

Multiple Myeloma: An Overview in 1996

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Multiple myeloma (MM) is characterized by the neoplastic proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin. The plasma cell proliferation usually results in extensive skeletal destruction with osteolytic lesions, hypercalcemia, anemia, and occasionally, plasma cell infiltration in different organs.⁽¹⁾ The excessive production of an monoclonal (M-) protein can lead to renal failure and/or hyperviscosity syndrome.

Etiology and Epidemiology

The cause of MM is unknown. Radiation may be a factor in some cases. An increased incidence of MM has been reported in atomic bomb survivors exposed to more than 50 cGy as well as in radiologists who had relatively large doses of long-term radiation. Exposure to asbestos, benzene or industrial and agricultural toxins, a genetic element, and viruses have all been considered possible causes, but proof is meager.

Multiple myeloma accounts for about 1% of all types of malignant disease and slightly more than 10% of hematologic malignancies. The incidence of MM is approximately 4 per 100,000 per year.⁽²⁾ The apparent increase of rates in recent years is probably related to increased availability and utilization of medical facilities and improved diagnostic techniques, particularly in the older population. The incidence in Blacks is twice that in Whites and is slightly more frequent in men than women. The median age at diagnosis is approximately 65 years. Less than 3% of patients are younger than 40 years of age.⁽³⁾

Biologic and Molecular Aspects

Myeloma cells express CD38 and PCA-1 and are CIg positive. Most plasma cells express IL-1b and CD56. Only a minority express CD10, HLA-DR, and CD20. However, the nature of the clonogenic cell in MM is still unknown. It is likely that plasma cell precursors of myeloma circulate in the peripheral blood. These circulating clonogenic pre-myeloma cells may home to the bone marrow by means of adhesion molecules where they find an appropriate micro-environment in which to differentiate and proliferate. T cells may play an important role. Expansion of T-cell subsets has been recognized in multiple myeloma. Resting B cells enter into DNA synthesis stimulated by interleukin-4 (IL-4), proliferate with IL-5, and differentiate into plasma cells with IL-6. IL-6 is an important growth factor for myeloma cells. Elevated IL-6 levels have been found in many patients with progressive, terminal MM and in those with plasma cell leukemia in contrast to patients with monoclonal gammopathy of undetermined significance (MGUS),

Increased expression of C-myc, N-ras, K-ras, and BCL-2 have been found in myeloma. Ras mutations have been reported in about 40% of patients with multiple myeloma. Shorter survival has been seen in those with a mutation in the K-ras gene. Point

mutations of the tumor suppressor gene, P53, occurs in about 15%. Thus, C-myc, N-ras, K-ras, and P53 genes may be involved in the pathogenesis of myeloma. Flow cytometric analysis has led to the demonstration of an aneuploid myeloma cell population in approximately 80% of patients. Hyperdiploidy occurs in 70% and hypodiploidy in about 10%. Cytogenetic studies have been hindered because of the low proliferative activity of plasma cells. Cytogenetic abnormalities have been detected in about half of patients. No specific abnormality has been demonstrated. It has been reported that patients with partial or complete deletions of chromosome 13 or abnormalities involving 11q are associated with a poor prognosis.⁽⁴⁾

Clinical Manifestations

Bone pain, particularly in the back or chest and less often in the extremities, is present at diagnosis in more than two-thirds of patients. Weakness and fatigue are common and are often associated with anemia. Fever from the disease itself is rare; most patients with multiple myeloma and fever have an infection. Epistaxis or purpura may occur. Symptoms from hypercalcemia, renal insufficiency, acute infection, or amyloidosis may be the initial manifestation.

Pallor is the most common physical finding. The liver is palpable in about 20% of patients and the spleen in 5%. Extramedullary plasmacytomas are not common and are usually seen late in the course of the disease as large, vascular, subcutaneous masses with a purplish hue.

Renal Involvement

The serum creatinine is increased (2 mg/dL or greater) in almost one-fourth of patients at diagnosis. The two major causes of renal failure are “myeloma kidney” and hypercalcemia. Myeloma kidney is characterized by the presence of large, waxy, laminated casts in the distal and collecting tubules. The casts are mainly composed of precipitated monoclonal light chains. The extent of cast formation correlates with the severity of renal insufficiency. Nausea, vomiting, and dehydration may contribute to acute renal failure. Hypercalcemia is present at diagnosis in 25% of patients and is a major and treatable cause of renal insufficiency. Hyperuricemia may contribute to renal insufficiency. Amyloidosis occurs in 10% to 15% of patients and may produce a nephrotic syndrome or renal failure or both. Acquired Fanconi’s syndrome, which is characterized by proximal tubular dysfunction, results in glycosuria, phosphaturia, and aminoaciduria. A low serum uric acid level in the absence of ingestion of allopurinol is an important clue to the diagnosis. Deposition of monoclonal light chains, especially κ , in the renal glomeruli (light-chain deposition disease) may produce renal insufficiency or nephrotic syndrome.

Skeletal Involvement

Conventional roentgenograms show abnormalities consisting of punched-out lytic lesions, osteoporosis, or fractures in 75% of patients at diagnosis. Technetium-99m-labeled bone scans are inferior to conventional radiographs for the detection of lytic lesions. Computed tomography (CT) and magnetic resonance imaging (MRI) are more

sensitive and may be useful when skeletal pain is atypical and radiographs show no abnormalities.

Other Organs

Radiculopathy is the single most frequent neurologic complication. It results from compression of the nerve by epidural extension from a vertebral lesion or by the collapsed bone itself and is usually in the thoracic or lumbosacral area. Compression of the spinal cord occurs in 5% to 10% of patients. Peripheral neuropathy is uncommon in multiple myeloma and when present is usually due to amyloidosis. Leptomeningeal myelomatosis is rare but is being recognized more frequently.

The incidence of infection is increased in multiple myeloma. Diplococcus pneumoniae and Staphylococcus aureus were the most frequent pathogens but more recently gram-negative organisms are more common. Impaired antibody response, deficient normal immunoglobulins, impaired serum opsonic activity, and neutropenia all contribute to the increased incidence of infections. Herpes zoster is common.

Laboratory Findings

Normocytic, normochromic anemia is present at diagnosis in about two-thirds of patients. The leukocyte count is usually normal but leukopenia may occur. Thrombocytopenia is present in approximately 15% of patients at diagnosis.

The serum protein electrophoretic pattern shows a peak or localized band in 80% of patients. Hypogammaglobulinemia or a normal pattern is seen in the remainder. An M-protein is found in the serum in about 90% of patients at diagnosis. More than 15% have a free monoclonal κ or λ protein (Bence Jones proteinemia). Immunoelectrophoresis or immunofixation of the urine reveals an M-protein in 75%. About two-thirds are κ . A monoclonal protein is found in the serum or urine in 99% of patients during the course of their disease.

Plasma cells usually constitute more than 10% of all nucleated cells in the bone marrow. However, the number may range from less than 5% to almost 100%. Bone marrow involvement may be more focal than diffuse, and some patients may require repeat bone marrow examinations for diagnosis. The presence of a monoclonal immunoglobulin in the cytoplasm of plasma cells with immunofluorescence or immunoperoxidase staining is helpful in differentiating multiple myeloma from reactive plasmacytosis.

Diagnosis and Differential Diagnosis

Minimal criteria for the diagnosis of multiple myeloma are a bone marrow containing greater than 10% plasma cells or a plasmacytoma plus at least one of the following: 1) M-protein in the serum (usually > 3 g/dL), 2) M-protein in the urine, and 3) lytic bone lesions. The main conditions to consider in the differential diagnoses are MGUS, smoldering multiple myeloma (SMM), primary amyloidosis (AL), and metastatic carcinoma. An M-protein of less than 3 g/dL, less than 10% bone marrow plasma cells, absence of lytic lesions, anemia, hypercalcemia, or renal insufficiency are characteristic

of MGUS. An M-protein of greater than 3 g/dL and more than 10% bone marrow plasma cells fulfill the diagnostic criteria for smoldering multiple myeloma in asymptomatic patients.⁽⁵⁾

The plasma cell labeling index (PCLI) may differentiate patients with MGUS or SMM from those with MM.⁽⁶⁾ The PCLI of peripheral blood correlates well with the bone marrow labeling index. An elevated value strongly suggests that the patient has or will soon have symptomatic disease. It must be emphasized that patients with symptomatic MM requiring therapy may have a normal PCLI. Monoclonal plasma cells are detected in the peripheral blood of 80% of patients with symptomatic multiple myeloma and in more than 90% of those with relapsed or refractory myeloma. In contrast, patients with MGUS or SMM have few or no circulating plasma cells.⁽⁷⁾

In summary, no single factor can differentiate a patient with MGUS from one in whom MM or other malignant disease will subsequently develop. The serum and urinary M-protein should be periodically measured, and clinical and other laboratory features should be reevaluated to determine whether MM, amyloidosis, macroglobulinemia, or other lymphoproliferative disorders have developed.

Prognosis

Multiple myeloma has a progressive course with a median survival of six months when no treatment is given. The current median survival with chemotherapy is about three years. The bone marrow plasma cell labeling index and β_2 -microglobulin (β_2 -M) levels are the most important prognostic factors in previously untreated patients.^(8,9) In addition, elevated soluble IL-6 receptor (sIL-6R), lactate dehydrogenase and C-reactive protein (CRP) levels, presence of plasmablastic morphology, older age, presence of circulating plasma cells in the peripheral blood, increased colony growth, and increased levels of IL-6 are all associated with a poorer prognosis.

Treatment

Not all patients who fulfill the minimal criteria for the diagnosis of MM should be treated. Patients with SMM or MGUS should not be treated. The patient's symptoms, physical findings, and all laboratory data must be considered. If there is doubt in the physician's mind, it is usually better to withhold therapy and to reevaluate the patient in two or three months.

Chemotherapy is the preferred initial treatment for overt, symptomatic MM. In most instances, analgesics, together with chemotherapy, can control the pain. This combination is preferred to focal irradiation because the bone marrow reserve of many patients is limited and focal irradiation does not benefit systemic disease.

The oral administration of melphalan and prednisone produces objective response in 50% to 60% of patients. Leukocyte and platelet levels should be determined every three weeks after beginning each cycle of chemotherapy, and the melphalan and prednisone should be repeated every six weeks. The dosage of melphalan must be adjusted until mid-cycle cytopenia occurs because absorption of the agent is variable.

Because of the obvious shortcomings of melphalan and prednisone, various combinations of therapeutic agents have been tried. One of the best-known combinations is the M2 Protocol, which includes vincristine, Carmustine (BCNU), melphalan, cyclophosphamide, and prednisone (VBMCP). This regimen produces an objective response in about 70% of patients. In a recent Eastern Cooperative Oncology Group (ECOG) study, the addition of α_2 -interferon (α_2 -IFN) to VBMCP produced a higher percentage of complete responses, but the overall survival of 43 months was the same as for VBMCP. In a meta-analysis of 18 published trials, no difference in efficacy was shown between melphalan/prednisone and combination chemotherapy.⁽¹⁰⁾ However, there was an implication that melphalan/prednisone was superior for patients with a good prognosis and inferior to combination therapy for those with a poor prognosis.

Chemotherapy should be continued for at least one year or until the patient is in a plateau state. This is defined as a stable serum and urine M-protein level and no evidence of progression. Continued chemotherapy may lead to the development of a myelodysplastic syndrome or acute leukemia.⁽¹¹⁾ α_2 -IFN appears to prolong the duration of the plateau state but does not significantly influence survival.⁽¹²⁾ Patients should be followed closely during the plateau state, and the same chemotherapy should be reinstated when relapse occurs. The treatment of multiple myeloma has recently been reviewed.⁽¹³⁾

Peripheral Blood Stem Cell or Bone Marrow Transplantation

Bone marrow transplantation from an identical twin donor (syngeneic) has been associated with occasional prolonged survival, but most patients die of their MM. Allogeneic bone marrow transplantation is advantageous in that the graft contains no tumor cells that can subsequently lead to a relapse.⁽¹⁴⁻¹⁶⁾ However, only 5% to 8% of patients with MM are eligible for this procedure because an HLA-compatible donor is available to only one-third of patients, 80% are greater than 50 years of age, and renal insufficiency (creatinine > 2 mg/dL) occurs in 20%. In addition, a significant mortality of 25% within six months, the risk of graft-versus-host disease, and the eventual relapse in most patients makes allogeneic bone marrow transplantation of limited use.

Autologous peripheral blood stem cell or bone marrow transplantation is applicable to more patients because the age limit is higher (65-70 years) and a matched donor is unnecessary.⁽¹⁶⁾ However, two major problems exist: 1) eradication of MM from the patient usually does not occur even with large doses of chemotherapy and irradiation, and 2) reinfusing autologous peripheral blood stem cells or bone marrow contaminated by myeloma cells or their precursors is a major concern. Selection of CD34⁺ Lin⁻ Thy⁺ stem cells may be a useful approach.⁽¹⁷⁾ Purging of the marrow in vitro with a combination of monoclonal antibodies⁽¹⁸⁾ or cytotoxic agents is not effective for routine clinical use. Prospective studies comparing transplantation and chemotherapy are underway in a number of centers.

It is essential to develop more sensitive techniques for detection of residual myeloma with the advent of more aggressive therapy. When the M-protein is not detected in the serum and urine with immunofixation and the bone marrow contains no identifiable myeloma cells, the patient still frequently relapses with myeloma of the same isotype that was present initially. Oligonucleotide primers to amplify regions of rearranged heavy-

chain alleles with polymerase chain reaction can detect one myeloma cell in 100,000 cells.

Treatment of Refractory Multiple Myeloma

Almost all patients with MM who respond to chemotherapy eventually relapse. The highest response rates for patients resistant to alkylating agents have been with VAD (vincristine, Adriamycin [doxorubicin], and dexamethasone). Most of the activity of VAD is from dexamethasone. Intravenous methylprednisolone (2 g three times weekly intravenously for a minimum of 4 weeks) is helpful for patients with pancytopenia, and we find fewer side effects than from dexamethasone. If there is a response, methylprednisolone is reduced to once or twice weekly. VBAP (vincristine, Carmustine [BCNU], and Adriamycin [doxorubicin] on day 1 and prednisone daily for 5 days every 3-4 weeks) benefits 30% of patients. α_2 -IFN produces objective response in 10% to 20% of patients with myeloma refractory to alkylating agents. Cyclophosphamide (600 mg/M² intravenously daily for 4 days) plus prednisone followed by granulocyte-colony stimulating factor (G-CSF) has been helpful in refractory patients with advanced disease.

Other Therapeutic Approaches

A reversal of resistance to chemotherapeutic agents is an important area of research. The use of verapamil or quinine to reverse the resistance to doxorubicin (Adriamycin) has been disappointing. PSC 833, an analog of cyclosporin, is being investigated in an effort to reduce multidrug resistance (MDR) to vinca alkaloids and anthracyclines. It appears to be a much more effective inhibitor of MDR than cyclosporin A.

Taxol has been disappointing in that it produces an objective response in about 25% of patients and it is associated with considerable neutropenia. Topotecan has also produced some objective responses. The use of monoclonal antibodies to IL-6, a potent growth factor for plasma cells, has produced some response in patients with advanced myeloma and plasma cell leukemia, but it is not a practical approach. New agents for the treatment of MM are needed.

Management of Complications

Hypercalcemia must be suspected if the patient has anorexia, nausea, vomiting, polyuria, increased constipation, weakness, confusion, stupor, or coma. Treatment is urgent because renal insufficiency commonly develops. Hydration, preferably with isotonic saline, is essential. In addition, oral prednisone in an initial dose of 25 mg q.i.d. should be given, but the dose must be reduced and the drug discontinued as soon as possible. If these fail to control the hypercalcemia, pamidronate (Aredia), etidronate (Didronel), or gallium nitrate is useful.

Maintenance of a high fluid intake (3 L of urine/24 hours) is important in preventing renal failure. Allopurinol is necessary if hyperuricemia is present. Patients with acute renal failure should be treated promptly with fluid and electrolyte correction and then with hemodialysis if necessary. Peritoneal dialysis is useful in patients with

hypotension from hemodialysis. Plasma exchange may be helpful for regaining renal function, but patients with severe myeloma cast formation or other irreversible renal changes are not likely to benefit from plasmapheresis. Renal transplantation for myeloma kidney has been followed by prolonged survival.

Prompt and appropriate treatment of bacterial infections is necessary. Pneumococcal and influenza vaccines should be given to all patients despite their suboptimal antibody response. Intravenously administered gamma globulin may be helpful for patients with recurrent infections, but it is very expensive for long-term therapy. Prophylactic daily oral penicillin often benefits patients with recurrent pneumococcal pneumonia infections. Patients should be encouraged to be as active as possible, because confinement to bed increases demineralization of the skeleton. Trauma must be avoided because even mild stress may result in a fracture. Fixation of long-bone fractures or impending fractures with an intramedullary rod and methyl methacrylate has given excellent results. Bisphosphonates such as pamidronate may be of benefit for reduction of skeletal complications.⁽¹⁹⁾ Erythropoietin is helpful for many patients with symptomatic anemia when the plateau state has been reached.⁽²⁰⁾

Symptoms of hyperviscosity include oronasal bleeding, blurred vision, neurologic symptoms, and congestive heart failure. Hyperviscosity is more common in IgA myeloma than in IgG myeloma. Plasmapheresis will promptly relieve the symptoms of hyperviscosity. If spinal cord compression is suspected, MRI, CT, or myelography must be done immediately to determine whether an extradural mass is causing the symptoms. Radiation therapy to the lesion is usually beneficial.

References

1. Kyle RA, Greipp PR: Plasma cell dyscrasias: current status. *CRC Crit Rev Oncol Hematol* 8:93, 1988
2. Kyle RA, Beard CM, O'Fallon WM, Kurland LT: Incidence of multiple myeloma in Olmsted County, Minnesota: 1978 through 1990, with a review of the trend since 1945. *J Clin Oncol* 12:1577, 1994
3. Blade J, Kyle RA, Greipp PR. Presenting features and prognosis in 72 patients with multiple myeloma who were younger than 40 years. *Br J Haematol* (in press).
4. Tricot G, Barlogie B, Jagannath S, Bracy D, Mattox S, Vesole DH, Naucke S, Sawyer JR. Poor prognosis in multiple myeloma is associated only with partial or complete deletions of chromosome 13 or abnormalities involving 11q and not with other karyotype abnormalities. *Blood* 86:42, 1995
5. Kyle RA, Greipp PR: Smoldering multiple myeloma. *N Engl J Med* 302:1347, 1980
6. Greipp PR, Witzig TE, Gonchoroff NJ, Habermann TM, Katzmann JA, O'Fallon WM, Kyle RA: Immunofluorescence labeling indices in myeloma and related monoclonal gammopathies. *Mayo Clin Proc* 62:969, 1987
7. Witzig TE, Kyle RA, Greipp PR: Circulating peripheral blood plasma cells in multiple myeloma. *Curr Top Microbiol Immunol* 182:195, 1992

8. Greipp PR, Lust JA, O'Fallon M, Katzmann JA, Witzig TE, Kyle RA: Plasma cell labeling index and β_2 -microglobulin predict survival independent of thymidine kinase and C-reactive protein in multiple myeloma. *Blood*, 81:3382, 1993
9. Kyle RA: Prognostic factors in multiple myeloma. *Stem Cells* 13(Suppl 2):56, 1995
10. Gregory WM, Richards MA, Malpas JS: Combination chemotherapy versus melphalan and prednisolone in the treatment of multiple myeloma: an overview of published trials. *J Clin Oncol* 10:334, 1992
11. Kyle RA, Gertz MA: Second malignancies after chemotherapy. P. 689 In: *The Chemotherapy Source Book*. Perry MC (ed.). Baltimore, Williams & Williams, 1992
12. Westin J, Rodger S, Turesson I, Cortelezzi A, Hjorth M, Zador G: Interferon alfa-2b versus no maintenance therapy during the plateau phase in multiple myeloma: a randomized study. *Br J Haematol* 89:561, 1995
13. Alexanian R, Dimopoulos M: The treatment of multiple myeloma. *N Engl J Med* 330:484, 1994
14. Fermand JP, Brouet JC: Marrow transplantation for myeloma. *Annu Rev Med* 46:299, 1995
15. Gahrton G, Tura S, Ljungman P, Blade J, Brandt L, Cavo M, Facon T, Gratwohl A, Hagenbeek A, Jacobs P, de Laurenzi A, Van Lint M, Michallet M, Nikoskelainen J, Reiffers J, Samson D, Verdonck L, de Witte T, Volin L: Prognostic factors in allogeneic bone marrow transplantation for multiple myeloma. *J Clin Oncol* 13:1312, 1995
16. Barlogie B, Jagannath S, Vesole D, Tricot Guido: Autologous and allogeneic transplants for multiple myeloma. *Semin Hematol* 32:31, 1995
17. Gazitt Y, Reading CC, Hoffman R, Wickrema A, Vesole DH, Jagannath S, Condino J, Lee B, Barlogie B, Tricot G: Purified CD34⁺ Lin⁻ Thy⁺ stem cells do not contain clonal myeloma cells. *Blood* 86:381, 1995
18. Seiden MV, Schlossman R, Andersen J, Freeman A, Robertson M, Soiffer R, Freedman A, Mauch P, Ritz J, Nadler L, Anderson KC: Monoclonal antibody-purged bone marrow transplantation for multiple myeloma. *Leuk Lymphoma* 17:87, 1995
19. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, Lipton A, Keller A, Ballester O, Kovacs J, Blacklock HA, Bell R, Simeone J, Reitsma DJ, Heffernan M, Seaman J, Knight D: Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *N Engl J Med* 334:448, 1996
20. Garton JP, Gertz MA, Witzig TE, Greipp PR, Lust JA, Schroeder G, Kyle RA: Erythropoetin alfa for the treatment of the anemia in multiple myeloma. A prospective, randomized, placebo-controlled, double-blind trial. *Arch Intern Med* 155:2069, 1995