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Original Research Paper

Epidemology

MULTIPLE MYELOMA: NARRATIVE REVIEW

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ABSTRACT Multiple myeloma (MM) is a disease of unknown etiology, characterized by the accumulation of malignant clonal plasma cells in the bone marrow. Among its possible causes, exposure to toxins or viruses and in some cases, radiation has been considered, representing around 10% of malignant hematological neoplasms. Chromosomal abnormalities related to the immunoglobulin heavy chain change region located on the long arm of chromosome 14 have been seen. Among its clinical manifestations, bone pain, pathological fractures, anemia, frequent infections, hypercalcemia, kidney failure and episodes of abnormal bleeding will be highlighted. Its diagnosis is based on the demonstration of an increase in plasma cells >10% in the bone marrow. There is no known cure for MM. However, in recent years a stable remission of the disease has been achieved in patients that can last up to several years through a combination of chemotherapy and autologous stem cell transplantation.

KEYWORDS : microenvironment; multiple myeloma; staging.

INTRODUCTION

Multiple myeloma (MM) is characterized by the neoplastic proliferation of malignant plasma cells in the bone marrow that produce a monoclonal immunoglobulin, when they proliferate in the bone marrow, they cause extensive skeletal destruction with osteolytic lesions, osteopenia and/or the presence of pathological fractures. It is important to distinguish MM from other plasma cell dyscrasias for prognostic and therapeutic purposes.

METHODS

This narrative review was based on a search strategy that was carried out in databases such as PubMed/Medline, Lilacs and Redalyc, EBSCO. The MeSH and DeCS thesauri were used. Articles such as clinical trials, systematic reviews, topic reviews between the years of 1949 and 2022 were included (Figure 1).

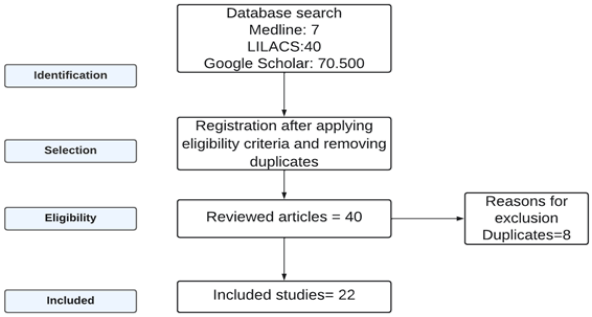

Figure 1. PRISMA.

Epidemiology

Multiple myeloma is a rare cancer, accounting for about 2% of all cancers and about 10% of hematologic malignancies. It is more common in men and in people of African American descent, with a median age of 65 to 74 years (1,2). Worldwide, according to figures from Globocan, there are approximately 180,000 cases with a total of 117,000 deaths/year. In the USA, 34,000 new cases of MM are estimated per year with a total of 13,000 deaths, which represents an incidence of 7/100,000 inhabitants/year (3), a similar incidence has been reported in Europe (4). In the case of Colombia, by mid-2020, an incidence of 1,376 cases/year was reported (5).

Pathophysiology

Myeloma arises from the proliferation of monoclonal plasma cells that are derived from postgerminal center B cells, genetic and microenvironmental changes lead to the transformation of these cells into a malignant neoplasm, myeloma is thought to evolve from a monoclonal gammopathy of clinical significance undetermined (MGUS). The initial step for the development of malignancy is the acquisition of hyperploidy or a translocation involving the immunoglobulin heavy chain gene locus (6). These clonal events can occur in almost all cells and are present in the precursor conditions of monoclonal gammopathy of undetermined significance (MGUS). Aetiological translocations mean that oncogenes are controlled by the immunoglobulin heavy chain gene enhancer, for example translocation t(4.14) deregulates MMSET and FGFR3, t(6;14) CCND3, t(11;14) CCND1, t(14;16) MAF and t(14;20) MAFB (7).

Genetic events are evidenced more frequently as the disease

evolves from a precursor condition to multiple myeloma, acquired genetic events refer to copy number abnormalities, somatic mutations, and secondary translocations with subsequent cell cycle dysregulation (8). Copy number abnormalities result in chromosomal regions of loss or gain. Loss of tumor suppressor genes occurs as a result of deletion, del(1p) results in loss of CDKN2C, FAF1 and FAM46C (also known as TENT5C), del(11q) BIRC2 and BIRC3, del(13q) RB1 and DIS3 , and del(17p)TP53. Common secondary translocations involve MYC, either through t(8;14) or without involving the immunoglobulin heavy chain gene, mutation rates are highly variable between patients and occur most frequently in genes of the pathway RAS/MAPK; about 50% of patients have this mutation (KRAS 22%, NRAS 17%, BRAF 8%). Other commonly mutated genes include TENT5C (previously known as FAM46C) and DIS3, in about 10% of patients (9). Other affected signaling pathways include the NF- B pathway, and the PI3K pathway (dysregulated in the absence of genetic changes). Dysregulation of the apoptotic pathway occurs, with BCL2 dependence in patients with t(11;14) and MCL1 dependence in other patients (10). Normal signaling of plasma cell differentiation is altered, with upregulation of IRF4 occurring through a positive autoregulatory loop and loss of negative feedback to MYC expression via PRDM1(11,12).

Anemia

It was evidenced in 73% of the patients at the time of diagnosis, of a normochromic normocytic nature, explained by the replacement of bone marrow with tumor infiltrate, relative deficiency of erythropoietin and dilution (12).

Bone pain

The osteolytic bone disease seen in MM can cause bone pain and pathological fractures. Pathological fractures, compression fractures and osteoporosis are evident in 20-25% of patients at the time of MM diagnosis (12).

Renal disease:

The serum creatinine concentration increases in almost half of the patients at the time of diagnosis, seeing values >2 mg/dl in 20% of the patients, this renal failure is due to the presence of immunoglobulin light chain cylinders and hypercalcemia, other reported causes are light chain amyloidosis and drug-induced kidney damage (13).

Hypercalcemia:

It can occur in MM secondary to bone demineralization due to altered bone resorption, with osteoclastic hyperactivity and osteoblastic inhibition (13).

Diagnosis

Patients with MM are often identified by elevated M protein values either in urine or blood. However, many patients arrive with signs and symptoms of organic damage (bone pain, fractures, anemia, infections, kidney failure), for which it is essential to perform a good clinical history and physical examination to guide the request for laboratories and images. In patients with asymptomatic precursor conditions such as monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma, additional morphological, biochemical, and imaging studies are needed (14). The acquisition of clonal plasma cells from the bone marrow is of great help, which, depending on their quantity, determine the type of precursor condition (Table 1). If there are symptoms or an increase in plasma cells >10% in the bone marrow demonstrated by biopsy, the diagnosis of MM is established. It is recommended that for the initial study of osteolytic lesions, a low-dose total body CT be performed, in case of suspicion of central nervous system involvement, an MRI would be the image of choice (15). Molecular tests, especially cytogenetic analysis by fluorescence in situ hybridization, should include tests for high-risk lesions, among which are: t(4;14), t(14;16) and del(17p) (16).

Table 1. Diagnosis.

	Monoclonal gammapaty	Smouldering myeloma	Multiple myeloma
M-protein and clonal bone marroy plasma cells	M-protein < 30 gr/L, and urinary M-protein <500 mg/24 h, and clonal bone marrow plasma cells <10%	M-protein >= 30 gr/L, or urinary M-protein >=500 mg/24 h, or clonal bone marrow plasma cells >=10% to <60%	Clonal bone marrow plasma cells >= 10% or bony or extramedullary plasmacytoma proved by biopsy.
Myeloma-defining events: biomarker of malignancy or end-organ damage	No	No	Yes

Clasification

The international staging system for MM is based on serum albumin and B2 microglobulin concentrations; this system reflects the tumor burden and the patient's condition (Table 2) (17). However, this system was updated, now called the revised international staging system (18), which contains information on the presence of high-risk genetic lesions: t(4;14), t(14;16) or del(17p) and lactate dehydrogenase levels, these inclusions provide more detailed information about the prognosis.

Table 2. Classification.

Stage	Criteria
I	Serum B2- macroglobulin <3,5 mg/L, Serum albumin >= 3,5 g/dL
II	Not stage I or III
III	Serum B2-microglobulin >=5,5 mg/dL

Treatment

Although no treatment is completely curative for MM, today there are multiple strategies for managing this disease, all efforts are focused on inducing a profound response, which is why autologous stem cell transplantation and chemotherapeutic regimens.

Autologous stem cell transplant

The first-line therapy in young patients (<65 years) is autologous stem cell transplantation (ASCT). The evidence supports the use of induction therapy, with subsequent autologous transplantation, in a randomized controlled clinical trial ASCT vs chemotherapy was evaluated, patients in the ASCT groups achieved longer progression-free survival of the disease, however, survival times were similar (19). It should be remembered that patients are selected for ASCT based on their age, performance status, and response to induction therapy; it should be clear that patients with refractory or progressive disease do not benefit from ASCT (20). Patients typically receive three to six induction cycles, after which the hematopoietic stem cells move into the peripheral blood, where they are collected and later frozen for reinfusion after high-dose chemotherapy (melphalan) from there the term autologous, the aim is generally to collect enough stem cells to have a reserve in case of relapse. The induction regimen is a regimen of bortezomib, combined with dexamethasone and an immunomodulatory drug (Thalidomide, Lenalidomide, Cyclophosphamide). Recently, the benefit of adding a CD38 antibody (Daratumumab) was reported in one trial, higher complete response rates (39% with daratumumab added vs. 26% without), and improved progression-free survival (21,22).

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