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Low-dose carfilzomib induced a dramatic response of the symptoms and paraproteinemia in a heavily pre-treated multiple myeloma patient refractory to lenalidomide-bortezomib-dexametasone

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ABSTRACT

Carfilzomib is a novel proteasome inhibitor, structurally and mechanistically distinct from bortezomib, which has been shown to be useful in the management of relapsed and/or refractory patients with multiple myeloma (MM), its recommended dose being 27 mg/m^2 biweekly. This paper reports the case of a 55-year-old female patient with IgA kappa MM who had been treated sequentially with thalidomide, dexametasone, bortezomib, lenalidomide and cyclophosphamide. She had become refractory to the combination of bortezomib, dexametasone and lenalidomide. She was given treatment with a reduced dose (50%) of carfilzomib, 27 mg/m^2 once a week. Along a 4-week period, the paraproteinemia dropped from 2.9 to 0.5 g/dL and the symptoms disappeared. A reduced dose of carfilzomib (50%) was able to induce a significant clinical and response in a patient with mieloma múltiple heavily pre-treated and who had become refractory to bortezomib-lenalidomide-dexametasone. Studies are needed to analyze if reduced doses of the drug, associated with diminished costs, are appropriate in the treatment of this disease. This information is critical in conditions of economic restrains.

Key words: multiple myeloma, treatment, carfilzomib, lenalidomide, bortezomib, dexametasone, paraproteniemia.

El carfilzomib a dosis bajas indujo una importante reducción de los síntomas y la paraproteinemia en una paciente con mieloma múltiple multitratada resistente a lenalidomida-bortezomib-dexametasona

RESUMEN

El carfilzomib es un nuevo inhibidor de proteasomas, diferente del bortezomib, que ha mostrado ser útil en el tratamiento de pacientes con mieloma múltiple en recaída o con resistencia. La dosis recomendada es

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de 27 mg/m^2 por vía endovenosa, dos veces a la semana. Se comunica el caso de una paciente de 55 años de edad con mieloma múltiple IgA kappa que había sido tratada con talidomida, dexametasona, bortezomib y ciclofosfamida y se había hecho resistente a la combinación bortezomib-dexametasona-lenalidomida; la paraproteinemia aumentaba y tenía mucho dolor lumbar. Recibió una dosis reducida (50%) de carfilzomib: 27 mg/m^2 una sola vez a la semana y dexametasona. En un periodo de cuatro semanas, la paraproteinemia se abatió de 2.9 a 0.5 g/dL y los síntomas desaparecieron. Una dosis reducida (50%) de carfilzomib fue capaz de producir una respuesta clínica y de laboratorio muy significativa en una paciente con mieloma múltiple multitratada, que se había hecho resistente a lenalidomida-bortezomib-dexametasona. Se necesitan estudios para analizar la eficacia de las dosis reducidas del carfilzomib, lo que es particularmente importante en circunstancias de restricción económica.

Palabras clave: mieloma múltiple, tratamiento, carfilzomib, lenalidomida, bortezomib, dexametasona, paraproteinemia.

BACKGROUND

Advances in drug therapy for multiple myeloma (MM) during the previous decade have improved survival outcomes; however, the disease remains incurable as patients eventually relapse or become refractory to all available therapies; therefore, there is a clear need for more effective and well-tolerated treatments. Carfilzomib is a novel proteasome inhibitor that is structurally and mechanistically distinct from bortezomib employed in the treatment of MM patients and represents a significant advance in the management of relapsed and/or refractory MM patients, including those intolerant or resistant to bortezomib.[1] High response rates have been demonstrated with carfilzomib as a single agent or in combination with alkylating agents, immunomodulators and/or corticosteroids, even among patients who have failed multiple prior therapies. Carfilzomib also has significant potential in the frontline setting, with encouraging response and survival rates observed for combination regimens.[1,2] Carfilzomib is now licensed in the United Stated for the treatment of relapsed/progressive MM and has had a major impact on the improvement in the treatment of MM in the last few years.[2] In Mexico, carfilzomib has not been licensed and is not yet commercially available. We describe here the case of a heavily pre-treated patient with MM who had become refractory to lenalidomida-bortezomib-dexametasone and who experienced a dramatic response, both clinical and in the paraproteinemia, to the compassionate use of low-dose weekly carfilzomib associated with dexametasone. This seems to be the first therapeutic experience with this novel drug in Mexico.

CLINICAL CASE

As the result of low-back pain, the diagnosis of IgA kappa MM, stage ISS I was done in this 55-year old woman in February 2003. The paraproteinemia was then 3.8 g/dL. She was initially treated with daily thalidomide (100 mg) and weekly dexametasone (40 mg) (thal/dex) and a complete response was obtained eight months later. She was offered an autologous stem cell

transplant, which she rejected. The patient remained in a sustained remission until February 2006, when the paraproteinemia reappeared (4.4 g/dL). She was given again thal/dex and entered another remission until June 2009, when she was started on lenalidomide 25 mg/day and bortezomib (2.2 mg/week). The Figure 1 depicts the evolution of the monoclonal spike. In May 2011 weekly dexametasone (40 mg) was added, the paraproteinemia remaining relatively stable. Facing a rise in the monoclonal spike and reappearance of the low back pain which required treatment with opioids, in July 2014 two doses of cyclophosphamide (1000 mg every 3 weeks) were added, without a significant response. In August 2014, carfilzomib (27 mg/m^2/week) was started, together with dexametasone (40 mg/week), the monoclonal spike dropping from 2.9 to 0.5 g/dL along a 4-week period and the low back pain resolving (Figure 1). Lenalidomide, 15 mg/day was added at this point.

DISCUSSION

The monoclonal plasmaproliferative disorders encompass a broad spectrum of diseases ranging from the often benign monoclonal gammopathy of undetermined significance (MGUS) and the potentially curable solitary plasmacytoma, to life-threatening MM and light chain amyloidosis (AL). All these conditions have a racial distribution[3-8] and in Mexican mestizos, the incidences of amyloidosis,[3] monoclonal gammopathy of undetermined significance,[4-6] MM,[7] and Waldenström's macroglobulinemia[8] have been shown to be substantially lower than in Caucasians. Despite the fact that MM is considerably less frequent in Mexico than in other countries,[7,9] there is a growing interest in the disease in the country, stemming mainly from the significant advances in the treatment of the condition, which have led into the improvement of the prognosis of patients afflicted by this malignancy.

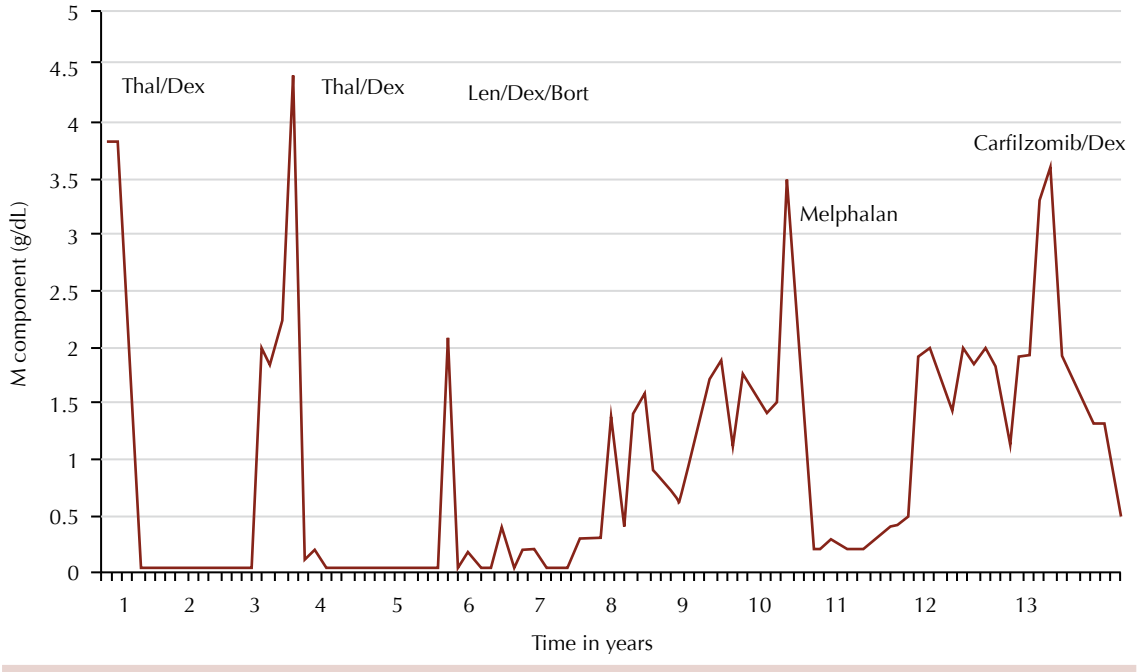

Figure 1. Evolution of the IgA kappa paraproteinemia along time in the patient described. Thal: thalidomide; Dex: dexametasone; Len: lenalidomide; Bort: bortezomib.

Accordingly, therapeutic guides for the treatment of MM adapted to the practice of medicine in Mexico have been prepared and published.[9] In the above mentioned guides, carfilzomib was not even mentioned, since it was not available yet.

Up to now, the best available therapy for patients with MM is high-dose therapy followed by hematopoieic rescue with autologus stem cell transplant (ASCT).[9-12] Even in the era of novel drugs ASCT continues to be considered for eligible patients.[12] There are, however, patients who are either ineligible for autografting or who reject the procedure, such as the one which we are presenting here; in this subset of patients, the availability of the novel anti-myeloma drugs is critical in order to improve the prognosis. In clinical studies in relapsed and refractory MM, and in combinations in newly diagnosed MM, single-agent carfilzomib demonstrated significant durable activity, good tolerability and a favorable safety profile, supporting its extended use.[1,2] Carfilzomib dosing is based on body surface area, and is given on days 1, 2, 8, 9, 15 and 16 of a 28-day cycle, at a dose of 27 mg/m^2/biweekly.[1,2] Based on the information of the usefulness of weekly bortezomib instead of its initially recommended bi-weekly administration,[13] we elected to employ weekly and not bi-weekly carfilzomib, mainly as a result of economic reasons, since carfilzomib is an expensive drug; thus, we employed 50% of the recommended dose. There is previous data of the use of reduced doses of carfilzomib in MM patients (20 mg/m^2/bi-weekly), which represents 74% of the currently recommended doses.[14] Along this line, stemming from economic restrains, the therapeutic approaches of several diseases have to be modified in developing countries, as well as drug dosing. For example, we have shown that the late introduction of lenalidomide in the treatment pathway of MM patients in Mexico leads to both substantial savings and adequate results,[15] and that thalidomide seems to be better tolerated by MM patients if it is used in doses not above 100 mg/day.[9] It is clear that the practice of medicine in general and hematology in particular has to be adapted to the economy of each of the countries and/or areas of the world.

In summary, we have shown that a reduced dose of carfilzomib (50%) was able to induce a significant response in a patient with MM, heavily pre-treated and who had become refractory to bortezomib-lenalidomide-dexametasone. Additional studies are needed to analyze if reduced doses of the drug, in turn associated with diminished costs, are appropriate in the treatment of this disease.

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