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Diagnosis and Treatment of Multiple Myeloma in 2010

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SUMMARY/ABSTRACT

Multiple myeloma is a plasma cell neoplasm that accounts for slightly more than 10% of hematologic malignancies. The diagnosis requires the presence of monoclonal bone marrow plasma cells, serum and/or urinary M protein and evidence of end organ damage (CRAB - hypercalcemia, renal disease, anemia or lytic bone lesions). Multiple myeloma may be divided into high-risk or standard-risk disease based upon fluorescence in situ hybridization (FISH), metaphase cytogenetics and the plasma cell labeling index. The physician must determine initially if the patient is eligible for an autologous stem cell transplant. If the patient is eligible, alkylating agents should be avoided because they may damage the hematopoietic stem cells. We prefer lenalidomide plus dexamethasone weekly but bortezomib or thalidomide both with dexamethasone are reasonable regimens. Autologous stem cell transplant may be performed immediately after induction therapy or delayed until relapse. Patients deemed ineligible for an autologous stem cell transplant may be given melphalan, prednisone and thalidomide (MPT). Lenalidomide and bortezomib are other options. The novel agents (thalidomide, bortezomib and lenalidomide have improved the survival of patients with multiple myeloma). Management of the complications which include skeletal disease, renal insufficiency, anemia, hypercalcemia, recurrent infections, spinal cord compression and thromboembolic phenomena must be managed appropriately.

Keywords
Multiple myeloma
Diagnosis
Therapy

RESUMEN

El Mieloma Múltiple es una neoplasia de células plasmáticas, que ocupa aproximadamente un 10% de todas las enfermedades hematológicas malignas. Para establecer el diagnóstico se requiere de la presencia de células plasmáticas monoclonales en médula ósea, la presencia de una proteína M (monoclonal) en suero y/o plasma así como la evidencia de lesiones en órganos blanco El Mieloma Múltiple se puede catalogar como de alto riesgo o de riesgo normal, de acuerdo a los resultados de los estudios de hibridación fluorescente in situ (FISH), los estudios citogenéticos y el índice de marca de las células plasmáticas anormales.

El medico debe determinar inicialmente si el paciente es candidato o no para un transplante de médula ósea autólogo. Si el paciente es candidato, se deben evitar los agentes alquilantes, ya que estos dañan la producción de células hematopoyéticas en la médula ósea. Nosotros preferimos iniciar el tratamiento con la combinación de lenalidomida y dexametasona semanal, pero también es adecuado el tratamiento inicial con bortezomib o talidomida. El transplante autólogo de médula ósea, se debe realizar inmediatamente después de una terapia de inducción, o retrasarse hasta que se presente una recaída. Para aquellos pacientes quienes no son candidatos para transplante autólogo de células hematopoyéticas, se recomienda el tratamiento con melfalán / prednisona y talidomida (MPT). Otras opciones de tratamiento son lenalidomida y bortezomib. Se ha visto que los agentes novedosos (talidomida, bortezomib y lenalidomida) prolongan de manera significativa la supervivencia de los pacientes. El manejo de los pacientes quienes presentan lesiones osteolíticas, Insuficiencia renal, anemia, hipercalcemia, infecciones recurrentes, aplastamiento de vértebras y fenómenos tromboembólicos, se deben de realizar de acuerdo a la complicación que se presente.

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Multiple myeloma (MM) is a plasma cell neoplasm that accounts for slightly more than 10% of hematologic malignancies. A historical overview of multiple myeloma has been published [1]. The annual incidence, age-adjusted to the 2000 U.S. popula-

tion, is 4.3 cases per 100,000, resulting in up to 20,000 new patients in the United States each year [2]. Multiple myeloma is twice as common in African-Americans as in the white population and is slightly more common in men than in women. The median age at diagnosis is 66 years and only 2% of patients are younger than 40 years at diagnosis [3].

In a report of 773 patients with MM from Malmö, Sweden, survival improved from 24 to 56 months in patients diagnosed from 1960 to 1969 and 2000 to 2005, respectively. Survival did not improve significantly in those > 65 years of age [4]. The reported increased incidence during the last several decades is probably related to the increased availability of medical facilities for elderly inpatients and to improved diagnostic techniques rather than to an actual increased incidence.

Multiple myeloma evolves from monoclonal gammopathy of undetermined significance (MGUS) in virtually all patients. MGUS was present in 100% of 71 patients 2 years prior to the development of multiple myeloma. Ninety-five percent of MM patients had a MGUS 5 years before diagnosis, while 82% had MGUS 8 years prior to the diagnosis of MM [5].

Diagnostic Criteria

The most common presenting symptoms of MM are fatigue, bone pain and recurrent infections. Anemia is present in 70% of patients at diagnosis and occurs in almost all during the course of the disease. Hypercalcemia is found in one-fourth of patients while the serum creatinine is elevated in almost one-half. Conventional radiography reveals skeletal abnormalities in approximately 80% of patients at diagnosis. Serum protein electrophoresis shows a protein spike in approximately 80% of patients while immunofixation is present in slightly more than 90%. Between 15% and 20% of patients have no heavy chain expression and are considered to have light chain MM. The M protein in these patients is always detected in the urine. Three percent of MM patients have no detectable M protein in serum or urine and are considered to have nonsecretory MM. The serum free light chain (FLC) assay is abnormal in about 70% of nonsecretory MM. The bone marrow usually contains more than 10% monoclonal plasma cells. The diagnosis of MM requires the presence of monoclonal bone marrow plasma cells, serum and/or urinary M protein, and evidence of end organ damage that can be attributed to the plasma cell proliferative disorder (CRAB – hypercalcemia, renal insufficiency, anemia, and/or bone lesions) [6].

Differential Diagnosis

The most important differential diagnoses includes MGUS, smoldering (asymptomatic) multiple myeloma (SMM), primary (AL) amyloidosis and solitary plasmacytoma.

MGUS is found in 3% of persons ≥ 50 years of age and in 5% of those ≥ 70 years of age [7]. It is characterized by the presence of an M protein < 3 g/dL and a bone marrow containing fewer than 10% monoclonal plasma cells and no evidence of end organ damage. Multiple myeloma develops in approximately 1% of MGUS patients each year. It is a challenge to differentiate patients with MGUS from MM when MGUS is found in the presence of postmenopausal osteoporosis, renal insufficiency from another cause such as diabetes or hypertension, or hypercalcemia due to hyperparathyroidism. Up to one-half of women older than 60 years of age have osteopenia and a number of these have a vertebral compression fracture. A CT scan of the spine may help in differentiating between postmenopausal osteoporosis and myelomatous bone disease. The most important point to decide is whether the damage is attributable to the plasma cell proliferative disorder or an unrelated cause.

Smoldering multiple myeloma must also be considered in the differential diagnosis. It is characterized by an M protein ≥ 3 g/dL and/or ≥ 10% bone marrow plasma cells but no evidence of anemia, hypercalcemia, renal insufficiency or lytic bone lesions (CRAB) [8]. These patients must be followed up closely because symptomatic MM develops at a rate of 10% per year for the first 5 years of follow-up. The risk decreases to 3% per year for the next 5 years and then falls 1% to 2% per year.

Primary systemic amyloidosis (AL) is a rare disorder that is characterized by the deposition of amyloid fibrils which are composed of monoclonal immunoglobulin light chain fragments. The diagnosis should be suspected when a patient with an M protein in the serum or urine presents with nephrotic-range proteinuria with or without renal insufficiency, cardiomyopathy, hepatomegaly, or autonomic or peripheral neuropathy. Amyloid appears as an apple-green birefringence under polarized light when using a Congo Red stain. The type of amyloid is best determined by laser microdissection of Congo Red

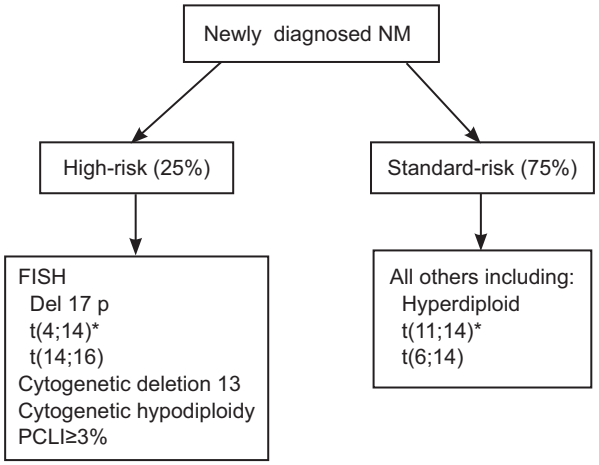
staining tissue from the biopsy of an involved organ and then subjected to tandem mass spectrometry [9].

Risk Stratification of Newly Diagnosed MM

Multiple myeloma has very different outcomes from patient to patient. At one end of the spectrum are patients with low-grade disease who require intermittent therapy and have a long survival. At the other end are patients with aggressive disease that becomes rapidly resistant to therapy and results in a short survival. We utilize mSMART which is based upon fluorescence in situ hybridization (FISH), metaphase cytogenetics, and the plasma cell labeling index (PCLI) (Fig. 1) [10]. High-risk disease accounts for approximately 25% of MM patients and is characterized by del 17p, t(4; 14) or t(14;16) by FISH, deletion of chromosome 13 or hypodiploidy by metaphase cytogenetics or PCLI $\geq$ 3%. Standard risk myeloma, accounting for three-fourths of patients, is characterized by hyperdiploidy which is characterized by trisomies of several odd-numbered chromosomes, especially 3, 5, 7, 9, 11, 15, 19 or 21 and is found in 50% to 60% of patients. The presence of t(11;14) and t(6;14) by FISH are found in standard-risk myeloma [10].

We strongly recommend clinical trials, but if the patient is not eligible or if clinical trials are not available, we separate those patients who are eligible for an autologous stem cell transplant from those who are not and proceed with the mSMART approach [11]. Criteria for diagnosis, staging, risk stratification and response assessment of MM have recently been described in detail [12]. The treatment of newly diagnosed multiple myeloma has recently been discussed in detail [11].

Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART).



Kumar S K et al. Mayo Clin Proc. 2009;84:1095-1110

Initial therapy for Transplant Eligible Patients

Alkylating agents must be avoided because they may damage stem cells and prevent mobilization of sufficient stem cells for a successful transplant. One may use granulocyte colony-stimulating factor (GCSF) with or without cyclophosphamide for stem cell collection. Plerixafor may also be useful for mobilization of hematopoietic stem cells. One should collect enough cells for two transplants [13].

We prefer lenalidomide 25 mg daily days 1-21 plus dexamethasone 40 mg given weekly for each 28-day cycle [14] as initial therapy. The addition of clarithromycin to lenalidomide and weekly dexamethasone is another option and produces an objective response in 90% of patients [15].

Thalidomide plus dexamethasone is an option. In a randomized study, 470 patients with symptomatic previously untreated MM were randomized to receive thalidomide in a dose of 50 mg daily with escalation to 200 mg daily if tolerated plus dexamethasone 40 mg (days 1-4, 9-12, 17-20) versus placebo plus dexamethasone 40 mg (days 1-4, 9-12, and 17-20). Thalidomide/dexamethasone produced a complete response or partial response in 63% of patients with a time to progression of 22.6 months. Dexamethasone alone produced an objective response in 40% with a time to progression of 6.5 months. Deep venous thrombosis occurred in 12% of patients receiving thalidomide/dexamethasone compared to 2% for the dexamethasone-alone regimen [16].

Bortezomib-based regimens

Bortezomib plus dexamethasone is another option for induction therapy. Bortezomib 1.3 mg/m^2 twice weekly for 2 weeks every 3 weeks plus dexamethasone 40 mg on the day of or day after bortezomib produced an objective response in 90% of 48 untreated symptomatic myeloma patients [17]. This study has recently been updated and reported an estimated survival of 67% at 4 years [18]. Bortezomib appears to overcome the adverse effect of unfavorable cytogenetic abnormalities [19]. Bortezomib plus dexamethasone is recommended for patients with acute renal insufficiency. Bortezomib may be combined

with alkylating agents or with liposomal doxorubicin. The combination of cyclophosphamide, bortezomib and dexamethasone was associated with an objective response in 88%; 61% had a VGPR and 39% had CR or near complete response (NCR) [18].

The combination of thalidomide, bortezomib and dexamethasone produced an objective response of 94%, with VGPR 68%, compared to 79% and 29% with thalidomide plus dexamethasone [19].

Autologous Stem Cell Transplantation

The stem cells must be collected following 3 to 4 months of induction therapy with lenalidomide, thalidomide or bortezomib – all with dexamethasone. We have found no significant difference in response rates, post-transplant complications or treatment-related mortality in patients who received VAD; dexamethasone alone; thalidomide plus dexamethasone; or lenalidomide plus dexamethasone [22]. We have failed to show that the depth of response before transplantation is associated with improved long-term survival. On the other hand, two recent studies suggest that induction therapy associated with greater depth of response (VGPR or CR) before transplantation results in a better progression-free survival following transplantation[20, 21].

Selection of the CD34+ cells has resulted in a large reduction of tumor cells but no difference in disease-free survival or overall survival [22].

The mortality of an autologous stem cell transplant is about 1% and is available for up to one-half of patients with MM. Approximately 40% of our patients undergo stem cell transplantation as an outpatient. Unfortunately, the procedure is not curative and most patients relapse in approximately two years.

The autologous stem cell transplant may be given immediately after induction therapy or delayed until relapse. There is no overall difference in survival. However, early autologous transplantation results in a superior quality of life and a shorter period of chemotherapy.

In a randomized trial of 282 newly diagnosed symptomatic myeloma patients aged < 65 years received melphalan 140 mg/m^2 plus 8 Gy total body irradiation or melphalan 200 mg/m^2 [26]. Patients had a more rapid hematologic recovery, lower incidence of severe mucocystitis, fewer transfusions and shorter hospitalization with melphalan 200 mg/m^2. In addition, survival at 45 months was superior in patients receiving melphalan 200/m^2 (66% vs. 46%).

In a large randomized study, autologous stem cell transplantation was superior to combination chemotherapy. Four-hundred and one patients with newly diagnosed symptomatic MM were randomized to receive melphalan 200 mg/m^2 followed by stem cell rescue or chemotherapy consisting of doxorubicin, carmustine, cyclophosphamide and melphalan. The CR rate was superior in the transplantation group (44% vs. 8%), while PFS was 32 months vs. 20 months and OS was 54 months vs.42 months, favoring transplantation [23]. Autologous stem cell transplantation can be performed in patients with renal failure, but the morbidity is higher even though transplantation-related mortality is not increased.

The cost of autologous stem cell transplantation has been reduced by keeping the cells in a refrigerator without freezing [24]. In a recent review, Harousseau and Moreau recommended the continued use of autologous stem cell transplantation despite the introduction of the novel agents lenalidomide and bortezomib [25].

Single versus tandem transplantation

In a randomized study comparing single and tandem transplantation, a superior EFS (21% vs. 10%) and OS (42% vs. 21%) favored a tandem transplant after 7 years follow-up [26]. After reanalysis of their data, the investigators concluded that those patients who obtained a CR or a VGPR with the first autologous transplantation did not benefit from a second transplantation. Cavo et al. reported an OS of 71 months for tandem transplantation versus 65 months for those with a single transplantation in a randomized study of 321 patients [31]. On the other hand, others have shown no difference in survival between single and tandem transplantation [27].

Maintenance Therapy Following Autologous Stem Cell Transplantation

The Intergroupe Francophone du Myelome (IFM) performed a tandem autologous transplant in 597 myeloma patients and then randomized them to no maintenance or pamidronate plus thalidomide maintenance. Although thalidomide improved the response rate and OS, it frequently resulted in peripheral neuropathy [28]. Initially thalidomide produced a superior OS but with longer follow-up. this difference has lost its statistical signifi-

cance. Intensive chemotherapy and a tandem autologous stem cell transplantation were performed in 868 patients who were randomized to receive or not receive thalidomide during the entire treatment period. There was a superior CR rate (62% vs. 42%) and 5-year EFS of 56% vs. 44%, respectively [29, 30]. This study does not allow one to determine the benefit of maintenance therapy because when randomized to thalidomide patients received it throughout the entire treatment period. It appears that thalidomide benefits only those who were not in VGPR after transplantation.

Alpha-2-interferon has been used for maintenance, but a large meta-analysis of 24 randomized trials involving 4,012 patients, alpha-2-interferon showed only a modest prolongation of PFS and OS [31]. In a large randomized study, interferon produced no benefit when given as maintenance therapy [37]. Currently, we recommend that patients who have obtained a response from stem cell transplantation be followed without maintenance therapy unless they are part of a clinical trial.

Allogeneic Transplantation

The advantage of allogeneic transplantation is that there is no contamination of hematopoietic stem cells by tumor cells. However, more than 90% of patients with MM are ineligible because of their age or lack of an HLA-matched donor. The mortality has been reduced from 40% to about 25%. We do not recommend conventional allogeneic transplantation in MM.

Nonmyeloablative (reduced intensity or mini allogeneic) stem cell transplantation regimens have been used for MM. It is best to perform a nonmyeloablative allogeneic stem cell transplantation following recovery from an autologous stem cell transplant. Initially, the mortality was 25% with a 3-year OS and PFS of 41% and 21%, respectively [32]. In a prospective study, 162 patients with newly diagnosed MM were treated initially with VAD followed by mobilization of stem cells with cyclophosphamide and GCSF. Patients with an HLA-identical sibling received an autologous transplantation followed by a nonmyeloablative allogeneic transplantation using the sibling donor. Those without an HLA-identical sibling received a double autologous stem cell transplant. The mortality was 2% for the double autologous transplant and 10% for patients receiving an autologous and nonmyeloablative transplant. The disease-related mortality was 43% for the tandem transplant versus 7% for the autologous allogeneic transplantation after a follow-up of 45 months [33].

Initial Therapy for Patients Ineligible for an Autologous Stem Cell Transplant

Since the 1960s, melphalan and prednisone has been the standard of therapy, but the response rate is only 50% to 60%. Many combinations of chemotherapy were developed over the next three decades, but a large meta-analysis of 4,930 symptomatic multiple myeloma patients in 20 prospective trials revealed a response rate of 60% for combination chemotherapy versus 53% from melphalan and prednisone. Unfortunately, there was no difference in survival and no subsets benefited from either single or multiple combinations of chemotherapy [34, 35].

The International Myeloma Working Group has recently published guidelines for the management of MM patients ineligible for autologous stem cell transplant (Palumbo, Sezer et al. 2009).

Two-hundred and fifty-five patients with newly diagnosed myeloma deemed ineligible for an autologous stem cell transplant were randomized to receive melphalan, prednisone and thalidomide (MPT) or melphalan and prednisone (MP). MPT produced a response rate of 76%, compared with 48% for MP. The three-year overall survival was 80% versus 64%, favoring the MPT regimen [36]. The IMF randomized 447 previously-untreated patients who were ineligible for a transplant to MPT or MP or melphalan 100 mg/m^2 x 2 followed by stem cell rescue. The overall survival was 52 months, 33 months and 38 months, respectively [37]. In another IMF study of 229 patients with previously-untreated MM aged > 75 years randomized to melphalan and prednisone or melphalan, prednisone plus thalidomide. The overall survival was 45.3 months, compared to 27.7 months for MP alone[38]. Palumbo et al. recently reported a large prospective randomized study comparing melphalan, prednisone and lenalidomide versus melphalan and prednisone [39]. On the other hand, a study of 289 elderly patients randomized to thalidomide and dexamethasone or to melphalan and prednisone revealed an overall survival of 41.5 months versus 49.4 months. Toxicity was greater with thalidomide and dexamethasone, especially in patients older than 75 years with poor performance[40].

Bortezomib is another option for patients ineligible for an autologous transplantation. In a randomized study comparing bortezomib, melphalan and prednisone with melphalan and prednisone in the same dose and schedule, CR plus VGPR was 45% for VMP compared to 10% for MP [41]. Peripheral neuropathy occurred in 44% of the VMP group, compared to 5% in those receiving MP.

We continue the initial chemotherapy regimen until the patient reaches a plateau state. There is no convincing evidence that continued chemotherapy with MP is of benefit after achieving a plateau state and there is a risk of myelodysplasia from continued therapy.

Treatment of Relapsed or Refractory Multiple Myeloma

Almost all patients with MM will eventually develop resistant or refractory disease. Thus, treatment of patients with relapsed MM is important. The overall survival rates at 1, 2, and 5 years in 578 patients with symptomatic MM from the Mayo Clinic were 72%, 55% and 22%, respectively. The median OS was 28.4 months. The median survival of the 355 patients who relapsed after initial therapy was 17.1 months from the time of institution of the second therapy. The duration of response decreased with each successive relapse. The median duration from diagnosis to the first relapse was 9.9 months but was 7.3, 6.0, 4.5, 4.0 and 3.2 months, respectively for the second, third, fourth, fifth, and sixth relapses [42].

The initial chemotherapy regimen should be reinstituted in most instances when relapse occurs more than six months after therapy has been discontinued. The major agents for the treatment of relapsed myeloma are thalidomide, bortezomib and lenalidomide at present, but a number of new agents are in Phase I/II studies.

Thalidomide produced a response in 32% of 84 patients with relapsed/refractory myeloma. [43]. The median duration of response was approximately one year [49]. The response rate with thalidomide increases to approximately 50% when corticosteroids are added. Side effects from thalidomide are troublesome and include sedation, fatigue, constipation, rash, peripheral neuropathy, deep vein thrombosis, bradycardia and hypothyroidism. Thalidomide is absolutely contraindicated in pregnancy and the S.T.E.P.S. Program must be followed carefully [44].

Bortezomib, a proteasome inhibitor, has shown significant activity in MM. Bortezomib produced an objective response in 35% of 193 patients with refractory MM with a median duration of one year [45]. In a report of 669 patients who had either not responded to therapy or who had relapsed after initial therapy were randomized to receive bortezomib or dexamethasone. The time to progression was 6.2 months versus 3.5 months, while the OS was 29.8 months versus 23.7 months, respectively, favoring bortezomib [46]. Bortezomib usually produces a response within one or two cycles of therapy and can be used in the presence of renal failure. Side effects are common and include gastrointestinal symptoms, cytopenias, fatigue and, most importantly, peripheral neuropathy which occurs in 30% to 40% of patients. Bortezomib appears to overcome the effect of adverse chromosomal features such as hypodiploidy and deletion of chromosome 13 as well as adverse cytogenetic changes such as t(4;14), t(4;16) or 17p-.

Lenalidomide produces an objective response in approximately 30% of patients with relapsed/refractory MM [47]. In a large randomized study of 704 patients randomized to lenalidomide plus dexamethasone or a placebo plus dexamethasone, the response rate was 60.5% versus 22%, favoring lenalidomide plus dexamethasone. The time to progression was 11.2 months for lenalidomide/dexamethasone, compared to 4.7 months for dexamethasone alone[48, 49]. Lenalidomide is associated with thrombocytopenia, neutropenia and anemia but neuropathy, sedation and gastrointestinal side effects are not a problem.

A number of novel agents such as pomalidomide[50], vorinostat, a histone deacetylase inhibitor and carfilzomib are promising new agents which have recently been reviewed [51].

Are We Making Progress?

Prior to the introduction of melphalan, median survival for multiple myeloma was less than one year. The introduction of melphalan over a half-century ago was a major advance [52]. The introduction of autologous stem cell transplantation and thalidomide, bortezomib and lenalidomide have improved survival.

In a series of 2,981 multiple myeloma patients from Mayo Clinic, the median survival was 29.9 months for those seen between 1971 and 1996, while those diagnosed after 1996 had median survival of 44.8 months [53]. The improved survival after 1996 is due to the availability of autologous stem cell transplantation and the novel agents.

The median survival following relapse after an autologous stem cell transplant was 14.8 months in 226 patients who did not receive thalidomide, bortezomib or lenalidomide compared to a median survival of 30.9 months for those who did receive one of these novel agent [53].

Treatment of Complications

Skeletal disease

Conventional skeletal radiographs reveal abnormalities in 80% of MM patients at the time of diagnosis. Abnormalities are found in more than 90% of patients utilizing magnetic resonance imaging (MRI), but we do not recommend it routinely unless the patient has localized symptoms in the absence of abnormalities on conventional radiographs. Technetium bone scans should not be performed because they are inferior to radiographs. Intravenous pamidronate 90 mg given over at least 2 hours [54]or zoledronic acid given over a period of 15 minutes every 3 to 4 weeks is recommended for patients with MM who have lytic lesions or osteopenia on the basis of plain radiographs, MRI or computed tomography [55]. Pamidronate should be reduced in patients with renal insufficiency while zoledronic acid is best avoided in patients with severe renal insufficiency. The bisphosphonates should be continued for one to two years, and at that point the bisphosphonate may be discontinued if the patient has responded to therapy. The bisphosphonate should be reinstituted in the event of relapsed multiple myeloma with progressive skeletal involvement. Bisphosphonates are not indicated for patients with MGUS, SMM or solitary plasmacytoma of bone. It is advisable to have a comprehensive dental examination and appropriate preventive dentistry before bisphosphonate therapy is started because osteonecrosis of the jaw is a potential complication. Patients should practice oral hygiene and avoid invasive dental procedures while on bisphosphonate therapy[56].

Vertebroplasty involves the percutaneous injection of methylmethacrylate under fluoroscopic guidance into the collapsed vertebral body while kyphoplasty involves the introduction of an inflatable balloon into the vertebral body which is then filled with methylmethacrylate [57].

Trauma must be avoided by patients with MM, but they should be encouraged to be as active as possible. Fixation of fractures or impending fractures of long bones with an intramedullary rod and methyl methacrylate has produced good results.

Renal insufficiency

Renal insufficiency is present in approximately one-half of patients with MM at diagnosis; 20% have a serum creatinine > 2 mg/dL. Cast nephropathy from excessive production of monoclonal light chains or hypercalcemia are the two major causes of renal failure. Dehydration may precipitate acute renal failure. AL amyloidosis or light chain deposition may also produce renal failure. Bortezomib and dexamethasone is the favored therapeutic regimen. Plasmapheresis is a consideration for patients with acute renal failure. Patients with Bence Jones proteinuria should be encouraged to drink enough fluids to produce three liters of urine daily.

Anemia

Anemia develops in nearly all patients with MM. Erythropoietin often increases the hemoglobin level. Iron, folate or vitamin B12 deficiencies must be treated if present. Erythropoietin should not be given unless the hemoglobin is < 10 g/dL and should be discontinued when the hemoglobin reaches 11 g/dL. Blood transfusions are indicated for severe anemia. Guidelines for the use of erythropoietin have been published [58].

Hypercalcemia

Hypercalcemia is found in 15% to 20% of patients with MM at the time of diagnosis. It may produce anorexia, nausea, vomiting, polyuria, polydipsia, increased constipation, weakness, confusion or stupor. Hypercalcemia is a major cause of renal insufficiency. Hydration, preferably with isotonic saline and prednisone 25 mg 4 times daily is effective in most patients. If the patient has severe hypercalcemia or does not respond to hydration and prednisone, zoledronic acid 4 mg intravenously over 15 minutes is recommended [59].

Infections

Reduction of humoral and cell-mediated immunity from MM and neutropenia from chemotherapy increases the frequency of infections. Herpes zoster is also common and requires antiviral therapy to prevent dissemination. Intravenous immunoglobulin infusions are expensive and may be associated with undesirable side effects. Immunization with pneumococcal and influenza vaccine should be done. Guidelines for the management of infections have been published [60].

Spinal cord compression

Spinal cord compression from an extramedullary plasmacytoma should be suspected in patients with weakness or paresthesias of the lower extremities or bladder or bowel dysfunction. MRI or CT myelography of the entire spine must be performed immediately. Dexamethasone and radiation therapy are often helpful so surgical decompression is usually unnecessary.

Thromboembolic risks

Patients receiving single-agent thalidomide or lenalidomide do not require anticoagulation unless they are at increased risk because of a prior thromboembolic event, obesity or at bed rest. If low-dose dexamethasone or prednisone is given with thalidomide or lenalidomide, aspirin in a dose of 325 mg daily is advised [61]. If thalidomide or lenalidomide is given with high-dose dexamethasone, doxorubicin, liposomal doxorubicin or erythropoietin, full-dose warfarin or low-molecular-weight heparin should be given. Bortezomib does not produce a greater risk of thromboembolic events.

Any patient with a serious disease such as MM needs substantial continuing emotional support. The physician must be positive and have confidence in his ability to cope with the patient's problems, and the patient should be able to sense this confidence. Potential benefits of therapy should be emphasized. It reassures the patient to know that some patients survive for more than a decade. Patient support groups are very helpful. It is essential that the physician caring for the MM patient has the interest and capacity to deal with incurable disease over a span of months to years with assurance, sympathy and resourcefulness.

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