

Conventional Chemotherapy for Multiple Myeloma

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Minimal criteria for the diagnosis of multiple myeloma consists of more than 10% plasma cells in the bone marrow or a plasmacytoma and one of the following: 1) M-protein in the serum (usually > 3g/dL); 2) M-protein in the urine; or 3) lytic bone lesions. These findings must not be related to metastatic carcinoma, lymphoma, connective tissues disorders, or chronic infections. It is also necessary that the patient have the usual clinical features of multiple myeloma. Monoclonal gammopathy of undetermined significance (MGUS)⁽¹⁾, smoldering multiple myeloma (SMM)⁽²⁾ and primary systemic amyloidosis (AL)⁽³⁾ must be included in the differential diagnosis. The size of the M-protein in the serum and the urine and the number of bone marrow plasma cells are helpful in the differential diagnosis. In the asymptomatic patient, an M-protein value < 3g/dL, fewer than 10% bone marrow plasma cells and absence of osteolytic lesions, anemia, hypercalcemia, and renal insufficiency are characteristic of MGUS. In asymptomatic patients an M-protein value > 3g/dL and more than 10% bone marrow plasma cells fulfill the diagnostic criteria for SMM. Reduction of uninvolved immunoglobulins are usually decreased in multiple myeloma and macroglobulinemia but reduction also occurs in almost one-third of all patients with MGUS⁽⁴⁾. The plasma cell labeling index (PCLI) is helpful in the differentiation of MGUS or SMM from multiple myeloma⁽⁵⁾. An increased value strongly suggests that the patient has or will soon have symptomatic multiple myeloma, but it must be emphasized that patients with overt multiple myeloma may have a normal plasma cell labeling index. Monoclonal plasma cells of the same isotype can be detected in the peripheral blood in 80% of patients with active multiple myeloma, whereas those with MGUS or SMM have few or no circulating plasma cells⁽⁶⁾. No single factor can differentiate a patient with MGUS from one in whom multiple myeloma or other malignant disease will eventually develop. The serum and urine M-protein value should be measured periodically, and clinical and other laboratory features should be evaluated to determine whether multiple myeloma, AL, macroglobulinemia, or related disorders have developed.

Therapy

Although most patients with multiple myeloma have symptomatic disease at diagnosis and require therapy, some are asymptomatic and should not be treated. All symptoms, physical findings, and laboratory data must be considered. An increasing level of the M-protein in the serum or urine, development of anemia, hypercalcemia, or renal insufficiency, and the occurrence of lytic lesions or extramedullary plasmacytomas are all indications for therapy. If there

is doubt about beginning treatment, the most reasonable approach is to reevaluate the patient in two months and to delay therapy until progressive disease is evident.

If the patient is younger than 70 years, the physician should discuss the possibility of autologous peripheral blood stem cell transplantation. This should be done as part of a prospective study. Hematopoietic stem cells should be collected before the patient is exposed to alkylating agents. Chemotherapy is the preferred initial treatment for overt, symptomatic multiple myeloma in persons older than 70 years or in younger patients in whom transplantation is not feasible. Oral administration of melphalan and prednisone produces an objective response in 50%-60% of patients. I prefer to give melphalan orally in a dosage of 8-10mg/day for seven days and prednisone, 20mg/tid orally for the same seven days. The melphalan should be given when the patient is fasting because absorption is reduced after food is eaten. Leukocyte and platelet counts must be determined at three-week intervals after the start of therapy, and the melphalan dosage should be altered until mid-cycle neutropenia or thrombocytopenia occurs. Melphalan and prednisone should be repeated every six weeks. Unless the disease progresses rapidly, at least three courses of melphalan and prednisone should be given before this regimen is discontinued. An objective response might not be achieved for six to twelve months or even longer in some patients.

Because of the obvious shortcomings of melphalan and prednisone, various combinations of therapeutic agents have been tried. One of the most commonly used, the M-2 protocol, consists of vincristine, carmustine (BCNU), melphalan, cyclophosphamide, and prednisone (VBMCP)⁽⁷⁾. This produces an objective response in up to 70% of patients. In an overview of individual data in 4,930 persons from 20 randomized trials comparing melphalan and prednisone with a variety of combinations of therapeutic agents, the response rates were significantly higher with combination chemotherapy (60%) compared to melphalan/prednisone (53%) ($p < 0.00001$). There was no evidence that any group of patients benefited from receiving combination therapy. In fact, there was nothing to indicate that high-risk patients benefited from combination chemotherapy. There was also no significant difference in response duration between single and multiple agents.⁽⁸⁾

Chemotherapy should be continued until the patient is in a plateau state or for at least one year. A plateau state is defined as stable serum and urine M-protein levels and no other evidence of progression. Chemotherapy should be discontinued when a plateau state occurs because continued therapy may lead to the development of a myelodysplastic syndrome or acute leukemia⁽⁹⁾.

Maintenance Therapy

It would be desirable to keep the patient in a plateau state forever, but this is not possible. The Italian Myeloma Study Group reported a superior response duration (26 vs. 14 months) favoring interferon maintenance after one year of induction therapy. There was no significant prolongation of survival⁽¹⁰⁾. An overview by the Myeloma Trialist Group revealed lapse-free survival at five years in 23% receiving alpha-2 interferon vs. 16% without interferon ($p < .001$). The overall survival at five years was modestly prolonged (31% vs 28%) ($p = .008$) (personal communication, Dr. K Wheatly, Myeloma Trialists: 1998). Patients should be monitored closely during the plateau state, and the same therapy should be reinstated if relapse occurs more than six months after the plateau state has begun.

Supportive Care

Skeletal complications

Skeletal involvement may lead to pain, hypercalcemia, pathologic fractures, or spinal cord compression. These complications result from increased osteoclastic bone resorption that is not accompanied by a comparable increase in bone formation⁽¹¹⁾. The increase in osteoclastic activity in multiple myeloma is mediated by the release of osteoclast-stimulating factors which include IL-1, IL-6 and tumor necrosis factor (TNF). These factors are produced locally in the bone marrow microenvironment by cells of both tumor and nontumor origin^(12,13). The cytokines can also serve as myeloma growth factors and prevent apoptosis.

Bisphosphonates are specific inhibitors of osteoclastic activity and have been evaluated as adjunctive therapy to chemotherapy for multiple myeloma^(14,15). Three hundred and seventy-seven patients with Stage III myeloma with at least one lytic lesion were randomized to receive pamidronate 90mg intravenously or placebo. The patients were stratified at study entry to those receiving first-line therapy (stratum 1) and patients who had failed first-line chemotherapy and were on subsequent therapy regimens (stratum 2). Skeletal events were defined as pathologic fractures, need for surgery to treat or prevent pathologic fracture, and need for radiation to bone or spinal cord compression. There was a significant reduction in both the proportion of patients experiencing skeletal events as well as the number of skeletal events annually in patients receiving pamidronate. In addition, there was a reduction in the number of patients developing new pathologic fractures as well as requiring radiation therapy in the pamidronate group. There was a significant reduction in bone pain, a lesser requirement for analgesic drugs, and improved quality of life in the pamidronate group. There was a slight survival advantage in the stratum 2 patients who received pamidronate compared to placebo (median 21 vs. 14 months). In addition, pamidronate and zoledronate reduced apoptosis of myeloma cells in human myeloma cell cultures and thus may have a direct effect on multiple myeloma⁽¹⁶⁾.

Patients should be encouraged to be as active as pos-

sible but they must avoid undue trauma. Fixation of fractures or impending fractures with an intramedullary rod and methyl methacrylate has produced good results. Bone pain should be treated with analgesics or narcotics as necessary.

Hypercalcemia

This occurs in up to one-fourth of patients with multiple myeloma and should be suspected with loss of appetite, nausea, vomiting, polydipsia, polyuria, constipation, weakness, changes in mental alertness, or confusion. Treatment is urgently important because kidney failure frequently occurs. The patient should be hydrated with intravenous fluids and started on prednisone, 25mg/qid. The prednisone should be reduced and discontinued as soon as the serum calcium becomes normal. If hypercalcemia persists, pamidronate or Didronel is effective.

Anemia

Anemia occurs in almost all patients during the course of multiple myeloma. A prospective, randomized, placebo-controlled blind clinical trial of 25 patients with hematocrit < 30 and in a stable phase of their multiple myeloma was performed. They were given erythropoietin, 150u/kg or placebo subcutaneously, three times weekly. After six weeks, the code was broken for all patients and those, who had been randomized to placebo were crossed over to an open-label phase in which they were given erythropoietin. Overall, 9 of 20 evaluable patients (45%) had a complete response and two (10%) had a partial response⁽¹⁷⁾. Osterborg et al⁽¹⁸⁾ reported a 60% response in patients with multiple myeloma or non-Hodgkin's lymphoma. They found that the serum erythropoietin concentration was the most important factor predicting response. Ludwig et al⁽¹⁹⁾ reported beneficial effects of erythropoietin in anemia associated with multiple myeloma. They also found a significant improvement in the patient's quality of life and an improved sense of well-being as measured by a self-assessment questionnaire. In another study, one-third of severely anemic patients with advanced multiple myeloma unresponsive to chemotherapy benefited from erythropoietin therapy⁽²⁰⁾.

Renal Failure

Approximately 20% of patients with multiple myeloma have a creatinine level ~ 2.0 mg/dL at the time of diagnosis. Two major causes of renal insufficiency are "myeloma kidney" and hypercalcemia. "Myeloma kidney" is characterized by the presence of large, waxy, laminated casts in the distal and collecting tubules. Although casts consist mainly of monoclonal light chains, there is no specific amino acid sequence of the light chain that has been associated with nephrotoxicity. In addition to hypercalcemia and "myeloma kidney," dehydration, infection, nonsteroidal anti-inflammatory agents, and roentgenographic contrast media may contribute to acute renal failure. Amyloid deposition occurs in 10-15% of patients with multiple myeloma and results in a nephrotic syndrome and/or renal insufficiency. It is important to determine whether the proteinuria in a pa-

tient with multiple myeloma consists of a globulin spike (Bence Jones proteinuria) or mainly albumin because large amounts of the latter indicate a nephrotic syndrome. Nephrotic syndrome rarely occurs in multiple myeloma unless amyloidosis is present.

A urinary output of 3L/24 hrs is helpful in preventing renal insufficiency in patients with light-chain proteinuria. Correction of dehydration and electrolyte imbalance is crucial as is the treatment of hypercalcemia. Allopurinol should be administered if hyperuricemia is present.

Patients with acute renal failure should be treated with appropriate fluid and electrolyte replacement. Alkalinization of the urine is useful. Plasmapheresis may be beneficial in acute renal failure⁽²¹⁾. In a prospective randomized study in which renal biopsies were performed, once cast formation reached an advanced stage, irreversible renal damage had already occurred and few of the patients responded to vigorous plasmapheresis⁽²²⁾. Patients with acute or subacute renal failure who have multiple myeloma should be treated with a regimen such as VAD (vincristine, Adriamycin, and doxorubicin). Since renal biopsy is usually impractical in patients with acute or subacute renal failure, we often proceed with a trial of plasmapheresis in those with acute renal failure. Hemodialysis or peritoneal dialysis must be provided for patients with irreversible renal failure.

Infection

Appropriate therapy for bacterial infections is essential. Patients who present with high fever and chills should have blood and urine cultures and a chest x-ray.

Antibiotics should be started immediately and changed if indicated by the results of cultures. Patients should receive pneumococcal and influenza vaccination despite their suboptimal antibody response. Prophylactic daily oral penicillin often benefits patients with recurrent pneumococcal infections. Since many infections occur in the first two months after instituting therapy, trimethoprim-sulfamethoxazole is useful⁽²³⁾. Intravenously administered gamma-globulin may be helpful for patients with recurrent bacterial infections but it is inconvenient and very expensive.

Neurologic

Spinal cord compression should be suspected in patients with severe back pain who develop weakness or paresthesias of the lower extremities. Bladder or bowel dysfunction is common. Magnetic resonance imaging (MRI) or computerized tomography (CT) must be done immediately. An MRI is particularly useful in demonstrating extramedullary plasmacytoma. Radiation therapy and dexamethasone are usually effective.

Hyperviscosity

Hyperviscosity is characterized by oral or nasal bleeding, blurred vision, neurologic symptoms, or congestive heart failure. It may occur from high concentrations of IgA or, rarely, IgG. Serum viscosity levels do not correlate well with the symptoms or the clinical findings. Consequently,

the decision to perform plasmapheresis depends on the symptoms as well as changes in the ocular fundus. Plasmapheresis promptly relieves the symptoms and should be done regardless of the viscosity level if the patient has signs or symptoms of hyperviscosity⁽²⁴⁾.

Emotional Support

All patients with multiple myeloma need substantial and continuing emotional support. The approach must be positive and emphasize the potential benefits of therapy. It is reassuring to know that some patients survive for ten years or more. It is vital that the physician caring for patients with multiple myeloma has the interest and capacity to deal with an incurable disease over a span of years with assurance, sympathy, and resourcefulness.

References

1. Kyle RA: "Benign" monoclonal gammopathy—After 20 to 35 years of follow-up. *Mayo Clin Proc* 68:26-36;1993
2. Kyle RA, Greipp PR: Smoldering multiple myeloma. *N Engl J Med* 302:1347-1349;1980.
3. Kyle RA, Gertz MA: Primary systemic amyloidosis: Clinical and laboratory features in 474 cases. *Semin Hematol* 32:45-59;1995.
4. Blade J, Lopez-Guillermo A, Rozmál C et al: Malignant transformation and life expectancy in monoclonal gammopathy of undetermined significance. *Br J Haematol* 81:391-394; 1992.
5. Greipp PR, Witzig TE, Gonchoroff NJ, et al: Immunofluorescence labeling indices in myeloma and related monoclonal gammopathies. *Mayo Clin Proc* 62:969-977;1987.
6. Witzig TE, Gertz MA, Lust JA, et al: Peripheral blood monoclonal plasma cells as a predictor of survival in patients with multiple myeloma. *Blood* 88:1780-1787;1996.
7. Case DC Jr, Lee DJ III, Clarkson BD: Improved survival times in multiple myeloma treated with melphalan, prednisone, cyclophosphamide, vincristine, and BCNU:M-2 protocol. *Am J Med* 63:897-903;1977.
8. Myeloma Trialists' Collaborative Group: Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: An overview of 6,633 patients from 27 randomized trials. *J Clin Oncol* 16:3832-3842; 1998.
9. Kyle RA, Gertz MA: Second malignancies after chemotherapy. In: Perry MC ed. *The Chemotherapy Source Book*. Baltimore, MD: Williams and Wilkins: 69-702;1992.
10. Mandelli F, Avvisati G, Amadori S, et al: Maintenance treatment with recombinant interferon alpha-2b in patients with multiple myeloma responding to conventional induction chemotherapy. *N Engl J Med* 322: 1430-1434; 1990.
11. Kanis JA McCloskey EV, Taube T, et al: Rationale for the use of bisphosphonates in bone metastases. *Bone* 12:S13-18;1991.
12. Bataille R, Chappard D, Basle M: Excessive bone resorption in human plasmacytomas: Direct induction by tumor cells in vivo. *Br J Haematol* 90:721;1995.
13. Mundy GR: Mechanisms of osteolytic bone destruction. *Bone* 12:S 1-6; 1991.
14. Berensoll JR, Lichtenstein A, Porter L, et al: Efficacy of pamidronate in reducing the skeletal events in patients with

- advanced multiple myeloma. *N Engl Med* 334:488; 1996.
15. Berensoll JR, Lichtenstein A, Porter L, et al: Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. *J Clin Oncol* 16:593-602;1998.
 16. Green JR, Muller K, Jaeggi KA: Preclinical pharmacology of CGP 42446, a new, potent, heterocyclic bisphosphonate compound. *J Bone Miner Res* 9:745;1994.
 17. Gartoll JP, Gertz MA, Witzig TE, et al: Epoetin alfa for the treatment of anemia of multiple myeloma. *Arch Intern Med* 155:2069-2074;1995.
 18. Osterborg A, Boogaerts MA, Cimino R, et al: Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lymphoma—a randomized multicenter study. *Blood* 87:2675-2682;1996.
 19. Ludwig H, Leitgenb C, Pecherstorfer M, Fritz E: Quality of life during erythropoietin therapy in chronic anemia of cancer. (Abstract). *Proc Am Soc Clin Oncol* 12:401;1993.
 20. Musto P, Falcone A, D'Arena G, et al: Clinical results of recombinant erythropoietin in transfusion-dependent patients with refractory multiple myeloma: Role of cytokines and monitoring of erythropoiesis. *Eur J Haematol* 58:314-319; 1997.
 21. Misiani R, Tiraboschi G, Mingardi G, Mecca G: Management of myeloma kidney: An anti-light chain approach. *Am J Kidney Dis* 10:28-33;1987.
 22. Johnson WJ, Kyle RA, Pineda AA, et al: Treatment of renal failure associated with multiple myeloma. *Arch Intern Med* 150:863-869;1990.
 23. Oken MM, Pomeroy C, Weisdorf D, et al: Prophylactic antibiotics for the prevention of early infection in multiple myeloma. *Am J Med* 100:624-628; 1996.
 24. Gertz MA, Kyle RA: Hyperviscosity syndrome. *J Intensive Care Med* 10:128-141;1995.