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Artículo original

Lenalidomide maintains remissions in persons with multiple myeloma intolerant to thalidomide

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RESUMEN

Antecedentes: la lenalidomida es un modificador de la respuesta inmune que ha mostrado utilidad en el tratamiento de pacientes con mieloma múltiple. Su indicación se ha limitado en México por el costo alto. El tratamiento óptimo del mieloma múltiple en México es la inducción a la remisión con talidomida-dexametasona seguida de trasplante de células hematopoyéticas autólogas y, posteriormente, mantenimiento con inmunomodulación.
Objetivo: analizar si la introducción tardía de lenalidomida en el tratamiento de pacientes con mieloma múltiple es útil como parte del tratamiento de mantenimiento.
Material y métodos: se trataron ocho pacientes consecutivos con mieloma múltiple con talidomida-dexametasona hasta inducir la remisión parcial o completa. Posteriormente, cuatro de ellos recibieron quimioterapia a dosis altas (melfalán 200 mg/m^2) rescatada con trasplante de células hematopoyéticas autólogas y todos recibieron tratamiento de mantenimiento con talidomida, 100 mg/día. A la aparición de síntomas de intolerancia a la talidomida, a los ocho pacientes se les cambió a lenalidomida, 25 mg/día.
Resultados: en todos los pacientes se mantuvo la remisión de la enfermedad y en dos se abatió aún más la magnitud de la paraproteinemia; en todos desaparecieron los datos de intolerancia a la talidomida.
Conclusión: la introducción tardía de la lenalidomida al armamentario terapéutico del mieloma múltiple se asocia con resultados favorables y disminuye los costos cuando se compara con la indicación temprana de este fármaco.
Palabras clave: lenalidomida, talidomida, mieloma múltiple.

ABSTRACT

Background: The most recommended therapy-approach in patients with multiple (MM) myeloma in México is induction with thalidomide and dexametasone (Thal/Dex) followed by autologous hematopoietic stem cell transplantation, followed by Thal maintenance; however, the toxicity of Thal develops eventually in most patients with MM. Lenalidomide (Len) is an expensive drug.
Material and methods: In a single institution in México, patients with MM intolerant to Thal were switched to Len during maintenance therapy. Eight of twelve subjects with MM who were able to defray the cost of Len were switched from Thal to Len as remission maintenance after developing peripheral neuropathy.
Results: Amount of monoclonal protein when Len was started dropped or remained stable. One subject had amyloidosis-related nephrotic syndrome; the amount of urinary albumin dropped following Len therapy. Side-effects of Thal remained stable or improved, as judged subjectively by the patients.
Conclusions: A delay in the introduction of Len in the treatment of patients with MM results in lower costs.
Key words: Lenalidomide, talidomide, multiple myeloma.

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Autologous hematopoietic cell transplantation (AHCT) is widely used to treat young persons with multiple myeloma (MM), but almost all recipients relapse.[1] Prior to the advent of immunomodulatory drugs (IMiDs) and proteosome inhibitors, survival in patients receiving two or more prior treatments was characteristically brief with a median of less than one year;[2] the introduction of novel drugs, like bortezomib, thalidomide (Thal) and, most recently, lenalidomide (Len) has transformed the management of MM.[3] Lenalidomide is an IMiD active alone and with low-dose dexamethasone

in persons with relapsed or refractory MM in phase-1 and phase-2 studies. Two large phase-3 studies showed Len combined with dexamethasone was superior to dexamethasone only in persons with relapsed or refractory MM receiving 1 or more prior therapies.[3-5]

Len is an expensive drug in México; Thal is considerably cheaper and dexametasone is also inexpensive.[6,7,8] Accordingly, the current recommendation for initial therapy of MM in México is Thal/dexametasone (Thal/Dex)[7] followed by AHCT in appropriate subjects.[8] Posttransplant maintenance with Thal is a reasonable option in México[1,6,7,8] but most people become intolerant to Thal because of peripheral neuropathy or other side-effects.[9,10]

PATIENTS AND METHODS

Eight persons with MM diagnosed at the *Centro de Hematología y Medicina Interna de Puebla* were included in the study. All subjects provided informed consent before participating in the study. Table 1 shows some characteristics of the subjects; persons with light chain myeloma had positive urine immunofixation. Thal was given by mouth at a dose of 100 mg/d. Dexametasone was given by mouth at a dose of 36-40 mg once weekly. Aspirin 100 mg/d was given to prevent thrombosis. All subjects received Thal/Dex until achieving a complete remission or a very good partial remission. Subjects were offered an AHCT; 4 subjects chose this therapy. After achieving a remission or having the AHCT, per protocol, all patients were given Thal by mouth at a dose of 100 mg/d. When patients developed Thal-induced peripheral neuropathy they were offered Len, 25 mg/d by mouth given 21 d of 28 d cycles.

RESULTS

Eight of twelve subjects able to defray the cost of the drug were switched from Thal to Len as remission maintenance after developing peripheral neuropathy. Important features are indicated in Table 1. Amount of monoclonal protein when Len was started dropped (2 cases) or remained stable (6 cases). One subject (number three) had amyloidosis-related nephrotic syndrome; the amount of urinary albumin dropped from 4 g to 2 g following Len therapy. Len was given for 2-14 mo. Side-effects of Thal remained stable or improved, as judged subjectively by the patients. The initial dose of Len was switched to a 14 d schedule every 28 d in cases of myelosuppression.

DISCUSSION

The use of novel drugs in MM has challenged the practice of high-dose therapy AHCT.[6,10] Since the use of novel therapies in MM results in substantially higher costs, the debate about the role of AHCT is different in countries with restricted economies.[6] In developing countries, AHCT is cheaper than the use of novel anti-MM drugs.[6,7,8] Accordingly, the use of Len as initial therapy for people with MM in these countries is difficult.

Currently, the most recommended therapy-approach in Mexico is induction with Thal/Dex followed by AHCT followed by Thal maintenance.[7] The toxicity of Thal, which develops eventually in most patients with MM,

Table 1. Salient features of the eight persons with multiple myeloma included in ths study. * amyloid patient. F = female, M = male, AHCT = Autologous hematopoietic stem cell transplantation. 2 indicates that two autografts were done.

Case	*1*	*2*	*3 **	*4*	*5*	*6*	*7*	*8*
Age	55	63	53	54	54	73	68	81
Sex	F	M	F	M	M	M	M	F
Paraprotein	IgA kappa	Lambda	IgA lambda	IgG kappa	IgG kappa	Kappa	IgG kapppa	IgG kappa
M spike at diagnosis (gr/dl)	3.8	0.0	1.1	4.6	1.1	0.0	6.3	2.8
AHCT	No	No	Yes	Yes	Yes (2)	No	Yes	No
M spike at starting lenalidomide (gr/dl)	1.4	0.0	0.0	0.0	0.7	0.0	0.3	1.5
Last M spike (gr/dl)	0.6	0.0	0.0	0.0	0.6	0.0	0.3	1.5
Time since diagnosis, months	92	42	100	33	108	16	56	222
Time since starting lenalidomide, months	14	11	12	2	2	10	4	2

results in either stopping or switching to Dex. This small study shows that Len can be effectively and safely used instead of Thal. A delay in the introduction of Len in the treatment of patients with MM results in lower costs. Additional studies are needed to define if the use of Len in this setting is appropriate.

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