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PROMOTION OF HEALTH-RELATED QUALITY OF LIFE IN THE TREATMENT OF ELDERLY PATIENTS WITH MULTIPLE MYELOMA: AN INTEGRATIVE REVIEW

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Abstract: Multiple myeloma (MM) is a hematological neoplasm with malignant transformation of plasma cells, resulting in uncontrolled growth in the bone marrow and secretion of non-functional monoclonal antibodies into the circulation. It causes damage to target organs due to the clinical manifestation of "CRAB" symptoms: hypercalcemia, renal failure, anemia and lytic bone lesions. MM is the second most common hematological malignancy after lymphomas. From 1990 to 2016, its global incidence increased by 126%, being related to population aging, as the disease typically occurs in the elderly, on average at age 70. Considering the impact on the health of those affected by MM and the greater prevalence of the disease in old age, this work aims to analyze evidence about treatment and care, which provide a better quality of life for those with the pathology, especially elderly patients. This is a qualitative, retrospective and cross-sectional study carried out through an integrative literature review. The databases used were PubMed and LILACS. The search considered the descriptors "aged", "multiple myeloma", "quality of life", using the Boolean operator "AND". Articles published in the last 11 years were included; in English, Spanish and Portuguese, free access and articles whose studies were clinical trials and controlled and randomized clinical trials. After applying the criteria, 10 articles were selected. Treatment with daratumumab, lenalidomide and dexamethasone, compared to lenalidomide and dexamethasone, presents greater efficacy with faster and more sustained clinically significant improvements, including pain, without resulting in an increase in adverse events. The inclusion of prophylactic levofloxacin in the treatment of MM resulted in a reduction in mortality from infectious events. Melphalan, prednisone and lenalidomide followed by lenalidomide maintenance, compared

to the melphalan-prednisone regimen, prolonged disease progression-free survival. Daratumumab – bortezomib -melphalan -prednisone guaranteed functional and symptom improvements. Comprehensive geriatric assessment is useful in classifying risk and directing care in elderly people with MM. Predictive prognostic scales help define and optimize care, through minimal clinically important differences. To assess the prognosis, it is useful to base it on age and easily identifiable laboratory parameters such as LDH, CRP, lymphocyte/total white blood cell ratio. It is concluded that strategies to establish the diagnosis early, the cautious use of medications, management of polypharmacy and application of prognostic scales are essential in the management of the pathology, in order to guarantee a better quality of life in elderly patients affected by this condition. Regarding physical function, there is still a lack of studies aimed at improving physical capacity in this population.
Keywords: Multiple Myeloma; Elderly; Quality of life.

INTRODUCTION

Multiple myeloma (MM) is a hematological neoplasm with malignant transformation of plasma cells, resulting in their uncontrolled growth within the bone marrow (BM) and secretion of large amounts of non-functioning monoclonal antibody, known as M protein, into the circulation.[1; 2] The MM normally causes damage to target organs, causing clinical manifestations such as "CRAB" symptoms: hypercalcemia, renal failure, anemia and lytic bone lesions, which result in pain and bone fracture.[3]

The diagnosis of MM is made by the mandatory criterion of the presence of ≥10% of medullary plasmacytosis and/or plasmacytoma (confirmed by biopsy), in addition to at least one of two additional criteria, the first being evidence of target organ damage (CRAB symptoms) and the second, the presence of some biomarker. Among the biomarkers, there is medullary plasmacytosis ≥60%, measurement of free light chains in the serum with a ratio of involved chains/uninvolved chains ≥ 100 and the presence of > 1 focal lesion shown on magnetic resonance imaging.[4]

The MM comprises 1% of all malignancies, and is the second most common hematological malignancy after lymphomas, representing 10% of blood malignancies.[5] From 1990 to 2016, the global incidence of MM increased by 126%.[6] This increase is explained by the exponential aging of the population, as this neoplasm typically occurs in the elderly, being diagnosed on average at 70 years of age.[7] In the first 5 years after diagnosis, the risk of progression is about 10% per year.[8] In 2018, around 106,000 people died globally from MM, representing 1.1% of all cancer deaths.[9] Individuals of black ethnicity have twice the risk of MM compared to white individuals, while the incidence of MM is markedly lower in Asians.[10] Furthermore, males have a 20% greater chance of being diagnosed with MM than females.[11]

Some known risk factors include ethnicity, aging, positive family history, and the presence of a precursor disease state such as monoclonal gammopathy of undetermined significance (GMUS) and smoldering multiple myeloma (SM).[12] Furthermore, there is a strong association between obesity and MM [13], Evidence has demonstrated an increased risk of transformation from GMUS to MM in overweight and obese individuals.[14] Other possible risk factors include specific occupations correlated with high exposure to organic solvents, such as painters, printers and oil workers.[15; 16]

During MM, patients, especially elderly people, experience pronounced symptoms

that substantially reduce their health-related quality of life. (QVRS).[17] Osteolytic lesions are present in 80% of patients, which often result in spontaneous fractures [18; 19], anemia occurs in 73%.[20] and renal failure affects 30% of patients.[21] Additionally, fatigue, weight loss and recurrent infections are notorious.[22] Such symptoms, combined with the adverse effects of treatment and the common comorbidities of the elderly population, are responsible for substantially reducing HRQoL.

The establishment of a treatment plan for newly diagnosed MM is based on eligibility for autologous stem cell transplantation (ASCT), considered the gold standard in its conduct.[24] However, the frailty of certain elderly individuals, such as chronic disorders and frailty syndrome, does not allow intensive treatments like this to be carried out. [25].

In view of this, the use of tools that add to geriatric assessment, such as the Eastern Cooperative Oncology Group (ECOG) Scale and the Charlson Comorbidity Index (CCI), are of great value in determining the conditions of patients ineligible for TACT and follow-up. to alternative treatment. With the help of these markers, prognostic assessment in the choice of management becomes possible. Thus, the effects of MM on physical function and performance status are assessed using the ECOG Scale, while the CCI is able to collaborate by calculating the risk of mortality in 1 year, via scores that include comorbidities at certain levels with different scores.[26]

It is essential that medication management is appropriate for patients not eligible for TACT, whose alternative first-line therapy includes proteasome inhibitors, immune modulators and corticosteroids, respectively to the bortezomib + lenalidomide + dexamethasone (RVD) regimen. However, these patients are not exempt from adverse effects and drug toxicities, such as renal impairment, venous thromboembolism, peripheral neuropathy and cardiac injuries.[27]

Age is a relevant factor in determining mortality and morbidity from the disease, since survival decreases with senility, especially after the age of 70. In this regard, adverse effects that affect HRQoL stand out, imposing physical (fatigue, skeletal pain, mobility) and emotional (distress, depression, anxiety) burdens. However, overall response to therapy and complete remission can significantly improve many aspects of HRQoL, considered the primary objective in patients with MM, with strict follow-up and adherence to therapy to improve prognosis.[28]

GOAL

Considering the great impact on the health of those affected by multiple myeloma, associated with a higher prevalence of the disease in old age. This work aims to analyze recent literature evidence about treatment and care in MM, in order to provide a better quality of life for those with the pathology, especially elderly patients.

METHODOLOGY

This is a qualitative, retrospective and cross-sectional study carried out through an integrative literature review. The databases used were the National Library of Medicine (PubMed) and Latin American and Caribbean Literature in Health Sciences (LILACS). The search for articles was carried out considering the descriptors "aged", "multiple myeloma", "quality of life", using the Boolean operator "AND". The literature review was carried out following the following steps: establishment of the theme; definition of eligibility parameters; definition of inclusion and exclusion criteria; verification of publications in databases; examination of the information found; analysis of the studies found and presentation of the results. The study included articles published in the last 11 years (2013-2023); in

English, Spanish and Portuguese, free access and articles whose studies were clinical trials and controlled and randomized clinical trials. Articles that did not have a clear definition of theoretical and thematic basis in line with the objects of the study and articles outside the topic covered were excluded.

RESULTS

The search, considering works from the last 11 years (2013 – 2023), resulted in a total of 572 works. Of these, 346 corresponded to studies from the last 10 years, 339 were from the PubMed database and 7 from the LILACS database. After applying the inclusion criteria, a total of 10 articles were selected, 9 in the PubMed database and 1 article in LILACS, as shown in figure 1. Of the 10 articles selected, 9 corresponded to a controlled and randomized clinical trial and one to a controlled clinic.

Among the selected articles, five evaluated elderly patients with MM and ineligible for bone marrow transplantation, the adoption of therapeutic regimens with medications to control symptoms and improve quality of life.

Two studies discussed the medications. The first demonstrated that treatment with daratumumab, lenalidomide and dexamethasone compared to treatment with lenalidomide and dexamethasone alone, is more effective in improving quality of life, without resulting in an increase in adverse events in this population. In a second study, therapy with daratumumab, lenalidomide, and dexamethasone compared with lenalidomide and dexamethasone was associated with faster and more sustained clinically significant improvements, including pain, in transplant-ineligible patients with newly diagnosed MM. The results are independent of age, initial ECOG status or depth of response to treatment.

The inclusion of prophylactic levofloxacin in the treatment of MM resulted in a reduction in mortality and common infectious syndromes of the disease, and the use of the drug was not related to a greater risk of kidney disease due to the drug.

Melphalan, prednisone and lenalidomide followed by lenalidomide maintenance (MPR-R) compared to the regimen containing melphalan and prednisone (MP), significantly prolonged disease progression-free survival. Finally, in another clinical trial, treatment with daratumumab, bortezomib, melphalan and prednisone (D-VMP) ensured early and continuous improvements in health-related quality of life, including functional and symptom improvements.

Another four studies addressed the use of assessment scales based on physical examination and laboratory tests to determine prognosis and treatment of the disease. The first demonstrated that the application of comprehensive geriatric assessment (CGA) is useful in classifying risk and directing care in patients with multiple myeloma, even in those with preserved functional capacity. Another study used the ECOG and CCI predictive prognosis scales, demonstrating improvement in the definition and optimization of care through them. Furthermore, a third study suggests an approach based on the patient's ECOG score to define minimal clinically important differences for the treatment of MM in the elderly.

Furthermore, to assess the prognosis and better define the treatment of patients with multiple myeloma, an assessment based on age and easily identifiable laboratory parameters such as LDH, CRP, lymphocyte/total white blood cell ratio is useful. The higher the age and the aforementioned indices, the higher the mortality and the worse the outcomes in terms of quality of life in these patients.

Finally, a Danish study demonstrated significant differences regarding the loss of physical and muscular function in patients

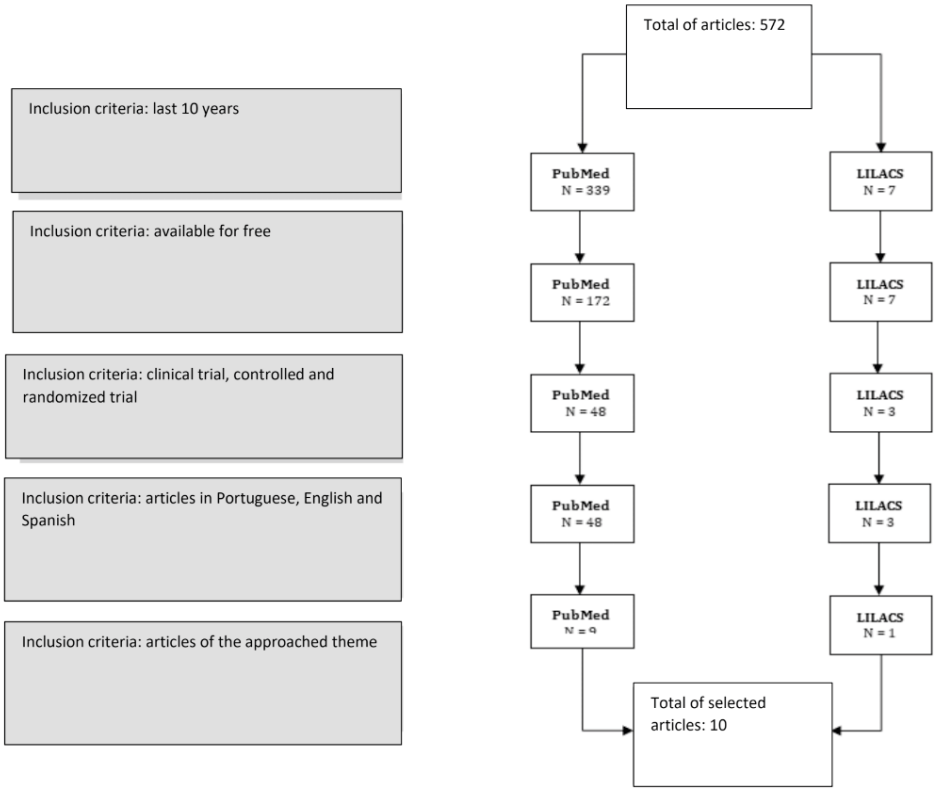

Figure 1: Flowchart of identification and selection of articles selected in the PubMed and LILACs databases

Source: Authors (2023).

Authors	Year	Kind of study	Sample	Main results
Li S, Zhang D, Yang L, Huang C, Niu T, Gong Y.	2023	Controlled and randomized study	N = 42.	Patients with newly diagnosed Multiple Myeloma were followed for 13 months, analyzing two treatment regimens Ixazomib + cyclophosphamide + dexamethasone (ICd) and Ixazomib + dexamethasone (Id). The regimens demonstrated efficacy and good tolerability in frail elderly people. The study suggests that ICd causes better and faster remission than the Id regimen, without increasing the risk of adverse events. The long-term efficacy and safety of the two regimens needs further investigation.
Jensen CE, Vohra SN, Nyrop KA, Deal AM, Muss HB, Lichtman EI, et al	2022	Clinical trial	N = 89	A brief AGA identifies clinically important deficits in individuals with MM, including among those with normal performance status on routine clinical assessment.
Knop S, Mateos MV, Dimopoulos MA, Suzuki K, Jakubowiak A, Doyen C, et al	2021	Controlled and randomized trial	N = 706	Patients with newly diagnosed myeloma who are ineligible for transplantation demonstrated early and ongoing improvements in health-related quality of life, including improvements in functioning and symptoms, following treatment with daratumumab, bortezomib, melphalan, and prednisone (D-VMP).
Perrot A, Facon T, Plesner T, Usmani SZ, Kumar S, Bahlis NJ, et al.	2021	Controlled and randomized trial	N = 737	Therapy with daratumumab, lenalidomide and dexamethasone compared to lenalidomide and dexamethasone was associated with faster and more sustained clinically meaningful improvements, including pain, in transplant-ineligible patients with newly diagnosed multiple myeloma, regardless of age, initial ECOG status, or depth of treatment response.

Tremblay G, Daniele P, Breeze J, Li L, Shah J, Shacham S, et al	2021	Controlled and randomized trial	N = 80	The majority of patients experienced no decline in HRQoL based on minimal clinically important differences during the first cycles of selinexor and dexamethasone treatment. A patient-level-based approach (ECOG PS score) to define minimal clinically important differences for treatment and delivery-based approach is suggested.
Larsen, R.F., Jarden, M., Minet, L.R, et al	2020	Controlled and randomized trial	N = 100	Patients with MM had significantly worse physical function compared to normative data, both in relation to aerobic capacity and muscle strength, although not grip strength. No differences in physical function were found between patients with multiple myeloma and other cancer populations. Exercise intervention studies are needed to explore the value of physical exercise on HRQoL in these patients.
Facon T, Dimopoulos MA, Meuleman N, Belch A, Mohty M, Chen WM, et al.	2020	Controlled and randomized trial	N= 1618	The use of a frailty scale containing Eastern Cooperative Oncology Group performance status (ECOG PS) as a predictive measure of clinical outcomes in patients with newly diagnosed myeloma and ineligible for transplantation is very useful. This score, based on age, Charlson Comorbidity Index (CCI) and ECOG PS, can be easily replicated, and also assists in designing future myeloma studies in frail and non-frail elderly patients.
Drayson MT, Bowcock S, Planche T, Iqbal G, Pratt G, Yong K, et al.	2019	Controlled and randomized trial	N=997	For 12 weeks from MM diagnosis, the addition of prophylactic levofloxacin to active myeloma treatment significantly reduced febrile episodes and deaths without increasing HAIs or carriage.
Cook G, Royle KL, Pawlyn C, Hockaday A, Shah V, Kaiser MF, et al.	2019	Controlled and randomized study	N =2372	The study defined a risk profile for treatment of newly diagnosed MM ineligible for marrow transplantation, using assessment of performance status (ECOG), neoplasm staging, age, LDH, ratio of lymphocytes to total white blood cells and protein concentration C reactive. The risk profile is associated with progression-free survival, early mortality and the percentage of the protocol dose administered, maintaining potential prognosis in patients treated with different mechanisms of action: alkylating agent regimens, immunomodulatory triplets and in patients treated with a sequential combination of immunomodulatory agents and proteasome inhibitors.
Dimopoulos MA, Palumbo A, Hajek R, Kropff M, Petrucci MT, Lewis P, et al.	2014	Controlled and randomized trial	N = 459	Melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance (MPR-R) significantly prolonged progression-free survival versus melphalan-prednisone (MP) in newly diagnosed multiple myeloma patients aged ≥ 65 years.

Table 1. Characterization of articles and main conclusions

Source: Authors (2023).

with MM, compared to individuals of the same age without the disease. Elderly people with MM had significantly worse physical function, in relation to aerobic capacity and also muscle strength, although not grip strength. No differences in physical function have been described between patients with multiple myeloma and other oncological populations. However, there is still no concrete evidence regarding the benefit of practicing physical activity in this population, in order to improve outcomes in relation to muscle function and physical capacity. The main results are shown in table 1.

DISCUSSION

In general, studies demonstrate benefits from treatment with immunomodulatory drugs and cytotoxic agents. However, the use of these therapeutic classes implies a high risk for neuropathy and fall-related events. Special attention is needed in the geriatric population, where polypharmacy and the use of other drugs with the potential to induce the same outcomes are common. Therefore, it is necessary to guide actions to prevent falls and promote the safe use of medications in elderly people with MM.[29]

Regarding the use of corticosteroids, in Brazil it is recommended to carry out a serological test to screen for strongyloidiasis in all asymptomatic patients (without suspicion of active strongyloides infection and without eosinophilia) before starting a course of corticosteroids with a dose equivalent to prednisone 20 mg/day or greater, lasting at least 2 weeks. Serological tests for strongyloides are very specific and sensitive, presenting a high negative predictive value, being useful for ruling out infection. In the face of negative results, it is not necessary to carry out prophylaxis. In immunocompromised patients (mainly due to hematological malignancies or undergoing chemotherapy) sensitivity is reduced. If it is necessary to immediately start corticosteroids, if it is impossible to wait for test results or if serological tests are unavailable, empiric treatment is indicated. The first choice is ivermectin at a dose of 200 mcg/kg/day for 2 consecutive days, without the need to add albendazole. The association of ivermectin with albendazole is indicated for the treatment of strongyloides hyperinfection.[30]

Levofloxacin, an antibiotic effective in reducing infectious events in patients with MM, is an antimicrobial belonging to the respiratory quinolone family. In the elderly, changes in renal elimination and hepatic metabolism may contribute to its accumulation and toxicity, and it is important to assess renal function before its use. In 0.9% to 11% of patients, there may be neurological changes, such as: dizziness, headache, insomnia, mood changes, attention disorders, memory changes, confusion, loss of appetite and tremors, which are often misinterpreted as part of the normal behavior of the geriatric patient. There are rare cases of hallucinations, delirium and psychoses, mainly described in senile and previously neuropathic patients.[31]

The use of comprehensive geriatric assessment was found to be effective in managing MM treatment in one of the studies. It is worth highlighting that its application improves the quality of life and care in geriatric patients as a whole. However, its applicability is often forgotten by some professionals, given the time and costs required to carry it out. In general, a comprehensive assessment of elderly people with cancer is recommended, since AGA, through different scopes, whether prognostic or interventional, plays a fundamental role in preserving the quality of life of this population. The need to create strategies for incorporating AGA into the care of elderly people with cancer is highlighted.[32]

CONCLUSION

It is possible to conclude that Multiple Myeloma has a major impact on health-related quality of life, especially as it affects mainly elderly patients, often with previous chronic diseases. In this sense, in order to provide greater quality survival for these patients, it is the doctor's duty to use medications cautiously, with special attention to the management of polypharmacy, to avoid drugs with synergistic adverse effects.

Furthermore, the application of prognostic scales is essential in these patients. It is worth highlighting the Comprehensive Geriatric Assessment, an important instrument for therapeutic assistance in the elderly, whether affected by pathologies or not. It is a useful tool for risk stratification and prognosis of patients, including those with normal performance according to clinical assessment. Its applicability must not be overlooked by medical professionals.

Other scales used in cancer patients, such as the Eastern Cooperative Oncology Group (ECOG) Scale and the Charlson Comorbidity Index (CCI) are also important prognostic definers and assist in the therapeutic management of these patients.

Regarding the preservation of physical capacity, an important definer of health-related quality of life in the elderly, there is a lack of studies aiming at functional improvement through exercise in this group. It is not possible to guarantee the safety of performing physical activity to maintain the quality of life in elderly people with Multiple Myeloma.

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