg		
Day	**Dilution**	**Dose**	**Day**	**Dilution**	**Dose**
1	1/100	0.1 mg	**1**	0.4/100	0.1 mg
2	5/100	0.5 mg	**2**	2/100	0.5 mg
3	10/100	1 mg	**3**	4/100	1 mg
4	25/100	2.5 mg	**4**	10/100	2.5 mg
5	50/ 100	5 mg	**5**	20/100	5 mg
6	75/100	7.5 mg	**6**	30/100	7.5 mg
7	100/100	10 mg	**7**	40/100	10 mg
			8	60/100	15 mg
			9	80/100	20 mg
			10	100/100	25 mg

Abbreviations: mg, milligrams.

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