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THERAPEUTIC STRATEGIES FOR MULTIPLE MYELOMA: AN ANALYSIS OF CURRENT PRACTICES

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ABSTRACT

Multiple myeloma (MM) is a hematological neoplasm characterized by the clonal proliferation of plasma cells, which accumulate in the bone marrow and frequently produce the monoclonal protein M. Comprising 10-15% of hematological cancers, MM has a heterogeneous profile, requiring diversified therapeutic strategies. This study reviews contemporary therapeutic practices, emphasizing the evolution provided by immunomodulators, proteasome inhibitors, monoclonal antibodies, and emerging therapies, such as CAR-T cells. Advances such as autologous stem cell transplantation (ASCT) and the combination of therapeutic agents have prolonged overall survival and improved disease control. However, challenges such as toxicity, high cost, and clinical heterogeneity remain. Personalized approaches and the use of biomarkers emerge as promising, allowing for more effective and targeted treatments. This paper summarizes the main innovations in the management of MM, highlighting perspectives and challenges of current practices.

Keywords: Multiple Myeloma. Treatment. Immunomodulators. Proteasome Inhibitors. Stem Cell Transplantation.

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INTRODUCTION

Multiple myeloma (MM) is a hematological neoplasm characterized by the clonal proliferation of plasma cells, which accumulate in the bone marrow and, in many cases, produce a monoclonal protein, called the M protein. This malignancy is the second most frequently diagnosed hematologic malignancy, accounting for about 10-15% of blood cancers and 1-1.8% of all cancer cases. In Europe, the incidence of MM varies between 4.5 and 6.0 cases per 100,000 inhabitants per year. In the Polish context, for example, almost 2,600 new cases were registered in 2016 (National Health Fund (NFZ)). The average age at diagnosis of MM is 72 years, and more than 90% of patients are over 50 years old, while only 2% are under 40 years old. (CHARLIŃSKI; JURCZYSZYN, 2021)

Therapeutic advances in recent decades have brought a significant increase in patient survival. The median overall survival (OS) is approximately six years, but this expectation may vary according to the clinical profile of the patient and the therapeutic regimen employed. In patients undergoing autologous stem cell transplantation (ASCT), for example, the average survival can reach about eight years, while in patients with advanced age, over 75 years, the survival is, on average, five years. (CHARLIŃSKI; JURCZYSZYN, 2021; MINNIE; HILL, 2020; RAJKUMAR; KUMAR, 2020) This variation in survival expectancy reflects not only the biological characteristics of the disease and the patient, but also the therapeutic innovations and individualized management strategies that have emerged.

The criteria for the diagnosis of MM were revised in 2014, and one of the main diagnostic criteria is the detection of plasma cells that produce the M protein. The production of M protein is predominantly associated with IgG and IgA immunoglobulins, as well as kappa and lambda light chains, present in 54%, 21%, and 16% of cases. respectively. MM with monoclonal IgD protein production is rare, occurring in less than 2% of patients, and there are also cases in which the M protein is not detected in serum or urine. The latter group, classified as non-secretory MM (NS), represents about 3-5% of diagnoses, but advances in laboratory diagnosis with the use of serum free light chain (sFLC) testing have helped to redefine the prevalence of MMNS, estimating that approximately 2% of patients with MM have the true subtype of non-secretory MM. (CHARLIŃSKI; JURCZYSZYN, 2021; PADALA et al., 2021)

In recent years, the treatment of MM has undergone a revolution with the introduction of new therapeutic agents, which include immunomodulators, proteasome inhibitors, and monoclonal antibodies. These drugs have enabled the development of highly effective combination regimens, tailored to specific patient profiles, such as those eligible or

ineligible for ASCT, as well as for refractory and relapsed cases. (FACON; The moon; MANIER, 2024) The combination of therapies based on immunomodulators and proteasome inhibitors with monoclonal antibodies and stem cell transplantation have shown significant results in terms of therapeutic response and prolonged survival, although challenges such as the high cost and toxicity of treatments remain.

Given the complexity of MM and the various therapeutic approaches available, this study aims to review current therapeutic strategies for MM, emphasizing the combinations of agents that have demonstrated greater efficacy in different clinical contexts, in addition to discussing the impact of these advances on patients' quality of life and survival. The review is based on an in-depth analysis of the current literature, highlighting the perspectives and challenges of the latest therapies and their implications for the management of MM.

METHODOLOGY

This study was conducted through a systematic literature review, with the objective of synthesizing the most recent and relevant information on the topic of multiple myeloma. The database used to collect the articles was PubMed, chosen for its wide coverage in the area of health and biomedicine. For the search, the descriptors "multiple myeloma", "treatment" and "management" were selected in order to identify studies published in the last five years and ensure the updating of information, allowing an analysis in line with contemporary practices.

The selection of articles followed strict inclusion and exclusion criteria to ensure the relevance and quality of the information collected. Articles published between 2019 and 2024 that were available in full in the PubMed database, written in English, and that addressed the treatment and management of multiple myeloma as the main focus were included. Original article publications, literature reviews, clinical trials, and meta-analyses were considered, as long as they presented results and discussions pertinent to therapeutic strategies and disease management.

The exclusion criteria involved articles published outside the defined period, studies that were not available in PubMed, and studies that, despite mentioning multiple myeloma, did not specifically focus on therapeutic approaches or management of the disease. Publications that were not available in full text, articles in languages other than English, duplicates, and systematic reviews that included studies that had already been analyzed were disregarded.

The selection process involved an initial screening, where all titles and abstracts were analyzed, ensuring the strict application of the inclusion and exclusion criteria. The

studies that went through this stage were read in full for a thorough analysis of the data and information.

The systematic and judicious approach used ensured the reproducibility of the study and transparency in the article selection process. This methodology allowed the compilation of a comprehensive and updated review of treatment practices for multiple myeloma, contributing to the understanding of therapeutic alternatives and the clinical management of this condition.

RESULTS AND DISCUSSION

The treatment of MM has advanced substantially in recent decades, with the introduction of new therapeutic agents and drug combinations that have significantly improved patient survival. The main therapeutic strategies for MM involve the use of alkylating agents, corticosteroids, immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies. In addition, the growing importance of immunotherapy and the adaptation of regimens for patients with different clinical characteristics, such as age and comorbidities, have also been highlighted. Below, we detail the main treatments used and their clinical implications.

ALKYLATING AGENTS AND CORTICOSTEROIDS

Alkylating agents, such as melphalan and cyclophosphamide, continue to be used in the treatment of MM, especially in combination with other drugs. Although these drugs have limited activity in isolation, their efficacy increases when combined with other agents. Corticosteroids, such as dexamethasone and prednisone, are also often used in combination with alkylating agents, immunomodulators, and proteasome inhibitors. The D-VMP regimen (daratumumab, bortezomib, melphalan, and prednisone), for example, has shown good results in elderly patients and those ineligible for autologous stem cell transplantation (ASCT), with good response rates and effective management of comorbidities associated with advanced age. (Prince; Kumar, 2020)

IMMUNOMODULATOR DRUGS AND PROTEASSOME INIBITORS

The introduction of immunomodulatory drugs, such as thalidomide, lenalidomide, and pomalidomide, has revolutionized the treatment of MM. These agents work by binding to the cereblon and activating the E3 ligase of cereblon, which results in the rapid ubiquitination and degradation of B-cell-specific proteins, such as Ikaros (IKZF1) and Aiolos (IKZF3). This results in direct cytotoxicity, with immune system activation, antiangiogenesis,

and tumor necrosis factor-alpha inhibition. When combined with other agents, such as dexamethasone and bortezomib, these drugs demonstrate superior response rates and increased progression-free survival (PFS) and overall survival (OS). (Prince; Kumar, 2020)

Proteasome inhibitors, such as bortezomib, carfilzomib and ixazomib, are essential agents in the treatment of MM, since they block the degradation of regulatory proteins inside tumor cells, resulting in cell death. These agents have been combined with immunomodulatory drugs in regimens such as DVV (bortezomib, lenalidomide, and dexamethasone), which is widely used in the induction and maintenance of patients with MM, especially in patients with standard-risk myeloma. The VRd regimen has demonstrated benefits in terms of progression-free survival and overall survival, with an overall survival rate of over 80% at four years, regardless of early ASCT performance. (PADALA et al., 2021)

MONOCLONAL ANTIBODIES

In recent years, monoclonal antibodies have been prominent in the treatment of MM. Daratumumab and isatuximab are CD38-targeted monoclonal antibodies, which have been shown to be highly effective, especially in the treatment of relapsed and refractory MM. Daratumumab, in particular, has been approved for use in combinations with other drugs, such as bortezomib and lenalidomide, significantly improving therapeutic response. Clinical trials with daratumumab have demonstrated an increase in progression-free survival in patients with relapsed MM compared with previous regimens such as Rd (lenalidomide and dexamethasone). (CHARLIŃSKI; JURCZYSZYN, 2021)

Another monoclonal antibody, elotuzumab, is also effective in treating MM, although it does not show significant activity alone. It has been combined with medications such as lenalidomide and dexamethasone, contributing to a more robust therapeutic response. Although monoclonal antibodies are effective, their use may be restricted due to their high cost and the need for close monitoring. (Prince; Kumar, 2020)

TREATMENT OF PATIENTS INELIGIBLE FOR TRANSPLANTATION

Patients with advanced MM or with significant comorbidities may not be candidates for autologous stem cell transplantation (ASCT). For these patients, initial treatment usually involves triple-combination regimens. The DRd regimen (daratumumab, lenalidomide, and dexamethasone) has been shown to be particularly effective, offering a viable alternative to the VRd regimen, especially in patients with comorbidities or severe neuropathy. (FACON; The moon; MANIER, 2024) Other regimens, such as D-PMV (daratumumab, bortezomib,

melphalan, and prednisone), have also been widely used for elderly patients and those with contraindications to transplantation, ensuring a good therapeutic response.

However, for patients with non-secretory MM (MMNS), a rare subtype of myeloma, the efficacy of treatment does not appear to differ substantially from cases of secretory MM. Retrospective studies indicate that conventional treatments, such as high-dose chemotherapy followed by ASCT, can be effective, with a median survival exceeding 99 months in some cases. Although data on MMNS are limited, the available evidence suggests that patients with this subtype respond well to the same regimens used for secretory MM, with some studies indicating longer survival in patients with MMNS. (CHARLIŃSKI; JURCZYSZYN, 2021)

IMMUNOTHERAPY AND EMERGING THERAPIES

Although immunotherapy has shown promise for the treatment of MM, its clinical applicability is still limited. The combination of immunomodulators with proteasome inhibitors, monoclonal antibodies, and autologous stem cell transplantation (ASCT) represents a growing strategic approach. Immunotherapy, in turn, still faces challenges in generating long-lasting and functional anti-myeloma T cell responses. However, there is a growing interest in starting immunotherapy earlier, especially at a time of increased T-cell fitness, with the hope of generating more durable and effective responses. (MINNIE; HILL, 2020)

Recently, therapies such as CAR-T (chimeric antigen receptor) cells and vaccination have been explored as complementary strategies to restore immune control and provide long-term control of the disease. In addition, incorporating immunological endpoints into future clinical trials may improve our understanding of how these therapies can be more effectively combined and applied in the treatment of MM. (MINNIE; HILL, 2020)

CONCLUSION

The treatment of multiple myeloma (MM) has evolved substantially in recent decades, providing patients with a considerable increase in survival and an improvement in quality of life. This progress is mainly due to the introduction of new therapeutic classes, such as immunomodulators, proteasome inhibitors, and monoclonal antibodies, which, combined with autologous stem cell transplantation (ASCT), have transformed the therapeutic landscape of MM. For patients eligible for ASCT, this procedure continues to be the backbone of the treatment, allowing a higher mean overall survival than that observed in groups not candidates for this treatment. (FACON; LELEU; MANIER, 2024; PADALA et

al., 2021; RAJKUMAR; KUMAR, 2020) Still, even elderly patients and those with comorbidities who are not eligible for transplantation benefit from combined regimens involving the new therapeutic agents, achieving prolonged survival and better disease control.

The incorporation of monoclonal antibodies and the possibility of sequential use of various treatments have created new perspectives for refractory and relapsed patients, who previously had limited treatment options and a significantly reduced survival expectancy. However, the management of these cases still presents challenges, such as the need for close monitoring to prevent and manage toxicities associated with new treatments, as well as the issue of the high cost of these therapies, which directly impacts access and long-term sustainability of treatments. (CHARLIŃSKI; JURCZYSZYN, 2021; MINNIE; HILL, 2020)

The heterogeneity of MM, characterized by clinical and molecular variations, requires a personalized approach to maximize therapeutic benefits, and the use of emerging biomarkers has shown promise to guide treatment with greater precision. The diagnosis of MM, especially in cases such as non-secretory MM (NS), which represents a small percentage of patients and requires advanced laboratory techniques such as serum free light chain (sFLC) testing, has become more accurate with the revisions in the diagnostic criteria carried out in 2014. (CHARLIŃSKI; JURCZYSZYN, 2021) These diagnostic innovations have allowed the identification of patients with rare subtypes of MM, enabling more targeted treatments.

In conclusion, the treatment of MM has become a dynamic and complex field, with several management strategies that must be adapted to the individual characteristics of each patient. Advances in diagnosis and the development of new therapies, together with the combination of these approaches, offer a promising scenario for the management of MM, but also pose new clinical and economic challenges that need to be addressed. The continuity of scientific development and the refinement of therapeutic practices are essential so that, in the near future, MM can be treated with even greater effectiveness, extending survival and improving the quality of life of patients.

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