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Review Article

MULTIPLE MYELOMA: A REVIEW

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ABSTRACT

Multiple myeloma is an incurable malignancy of plasma cells, and its pathogenesis is poorly understood. Multiple myeloma is the second most frequent haematological disease. There have been major advances in the past decade in the continuum of therapy for transplant –eligible and transplant non-eligible multiple myeloma patients. The pathogenesis of multiple myeloma is becoming clearer emanating from analysis of multiple myeloma cell genomes which reveals new mechanisms of transformation including mutations in the RNA exonuclease DIS3 and other genes involved in protein translation and homeostasis. This is in addition to previously suspected roles of NF-kB (Nuclear Factor Kappa B; a transcription factor) activation and HMT (Haematopietic Marrow Tissue) dysfunction in the biology of multiple myeloma.

This review therefore summarizes the current knowledge of multiple myeloma from the perspective of epidemiology, pathogenesis, clinical presentations, treatment and prognosis.

Introduction

The term 'Multiple Myeloma' was introduced by a Russian doctor, Von Rustizky in 1873, who had worked in von Recklinghausen's laboratory. During an autopsy, Von Rustizky found eight separate tumors of the bone marrow, which he designated as 'Multiple Myelomas', In Russia, the term 'Rustizky's disease' is often used for multiple myeloma. Multiple Myeloma is a debilitating disease that has gained the interest of physicians and scientists for decades. This disease has probably been present for centuries as cases of

possible multiple myeloma have been reported in American Indian skeletons from 200 AD. In 1848, Dr Bence Jones identified a metabolite of albumin in patients with this disease which was later named the Bence Jones protein.

Multiple myeloma (MM) refers to disseminated plasma cell malignancy. It is part of the spectrum of plasma cell dyscrasias, which includes monoclonal gammopathy of undetermined significance (MGUS), primary amyloidosis, non–secretory myeloma, smouldering multiple myeloma (SMM), solitary plasmacytoma, and multiple myeloma.
Multiple myeloma is characterized by proliferation of malignant plasma cells and subsequent production of monoclonal paraprotein (the M protein).

Multiple myeloma accounts for 1% of all cancers [1], 10% of all haematolgical malignancies [2,3] 19% of all deaths resulting from hematological malignancies, and 2% of all cancer-related mortality.[2] Although the incidence of multiple myeloma in Nigeria is uncertain, it is estimated to be 8 per 100 000 per year in Hospital based data.[4]
Blacks have at least double the risk of being diagnosed with multiple myeloma and have twice the mortality rate from the disease compared to whites.

Multiple Myeloma is the second most frequent haematological cancer. The occurrence of multiple myeloma is worldwide but there are considerable differences in the incidence and survival in different geographical areas. It primarily affects older individuals; the median age at diagnosis is 70years in caucasians and two-thirds of MM patients are more than 65 years of age when they are first diagnosed. In the United States, the lifetime risk of being diagnosed with MM is 1 in 161 (0.62%)[5] its incidence is higher in men and people of African descent. The male-to-female ratio of multiple myeloma is approximately 3:2. In patients seen in the University College Hospital (UCH) Ibadan, we observed that the median age at presentation for the patients with myeloma was 65 years, with age ranging from 36 to 85 years[6]. Four percent of patients were less than 40years, while 24% were greater than 70 years. Male: Female ratio was 1.4:1.The increased life expectancy of the general population and improved survival arising from better anti myeloma drugs means that an increase in the number of elderly MM patients is expected over time.

Pathophysiology

The precise etiology of MM has not yet been established. However, aetiological roles have been suggested for a variety of factors, including genetic causes, environmental or occupational causes, monoclonal gammopathy of undetermined significance (MGUS), radiation, chronic inflammation, and infection. Based on retrospective data, the risk of progression from SMM[7] to multiple myeloma is 10% per year for the first 5 years, 3 % per year for the next 5 years, and 1% for the subsequent 10 years. MGUS is associated with an

average 1% annual risk of progression to multiple myeloma[8]. The clinical course of SMM was described by kyle et al [9]

Multiple Myeloma is characterized by neoplastic proliferation of plasma cells constituting more than 10% of the cells in the bone marrow [10]. Increasing evidence suggests that the bone marrow microenvironment of tumor cells plays a pivotal role in the pathogenesis of myeloma. Myeloma cell growth and survival are augmented by direct physical interactions of plasma cells with bone marrow stromal cells, and this knowledge is providing a focus for new therapeutic approach and treatment options.

Genetic abnormalities in myeloma

About 40% of cases of myeloma harbour chromosome translocations resulting in overexpression of genes (including CCND1, CCND3, MAF, MAFB, WHSC1 (also called MMSET) and FGFR3) via their juxtaposition to the immunoglobulin heavy chain (IgH) locus[11]. Other cases exhibit hyperdiploidy.

However, these abnormalities are probably insufficient for malignant transformation because they are also observed in the pre-malignant syndrome known as monoclonal gammopathy of uncertain significance.

Malignant progression events include activation of MYC, FGFR3, KRAS and NRAS and activation of the NF-kB pathway[11-13].

More recently, loss-of-function mutations in the histone demethylase UTX (also called KDM6A) have also been reported[14].

Of potential immediate clinical relevance, activating mutations of the kinase BRAF were observed in 4% of patients, suggesting the evaluation of BRAF inhibitors in multiple myeloma clinical trials.

Genome sequencing and analysis of multiple myeloma revealed statistically significant protein-coding mutations in multiple myeloma to include NRAS, KRAS, FAM46C, DIS3, TP53, CCND1, PNRC1, ALOX12B, HLA-A and MAGED1[15].

The Role of Cytokines

The proliferation and survival of myeloma cells are dependent on several cytokines, most notably IL-6, which is an important growth factor for plasma cells. This cytokine is produced by the tumor cells themselves and marrow stromal cells. High serum levels of IL-6 are seen in patients with active disease and are associated with a poor prognosis. The role of cytokines in the pathogenesis of MM is an important area of research. Other cytokines such as tumor necrosis factor and IL-1b have also been implicated in the development of multiple myeloma.[16,17]

Myeloma-derived Macrophage inflammatory protein 1 alpha (MIP-1 alpha) is a member of the C-C sub-family of chemokines, a large superfamily of low-molecular weight inducible proteins that exhibit a variety of proinflammatory activities in vitro, including leukocyte chemotaxis. MIP-1 alpha is a particularly an interesting chemokine, because in addition to its proinflammatory activities, it inhibits the proliferation of hematopoietic stem cells in vitro and in vivo. MIP1α upregulates the expression of the receptor activator of NF-κB ligand (RANKL) by bone marrow stromal cells, which in turn activates osteoclasts, thereby playing a major role in bone resorption seen in MM patients[18,19].

Other factors released from tumor cells, such as modulators of the Wnt pathway, are potent inhibitors of osteoblast function. The net effect is a marked increase in bone resorption, which leads to hypercalcemia and pathologic fractures.[20]

Multiple myeloma is quite heterogeneous at the molecular level, and is associated with a diversity of chromosomal aberrations. *Many myelomas have rearrangements involving the Ig heavy-chain gene on chromosome 14q32.* Common translocation partners include *FGFR3* (fibroblast growth factor receptor 3) on chromosome 4p16- , a gene encoding a tyrosine kinase receptor implicated in the control of cellular proliferation; the gene for the transcription factor c-MAF on chromosome 16q23; and the gene encoding the transcription factor MUM1/IRF4 on chromosome 6p25.Frequently, there is dysregulation of the cell cycle–regulatory genes with translocations involving cyclin D1 on chromosome 11q13 and cyclin D3 on chromosome 6p21. Translocations involving cyclin D1 are associated with a good outcome, whereas deletions of 13q, deletions of 17p, and the t(4;14) portend a more aggressive course.[19]The malignant plasma cells of MM, and plasmacytoid lymphocytes are the most mature cells of the B-lymphocyte lineage. B-cell maturation is associated with a programmed rearrangement of DNA sequences in the process of encoding the structure of mature immunoglobulins. Mutations occurring during this process result in overproduction of monoclonal immunoglobulin G (IgG), immunoglobulin A (IgA), Ig E, IgM and/or light chains, which may be identified with serum protein electrophoresis or urine protein electrophoresis. Mehta KD et al has demonstrated M protein in bone morrow asprirate by agar gel electrophoresis in myloma.[21]

Clinical Features

In developed countries MM is often discovered through routine blood screening, when patients are being evaluated for unrelated problems. In one third of patients, particularly in developing countries MM is diagnosed after a pathologic fracture has occurred, usually involving the axial skeleton. In a study done by Madu AJ et al [29] in Enugu, Nigeria, the most common clinical features at presentation were anemia (71.9%) and bone pains (78.1%), while pathological fractures were found in 69%, and nephropathy in 13.8%.

The malignant proliferation of plasma cells in MM interferes with the normal production of other blood cells hence the anaemia and the other cytopaenias in advanced disease.These malignant plasma cells elaborate aberrant antibodies leading tothe impairment of humoral immunity. Other complications from the overproduction of these antibodies include hyperviscosity, amyloidosis, and renal failure.

The clinical features of multiple myeloma stem from (1) the effects of plasma cell growth in tissues, particularly the bones; (2) the production of excessive Igs, which often have abnormal physicochemical properties; and (3) the suppression of normal humoral immunity.

Plasma-cell proliferation causes extensive skeletal destruction with osteolytic lesions, anemia, and hypercalcemia.The presentation of MM can range from asymptomatic to severely symptomatic, with complications requiring emergency care such as paraplegia resulting from spinal cord compression, anaemic heart filure, septicaemia altered sensorium from hyperviscosity syndrome and or hypercalcaemia.

Table1. Clinical features of multiple myeloma patients at presentation in UCH Ibadan.[22]

Clinical features	Frequency (Percentage)
Anaemia with Fatigue / dizzy spell	26 (56.5)
Bone pain	19 (41.3)
Lumbo-Sacral pain	23 (50.0)
Inability to work	18 (39.10)
Fever	16 (34.8)
Cough	14(30.4)
Paraparesis	14 (30.4)
Oedema	5 (10.9)
Pathological fracture	14 (30.4)
Bleeding	8 (17.4)
Weight loss	8 (17.40)
Hepatomegaly	5 (10.9)
Splenomegaly	4(8.7)

Examination for MM may reveal the following:

Head,Eye and ENT examination: Exudative macular detachment, retinal hemorrhage, or cotton-wool spots

Dermatologic: Pallor from anemia, ecchymoses or purpura from thrombocytopenia;

extramedullary plasmacytomas (most commonly in aerodigestive tract but also in orbital, ear canal, cutaneous, gastric, rectal, prostatic, retroperitoneal areas)
Musculoskeletal: Bone tenderness or pain without tenderness
Neurologic: Sensory level changes (ie, loss of sensation below a dermatome corresponding to a spinal cord compression), neuropathy, myopathy, positive Tinel sign, or positive Phalen sign.
Hepatosplenomegaly
Cardiomegaly
In patients with multiple myeloma and amyloidosis, the characteristic examination findings include the following: Shoulder pad sign, macroglossia, typical skin lesion, carpal tunnel syndrome, and subcutaneous nodules.

Diagnosis

The diagnosis of multiple myeloma is often not that simple, [10, 23] it requires thoughtful synthesis of multiple variables from the patient's presentation. Approximately 20% of patients with multiple myeloma are recognized by chance without significant symptoms; such patients can be carefully monitored without instituting therapy. In addition to clinical features and basic investigations such as complete blood count, skeletal x-ray, serum creatinine, urea and calcium levels, extensive investigations might be required to determine whether the pathology is attributable to the myeloma or another cause.

The clinicopathologic diagnosis of multiple myeloma rests on radiographic and laboratory findings. Haematological tests include Full blood counts, ESR, Peripheral blood film which may show circulating plasma cells in buffy coat particularly in cases advanced disease and plasma cell Leukaemia.

The definitive diagnosis requires a bone marrow examination. Marrow involvement often gives rise to a normocytic normochromic anemia, sometimes accompanied by moderate leukopenia and thrombocytopenia. Bone marrow examination reveals replacement of the normal marrow cells by plasma cells that may show multi-nuclearity, prominent nucleoli, and cytoplasmic droplets containing Immunoglobulin.

Immunological Assessment

Serum and urine assessment for monoclonal protein (densitometer tracing and nephelometric quantitation; immunofixation for confirmation)
Serum free light chain assay (in all patients with newly diagnosed plasma cell dyscrasias)
Serum beta2-microglobulin, albumin, and lactate dehydrogenase measurement
Comprehensive metabolic panel (levels of total protein, albumin and globulin, BUN, creatinine, uric acid) 24-hour urine collection for quantification of the Bence Jones protein

(ie, lambda light chains), protein, and creatinine clearance; proteinuria greater than 1 g of protein in 24 hours is a major criterion
C-reactive protein
Standard metaphase cytogenetics which may show the known chromosomal abnormalities
Fluorescence in situ hybridization
Comprehensive metabolic panel (levels of total protein, albumin and globulin, BUN, creatinine, uric acid)

Table 2. Comparison of the multiple myeloma patients' biochemical profile with reference range

Parameter	Normal Range	Patients: Mean (SD)	P value
Total protein g/L	6.0-8.0	9.2 (2.1)	0.05
Corrected calcium mg/dl	9.0-11.0	10.3 (1.4)	>0.05
Uric acid mg/dl	2.0-7.0	5.6 (4.6)	0.05
PCV %	36.0 – 52.0	24.0 (7.0)	< 0.05
WBC /mm3	3000 – 9000	5167.9 (2241.7)	> 0.05
ESR mmhr	2 – 15	100.3 (37.3)	< 0.05
Platelet /mm	100 000 – 300 00	191786.2 (119420.1)	> 0.05
Globulin g/L	2.0-4.5	6.1 (2.2)	< 0.05
Albumin g/L	3.5 – 5.0	3.1 (0.9)	< 0.05

Imaging studies in the diagnosis of myeloma myeloma.

Radio diagnostic tests should include Skeletal survey, including the skull, long bones from which multiple myeloma can be strongly suspected when the distinctive radiographic changes are present: Sharply punched-out bone lesions that are most obvious in the calvarium spine MRI for detecting thoracic and lumbar spine lesions, paraspinal involvement, and early cord compression PET scanning in conjunction with MRI are also potentially useful

Management

The outcome of MM has significantly improved in the last decade because of new treatment modalities. The decision to treat is based on some established criteria. CRAB (which stands for "hyperCalcaemia, Renal failure, Anaemia, and Bone diseases") criteria are the most common reasons for initiating therapy. Other indications include symptomatic hyperviscosity, recurrent bacterial infections, and amyloidosis with organ involvement.

There is currently no cure for MM. However, advances in therapy have helped to lessen the occurrence and severity of adverse effects of this disease, such as autologous stem cell transplantation, radiation, and surgical care in certain cases.

The initial therapy for MM depends on the eligibility for Haemopioetic Stem Cell Transplantation (HSCT). The ultimate goal of therapy for non-transplantation-eligible MM patients is prolongation of disease- free survival and overall survival. Prolonged treatment –free intervals and good quality of life have also become important aims, especially for the elderly patients.

The transplantation- eligible patients may be defined by age and/or comorbidities. In some countries, most patients over age of 65 years do not undergo autologous Haemopoietic Stem Cell Transplantation (HSCT) however in the United States, age over 65years is not considered an absolute contraindication. Other factors, especially comorbidities and performance status influence the decision for a patient to undergo autologous HSCT.

Chemotherapy and immunosuppression

Chemotherapy regimen used in patients with MM include the following:

Thalidomide, either as a single agent or in combination with steroids or with melphalan

Lénalidomide plus dexamethasone

Bortezomib plus melphalan

VAD (vincristine, doxorubicin [Adriamycin], and dexamethasone)

Melphalan plus prednisone

The 2011 NCCN guidelines for MM added the following therapies:

The combination of bortezomib/cyclophosphamide/dexamethasone as primary induction

therapy for transplant candidates
The combination of bortezomib/dexamethasone (without cyclophosphamide) as primary induction therapy for patients who are not candidates for transplantation
The combination of melphalan/prednisone/lenalidomide for primary induction therapy for nontransplant candidates
Patients with refractory disease or relapse may be treated with the following:
Any of the agents not previously used
Bortezomib plus cyclophosphamide and dexamethasone
Carfilzomib (Kyprolis)
Thalidomide
Lenalidomide plus cyclophosphamide and dexamethasone
Pomalidomide
Patient education is very important in the management of MM and should address the following questions:
What is MM, and how does it affect the body?
What are the causes of MM?
What is the treatment for MM?
What are the adverse effects of medicine? (As an example, patients should be informed of the risk of osteonecrosis of the jaw, which has been associated with bisphosphonate therapy in MM.)
What are some of the complications of MM?
Where can additional information be found?

PROGNOSIS

The 5-year relative survival rate for MM is around 35%, with survival ranging from 1 year to more than 10 years. Median survival in unselected patients with MM is 3 years although patients benefit from treatment with improved survival and reduction in symptoms and complications (longer life, less pain, fewer complications), currently no cure exists.
Survival is higher in younger people and lower in the elderly. In Nigeria, late presentation and occurrence of complications adversely affect survival. Tumor burden and the proliferation rate are the two key indicators for assessing the prognosis in patients with MM.
The staging of MM is important for finding out how much the cancer has advanced. The stage is an important determinant of treatment options, prognosis, outcome and survival.
This International Staging System (ISS) divides myeloma into 3 stages based only on the serum beta-2 microglobulin and serum albumin levels.

Stage I

Serum beta-2 microglobulin is less than 3.5 (mg/L) and the albumin level is above 3.5 (g/L)

Stage II

Neither stage I nor III, meaning that either:

The beta-2 microglobulin level is between 3.5mg/l and 5.5mg/l (with any albumin level), or
The albumin is below 3.5g/dl while the beta-2 microglobulin is less than 3.5mg/l

Stage III

Serum beta-2 microglobulin is greater than 5.5mg/l

Factors other than the stage of the disease that affect survival includes age, plasma cell labeling index, kidney function (creatinine clearance) and chromosome abnormalities.

The prognosis in relation to the type of treatment areas are as follows:

Conventional therapy: Overall survival is approximately 3 years, and event-free survival is less than 2 years.

High-dose chemotherapy with stem-cell transplantation: The overall survival rate is greater than 50% at 5 years.

For patients with Serum amyloid P retention; more than 50% have a median survival of approximately 11 months.

The study by A.J Madu et al (2014)[29] showed the longest duration of survival of 288 and 252 weeks in patients on Melphalan and Prednisolone with or without thalidomide. Bacterial infection has been identified as the leading cause of death in patients with myeloma.

In conclusion, multiple myeloma is a heterogeneous disease with ongoing advances in the understanding of its aetiology, pathophysiology and treatment. The most important thrust of management of this fairly common hematological malignancy is early diagnosis and intervention to prevent complications.

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