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Mini Review

Multiple Myeloma Update

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This literature review presents the most recent developments in the management of multiple myeloma, which is characterized by the presence of abnormal plasma cells (myeloma cells) that accumulate into the bone marrow. Aspects related to pathophysiology, clinical manifestations, laboratory, study and treatment are described. These pieces of information are necessary to accomplish a better management of the disease, and a reduction in economic burden and incidence of multiple myeloma.

Keywords: Multiple myeloma, immunoglobulin, neoplasm, monoclonal antibody, Bence Jones protein

Multiple myeloma (MM) is characterized by the presence of abnormal plasma cells (myeloma cells) that accumulate into the bone marrow. These tumors prevent the bone marrow from making sufficient healthy blood cells and specific antibodies to protect against millions of antigens. In 1975, the Durie/Salmon (DS) system, a clinical staging system for multiple myeloma was put forth by Brian G. M. Durie and Sydney E. Salmon. This comprises three stages, stage 1 having the best prognosis, and stage 3 links to inadequate response to treatment and low survival rates (1). The DS-system served as the most widely used staging system for more than 25 years. Clinical features, such as hemoglobin, serum calcium, grade of bone lesions, M-component, serum creatinine, and myeloma cell mass were analyzed with response to treatment and survival to create the basis of the DS-system (1, 2). However, in 2005, the International Myeloma Working Group (IMWG) developed another three-stage system that was similar to the DS-system but considered some more factors, as well as advances in medicine that occurred since 1975, when the DS system was published. Serum beta 2 microglobulins (Sβ2M) and serum albumin were included among the already established parameters diagnosing and staging multiple myeloma, together with geographic location, age, and treatment type (3). This system also disapproved the use of bone lesions as a parameter, as it deemed "observer-dependent" (4). This new system was the International Staging System for MM. A Sβ2M of less than 3.5 mg/L, serum albumin less than 3.5 g/dL was classified as ISS stage 1; ISS stage 2 was neither ISS stage 1 or 3; and lastly, ISS stage 3 was marked by serum Sβ2M more than 5.5 mg/L (3).

Most recently, in 2015, the IMWG, to improve the prognosis and care for patients with MM, proposed the Revised International Staging System (R-ISS) for MM that was a model composed of the previous ISS and the newly added criteria: chromosomal abnormalities (CA), and serum lactate dehydrogenase (LDH) (5). The standard risk for CA was no high-risk chromosomal abnormalities, while a high risk was the presence of del (17p), translocation t (4; 14), or translocation t (14, 16). Normal serum LDH was defined as the upper limit of normal as determined by the reporting laboratory,

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and similarly high serum LDH more than the upper limit of normal as established by the reporting laboratory. Collectively, these three parameters serve as the R-ISS, which is also a three-stage algorithm. R-ISS stage 1 is characterized by ISS stage 1 and standard-risk CA and normal LDH. R-ISS stage 2 is neither R-ISS stage 1 or 3. R-ISS stage 3 is characterized by ISS stage 3 and either high-risk CA by fluorescent-in situ hybridization (iFISH) or high LDH (5-6).

Pathophysiology

MM is a cancer of plasma cells involving more than 10% of the bone marrow. The neoplastic cells that form the bone marrow microenvironment play a major role in the pathogenesis of myelomas (7).

The malignant cells of MM, plasma cells, and plasmacytoid lymphocytes are the most mature cells of B-lymphocytes. B-cell maturation is associated with a programmed rearrangement of DNA sequences during the process of encoding the structure of mature immunoglobulins (8). It is characterized by overproduction of monoclonal immunoglobulin G (IgG), immunoglobulin A (IgA), or light chains, which can be identified with serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP) (9).

Interleukin (IL)-6 participates in the growth of myeloma cells (10). Other cytokines are IL-1b and tumor necrosis factor. MM involves the skeletal, hematologic, renal, and nervous systems, as well as general processes discussed below.

Skeletal processes

Plasma-cell proliferation causes anemia, osteolytic lesions, and hypercalcemia with bony involvement. Isolated plasmacytomas produces the osteoclast-activating factor, which lead to hypercalcemia. Replacement of bones by the tumor cells may lead to spinal cord compression, and pathological fracture. The development of symptoms of an epidural mass or rarely, an extradural mass may be due to the mechanism of spinal cord compression. With a pathologic fracture, bony involvement is typically lytic (7).

Hematologic processes

Bone marrow infiltration by plasma cells results in thrombocytopenia and neutropenia. M components may interact specifically with clotting factors, leading to defective aggregation (11).

Renal problems

The most prevalent renal injuries in MM are direct tubular injury, amyloidosis, or involvement by plasmacytoma. Renal conditions that can be observed include light-chain nephropathy, hypercalcemic nephropathy, amyloidosis, hyperuricemia due to renal infiltration of plasma cells resulting in myeloma, and glomerulosclerosis (12-13).

Neurologic processes

The nervous system can involve radiculopathy, and cord compression due to nerve compression and skeletal destruction (amyloid infiltration of nerves) (14).

General processes

General pathophysiologic processes include hyperviscosity syndrome. This syndrome is infrequent in MM, and occurs with overproduction of antibodies including IgA, IgG1 or IgG3. Sludging in the capillaries can result in papilledema, purpura, or central nervous system (CNS) symptoms (e.g., seizures, confusion, and vertigo). Cryoglobulinemia causes thrombosis, Raynaud phenomenon, and gangrene in the extremities (7).

Clinical features

In MM, abnormal plasma cells (myeloma cells) build up in the bone marrow, and form tumors in many bones of the body. These tumors infiltrate the bone marrow keeping them from making enough healthy blood cells (3, 7-8). The primary clinical features of MM are:

1) Osteolytic bone lesions: these cause bone pain especially in the back or ribs. They may also cause pathological fractures (bones break easily) and vertebral collapse. Myeloma causes osteoclastic activation which damages the bone, allowing the release of calcium into the blood causing hypercalcemia (15-16) that can cause loss of

appetite, nausea or vomiting, feeling thirsty, frequent urination, constipation, feeling very tired, muscle weakness, and restlessness.

2) Thrombocytopenia, anemia or neutropenia: this is due to bone marrow infiltration of neoplastic plasma cells. When myeloma crowds the bone marrow, there are less hematopoietic stem cells, and therefore less platelets, erythrocytes, and leukocytes. Renal failure can also cause anemia due to the decrease of erythropoietin levels. In MM, there is hypo-gammaglobulinemia, in which there is a suppression of normal antibodies. Along with neutropenia secondary to bone marrow infiltration, hypo-gammaglobulinemia increases the risk for bacterial infections (17-18).

3) Renal impairment: the leading cause of renal impairment in MM is due to the Bence Jones protein (light chains). Bence Jones protein combines with Tamm Horsfall protein (abundant urinary protein) form casts that obstruct the lumens of tubules, inducing an inflammatory reaction damaging the kidneys. Additionally, lambda light chains that are made in AL amyloidosis type (immunoglobulin light chain amyloidosis) cause deposit in the glomeruli, and subsequent nephrosis leading to acute and chronic renal failure (19).

Diagnosis /laboratory investigations

Procedures and tests used to diagnose MM include the measurement of M proteins and beta-2-microglobulin in blood (20). Additionally, blood tests may examine kidney function, blood cell counts, calcium levels, and uric acid levels (16, 21). Urine tests can be performed to find Bence Jones proteins (16). Bone marrow examination can be performed to search for abnormal plasma cells (plasmacytomas), and FISH analysis may show chromosomal genetic abnormalities (8, 16). Imaging tests including X-ray, magnetic resonance imaging (MRI), computed tomography (CT) or positron emission tomography (PET) can also be performed (17, 22-23).

Differential diagnosis

Several diseases closely resemble, and show the presentation and laboratory findings of MM (23-25). This is the case of monoclonal gammopathy of undetermined significance, with a 1% yearly risk of progression to the full blown MM. Other defects are Waldenström's macroglobulinemia, amyloidosis with extracellular deposition of protein in an abnormal fibrillar form, metastatic bone disease, and primary (malignant) lymphoma of bone.

Treatment

There are various clinical features of MM that require management throughout the disease and its treatment. To enhance the overall quality of life, it is necessary to decrease patient morbidity and mortality.

Bisphosphonates (BPs) are the gold standard for treating ytic bone lesions. Current recommendations indicate that BPs should initiate in patients with or without detectable osteolytic bone lesions on conventional radiography, who are receiving anti-myeloma therapy. Patients with osteoporosis or osteopenia should also be on BPs. Intravenous zoledronic acid or pamidronate show comparable efficacy in reducing skeletal-related events (pathological fractures) in patients with MM. Calcium and vitamin D3 supplementation should be used to maintain calcium homeostasis. However, caution should be takenwith the use of calcium supplements in patients with renal impairment (26).

The anemia resulting anemia from MM is usually treated with erythropoietic stimulating agents (ESA) to decrease the transfusion requirements. It was pointed out that the rise in hemoglobin is due to the ESA therapy and not a change in the status of the underlying myeloma, which emphasizes the importance of depriving the malignant myeloma cells from the needed iron in controlling the disease (27-28).

Renal impairment and acute kidney injury may result from paraprotein cast formation, hypercalcemia, and recurrent infections. Thus, various potential mechanisms for kidney injury should be addressed simultaneously. Patients should drink approximately 3L of water daily to flush the

kidneys, and prevent cast formation. Hypercalcemia should be aggressively treated due to its systemic effects. Treatment protocols include rehydration with isotonic saline, a non-loop diuretic, and corticosteroids; patients should already be on bisphosphonates to control calcium homeostasis. Rasburicase can be indicated in patients with significant tumor lysis syndrome (29-30).

Complications and management

The most important complications of MM are spinal cord compression, recurrent pneumonia due to leukopenia, pathological fractures, secondary amyloidosis, thromboembolism, and renal impairment (23). Table 1 summarizes the current management of MM (29-41).

Conclusion

A better understanding of the pathophysiology, clinical manifestations, laboratory studies, and treatment of MM is necessary to accomplish a better management of the disease, and a reduction in economic burden and incidence of MM.

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Conflict of interest

The authors declared no conflict of interest.

Table 1. Therapy of multiple myeloma (MM)

Type of treatment	Comments	References
Lenalidomide plus dexamethasone; bortezomib, lenalidomide, dexamethasone; bortezomib, thalidomide, dexamethasone; and bortezomib, cyclophosphamide and dexamethasone	The most common regimens used in the treatment of newly diagnosed MM	(29-31)
Autologous stem cell transplantation	Prolongs median overall survival in MM by approximately a year	(32-35)
Maintenance therapy with lenalidomide, and with bortezomib	Post-transplant maintenance therapy	(36)
Carfilzomib and pomalidomide regimen	For the treatment of relapsed refractory MM in patients who have previously used lenalidomide and bortezomib	(37)
Panobinostat	Its mechanism of action is to allow an alternative route for cells to bypass the deleterious effects of proteasome inhibition	(38)
Daratumumab	A monoclonal antibody used for the treatment of relapsed MM	(39)
Elotuzumab	Used combined with lenalidomide plus dexamethasone in relapsed MM	(39)
Ixazomib	Oral proteasome inhibitor that is active in both the newly diagnosed and the relapsed MM	(39)
Marizomib, oprozomib, filanesib, and dinaciclib	They show single agent activity in relapsed MM	(40,41)

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