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## THE EFFECTIVENESS OF TREATING BONE COMPLICATIONS IN MULTIPLE MYELOMA

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**Abstract:** Multiple myeloma is a cancer that affects plasma cells in the bone marrow, causing damage to organs such as the kidneys and bones, which can lead to bone lesions. Despite the existence of several current treatments that generate responses, in many patients the disease is still incurable. In order to evaluate and analyze the approaches applied to intervention in multiple myeloma, an integrative literature review was carried out, consulting studies available on the National Library of Medicine (PubMed) and Virtual Health Library (VHL) platforms. The literature review shows that the treatment of multiple myeloma is constantly evolving, with the emergence of new therapies and approaches. These innovations are mainly aimed at improving existing therapies and minimizing negative impacts, ensuring a better quality of life for patients. Despite the advances, current methods and options have varying degrees of efficacy and there are still challenges related to toxicity, side effects and the impact on patients' quality of life.

**Keywords:** Myeloma, Multiple; Treatment; Therapies; Effectiveness.

## INTRODUCTION

Multiple myeloma (MM) is a plasma cell cancer that causes damage to organs such as the kidneys and bones, leading to bone lesions, hypercalcemia and anemia (KAHALE et al., 2022). It is a debilitating malignancy that is part of a spectrum of conditions, ranging from monoclonal gammopathy of undetermined significance to plasma cell leukemia (ANDERSON et al. 2015).

Although current treatments for multiple myeloma (MM) generate responses in a large proportion of patients, the disease remains incurable for the majority. Relapses are generally heterogeneous, often occurring biochemically, without clinical symptoms. Although these patients may not need

immediate treatment, they are at high risk of symptomatic progression, which eventually requires therapeutic intervention (GARCÍA-SANZ et al. 2015).

Multiple myeloma, a hematological neoplasm, is characterized by the abnormal growth of plasma cells in the bone marrow, often accompanied by bone pain and skeletal events such as pathological fractures and spinal cord compression (ANNIBALI et al., 2023). Changes in the bone marrow microenvironment, caused by increased osteoclastic activity and/or reduced osteoblastic activity due to myeloma-associated bone disease, negatively impact patients' quality of life (TANVEER et al., 2023).

Some treatments are used to prevent skeletal complications in patients with multiple myeloma (Chatziravdeli et al., 2022). The treatment approach is due to the frequent occurrence of debilitating events related to the skeleton (ASHCROFT et al. 2018).

Patients with multiple myeloma face complications such as bone destruction, toxicities from repeated treatments and age-related comorbidities. With improvements in treatment options, these patients have a prolonged survival but face specific challenges, so conditions need to be considered to improve quality of life and long-term survival (LECAT, et al. 2023).

This study aims to evaluate the efficacy and safety of different treatments for multiple myeloma, analyzing their impact on parameters such as response to therapy, survival, skeletal events, quality of life, toxicity and side effects.

## METHODOLOGY

In order to investigate the bone complications of multiple myeloma, this study adopted a qualitative, retrospective and cross-sectional approach, using an integrative literature review as its methodology. The search was carried out in the PubMed and Virtual Health Library (VHL) databases, using the terms “bone complications” and “multiple myeloma” combined by the Boolean operator “AND”.

In order to guarantee the relevance of the selected articles, inclusion criteria were established, prioritizing those that addressed the proposed themes and were published between 2014 and 2024, in English, Portuguese or Spanish, and available in full. Articles that did not fit the theme, did not meet the criteria or were duplicates were eliminated.

## RESULTS AND DISCUSSION

The initial search identified 5,663 papers, of which 6,637 were from PubMed and 1026 from the VHL. After reading and manually selecting 46 articles, 20 journals were selected for further analysis. Of these, 14 articles were chosen from PubMed and 6 from the BVS, as shown in Figure 1.

The 20 selected studies were analyzed and considered in order to formulate a table presenting the authors' main considerations. The main information is presented in Table 1 below, according to the case studies and randomized studies.

Multiple myeloma is a type of cancer that affects the plasma cells in the bone marrow. Several studies have investigated different treatments for this disease, seeking to improve the quality of life and survival of patients.

A study by Hilmelstein et al. (2017) evaluated the efficacy of different dosages of zoledronic acid. The results showed that administration every 4 weeks or every 12 weeks had no significant impact on

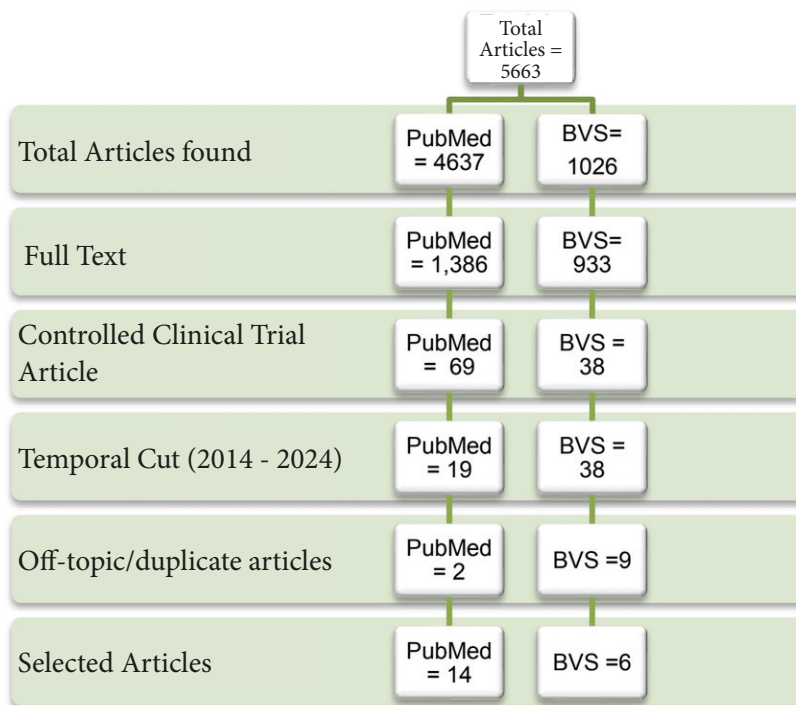
the occurrence of skeletal events, pain, performance, osteonecrosis of the jaw, renal dysfunction or skeletal morbidity over a 2-year period. However, the group that received the medication every 12 weeks showed greater bone renewal, evidenced by higher levels of C-terminal telopeptide.

Another study, by Sezer et al. (2017), compared consolidation with bortezomib versus observation in patients with myeloma who showed a partial or better response after high-dose therapy and autologous stem cell transplantation. Bortezomib showed no significant difference in bone mineral density, but had higher complete response rates, less disease progression and longer progression-free survival. However, bortezomib had more adverse events, such as diarrhea, neuropathy and nausea.

Radiotherapy is also used in the treatment of multiple myeloma, providing local pain relief in 31% of patients and partial relief in 54%. Higher doses of radiation and older age were associated with greater pain relief. Recalcification was observed in 48% of irradiated lesions, and was more frequent with higher doses. The side effects of radiotherapy were generally mild (MATUSCHEK et al., 2015)

Li et al. (2022) investigated CAR-T cell therapy in the treatment of relapsed/refractory multiple myeloma. Despite demonstrating efficacy, CAR-T cell therapy presents a significant challenge: severe hematologic toxicity. The study data showed high rates of severe cytopenia, including severe neutropenia (52%), severe anemia (28%) and severe thrombocytopenia (33%). Prolonged hematological toxicity was observed in 52% of patients on day 28 after infusion, associated with lower progression-free survival and overall survival.

Terao et al. (2021) evaluated loss of spleen visualization (LSV) in patients with multiple



**Figure 1.** Flowchart for identifying and selecting the selected articles  
Source: Authors (2024)

Author	Year	Type of study	Effectiveness	Approach
Sezer et al.	2017	Randomized study (n=104)	Yes	Bortezomib was associated with trends towards improved response and survival in patients with myeloma.
Himelstein et al.	2017	Study randomized (n=1822)	Yes	The use of zoledronic acid did not lead to an increased risk of skeletal events over 2 years.
Matuschek et al.	2015	Case series (n= 153)	Yes	Higher doses of total biological radiation were associated with better pain relief and recalcification.
Li et al.	2022	Case series (n=54)	Yes	The use of CART-T cells has shown that early detection and treatment of prolonged hematological toxicity can improve survival and prevent fatal complications.
Terao et al.	2021	Case series (n=111)	No	Loss of visualization of the spleen suggests an unfavorable prognosis, even with a response to treatment.
Iyer et al.	2014	Case series (n=28)	Yes	The monoclonal antibody BHQ880 was well tolerated and showed potential clinical activity in patients.
Hari et al.	2015	Case Series (n=61)	Yes	EVOMELA (melphalan without propylene glycol) can be used as a high-dose conditioning regimen for autologous stem cell transplantation.
García-Sanz et al.	2015	Study randomized (n=100)	No	Zoledronic acid did not directly impact the tumor, but it did reduce the risk of bone and skeletal complications.
Raje et al.	2016	Case series (n=1776)	No	The comparative use of denosumab and zoledronic acid showed inconclusive survival results.
Bethge et al.	2021	Case series (n=60)	Yes	Haploidentical hematopoietic stem cell transplantation with depleted grafts is a viable option for high-risk patients.
Khalafallah et al.	2017	Case series (n=73)	Yes	Long-term use of zoledronic acid is beneficial and safe in patients with advanced cancer and bone involvement.
Wu et al.	2015	Case study (n=176)	Yes	The preoperative use of zoledronic acid significantly reduced intraoperative bleeding.

Te Velde et al.	2023	Case series (n=127)	Yes	The Spinal Instability Neoplastic Score can be useful for predicting and preventing fractures in patients with multiple myeloma.
Abdulkadyrov et al.	2014	Study randomized (n=30)	Yes	Multiple doses of sotatercept plus an oral combination of melphalan, prednisolone and thalidomide appear to be safe and generally well tolerated.
Huang et al.	2020	Study randomized (n=196)	Yes	Denosumab could be an additional treatment option for Asian patients.
Cella et al.	2018	Study randomized (n= 646)	Yes	Treatment with elotuzumab, together with lenalidomide and dexamethasone, is effective in improving progression-free survival and response rates in patients.
Koutoukidis et al.	2020	Randomized Study (n=131)	Yes	Exercise can be beneficial for cancer patients, especially those suffering from clinical fatigue.
Abdelmonem et al.	2022	Case series (n=24)	Yes	The use of long stems for proximal femoral metastasis should be rethought, considering the expected survival of the patient and the low rate of complications.
Li et al.	2015	Case series (n=275)	Yes	del(12p) is a valuable prognostic marker and can help identify high-risk subpopulations.
Kernan et al.	2018	Case series (n=82)	Yes	Defibrotide may be a viable treatment option for hepatic veno-occlusive disease/sinusoidal obstruction syndrome unrelated to transplantation.

**Table 1.** Characterization of articles according to authors, year of publication, type of study, effectiveness and approaches

Source: Authors (2024)

myeloma using whole-body diffusion-weighted imaging (WB-DWI). Patients with LSV showed greater plasma cell infiltration in the bone marrow, greater total diffusion volume, lower spleen-to-spinal cord ratio and worse overall survival at 2 years. Even with a good response to treatment, those who did not recover visualization of the spleen during treatment had a worse prognosis.

Iyer et al. (2014) investigated the monoclonal antibody BHQ880, which neutralizes the Dickkopf-1 (DKK1) protein, associated with suppression of osteoblastic function. BHQ880 showed a tendency to increase bone mineral density, especially in the spine, without presenting dose-limiting toxicity.

Hari et al. (2015), state that EVOMELA, a new formulation of melphalan without propylene glycol, was tested in a phase IIb study. EVOMELA demonstrated efficacy in myeloablation, with a high overall response rate, a low incidence of grade 3 mucositis and no treatment-related mortality.

García-Sanz et al. (2015) evaluated the effect of zoledronic acid as monotherapy in patients with multiple myeloma in asymptomatic biochemical relapse. Zoledronic acid did not show an antitumor effect, but it did reduce the symptomatic progression of the disease and increased the average time until the onset of symptoms.

Raje et al. (2016) compared the use of denosumab and zoledronic acid in patients with bone metastases. Denosumab proved superior in preventing skeletal events, but zoledronic acid had better results in terms of overall survival.

Bethge et al. (2021) evaluated the procedure in 30 children and 30 adults. The results showed safety, with a low incidence of graft-versus-host disease, and good overall and disease-free survival.

Khalafallah et al. (2017), considered zoledronic acid (ZOL) in patients with metastatic bone cancer, beyond one year of treatment. The results showed that monthly ZOL continued to be effective in reducing

skeletal-related events (SREs) during the second year of treatment, with only 5.5% of patients developing a new SRE. Also looking at the zoledronic acid approach, Wu et al. (2017) considered its use before surgery to treat spinal tumors and their results showed that patients who received zoledronic acid before surgery had significantly less intraoperative bleeding than those who did not.

Te Velde, et al. (2023), found that there is an independent association between the Spinal Instability Neoplastic Score (SINS) and an increased risk of new fractures or progression of existing ones. On the other hand, the use of bisphosphonates has been shown to reduce this risk.

The study by Abdulkadyrov et al. (2014) looked at the use of the drug sotatercept and it proved to be effective in increasing hemoglobin levels, but it also had a worrying safety profile with serious adverse events.

Huang et al. (2020) compared the efficacy and safety of denosumab with zoledronic acid in Asian patients with newly diagnosed multiple myeloma and lytic bone lesions. Denosumab proved effective in reducing skeletal-related events, with a similar safety profile to zoledronic acid.

Cella et al. (2018) analyzed the impact of treatment with elotuzumab, together with lenalidomide and dexamethasone, on pain and health-related quality of life (HRQoL) in patients with relapsed/refractory multiple myeloma (RRMM). Elotuzumab did not have a negative impact on HRQoL, and patients with an objective response to treatment showed a significant improvement in pain.

Koutoukidis et al. (2020) found that an exercise program was safe for cancer patients undergoing treatment, improving muscle strength and cardiovascular fitness, but with limited impact on overall fatigue. However, participants who reported clinical fatigue at baseline tended to have less fatigue after 6 months of exercise.

Abdelmonem et al. (2022) compared the use of long stems versus standard stems for the treatment of proximal femoral metastasis. Although the complication rate was slightly higher in the standard group, the difference was not statistically significant. Mean survival was similar between the groups, but the long stem group had a slightly longer survival.

Li et al. (2015) evaluated the impact of the del(12p) deletion in patients with multiple myeloma. Patients with this deletion had a significantly worse prognosis in terms of progression-free survival and overall survival, even after treatment with bortezomib.

Kernan et al. (2018) analyzed patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) unrelated to transplantation who received defibrotide within 30 days of starting chemotherapy. Estimated survival at 70 days after starting defibrotide was 74.1%, with 80.1% survival in pediatric patients and 50.0% in adults.

## FINAL CONSIDERATIONS

The analysis of various studies on multiple myeloma indicates that the therapeutic landscape is constantly evolving, with new treatment options and strategies emerging to combat the disease. Current therapies demonstrate efficacy in different aspects, such as pain control, prevention of skeletal events and increased survival, but present challenges related to toxicity, side effects and impact on quality of life. The study of prognostic factors and the investigation of new therapies are crucial for the optimization of treatment and the search for more effective and safer approaches for patients with multiple myeloma.



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