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Review Article

Multiple Myeloma

Naghmi Asif and Khalid Hassan
Department of Pathology, Islamabad Medical & Dental College, Islamabad

(Bahria University, Islamabad)

Multiple myeloma is a neoplastic disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow, monoclonal proteins in the blood and/ or urine and associated organ dysfunction.[1] It accounts for approximately 1% of neoplastic diseases and 13% of hematologic cancers.[2] Multiple myeloma is slightly more common in men than in women and the median age at the time of diagnosis is about 65 years.[3] Unlike other malignancies that metastasize to the bone, bone lesions in multiple myeloma are lytic in nature rather than osteoblastic. Bone disease and renal failure are the main cause of morbidity. Other major clinical manifestations are anemia, hypercalcemia and an increased risk of infections. Approximately 1–2% of patients have extramedullary disease (EMD) at the time of initial diagnosis, while 8% develop EMD later on in the disease course.[4] There is an increased incidence of multiple myeloma in persons with rheumatoid arthritis or obesity (body mass index of more than 30 kg per m2).[5] Some environmental factors such as exposure to ionizing radiation, pesticides, or petrochemicals also seem to interact with underlying genetic factors and increase the risk of multiple myeloma. However, no clear risk factor can be identified in most patients.

Almost all patients with myeloma evolve from an asymptomatic premalignant stage termed monoclonal gammopathy of undetermined significance (MGUS).[6,7] MGUS is a premalignant disorder in which a clone of plasma cells produces a monoclonal paraprotein that does not cause end-organ damage. It is present in 2 % of persons older than 50 years, and the risk of progressing to multiple myeloma is 1 % each year.[8] Several familial aggregations have been observed with an autosomal dominant pattern, increasing the risk by two- to fourfold.[9,10,11] In some patients, an intermediate asymptomatic but more advanced premalignant stage referred to as smoldering multiple myeloma (SMM) can be recognized clinically. SMM progresses to myeloma at a rate of 10% per year over the first 5 years following diagnosis.[3]

Pathophysiology

Monoclonal myeloma plasma cells proliferate and overproduce M protein (abnormal IgG, IgM, or IgA, or rarely IgE or IgD); these cells also produce abnormal light chain proteins (κ or λ), cytokines that stimulate osteoclasts and suppress osteoblasts, and angiogenesis factors that promote new blood vessel formation. This process leads to an excessive M protein level, which causes hyperviscosity; light chain proteins that cause end-organ damage, especially in the kidneys; and bone lesions that cause bone pain, osteoporosis, and hypercalcemia. Bone marrow infiltration leads to anemia, and immunologic alterations contribute to recurrent infections. Most new cases of multiple myeloma are believed to arise de novo, although up to 20 percent evolve from MGUS.[12] It is not completely understood how MGUS develops into multiple myeloma. An elevated M protein level (1.5 g per dL [15g per L] or greater), non-IgG MGUS , and an abnormal free light chain ratio increase the risk of multiple myeloma, if all three risk factors are present. Patients with MGUS should be monitored with laboratory tests every six to twelve months.[13]

Clinical Presentation

Many patients with multiple myeloma initially present with unexplained backache or bone pain. The long bones, ribs, skull, and pelvis are commonly involved, and most patients have multiple lytic skeletal lesions. Pathologic fracture is the presenting symptom in 26 to 34 percent of patients.[12] Vertebral compression fractures can lead to weakness and paresthesias in the lower extremities. Carpal tunnel syndrome is the most common peripheral neuropathy in patients with multiple myeloma. Anorexia, nausea, somnolence, and polydipsia are common symptoms due to hypercalcemia. Weakness and malaise are usually associated with anemia in multiple myeloma. Impaired antibodies and leukopenia cause recurrent infections, usually from encapsulated organisms (pneumonia is the most common infection). Weight

loss occurs in less than one fourth of patients, and fever is rare at presentation. About 34 percent of patients are asymptomatic at presentation with incidental abnormalities on total protein, creatinine, calcium, or hemoglobin.[13] Myeloma related organ and tissue impairments include hypercalcaemia: serum calcium level greater than 11 mg per dL (2.75 mmol per L); renal insufficiency: serum creatinine level greater than 2 mg per dL (180 µmol per L); anaemia: haemoglobin level less than 10 g per dL (100 g per L); bone lesions: lytic lesions, compression fractures, or osteoporosis; and other impairments: symptomatic hyperviscosity, amyloidosis, and bacterial infections.[14] Other clinical manifestations include disorders of metabolism (hyperuricaemia), cryoglobulinaemia and the hyperviscosity syndrome,[15] soft tissue or solitary bone masses (plasmacytomas), and concomitant amyloidosis with gastrointestinal symptoms, peripheral neuropathy, or cardiomegaly.[16]

Renal Impairment

Renal impairment occurs in 20 to 40% of patients with newly diagnosed disease,[17,18] mainly as a result of direct tubular damage from excess protein load, dehydration, hypercalcemia, and the use of nephrotoxic medications.[19] Renal involvement in multiple myeloma is mainly due to the presence of light chains that are predominantly affect glomeruli, tubules and form casts. Myeloma cast nephropathy (or myeloma kidney) is the most frequent and most important renal manifestation of MM and is observed in more than 50% of the patients who die from MM and renal involvement, and in 40% to 60% of renal biopsies performed in subjects with MM.[20] Myeloma cast nephropathy is associated with exceptionally poor prognosis. This is an important cause of end stage renal disease (ESRD) and is associated with significantly worsened survival as compared to ESRD secondary to other forms of renal involvement due to MM.[21,22] Proteinuria is another common manifestation of renal involvement in MM; it is observed in up to 80% of the cases with renal manifestations, and in 15% to 20% of these cases it reaches the nephrotic range, i.e., exceeds 3.5 g/24 h.[21] Proximal tubular cell dysfunction resulting in glycosuria, aminoaciduria, hyperphosphaturia, and renal tubular acidosis secondary to bicarbonate loss is another manifestation of renal disease in MM.[23]

It has been observed that impairment of renal function significantly and adversely affects the prognosis in MM. Successfully treated MM can result in complete recovery of renal function. In these cases, an unfavorable effect of chronic kidney disease on prognosis can be fully reversed.

Haemostatic abnormalities

Patients with multiple myeloma having a higher titer of serum paraproteins can manifest haemostatic abnormalities. Most of these abnormalities predispose the patient to haemorrhage. Impaired platelet function, shown by prolonged bleeding time or abnormal platelet aggregation studies, have been associated with clinically significant bleeding and elevated serum paraproteins, particularly IgM. The proposed pathophysiology is nonspecific coating of platelets by immunoglobin. Control of bleeding and shortening of bleeding time following plasmapheresis indirectly supports this mechanism, but improvement may also be due to correction of hyperviscosity. Bleeding complications are more likely with IgM and IgA paraproteins than with IgG, and are associated with higher concentrations of serum immunoglobins, higher serum viscosity, and prolonged bleeding time. Coagulation abnormalities in patients with plasma cell dyscrasias, are also due to monoclonal protein interaction with clotting factors. Rare cases of multiple myeloma complicated by severe bleeding, paraproteins with specificity for thrombin and factor VIII have been identified.[24] Both solid tumours and multiple myeloma have been associated with rare cases of acquired hyperfibrinolysis due to excess release of tissue plasminogen activator or urokinase-type plasminogen activator and circulating heparin-like anticoagulants.[25]

Bone Lesions

Bone lesions in MM are caused by an imbalance in the function of osteoblasts and osteoclasts.

First, osteoblasts are suppressed by inhibition of the Wnt pathway, whereas the amplification of the RANK pathway and the action of macrophage inflammatory protein-1a activate osteoclasts.[26] The induction of proangiogenic molecules (e.g., vascular endothelial growth factor) enhances the microvascular density of bone marrow and accounts for the abnormal structure of myeloma feeding vessels.[27]

Emergencies in Multiple Myeloma

Spinal cord compression, hypercalcaemia, renal failure, hyperurecemia, fractures and bleeding are medical emergencies in multiple myeloma requiring immediate investigation and treatment.

Diagnosis

Investigation of a patient with suspected myeloma should include the screening tests (which include full blood count, ESR, serum or urine protein electrophoresis, X-rays of symptomatic areas and renal function tests), followed by further tests (including bone marrow aspirate/trephine biopsy, skeletal survey and quantification and immunofixation of serum or urine) to confirm the diagnosis. The diagnosis of myeloma is based on the presence of at least 10% clonal bone marrow plasma cells and monoclonal protein in serum and/or urine. In patients with non-secretory myeloma, which accounts for about 2% of MM, the diagnosis is based on the presence of 30% monoclonal bone marrow plasma cells or a biopsy-proven plasmacytoma.

MM is classified as asymptomatic or symptomatic, depending on the absence or presence of myeloma-related organ or tissue damage, including hypercalcemia (C), renal insufficiency (C), anemia (A), bone disease (B), and other myeloma-related symptoms (O), such as hyperviscosity syndrome and frequent infectious events, which are called the CRABO criteria.[28,29]

Several diagnostic criteria of MM have been proposed; the most recent diagnostic criteria were proposed by the International Myeloma Working Group (IMWG). IMWG recommends taking a detailed medical history and a physical examination, routine laboratory testing (complete blood count, chemical analysis, serum and urine protein electrophoresis with immunofixation, and quantification of monoclonal protein), and bone marrow examination (trephine biopsy plus aspirate for cytogenetic analysis or fluorescence *in situ* hybridization). Bone skeletal surveys are also essential components of the initial work-up for myeloma. A skeletal survey including X-rays of the skull, pelvis, ribs, vertebrae, shoulder girdle and long bones is required. Radiologically, typical myeloma lesions are multiple, osteolytic and have sharp punched-out margins. These lesions are well seen on X-rays of the skull, ribs and pelvic bones. In the vertebrae, there may be partial or complete compression. Spinal cord compression may occur secondary to extradural involvement or vertebral collapse.

Extramedullary myeloma generally occurs in the upper respiratory tract, usually in the paranasal sinuses or pharynx. Magnetic resonance imaging (MRI) is useful in patients with spinal cord compression and solitary plasmacytoma. Osteoporosis is a frequent finding in myeloma; it is multifactorial in etiology and includes diffuse marrow involvement. It may occur with or without bone lesions. A PET-CT scan is superior, identifying both extramedullary and medullary lesions in patients with negative X-rays. However whole-body MRI is considered to be better than PET in the assessment of disease activity with a higher sensitivity and specificity.[30]

Peripheral Blood:

Multiple myeloma anemia is typically normochromic and normocytic, although macrocytosis with vitamin B12 deficiency has been reported.[31] In patients with more advanced disease, there may be thrombocytopenia and neutropenia. A complete blood count showing circulating plasma cells is uncommon, unless the disease is advanced. Sedimentation rates are typically high. In most patients there is increased rouleaux formation and increased background basophilic staining due to the presence of paraproteins in blood. However these features are not seen in patients with non-secretory myeloma or those who secrete only Bence-Jones proteins. Small number of plasmacytoid lymphocytes or occasional plasma cells may be found in peripheral blood. However when large numbers of plasma cells are seen in peripheral blood the condition is referred to as plasma cell leukemia.

Bone marrow findings

The bone marrow findings are very variable. Plasma cells are usually increased often constituting between 30-90% of bone marrow nucleated cells. Morphologically these plasma cells are abnormal with nucleocytoplasmic asynchrony, diffuse chromatin pattern and prominent nucleoli. Other cytological abnormalities include marked pleomorphism, increased size of cells, high N/C ratio, binuclearity, multinuclearity and nuclear lobation. Flame cells (plasma cells with eosinophilic cytoplasmic margins) may be seen in some cases. Other specific findings include Mott cells (cells with prominent vacuoles or spherical cytoplasmic inclusions called Russell bodies) and Dutcher bodies (intranuclear inclusions). Both bone marrow aspiration and trephine biopsy are required for diagnosis. Though aspirate if adequate is usually sufficient for diagnosis, sometimes infiltration is patchy and we may not get the adequate aspirate. In such cases biopsy will be more useful. Bone marrow biopsy is of use both in the diagnosis and in assessing prognosis Trephine may show interstitial, nodular or diffuse involvement. On aspirate both increased number of plasma cells and high degree of dysplasia

of bone marrow trephine are associated with poor prognosis. Similarly nodular and diffuse involvement of bone marrow trephine is associated with worse prognosis. Response to treatment is also associated with reduction of plasma cell burden and reduced osteoclastic activity.

Immunological Makers:

Myeloma cells give negative reactions with most B-cell markers but positive reactions are obtained with CD79a. Both normal cells and plasma cells express CD 38 and 138. Normal plasma cells express CD19 and CD45 and not CD56 whereas myeloma cells often over-express CD56 and fail to express CD19 and CD45.

Paraproteins

Paraprotein secreted is IgG in about 60% cases and IgA in 20% cases. In some patients there is secretion of excess monoclonal light chain (Bence-Jones proteins). A minority of patients produce IgM, IgD or IgE Paraprotein. Occasional patients have two distinct paraproteins. A small minority have no paraprotein in the serum or urine (non-secretory myeloma). Any paraprotein as it arises from a single clone of cells, contains only a single light chain type, either κ or λ. Monoclonal immunoglobulins being of high molecular weight are usually detected mainly in serum (unless there is coexisting renal failure), whereas low molecular weight bence-Jones proteins are detected only in urine. Electrophoresis of serum and concentrated urine should be performed, followed by immunofixation to confirm and type of M-protein. Immunofixation and serum free light chain assessment are indicated in patients where there is a strong suspicion of myeloma but in whom routine serum protein electrophoresis is negative.

Quantification of serum M-protein should be performed by densitometry of the monoclonal peak on electrophoresis; immunochemical measurement of total immunoglobulin (Ig) isotype level can also be used and is particularly useful for IgA and IgD M-proteins. Quantification of urinary total protein and light chain excretion can be performed directly on a 24-hour urine collection or calculated on a random urine sample in relation to the urine creatinine.

The concentration of normal immunoglobulins is reduced in about 90% of patients. The probability of Myeloma is high if concentration of an IgG paraprotein exceeds 30g/l, an IgA paraprotein exceeds 25g/l or urinary light chains exceed 1 gm in 24 hours. It is important to distinguish smouldering or asymptomatic myeloma from other cases. 'Symptomatic' myeloma includes all cases with symptoms or organ damage.

Differential Diagnosis

There are different clinical entities of multiple myeloma which need consideration. These include:

Monoclonal Gammopathy of Un-determined Significance (MGUS)

MGUS is characterized by the presence of serum M protein (<30 g/l) and less than 10% plasma cells in the bone marrow with no evidence of other B cell lympho-proliferative disorder and no symptoms or organ or tissue impairment due to monoclonal gammopathy. The transformation rate to malignant plasma cell disorder is about 1%/year.

Smouldering multiple myeloma (SMM)

SMM is characterized by presence of serum M protein (>30g/l) and 10% or more plasma cells in the bone marrow in the absence of lytic bone lesions or clinical manifestations due to the monoclonal gammopathy. About 10% diagnosed with multiple myeloma have smouldering disease at the start. This situation is clinically and biologically very close to that observed in MGUS. However the plasma cell mass is much higher and most cases will eventually evolve into symptomatic MM. The risk of transformation is 10%/ year during the first five years and then decreases to 3% in the subsequent 5 years. Risk factors for transformation include high M- component, IgA isotype, more than 20% plasma cells in the bone marrow, presence of light chain ratio and presence of more than 95% phenotypically aberrant plasma cells within the bone marrow.

Plasma cell leukemia

Plasma cell leukemia (PCL) is a rare variant of multiple myeloma accounting for 2-3% of myeloma and other plasma cell dyscrasias.[32] It is a rare and aggressive variant of myeloma characterized by the presence of circulating plasma cells.[33] It is classified as either primary PCL occurring at diagnosis or as secondary PCL in patients with relapsed/refractory myeloma. Diagnosis is made when there are >2000/cmm circulating plasma cells in the peripheral blood and plasmacytosis >20% of total leucocyte count (TLC).[34] PCL patients usually have accompanying anemia, hypercalcemia, renal insufficiency and organomegaly.[35] It is an extremely aggressive disease with no standard treatment regime so far due to the

rarity of the disease. Prognosis is generally very poor with a median survival of 2-8 months.[36]

Nonsecretory multiple myeloma

Nonsecretory multiple myeloma is a rare variant of the classic form of MM and has a similar clinical and radiologic presentation except for the absence of the M- band. In non secretory myeloma while the clinical presentation is essentially similar to standard myeloma, anaemia and lytic lesions may be seen more frequently while renal failure is uncommon.

IgD, E and M Myelomas

Immunoglobulin (Ig) D multiple myeloma (IgD MM) is a rare subtype of myeloma, accounts for less than 2% of all myelomas and is accompanied with aggressive course, resistance to chemotherapy and poor outcome.[37] It is often associated with relatively high frequencies of renal failure, extra osseous disease, hypercalcemia, amyloidosis and Bence-Jones proteinuria. The survival of patients with IgD MM has been reported to be shorter than that of patients with other types of M-protein.

Relatively few cases of IgE myeloma have been reported in the literature. There may be clinical similarities with IgD myeloma and in both conditions the prognosis appears to be poor. With the increased use of bone marrow trephine biopsies and improved immunohistomorphology IgM myelomas are being recognized more frequently and may comprise up to 0.4% of all myelomas. [38,39] It is important that such cases are distinguished from other IgM secreting disorders particularly Waldenstrom macroglobulinaemia.[40] The morphology and immunophenotype of infiltrating cells and presence of lytic lesions (absent in Waldenstrom macroglobinemia) give definitive diagnosis. There is a high incidence of the t(11;14) and prognosis appears to be poor. [41]

Solitary Plasmacytoma of bone

This is seen in upto 3% of patients with plasma cell dyscrasias usually seen in vertebral column. The diagnostic criteria require the presence of solitary plasma cell tumor, in which biopsy confirms plasma cell histology, a negative skeletal survey, absence of plasma cell infiltration in bone marrow, no evidence of anemia, hypercalcemia or renal impairment. Treatment of choice is local radiotherapy and it is suggested that patients in whom paraproteins persist after eradication of plasmacytoma with local treatment should undergo review of diagnosis. Two third of patients with solitary plasmacytoma develop multiple myeloma at 10 years follow-up.

Extramedullary Plasmacytoma:

Extramedullary plasmacytoma is a plasma cell tumor that arises outside the bone marrow, most frequently in the upper respiratory tract (nose, paranasal sinuses, nasopharynx, and tonsils). Other sites include parathyroid gland, orbit, lung, spleen, gastrointestinal tract, testes and skin. Diagnosis is based on detection of plasma cell tumor in an extramedullary site, in the

Table 1: Diagnostic Criteria, Diagnostic Evaluation, and Staging System for Multiple Myeloma.

Diagnostic criteria
Diagnosis of myeloma
At least 10% clonal bone marrow plasma cells
Serum or urinary monoclonal protein
Myeloma-related organ dysfunction (CRAB criteria)
Hypercalcemia (serum calcium >11.5 mg/dl [2.88 mmol/liter])
Renal insufficiency (serum creatinine >2 mg/dl [177 µmol/liter])
Anemia (hemoglobin <10 g/dl or >2 g/dl below the lower limit of the
normal range)
Bone disease (lytic lesions, severe osteopenia, or pathologic fracture)

Diagnostic evaluation
Diagnosis
Medical history and physical examination
Routine testing: complete blood count, chemical analysis with calcium
and creatinine, serum and urine protein electrophoresis with immunofixation,
quantification of serum and urine monoclonal protein,
measurement of free light chains
Bone marrow testing: trephine biopsy and aspirate of bone-marrow cells
for morphologic features; cytogenetic analysis and fluorescence in situ
hybridization for chromosomal abnormalities
Imaging: skeletal survey, magnetic resonance imaging if skeletal survey is negative

Prognosis
Routine testing: serum albumin, β2-microglobulin, lactate dehydrogenase
Staging
International Staging System
Stage I: serum β2-microglobulin <3.5 mg/liter, serum albumin ≥3.5 g/dl
Stage II: serum β2-microglobulin, <3.5mg/liter plus serum albumin

<3.5 g/dl; or serum β2-microglobulin 3.5 to <5.5 mg/liter regardless of serum albumin level **Stage III:** serum β2-microglobulin ≥5.5 mg/liter **Chromosomal abnormalities** High-risk: presence of t(4;14) or deletion 17p13 detected by fluorescence in situ hybridization Standard-risk: t(11;14) detected by fluorescence in situ hybridization

absence of bone marrow plasma cell infiltration, osteolytic lesions and other signs of multiple myeloma (end-organ damage)

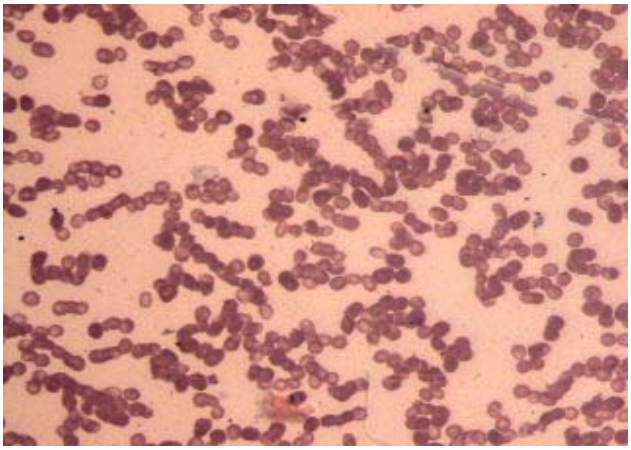

Figure 1: Multiple Myeloma (Peripheral film/ Rouleux formation)Wright Stain (10x100)

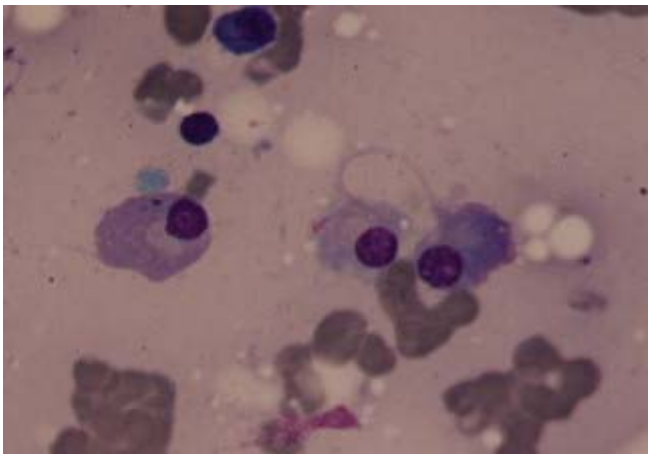

Figure 2: Multiple Myeloma (Bone marrow aspirate) Wright Stain (100x100)

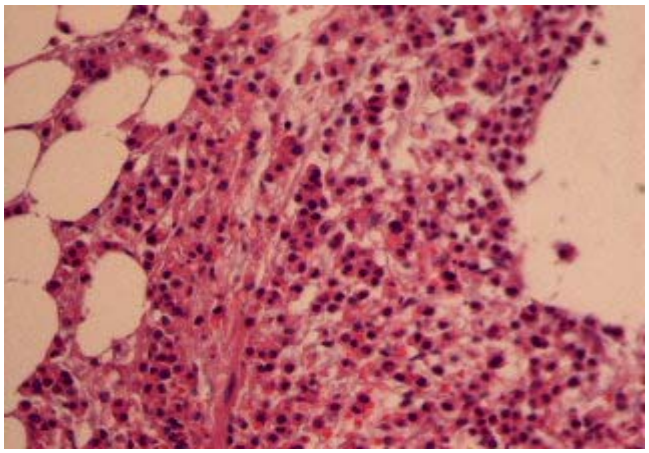

Figure 3: Multiple Myeloma (Trephine Biopsy) H & E stain (40x100)

Prognostic Factors and staging:

The natural history of myeloma is heterogeneous with survival times ranging from a few weeks to >20 years. Analysis of prognostic factors is essential to compare outcomes within and between clinical trials. The Durie/Salmon staging system was initially used for staging patients and was published in 1975.[42] This system was based upon the levels of haemoglobin, serum calcium, serum creatinine, serum and urine paraprotein (M protein), and the number and size of bone lesions.This provided a simple and practical estimate of tumour burden. Patients were categorized as stage I, II or III, depending on the degree of anaemia, hypercalcaemia, and levels of M protein in the serum and urine or bone lesions. In addition, patients without or with serum creatinine of >2 mg/dl were categorized A or B. One of the major limitations of this staging system was that the number of lytic bone lesions on plain X-ray were observer-dependent. This staging has now been replaced by the International Staging System (ISS) which has been validated in several clinical studies. ISS uses a combination of serum β2 microglobulin and serum albumin, and correlates well with long term outcome.[43,44] Staging of the disease, according to the International Staging System, defines three risk groups on the basis of serum β2-microglobulin and albumin levels. High risk disease and poor prognosis are defined by the presence of one of the following in each category: hypodiploidy, t(4;14), or deletion 17p13;high levels of serum β2-microglobulin or lactate dehydrogenase; and International Staging System stage III. Standard-risk disease is defined by the presence of hyperdiploidy or t(11;14), normal levels of serum β2-microglobulin or lactate dehydrogenase, and International Staging System stage I (Table1). Certain

cytogenetic and molecular genetic abnormalities have been shown to predict outcome in myeloma. It is generally accepted that the t (4;14), t (14;16) and deletion 17p, demonstrated by fluorescence in situ hybridisation (FISH), confer an adverse outcome in myeloma. It has therefore been proposed that these abnormalities define "high-risk" myeloma and should be specifically sought at diagnosis in all patients.[45]
However, ISS cannot distinguish MGUS or smoldering myeloma from active or symptomatic myeloma. However the use of staging systems to determine choice of therapy for individual patients remains unproven. It is essential that new prognostic indicators continue to be evaluated in prospective clinical trials.

Treatment

Treatment of multiple myeloma depends upon age of patient and stage of disease. All symptomatic patients should receive treatment and should be treated immediately, whereas asymptomatic (smoldering) myeloma requires only clinical observation, since early treatment with conventional chemotherapy has shown no benefit. Initial supportive treatment includes adequate hydration, bisphosphonates, management of renal failure, correction of anaemia and control of infection. Treatment strategies should include the use of induction regimens that are associated with high rates of complete response, followed by maintenance treatment. This approach combines maximal tumor reduction with continuous treatment, which is essential in delaying tumor regrowth.[46] Autologous stem-cell transplantation with a reduced-intensity conditioning regimen should be considered for older patients or those with coexisting conditions. The level of response, and in particular achievement of complete response, is associated with an improved long-term outcome. A complete response is defined as the elimination of detectable disease on routine testing.[47,48]

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