Tratamiento de primera línea para pacientes con mieloma múltiple no elegibles para trasplante autólogo de células progenitoras: revisión sistemática y meta-análisis (estudio del Hemo-ONCOLGroup)

First line therapy for patients with newly diagnosed multiple myeloma ineligible for autologous stem cell transplantation: a systematic review and meta-analysis (Hemo-ONCOLGroup study)

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Resumen

Antecedentes: Los pacientes con mieloma múltiple (MM) que no son elegibles para Trasplante de Médula Ósea han sido tratados con melfalán (M) más prednisona (P); sin embargo, el estándar de tratamiento ha cambiado a MP mas talidomida (T) debido a un beneficio en supervivencia. Bortezomib (B) y lenalidomida también han surgido como tratamientos efectivos.
Métodos: Se identificaron los ensayos clínicos aleatorizados y controlados (RCT) obtenidos en la Librería Cochrane, PUBMED, LILACS, EMBASE y Scirus. Sólo se consideraron los estudios que compararon melfalán-prednisolona (MP) con cualquier otro régimen.
Resultados: Se analizaron 22 RCTs, de 2.159 referencias. MP vs. M mas dexametasona (MD): 3 RCT. No hubo diferencias respecto de la supervivencia global (SG), la tasa de respuesta completa (TRC) y la toxicidad hematológica. MD fue superior en respuesta parcial (RR 1.54;1.32-1.80) y toxicidad no hematológica RR 2.15;1.36-3.41. MP vs. regímenes basados en talidomida: 4 RCT. Se encontraron diferencias a favor de la talidomida respecto de la TRC RR 3.44;1.86-6.39 y respuesta parcial (RP) RR 1.67;1.28-2.17. La supervivencia libre de progresión (SLP) fue superior con talidomida (p = 0.02). MP vs. regímenes basados en bortezomib: 1 RCT. Se encontraron diferencias significativas a favor de bortezomib en SG HR 0.61;0.42-0.89, tiempo a la progresión HR 0.48;0.41-0.56, TRC RR 8.35;4.68-14.89 y RP RR 1.30;1.06-1.59. MP vs. quimioterapia sin M: 3 RCT. Los esquemas con bendamustina lograron una mayor respuesta completa RR 2.55;1.22-5.30. MP vs. otros: 13 RCT. No se encontraron diferencias en la RP, SG ni en los efectos adversos.
Conclusiones: Los pacientes sintomáticos con MM no elegibles para trasplante de médula ósea deben recibir como primera línea una combinación de MP con bortezomib o talidomida. Se necesitan más estudios que permitan determinar el beneficio terapéutico basado en el fenotipo y la citogenética.

Palabras clave: mieloma múltiple, quimioterapia, ensayo clínico controlado, revisión sistemática, meta-análisis.

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Abstract

Background: Patients with multiple myeloma (MM) not eligible for SCT have been treated with melphalan (M) plus prednisone (P); however, the standard of care has shifted to MP plus thalidomide (T) due to a greater survival benefit. Bortezomib (B) and lenalidomide have also emerged as effective agents.
Methods: Randomized clinical trials (RCT) were identified from the Cochrane Library, PubMed, Lilacs, Embase and Scirus, that compare MP to any other regimen.
Results: Twenty-two trials were included from 2159 potentially eligible references. MP vs. M plus dexamethasone (MD): (3 RCT) MD was superior in partial response (PR) rate and non-hematological toxicity. MP vs. T-based regimens: (4 RCT) significant differences favoring T-based regimens in CR rate, PR rate, and progression-free survival (PFS). MP vs. B based regimens: (1 RCT) Significant differences in OS, TTP, CR rate and PR rate favored B-based regimens according to the EBMT criteria. MP vs. chemotherapy regimens without M: (3 RCT) A significantly higher number of patients treated with BP achieved a CR. TTP was also significantly longer in BP-treated patients ($p < 0.02$). MP vs. other polychemotherapy regimens: (13 RCT) No significant differences in PR, OS, hemathological or other type of toxicity were observed between MP and the other chemotherapy regimens.
Conclusions: Symptomatic MM patients ineligible for SCT should receive as first-line treatment a combination of MP plus B or T; these regimens are associated with improved outcome but greater toxicity compared to MP alone. More homogeneous clinical trials using a cytogenetic risk approach are required.

Key words: multiple myeloma, chemotherapy, randomized controlled trial, systematic review, meta-analysis.

Introduction

Multiple myeloma (MM) is a clonal malignancy characterized by proliferation of abnormal plasma cells that impair hematopoiesis, activate bone resorption, and secrete a monoclonal paraprotein in serum and urine[1]. MM accounts for about 1% of human neoplasms, almost 2% of cancer-related deaths, and 12-15% of hematological malignancies[2]. MM patients with symptomatic disease are usually considered candidates for chemotherapy-based treatment[3]: those who are eligible for high-dose therapy followed by stem cell transplantation (SCT), and those who are ineligible for SCT[4]. Criteria for deciding on eligibility for SCT generally include age, performance status (PS), and co-morbid conditions[5]. There is some variability in these parameters and how they are applied, since studies examining SCT have been carried out with heterogeneous criteria. For example, initial studies tended to include patients younger than 65 years of age, while more recent trials suggest that SCT is safe in a selected group of patients over 70[6]. On the other hand, since patients with poor-risk chromosomal features have a short progression free survival (PFS) after SCT, even younger patients with these alterations may not be candidates for transplantation[7].

Since the 1960s, the standard of care for patients ineligible for SCT has been melphalan plus prednisone (MP)[8]; this regimen has the advantages of an oral, outpatient administration schedule and is generally well-tolerated. Moreover, a classic study demonstrated that while combination chemotherapy tended to induce a more rapid response, and a higher overall response rate (ORR), these differences did not translate into a survival advantage compared to MP[9]. Though MP has been the standard of care for patients with newly diagnosed MM ineligible for SCT, other options include dexamethasone (D) alone and melphalan plus dexamethasone (MD)[4]. The Intergroupe Francophone du Myélome (IFM) randomized patients who were 65 to 75 years of age to receive MP, MD, D alone, or D plus interferon[10]. While none of these regimens induced a significant number of complete responses, patients receiving MD had a 70% ORR, defined as achieving at least a partial response (PR), which was significantly higher than that seen with any of the other three regimens; however, MD was also associated with a greater risk of toxicity, especially severe infections. Furthermore, the higher response rate with MD did not translate into either a significantly better median PFS or overall survival (OS)[10].

Thalidomide has also been added to MP (MPT)[11,12]. Recently, Palumbo et al found that newly diagnosed MM patients treated with MPT had a significantly higher ORR and longer PFS, as well as a trend towards longer OS, than those treated with MP[13]. In an updated analysis after a median follow-up of 38 months, median PFS was 21.8 months for MPT and 14.5 months for MP ($p = 0.004$), median OS was 45 months for MPT and 47.6 months for MP ($p = 0.79$). Moreover, PFS was longer with MPT regardless of age, serum concentrations of ß2-microglobulin, or high International Staging System (ISS)[14]. However, MPT failed to show any significant benefit in OS, which