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Pro studentů, aspirantů a vědeckých pracovníků

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MEDICÍNA

Porodnictví a gynekologie

Therapy

EKOLOGIE

Stav biosféry a její vliv na lidské zdraví

Radiační bezpečnost, sociální a environmentální problémy

FYZIKA

Využití fyzikálních metod v medicíně

Therapy

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State Establishment «Dnipropetrovsk Medical Academy»

THE CLINICIAN ABOUT MULTIPLE MYELOMA

Multiple myeloma (MM) is a cancer of plasma cells characterized by a proliferation of malignant cells that produce monoclonal immunoglobulin (paraprotein (M-protein)) and invade and destroy adjacent bone tissue. Common manifestations include bone pain, renal insufficiency, hypercalcemia, anemia, and recurrent infections. Diagnosis requires demonstration of M-protein (sometimes present in urine and not serum) and either lytic bone lesions, light-chain proteinuria, or excessive plasma cells in bone marrow. A bone marrow biopsy is usually needed.

The incidence of multiple myeloma is 2 to 4/100 000. Male:female ratio is 1,6:1, and the median age is about 65 years. Prevalence in blacks is twice that in whites.

The precise etiology of MM has not yet been established. Roles have been suggested for a variety of factors, including genetic causes, environmental or occupational causes, MGUS, radiation, chronic inflammation, and infection.

Myeloma develops in 4 per 100 000 people per year.

Slightly more common in men than in women

Higher incidence in afro-americas vs whites (2:1)

Median age at diagnosis is 69 years for men and 71 years for women

The M-protein produced by the malignant plasma cells is IgG in about 60 % of myeloma patients and IgA in about 25 %; of patients producing either IgG or IgA, 40 % also have Bence Jones proteinuria, which is free monoclonal Korl, light chains in the urine. In 20 % of patients, plasma cells secrete only Bence Jones protein. IgD myeloma accounts for about 1 % of cases.

Diffuse osteoporosis or discrete osteolytic lesions develop, usually in the pelvis (12%), spine (25%), ribs (45%), and skull (65%). Lesions are caused by bone replacement by expanding plasmacytomas or by cytokines that are secreted by malignant plasma cells that activate osteoclasts and suppress osteoblasts. The

osteolytic lesions are usually multiple; occasionally, they are solitary intramedullary masses. Enhanced bone loss may also lead to hypercalcemia. Extraosseous solitary plasmacytomas are unusual but may occur in any tissue, especially in the upper respiratory tract.

Renal failure (myeloma kidney) occurs in many patients at diagnosis or during the course of the disorder due to many causes, most commonly from deposition of light chains in the distal tubules and hypercalcemia. Patients also often develop anemia usually from kidney disease or suppression of erythropoiesis by cancer cells.

Susceptibility to bacterial infection may occur in some patients. Viral infections, especially herpes infections, are increasingly occurring as a result of newer treatment modalities. Secondary amyloidosis occurs in 10 % of myeloma patients, most often in patients with Bence Jones proteinuria (12%) of Å-type.

In 2003, the **International Myeloma Working Group** agreed on diagnostic criteria for symptomatic myeloma, asymptomatic myeloma and MGUS (monoclonal gammopathy of undetermined significance), which was subsequently updated in 2009:

• Symptomatic myeloma:

Clonal plasma cells >10 % on bone marrow biopsy or (in any quantity) in a biopsy from other tissues (**plasmacytoma**)

A monoclonal protein (paraprotein) in either serum or urine (except in cases of true non-secretory myeloma)

Evidence of end-organ damage felt related to the plasma cell disorder (related organ or tissue impairment, ROTI, commonly referred to by the acronym "CRAB"):

Hypercalcemia (corrected calcium >2,75 mmol/L) (39%)

Renal insufficiency attributable to myeloma (42%)

Anemia (hemoglobin <10 g/dL) (76%)

Bone lesions (lytic lesions or osteoporosis with compression fractures) (86%)

Recurrent infections alone in a patient who has none of the CRAB features is not sufficient to make the diagnosis of myeloma. Patients who lack CRAB features but have evidence of amyloidosis should be considered as amyloidosis and not myeloma. CRAB like abnormalities are common with numerous diseases, and it is imperative that these abnormalities are felt to be directly attributable to the related

plasma cell disorder and every attempt made to rule out other underlying causes of anemia, renal failure etc.

• Asymptomatic (smoldering) myeloma:

Serum paraprotein >30 g/L AND/OR

Clonal plasma cells >10 % on bone marrow biopsy AND

NO myeloma-related organ or tissue impairment

• Monoclonal gammopathy of undetermined significance (MGUS):

Serum paraprotein <30 g/L AND

Clonal plasma cells <10 % on bone marrow biopsy AND

NO myeloma-related organ or tissue impairment

Related conditions include solitary plasmacytoma (a single tumor of plasma cells, typically treated with irradiation), plasma cell dyscrasia (where only the antibodies produce symptoms, e.g. AL amyloidosis), and POEMS syndrome (peripheral neuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes).

The International Staging System of the International Myeloma Working Group is also based on 3 stages.

Stage I consists of the following:

(3-2 microglobulin less than or equal to 3,5 g/dL and albumin >3,5 g/dL

CRP >4,0 mg/dL

Plasma cell labeling index <1 %

Absence of chromosome 13 deletion

Low serum IL-6 receptor

Long duration of initial plateau phase Stage II consists of the following:

P-2 microglobulin level >3,5 to <5,5 g/dL, or

p-2 microglobulin <3,5 g/dL and albumin <3,5 g/dL

Stage III consists of the following:

P-2 microglobulin of 5,5 g/dL or more

Median survival is as follows:

Stage I, 62 months

Stage II, 44 months

Stage III, 29 months

The Salmon-Durie classification of MM is based on 3 stages and additional subclassifications.

In stage I, the MM cell mass is less than $0.6x10^{12}$ cells/m^2, and all of the following are present:

Hemoglobin value greater than 10 g/dL

Serum calcium value less than 12 mg/dL (normal)

Normal bone structure or only a solitary bone plasmacytoma on radiographs

Low M-component production rates (IgG value less than 5 g/dL, IgA value less than 3 g/dL, urine light-chain M component on electrophoresis less than 4 g/24 h)

In stage II, the MM cell mass is $(0,6\text{-}1,2)x10^{12}$ cells/m^2. The other values fit neither those of stage I nor those of stage III.

In stage III, the MM cell mass is greater than $1,2x\ ]\ 0^{12}$ cells/m^2, and all of the following are present:

Hemoglobin value equal to 8,5 g/dL

Serum calcium value greater than 12 mg/dL

Advanced lytic bone lesions on radiographs

High M-component production rates (IgG value greater than 7 g/dL, IgA value greater than 5 g/dL, urine light-chain M component on electrophoresis greater than 12 g/24 h)

A: serum creatinine <2 mg/dL (<177 umol/L)

B: serum creatinine >2 mg/dL (>177 umol/L)

Median survival is as follows:

Stage I, >60 months

Stage II, 41 months

Stage III, 23 months

Disease in subclassification B has a significantly worse outcome (e.g., 2-12 months survival in 4 separate series).

Diagnostic considerations. The most widely accepted schema for the diagnosis of multiple myeloma (MM) uses particular combinations of laboratory, imaging, and procedure findings as diagnostic criteria. The findings are as follows:

I = Plasmacytoma on tissue biopsy

II = Bone marrow with greater than 30 % plasma cells

III = Monoclonal globulin spike on serum protein electrophoresis, with an immunoglobulin (Ig) G peak of greater than 3,5 g/dL or an IgA peak of greater than 2 g/dL, or urine protein electrophoresis (in the presence of amyloidosis) result of greater than 1 g/24 h.

a = Bone marrow with 10-30 % plasma cells

b = Monoclonal globulin spike present but less than category 111

c = Lytic bone lesions

d = Residual IgM level less than 50 mg/dL, IgA level less than 100 mg/dL, or IgG level less than 600 mg/dL

The following combinations of findings are used to make the diagnosis of multiple myeloma:

I plus b, c, or d

II plus b, c, or d

III plus a, c, or d

a plus b plus c

a plus b plus d

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare syndrome consisting of polyneuropathy, organomegaly, endocrinopathy, M-protein deviations, and skin changes.

Amyloidosis is often secondary to MM, but it may develop without MM. Patients with amyloidosis typically lack sufficient numbers of plasma cells in the bone marrow or sufficiently high levels of M protein to meet the diagnostic criteria for MM.

Indolent MM is a subset of the disease in which patients have no (or very limited) bone disease, a performance status greater than 70 %, a hemoglobin level greater than 10 g/dL, a calcium level within the reference range, a creatinine level less than 2 mg/dL, no infections, and low (i.e., <7 g/dL for IgG, <5 g/dL for IgA) M-protein levels.

Smoldering MM is the same as indolent MM, except that these patients have less than 30 % plasma cells in their bone marrow, and they have no bone disease.

Evaluation of multiple myeloma

History and physical	
Blood workup	▪ CBC with differential and platelet counts, ESR ▪ BUN, creatinine ▪ Electrolytes, calcium, albumin, LDH, protein ▪ Serum quantitative immunoglobulins ▪ Serum protein electrophoresis and immunofixation ▪ Serum P-microglobuline ▪ Serum free light chain assay
Urine	▪ 24-hour protein ▪ Protein electrophoresis (quantitative Bence Jones protein) ▪ Immunofixation electrophoresis
Other	▪ Skeletal survey ▪ Unilateral bone marrow aspirate and biopsy evaluation with immunohistochemistry or flow cytometry, cytogenetics, and FISH ▪ Imaging as indicated, MRI, Bone marrow aspiration

Presenting symptoms of multiple myeloma include bone pain, pathologic fractures, weakness, anemia, infection (often pneumococcal), hypercalcemia, spinal cord compression, or renal failure. The diagnosis is incidental in 30 % of cases. MM is often discovered through routine blood screening when patients are being evaluated for unrelated problems.

Clinical Features at Presentation:

Monoclonal (M) protein: 93 %

Lytic bone lesions: 67 %

Increased plasma cells in the bone marrow: 96 %

Anemia (normochromic normocytic): 73 %

Hypercalcemia (corrected calcium >11 mg/dL): 13 %

Renal failure (serum creatinine >2,0 mg/dL): 19 %

Major Symptoms at Diagnosis:

Bone pain: 58 %

Fatigue: 32 %

Weight loss: 24 %

Paresthesias: 5 %

11 % of patients are asymptomatic or have only mild symptoms at diagnosis

Bone pain is the most common presenting symptom in MM. Most case series report that 70 % of patients have bone pain at presentation. The lumbar spine is one of the most common sites of pain.

Pathologic fractures are very common in MM; 93 % of patients have more than one site of bony involvement. A severe bony event is a common presenting issue.

The symptoms that should alert physicians to consider spinal cord compression are back pain, weakness, numbness, or dysesthesias in the extremities. Because spinal cord compressions in MM occur at multiple levels, comprehensive evaluation of the spine is warranted. Patients who are ambulatory at the start of therapy have the best likelihood of preserving function and avoiding paralysis.

Occasionally, a patient may come to medical attention for bleeding resulting from thrombocytopenia. Rarely, monoclonal protein may absorb clotting factors and lead to bleeding.

Confusion, somnolence, bone pain, constipation, nausea, and thirst are the presenting symptoms of hypercalcemia. This complication may be present in as many as 30 % of patients with MM at presentation. In most solid malignancies, hypercalcemia carries an ominous prognosis, but in MM, its occurrence does not adversely affect survival.

Abnormal humoral immunity and leukopenia may lead to infection. Pneumococcal organisms are commonly involved, but shingles (i.e., herpes zoster) and Haemophilus infections are also more common among patients with MM.

Hyperviscosity may be associated with a number of symptoms, including, generalized malaise, infection, fever, paresthesia, sluggish mentation, and sensory loss. Patients may report headaches and somnolence, and they may bruise easily and have hazy vision. Patients with MM typically experience these symptoms when their serum viscosity is greater than 4 times that of normal serum.

Epistaxis may be a presenting symptom of MM with a high tumor volume. Occasionally, patients may have such a high volume of monoclonal protein that their blood viscosity increases, resulting in complications such as stroke, myocardial ischemia, or infarction.

Carpal tunnel syndrome is a common complication of myeloma. Meningitis (especially that resulting from pneumococcal or meningococcal infection) is more common in patients with MM. Some peripheral neuropathies have been attributed to

MM. Long-term neurologic function is directly related to the rapidity of the diagnosis and the institution of appropriate therapy for MM.

Anemia, which may be quite severe, is the most common cause of weakness in patients with MM.

On head, ears, eyes, nose, and throat (HEENT) examination, the eyes may show exudative macular detachment, retinal hemorrhage, or cotton-wool spots. Pallor from anemia may be present. Ecchymoses or purpura from thrombocytopenia may be evident.

Bony tenderness is not uncommon in MM, resulting from focal lytic destructive bone lesions or pathologic fracture. Pain without tenderness is typical. Pathologic fractures may be observed. In general, painful lesions that involve at least 50 % of the cortical diameter of a long bone or lesions that involve the femoral neck or calcar femorale are at high (50 %) risk for a pathologic fracture. The risk of fracture is lower in upper-extremity lesions than in lower-extremity lesions. Even a small cortical defect can decrease torsional strength by as much as 60 % (stress riser effect).

Neurologic findings may include a sensory level change (i.e., loss of sensation below a dermatome corresponding to a spinal cord compression), neuropathy, myopathy, a Tinel sign, or a Phalen sign due to carpel tunnel compression secondary to amyloid deposition.

Extramedullary plasmacytomas, which consist of soft-tissue masses of plasma cells, are not uncommon. Plasmacytomas have been described in almost every site in the body. Although the aerodigestive tract is the most common location, reports also describe orbital, ear canal, cutaneous, gastric, rectal, prostatic, and retroperitoneal lesions.

On evaluation of the abdomen, hepatosplenomegaly may be discovered. Cardiovascular system examination may reveal cardiomegaly secondary to immunoglobulin deposition.

Amyloidosis may develop in some patients with MM. The characteristic physical examination findings that suggest amyloidosis include the following:

Shoulder pad sign

Macroglossia

Typical skin lesions

Postprotoscopic peripalpebral purpura

The shoulder pad sign is defined by bilateral swelling of the shoulder joints secondary to amyloid deposition. Physicians describe the swelling as hard and rubbery. Amyloidosis may also be associated with carpal tunnel syndrome and subcutaneous nodules.

Macroglossia may occur secondary to amyloid deposition in the tongue and is a common finding in patients with amyloidosis.

Skin lesions that have been described as waxy papules or nodules may occur on the torso, ears, or lips.

Postprotoscopic peripalpebral purpura strongly suggests amyloidosis. Patients may develop raccoonlike dark circles around their eyes following any procedure that parallels a prolonged Valsalva maneuver. The capillary fragility associated with amyloidosis may account for this observation. In the past, this correlation was observed when patients underwent rectal biopsies to make the diagnosis.

Perform a complete blood count (CBC) to determine if the patient has anemia, thrombocytopenia, or leukopenia. The CBC and differential may show pancytopenia, abnormal coagulation, and an increased erythrocyte sedimentation rate (ESR). The reticulocyte count is typically low. Peripheral blood smears may show Rouleau formation.

Obtain a comprehensive metabolic panel to assess levels of total protein, albumin and globulin, blood urea nitrogen (BUN), creatinine, and uric acid (uric acid will be high if the patient has high cell turnover or is dehydrated).

Obtain a 24-hour urine collection for quantification of the Bence Jones protein (i.e., lambda light chains), protein, and creatinine clearance. Quantification of proteinuria is useful for the diagnosis of MM (>1 g of protein in 24 h is a major criterion) and for monitoring the response to therapy. Creatinine clearance can be useful for defining the severity of the patient's renal impairment.

Serum protein electrophoresis (SPEP) is used to determine the type of each protein present and may indicate a characteristic curve (i.e., where the spike is observed). Urine protein electrophoresis (UPEP) is used to identify the presence of the Bence Jones protein in urine. Immunofixation is used to identify the subtype of protein (i.e., IgA lambda).

The 2011 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Oncology, Multiple Myeloma Version recommend the use of

serum free light chain assay as well as fluorescence in situ hybridization (FISH) for 1 q21 amplification as part of the initial diagnostic workup.

Chemical screening, including calcium and creatinine SPEP, immunofixation, and immunoglobulin quantitation, may show azotemia, hypercalcemia, an elevated alkaline phosphatase level, and hypoalbuminemia. A high lactic dehydrogenase (LDH) level is predictive of an aggressive lymphomalike course.

SPEP is a useful screening test for detecting M-proteins. An M-component is usually detected by means of high-resolution SPEP. The kappa-to-lambda ratio has been recommended as a screening tool for detecting M-component abnormalities. An M- component serum concentration of 30 g/L is a minimal diagnostic criterion for MM. In about 25 % of patients, M-protein cannot be detected by using SPEP.

Routine urinalysis may not indicate the presence of Bence Jones proteinuria. Therefore, a 24-hour urinalysis by means of UPEP or immunoelectrophoresis may be required. UPEP or immunoelectrophoresis can also be used to detect an M-component and kappa or lambda light chains. The most important means of detecting MM is electrophoretic measurement of immunoglobulins in both serum and urine.

Quantitative Immunoglobulin Levels (IgG, Ig.A, IgM). Suppression of nonmyelomatous immunoglobulin is a minor diagnostic criterion for MM. The level of MM protein (i.e., M-protein level), as documented by the immunoglobulin level, can be useful as a marker to assess the response to therapy.

P-2 Microglobulin is a surrogate marker for the overall body tumor burden. The level of beta-2 microglobulin is increased in patients with renal insufficiency without MM, which is one reason that it is a useful prognosticator in MM. The prognosis of patients with MM and impaired renal function is reduced.

C-reactive protein (CRP) is a surrogate marker of interleukin (IL)-6 activity. IL-6 is often referred to as the plasma cell growth factor. Like P-2 microglobulin, CRP is useful for prognostication.

Check the serum viscosity in patients with central nervous system (CNS) symptoms, nosebleeds, or very high M-protein levels.

Simple radiography is indicated for the evaluation of skeleton lesions, and a skeletal survey is performed when myeloma is in the differential diagnosis. Plain radiography remains the gold standard imaging procedure for staging newly diagnosed and relapsed myeloma patients, according to an International Myeloma Working Group consensus statement.

Perform a complete skeletal series at diagnosis of MM, including the skull (a very common site of bone lesions in persons with MM), the long bones and the spine.

Onventional plain radiography can usually depict lytic lesions. Such lesions appear as multiple, rounded, punched-out areas found in the skull, vertebral column, ribs, and/or pelvis. Less common but not rare sites of involvement include the long bones. Plain radiographs can be supplemented by computed tomography (CT) scanning to assess cortical involvement and risk of fracture. Diffuse osteopenia may suggest myelomatous involvement before discrete lytic lesions are apparent.

Findings from this evaluation may be used to identify impending pathologic fractures, allowing physicians the opportunity to repair debilities and prevent further morbidity.

Magnetic resonance imaging (MRI) is useful in detecting thoracic and lumbar spine lesions, paraspinal involvement, and early cord compression. Findings from MRI of the vertebrae are often positive when plain radiographs are not. MRI can depict as many as 40 % of spinal abnormalities in patients with asymptomatic gammopathies in whom radiographic studies are normal. For this reason, evaluate symptomatic patients with MRI to obtain a clear view of the spinal column and to assess the integrity of the spinal cord.

Comparative studies have suggested the possible utility of positron emission tomography (PET) scanning in the evaluation of MM. For example, a comparison study of PET scanning and whole-body MRI in patients with bone marrow biopsy-proven multiple myeloma found that although MRI had higher sensitivity and specificity than PET in the assessment of disease activity, when used in combination and with concordant findings, the 2 modalities had a specificity and positive predictive value of 100%.

These researchers suggest that the combination of modalities may be valuable for assessing the effectiveness of treatment, when aggressive and expensive regimens are used. However, PET scanning has not yet been integrated into standard practice. The International Myeloma Working Group notes the potential usefulness of PET scanning in selected patients but suggests that such studies ideally should be performed in the context of a clinical trial.

Do not use bone scans to evaluate MM. Cytokines secreted by MM cells suppress osteoblast activity; therefore, typically, no increased uptake is observed. On technetium bone scanning, more than 50 % of lesions can be missed.

MM is characterized by an increased number of bone marrow plasma cells. Plasma cells show low proliferative activity, as measured by using the labeling index. This index is a reliable parameter for the diagnosis of MM. High values are strongly correlated with progression of the disease.

Obtain bone marrow aspirate and biopsy samples from patients with MM to calculate the percentage of plasma cells in the aspirate (reference range, up to 3 %) and to look for sheets or clusters of plasma cells in the biopsy specimen. Bone marrow biopsy enables a more accurate evaluation of malignancies than does bone marrow aspiration.

Plasma cells are 2-3 times larger than typical lymphocytes; they have eccentric nuclei that are smooth (round or oval) in contour with clumped chromatin and have a perinuclear halo or pale zone. The cytoplasm is basophilic.

Many MM cells have characteristic, but not diagnostic, cytoplasmic inclusions, usually containing immunoglobulin. The variants include Mott cells, Russell bodies, grape cells, and morula cells. Bone marrow examination reveals plasma cell infiltration, often in sheets or clumps. This infiltration is different from the lymphoplasmacytic infiltration observed in patients with Waldenstrom macroglobulinemia.

Analysis of bone biopsy specimens may reveal plasmacytic, mixed cellular, or plasmablastic histologic findings. With the plasmacytic type, median survival is approximately 39,7 months. With the mixed cellular type, survival is 16,1 months, and with the plasmablastic type, survival is 9,8 months.

Cytogenetic analysis of the bone marrow may contribute significant prognostic information in multiple myeloma. The most significant cytogenetic abnormality appears to be deletion of 17p 13. This abnormality is associated with shorter survival, more extramedullary disease, and hypercalcemia. This locus is the site of the *TP53* tumor suppressor gene. Chromosome 1 abnormalities and *c-myc* defects are also significant prognostic factors in multiple myeloma.

Although not as well defined as in other hematologic malignancies, such as acute leukemia, risk-adapted therapy based on cytogenetic abnormalities is at the forefront of myeloma research.

Renal failure and insufficiency are seen in 25 % of patients with MM, including the following manifestations:

Myeloma kidney syndrome with multiple etiologies

Amyloidosis with light chains

Nephrocalcinosis due to hypercalcemia

Anemia, neutropenia, or thrombocytopenia is due to bone marrow infiltration of plasma cells. Thrombosis and Raynaud phenomenon due to cryoglobulinemia may be present.

Bone disease may result in the following:

Severe bone pain, pathologic fracture due to lytic lesions. Lytic disease or fracture may be observed on plain radiographs.

Increased bone resorption leading to hypercalcemia

Spinal cord compression. This is one of the most severe adverse effects of MM. Reports indicate that as many as 20 % of patients develop spinal cord compression at some point during the course of their disease. Symptoms typically inc!ude back pain, weakness or paralysis in the legs, numbness, or dysesthesias in the lower extremities. However, depending on the level of involvement, patients may present with upper-extremity symptoms.

Radiculopathy and/or cord compression may occur because of skeletal destruction and nerve compression.

Bacterial infection may develop; it is the leading cause of death in patients with myeloma. The highest risk is in the first 2-3 months of chemotherapy.

Purpura, retinal hemorrhage, papilledema, coronary ischemia, seizures, and confusion may occur as a result of hyperviscosity syndrome.

Hypercalcemia may cause polyuria and polydipsia, muscle cramps, constipation, and a change in the patient's mental status.

Differential diagnoses

Malignant Lymphoma

Metastatic Carcinoma

Monoclonal Gammopathies of Uncertain Origin

Waldenstrom Hypergammaglobulinemia Treatment

Chemotherapy for symptomatic patients

Thalidomide, bortezomib, or lenalidomide with corticosteroids and/or chemotherapy

Possibly maintenance therapy

Possibly stem cell transplantation

Possibly radiation therapy

Treatment of complications (anemia, hypercalcemia, renal insufficiency, infections, skeletal lesions)

Initial Approach to Treatment of MM

Nontransplantation candidate (based on age, performance score, and comorbidity. Induction treatment → Maintenance

Transplantation candidate: Induction treatment (nonalkylator-based induction x4-6 cycles) →Stem cell harvest →Stem cell transplantation →Maintenance

NCCN. Clinical practice guidelines in oncology: multiple myeloma Induction Therapies: Transplantation Eligible

NCCN Category 1

Bortezomib/dexamethasone (VD)

Bortezomib/thalidomide/dexamethasone (VTD)

Bortezomib/doxorubicin/dexamethasone (PAD)

Lenalidomide/dexamethasone (RD)

NCCN Category 2A

Bortezomib/cyclophosphamide/dexamethasone (CyBorD)

Bortezomib/lenalidomide/dexamethasone (VRD)

NCCN Category 2B

- Thalidomide/dexamethasone (TD)

Dexamethasone

Liposomal doxorubicin/vincristine/dexamethasone (DVD)

Induction Therapies: Transplantation Eligible

NCCN Category 1

Lenalidomide/low-dose dexamethasone (Rd)

Melphalan/prednisone/bortezomib (MPV)

Melphalan/prednisone/lenalidomide (MPR)

Melphalan/prednisone/thalidomide (MPT)

NCCN Category 2A

Bortezomib/dexamethasone (VD)

Melphalan/prednisone (MP)

NCCN Category 2B

Dexamethasone

-Liposomal doxorubicin/ vincristine/dexamethasone (DVD)

Thalidomide/dexamethasone (TD)

Vincristine/doxorubicin/dexamethasone (VAD)

Factors Affecting Transplant Eligibility:

•Age

Older than 65 years of age may not be eligible

Older patients more sensitive to toxicity; less physical reserve

Performance score

Comorbidities

Increased risk of infection

Decreased tolerability for high-dose therapy

Treatment of malignant cells: Until recently, conventional chemotherapy consisted only of oral melphalan and prednisonegiven in cycles of 4 to 6 weeks with monthly evaluation of response. Recent studies show superior outcome with the addition of either bortezomib orthalidomide. Other chemotherapeutic drugs, including other alkylating drugs (e.g., cyclophosphamide, doxorubicinand its newer analog liposomal pegylated doxorubicin) also are more effective when combined with thalidomide or bortezomib. Many other patients are effectively treatedwith bortezomib, thalidomide, or lenalidomide plus glucocorticoids and/or chemotherapy.

Chemotherapy response is indicated by decreases in serum or urine M-protein, increases in RBCs, and improvement in renal function among patients presenting with kidney failure.

Autologous peripheral blood stem cell transplantation may be considered for patients who have adequate cardiac, hepatic, pulmonary, and renal function, particularly those whose disease is stable or responsive after several cycles of initial therapy. Allogeneic stem cell transplantation after non-myeloablative chemotherapy (e.g., low-dose cyclophosphamide andfludarabine) or low-dose radiation therapy can produce myeloma-free survival of 5 to 10 years in some patients. However, allogeneic stem cell transplantation remains experimental because of the high morbidity and mortality from graft vs. host disease.

In relapsed or refractory myeloma, combinations of bortezomib, thalidomide, or its newer analog lenalidomide with chemotherapy or corticosteroids may be used.

These drugs are usually combined with other effective drugs that the patient has not yet been treated with, although patients with prolonged remissions may respond to retreatment with the same regimen that led to the remission.

Maintenance therapy has been tried with nonchemotherapeutic drugs, including interferon a, which prolongs remission but does not improve survival and is associated with significant adverse effects. Following a response to corticosteroid-based regimens, corticosteroids alone are effective as a maintenance treatment. Thalidomidemay also be effective as a maintenance treatment, and studies are evaluating maintenance therapy with bortezomiband lenalidomide among patients who have responded to these drugs alone or in combination therapeutic regimens.

Treatment of complications. In addition to direct treatment of malignant cells, therapy must also be directed at complications, which include anemia, hypercalcemia, renal insufficiency, infections, and skeletal lesions.

Anemia can be treated with recombinant erythropoietin (40 000 units sc once/week) in patients whose anemia is inadequately relieved by chemotherapy. If anemia causes cardiovascular or significant systemic symptoms, packed RBCs are transfused. Plasmapheresis is indicated if hyperviscosity develops.

Hypercalcemia is treated with saluresis, IV bisphosphonates, and sometimes withprednisone. Most patients do not require allopurinol. However, allopurinol is indicated for patients with high levels of serum uric acid or high tumor burden and a high risk of tumor lysis syndrome with treatment.

Renal compromise can be ameliorated with adequate hydration. Even patients with prolonged, massive Bence Jones proteinuria (>10 to 30 g/day) may have intact renal function if they maintain urine output >2000 mL/day. Dehydration combined with high- osmolar IV contrast may precipitate acute oliguric renal failure in patients with Bence Jones proteinuria.

Infection is more likely during chemotherapy-induced neutropenia. In addition, infections with the herpes zoster virus are occurring more frequently in patients treated with newer antimyeloma drugs. Documented bacterial infections should be treated with antibiotics; however, prophylactic use of antibiotics is not routinely recommended. Prophylactic use of antiviral drugs may be indicated for patients receiving specific drugs. Prophylactic IV immune globulin may reduce the risk of infection but is generally reserved for patients with recurring infections. Pneumococcal and influenza vaccines are indicated to prevent infection.

Skeletal lesions require multiple supportive measures. Maintenance of ambulation and supplemental Ca and vitamin D help preserve bone density. Analgesics and palliative doses of radiation therapy (18 to 24 Gy) can relieve bone pain. However, radiation therapy may impair the patient's ability to receive cytotoxic doses of systemic chemotherapy. Most patients, especially those with lytic lesions and generalized osteoporosis or osteopenia, should receive a monthly IV bisphosphonate (either pamidronate or zoledronic acid). Bisphosphonates reduce skeletal complications and lessen bone pain and may have an antitumor effect.

MM is a heterogeneous disease, with survival ranging from 1 year to more than 10 years. Median survival in unselected patients with MM is 3 years. The 5-year relative survival rate is around 35 %. Survival is higher in younger people and lower in the elderly. It was estimated that about 10 580 Americans (5 640 men and 4 940 women) would die of multiple myeloma in 2008.

The tumor burden and the proliferation rate are the 2 key indicators for the prognosis in patients with MM. Many schemas have been published to aid in determining the prognosis.

One schema uses C-reactive protein (CRP) and P-2 microglobulin (which is an expression of tumor burden) to predict survival as follows:

If levels of both proteins are less than 6 mg/L, the median survival is 54 months.

If the level of only one component is less than 6 mg/L, the median survival is 27 months.

If levels of both protein values are greater than 6 mg/L, the median survival is 6 months.

Poor prognostic factors include the following:

Tumor mass

Hypercalcemia

Bence Jones proteinemia

Renal impairment (i.e., stage B disease or creatinine level >2 mg/dL at diagnosis)

The prognosis by treatment is 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.

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

Serum amyloid P retention: median survival is 24 months.

Bacterial infection is the leading cause of death in patients with myeloma.

A study by Larsen et al., found that a significant reduction in plasma cell proliferation in patients with newly diagnosed MM is an important predictor of survival.

Clinical case. 52-year-old patient with multiple myeloma complicated with chronic renal failure.

Fig. 1. Skull X-ray showing multiple lucencies due to multiple myeloma.

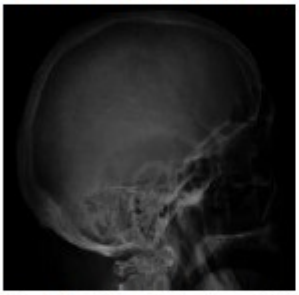


Fig. 2. Pathological fracture of the L-spine due to multiple myeloma.

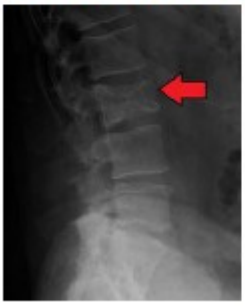


Fig. 3. Ultrasound diagnostic. Hypersplenism. Heterogeniety echo.

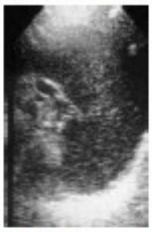
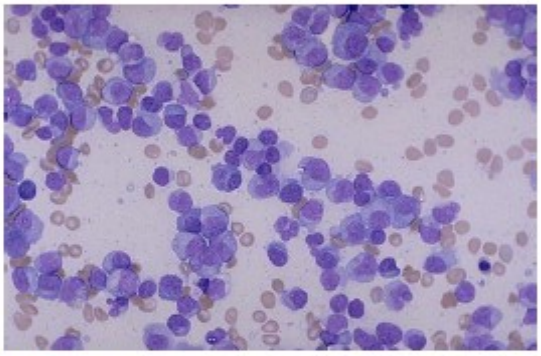


Fig. 4. Bone marrow morphology. Plasma cells.



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