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Systematic review on the efficacy of Thalidomide in the treatment of Multiple Myeloma / Revisión sistemática sobre la eficacia de la Talidomida en el tratamiento de Mieloma Múltiple

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ABSTRACT

Introduction: multiple mieloma , previously characterized by a por prognosis, has improved with immunomodulatory drugs (IMiDs) such as Thalidomide an its derivates. Althouhg effective, Thalidomide poses risks such as thrombosis andd teratogenicity, requiring strict safety protocols. Its use has significantly increased survival and life quality.
Method: a systematic review was conducted to evaluate the efficacy and safety of Thalidomide in the treatment of multiple myeloma
Results: a total of 354 articles were identified in Pubmed, Cochrane, Scielo Elsevier, and EBSCO. To eliminate duplicates and apply inclusión criteria, 15 studies were selected for analysis: 7 randomized clinical trials, 5 cohort studies, and 3 systematics reviews. These evaluated 3245 patientes with multiple mieloma. Most studies included both newly diagnosed and patienes in thes process of diagnosis.
Conclusions: both Thalidomide and new IMiDs, such as Lenalidomide and Pomalidomide, are effective treatments for multiple myeloma, with acceptable overall response rate. However secondary effects related to peripheral neuropathy and neutropenia continues to be a challenge, which require close monitoring during treatment. The combinations with Dexamethasone seem more effective than Thalidomide alone, and the bortezomibe-lenalidomide-Dexamethasone (VRD) scheme shows better results in terms of Progression-free survival.

Keywords: Multiple Myeloma; Multiple Myeloma/therapy; Thalidomide; Treatment Outcome; Humans.

RESUMEN

Introducción: el mieloma múltiple, previamente de mal pronóstico en la actualidad mejoró con drogas inmunomoduladoras (IMiDs) como la Talidomida y sus derivados. Aunque eficaz la Talidomida presenta riesgos como trombosis y teratogenicidad, requiriendo estrictos protocoloes de seguridad. Su uso ha incrementado significativamente la supervivencia y calidad de vida en pacientes con mieloma múltiple.
Método: se realizó una revisión sistemática para evaluar la eficacia y seguridad de la Talidomida en el tratamiento de mieloma múltiple, comparándola con otras IMiDs. Se incluyeron pacientes en edad reproductiva bajo estrictos criterios de control anticonceptivo, excluyendo embarazadas y tratamientos oncológicos paralelos.
Resultados: se identificaron 354 artículos en PubMed, Cochrane, Scielo, Elsevier y EBSCO. Tras eliminar duplicados y aplicar criterios de inclusión, se seleccionaron 15 estudios para análisis: 7 ensayos clínicos aleatorizados, 5 estudios de cohorte y 3 revisiones sistemáticas. Éstos evaluaron 3245 pacientes con mieloma múltiple. La mayoría de los estudios incluyó tanto pacientes recién

diagnosticados como en recaída.
Conclusiones: tanto la Talidomida como otras nuevas IMiDs , como la Lenalidomida y la Pomalidomida , son tratamientos efectivos para el mieloma múltiple , con tasas de respuesta global aceptables. Sin embargo, la seguridad sigue siendo un desafío, con efectos secundarios significativos como la neuropatía periférica y neutropenia, que requieren una vigilancia estrecha durante el tratamiento. La combinaciónes con Dexametasona parecen más eficaces que la Talidomida sola, y el esquema bortezomib-lenalidomida-Dexametasona (VRD) muestra mejores resultados en términos de respuesta de supervivencia libre de progresión de enfermedad.

Palabras clave: Multiple Myeloma ; Multiple Myeloma/therapy; Thalidomide; Treatment Outcome; Humans.

INTRODUCTION

Multiple myeloma is a hematological cancer caused by the proliferation of clonal plasma cells, leading to anemia, renal failure, hypercalcemia, and bone cell destruction. Overall survival has increased significantly with the introduction of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs).[1]

Less than a century ago, multiple myeloma was a disease with a poor prognosis. Fortunately, this has changed thanks to the current use of immunomodulatory drugs such as thalidomide and other new drugs.[2]

Thalidomide was created as a sedative drug in the 1950s but was withdrawn from the market due to its teratogenic effects. However, in 1990, thalidomide received renewed attention when its potential as an oncological and immunomodulatory drug was discovered, particularly for the treatment of multiple myeloma. Subsequently, two other IMiDs, lenalidomide and pomalidomide, were developed to treat tumors, with fewer adverse effects than thalidomide, both in newly diagnosed patients and in relapsed patients, and in combination with other agents such as proteasome inhibitors and monoclonal antibodies.[3]

Although many mechanisms have been proposed to explain the action of thalidomide in multiple myeloma, including angiogenic antigen, antiproliferative, and immunomodulatory effects, the precision of its effects on target cells and cellular mechanisms can only now be fully understood: It has been demonstrated that thalidomide identifies cereblons, which are proteins that play a crucial role in biological processes and even more so in immunomodulation, as its primary target. Subsequently, it was shown that myeloma requires these proteins, whose activity is inhibited by thalidomide and similar drugs known as immunomodulatory drugs (IMiDs).[4]

Thalidomide, from the first generation of IMiD drugs, is associated with significant toxicity in older adult patients, unlike newer generations such as second-generation lenalidomide, which is more potent and has fewer adverse effects, and is frequently used in patients who have recently been diagnosed with. Third-generation pomalidomide is 10 times more powerful and shows excellent results.[5]

When a patient is being treated with thalidomide for multiple myeloma, it is essential to bear in mind that there is a high risk of blood clots forming in the arms, legs, or lungs, especially when the treatment is combined with other drugs such as dexamethasone. It should also be

made very clear that female patients should not become pregnant while undergoing treatment with this drug, due to congenital disabilities such as phocomelia that can be caused to the embryo/fetus even with a single dose. For this reason, measures have been taken, such as protocols implementing the use of dual contraception, since drug interactions can alter oral contraceptives, and also a Thalidomide STEPS program to ensure that all individuals who have been prescribed thalidomide, including men, are registered with Thalidomide REMS, and that pharmacies require a prescription to provide them with this medication.[6]

The use of IMiDs such as thalidomide has led to a very significant increase in long-term survival and quality of life for cancer patients with multiple myeloma. Despite its adverse effects in older adults or those of reproductive age, after its initial ban, it has been rediscovered for cancer, and, as is often the case with first-generation drugs, it is more affordable than newer generations.

In recent years, thalidomide, together with other new drugs in the same family, has been very useful in the treatment of multiple myeloma, provided that pregnancy is avoided before, during, and after treatment, as well as interaction with other drugs for diseases such as HIV. Therefore, the following research question was posed:

Is the use of IMiDs such as thalidomide and its congeners safe and effective in the treatment of multiple myeloma?

METHOD

The objectives of this research were as follows:

Primary: the premise of the following study is to conduct a systematic review assessing the efficacy and safety of thalidomide treatment for multiple myeloma.

Specific

- To review the effects and restrictions of thalidomide use.
- To compare thalidomide with other IMiDs for the treatment of myeloma in terms of efficacy and safety.

A systematic review of the literature was conducted addressing the efficacy and safety of thalidomide and its congeners in the treatment of multiple myeloma. Articles will be searched in the following databases: PubMed, Cochrane, Elsevier, SciELO, and EBSCO, covering the last 18 years (in 2006, the US FDA approved the use of thalidomide under strict control for the treatment of multiple myeloma).

The study population comprised patients of both sexes of reproductive age affected by multiple myeloma and undergoing treatment with thalidomide and other IMiDs.

Inclusion criteria

Patients with multiple myeloma; patients undergoing treatment with thalidomide and IMiDs; female patients who are not pregnant; female patients who are not seeking pregnancy; female and male patients who are committed to not donating blood or sperm and who ensure double contraception before, during, and after treatment.

Exclusion criteria

Patients who, in addition to thalidomide, are undergoing other cancer treatments at the

same time; patients whose contraceptive method has failed; patients who use thalidomide for different diseases; patients with coagulopathies.

The most relevant variables to consider will be the efficacy of thalidomide in the initial treatment and in the recurrence of multiple myeloma, compared with other IMiDs, and the evaluation of its side effects during and after treatment.

RESULTS

A total of 453 articles were identified in the PubMed, Cochrane, Scielo, Elsevier, and EBSCO databases.

After removing duplicates and applying inclusion and exclusion criteria, 15 studies were selected for analysis, including seven randomized clinical trials (RCTs), 5 cohort studies, and three systematic reviews.

PRISMA diagram

- Articles identified: 354.
- Duplicates removed: 54.
- Articles selected for full-text review: 45.
- Studies included in the final analysis: 15.

Characteristics of studies included in the review

The selected studies evaluated 3245 patients with multiple myeloma, with a mean age of 65 years. Most studies included both newly diagnosed patients and those in relapse or refractory disease.

- Six studies evaluated thalidomide in combination with dexamethasone or bortezomib as initial treatment.
- Nine studies evaluated lenalidomide or pomalidomide in relapse or refractory disease.

Efficacy of thalidomide

- In the study by Dispenzieri A et al.[7], thalidomide combined with dexamethasone achieved an overall response rate of 63 % in patients with newly diagnosed multiple myeloma.
- Wang et al.[8] conducted a systematic review and meta-analysis comparing Bortezomib-Thalidomide-Dexamethasone (VTD) versus Bortezomib-Lenalidomide-Dexamethasone (VRD) in patients with newly diagnosed multiple myeloma who were eligible for transplantation. They found that VRD significantly improved complete response and progression-free survival (PFS), with a lower incidence of peripheral neuropathy compared to VTD.
- Thomas SK et al.[9] showed that Lenalidomide plus Dexamethasone improved progression-free survival (PFS) to 26 months versus 15 months in patients treated with Thalidomide.

Safety of thalidomide

- Mohty B et al.[10]: in a study of combination therapy with thalidomide and dexamethasone in newly diagnosed multiple myeloma, peripheral neuropathy was observed in 55 % of patients, with 23 % of cases being severe.
- Zangari M et al.[11]: an incidence of deep vein thrombosis of 14 % was reported in

patients treated with thalidomide, especially when combined with dexamethasone.

- Palumbo MA et al.[12]: in a phase III clinical trial, the combination of lenalidomide and dexamethasone in patients with refractory or relapsed multiple myeloma resulted in grade 3-4 neutropenia in 23 % of patients.
- Dimopoulos MA et al.[13]: in a study of pomalidomide alone or in combination with dexamethasone in refractory multiple myeloma, grade 3-4 neutropenia was observed in 48 % of patients treated with pomalidomide alone and in 41 % of those who received the combination.

DISCUSSION

The systematic review provides a comprehensive analysis of the efficacy and safety of thalidomide, lenalidomide, and pomalidomide in patients with multiple myeloma, based on 15 studies selected from 354 articles. These studies included randomized clinical trials, cohort studies, and systematic reviews, evaluating 3245 patients with multiple myeloma, with an average age of 65 years, most of whom were newly diagnosed or relapsed/refractory.

Efficacy of Thalidomide

Analysis of studies on the efficacy of thalidomide showed an overall response rate of 63 % in patients with newly diagnosed multiple myeloma when combined with dexamethasone.[6] This is consistent with the results of other studies demonstrating the effectiveness of thalidomide in the initial treatment of multiple myeloma. However, compared with the combination of bortezomib-lenalidomide-dexamethasone (VRD), the bortezomib-thalidomide-dexamethasone (VTD) regimen showed a significantly lower complete response rate and a higher incidence of peripheral neuropathy in patients, as noted in the meta-analysis by Wang et al.[8].

On the other hand, the combination of lenalidomide with dexamethasone is more effective than thalidomide, as it improves progression-free survival (PFS) at 26 months versus 15 months. This highlights the advantage of Lenalidomide over Thalidomide, especially in patients with refractory or relapsed myeloma.

Safety of thalidomide

Regarding the safety of thalidomide, the most common adverse effects were peripheral neuropathy and deep vein thrombosis. Thomas SK et al.[9] reported that peripheral neuropathy affected 55 % of patients, with an incidence of 23 % of severe cases. This data is consistent with other studies that also identified neuropathy as a significant adverse effect in patients treated with thalidomide. Mohty B et al.[10] reported a 14 % incidence of deep vein thrombosis in patients treated with thalidomide, particularly when combined with dexamethasone, highlighting the need to monitor coagulation in these patients.

In addition, it was observed that in treatments with other IMiDs, such as lenalidomide and pomalidomide, grade 3.

4 neutropenia was more frequent. Zangari M et al.[11] found that 23 % of patients treated with lenalidomide and dexamethasone had severe neutropenia, while Palumbo A et al.[12] reported an incidence of grade 3-4 neutropenia in 48 % of patients treated with pomalidomide, underscoring the hematologic toxicity associated with these treatments.

CONCLUSIONS

The results of this systematic review confirm that both thalidomide and other IMiDs, such

as lenalidomide and pomalidomide, are effective treatments for multiple myeloma, with acceptable overall response rates. However, safety remains a challenge, with significant side effects such as peripheral neuropathy and neutropenia requiring close monitoring during treatment. The combination of lenalidomide with dexamethasone appears to be more effective than thalidomide, and the bortezomib-lenalidomide-dexamethasone (VRD) regimen shows better response and progression-free survival rates. Future research should focus on optimizing treatment combinations and reducing their associated toxicity.

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CONFLICT OF INTEREST

None.

AUTHORSHIP CONTRIBUTION

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