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Introduction

Multiple myeloma accounts for one percent of all malignant tumors and causes the death of about 7,000 individuals in the United States each year. During the past 20 years, the frequency of diagnosis has increased, complications have been better controlled, and a variety of drug combinations have been evaluated. We summarize some of the major advances regarding the choice of initial therapy, the role of unmaintained remission, and the treatment available for resistant disease.

Localized and Indolent Myeloma

Solitary plasmacytoma of bone and indolent multiple myeloma represent two variants of plasma cell dyscrasias that should be considered separately. Each entity requires a different approach to staging and treatment.[1]

Approximately five percent of patients with plasma cell myeloma have a solitary lesion, which is defined by one area of bone destruction with no bone marrow plasmacytosis and no disease complication, such as anemia or hypercalcemia. At our institution, only one half of these patients had a serum or urine myeloma protein. In all patients, the IgG or IgA serum peak was less than 1.6 gm/100 ml, Bence Jones protein excretion was less than 500 mg/day, and normal immunoglobulin levels were preserved. When treated with 4,000 rad, most patients showed a marked diminution of the myeloma protein level. Eventual progression to overt multiple myeloma has occurred in two thirds of patients who present with a solitary bone lesion; the remaining one third have probably been cured.

Another five percent of patients have indolent myeloma. These patients are asymptomatic, but do show changes typical of multiple myeloma—monoclonal globulin peaks above 4 gm/100 ml, marrow plasmacytosis, and occasionally lytic bone lesions. Diagnosis often follows detection of an elevated serum protein on routine chemical survey. Such patients have been followed without treatment provided that serial electrophoretic studies are obtained every two to three months. Treatment should be initiated when there is a clear upward trend in myeloma protein and calculated tumor mass. About one half of patients have shown such slow elevations in myeloma protein that chemotherapy has been deferred for more than two years. As is true for patients with indolent lymphoma, the delay in treatment has not af-

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fected the long-term outcome.[1] These patients are eligible for one of the various interferons now available.

Staging of Overt Multiple Myeloma

Clinical features that correlate with measured tumor mass and survival have been used to define a clinical staging system for multiple myeloma.[2] We have refined this system to make the staging of patients more quantitative and more relevant to the clinical outcome (Table 1). We recognize that factors other than tumor load may contribute to anemia and hypercalcemia. Less emphasis has been placed on defining the extent of lytic lesions or bone demineralization since this variable is excessively subjective and often leads to the overstaging of individual patients. The degree of marrow plasmacytosis, the level of serum beta$_2$ microglobulin, and the levels of normal immunoglobulins also contribute to a more consistent staging of individual patients.[3,4]

Approach to Treatment

Before chemotherapy is begun, optimal control of reversible medical complications, such as overt infection, is desirable. Treatment should not be delayed for hypercalcemia, particularly since the therapeutic regimen always includes corticosteroids. For patients with severe vertebral fracture pain, at least one course of chemotherapy is useful before local radiation therapy is considered, unless the radiation therapy is required for spinal cord compression.

The effectiveness of chemotherapy should be monitored with serial measurements of the serum myeloma protein concentration and/or Bence Jones protein excretion. The true degree of tumor reduction will be underestimated if consideration is not given to the changing catabolic rate for different IgG levels, the reduction of plasma volume with therapy, and the possible effect of normal background globulin in the calculation of tumor mass change.[5] When the data are corrected for these factors, a reduction in a monoclonal IgG peak from four to two gm/100 ml conforms more closely to a 75-percent reduction in tumor mass.

While low monoclonal IgG peaks are best assessed from the routine serum electrophoresis, low monoclonal IgA globulins are frequently obscured by normal globulins. For this reason, IgA peaks below 2,000 mg/100 ml should be evaluated serially from direct quantitations. All of these factors are considered in a simple computer program that includes the serum myeloma protein component, albumin, hemoglobin, and body weight. Data obtained in this way permit the calculation of monthly changes in tumor mass from an arbitrarily assigned value of 100 percent at the start of therapy. Serial changes in each patient's tumor mass can be plotted and, when viewed in the context of sequential therapies or no-treatment follow-up, serve as invaluable aids in the management of these patients.

About two thirds of relapsing patients and about one third of unresponsive patients achieved a 75-percent reduction in tumor mass from a vincristine-Adriamycin-dexamethasone combination.

For patients undergoing initial treatment at our institution, response is defined by a 75-percent reduction in calculated tumor mass and/or disappearance of Bence Jones protein. Less strict criteria, such as a 50-percent reduction, will result in a 20-percent higher response rate. For patients responding to combination therapies, such as vincristine-cyclophosphamide-Adriamycin-prednisone (VCAP), the onset of remission is usually rapid so that the tumor-halving time is less than four months (median 1.5 months). Thus, a stable serum peak during the first few months usually indicates that a remission will probably never occur. When Bence Jones protein is present, either as the only abnormality or in combination with a serum peak, con-

clusions can be reached even earlier. Within two months, Bence Jones protein excretion was reduced by 50 percent in all patients who achieved a 75-percent reduction in tumor mass as defined by changes in their serum peak.[6] The failure to reduce Bence Jones protein by 50 percent within this period identified resistant patients.

Therapeutic Choices

In 1969, the Southwest Oncology Group reported that four-day courses of melphalan and prednisone given at six-week intervals reduced myeloma tumor mass by 75 percent in about 45 percent of patients.[7] Since this development, progress in controlling the disease has been limited. The major drug combinations that have been evaluated include combinations of different alkylating agents with or without a nitrosourea compound, and combinations of an alkylating agent with Adriamycin and/or vincristine.

The most important predictor of prolonged survival is the occurrence of response; the pretreatment tumor mass is a secondary factor.

Following reports that patients with myeloma resistant to melphalan might respond to either cyclophosphamide or a nitrosourea, several treatment centers evaluated combinations of different alkylating agents with or without a nitrosourea, such as BCNU. However, combinations such as melphalan-cyclophosphamide-prednisone, or the same drugs plus BCNU, did not consistently improve the results in comparison with melphalan-prednisone.

In contrast, a favorable experience was reported with a combination of vincristine-melphalan-cyclophosphamide-BCNU-prednisone (the M-2 protocol) in a study at Memorial Sloan-Kettering Cancer Center.[8] Using a reduction of 50 percent in myeloma protein as the criterion for response, the authors concluded that 78 percent of 81 patients responded, compared with only 33 percent of 46 patients in a historical control group treated with either melphalan or melphalan-prednisone. The median survival for patients on the M-2 protocol was significantly longer (38 months) than the median survival of the control group (15 months).

Many questions have been raised about this trial. About 70 percent of the patients were designated as having high tumor mass, even though anemia and hypercalcemia occurred only half as frequently as at other centers, where about 40 percent of patients had high tumor mass. The apparent superiority of the M-2 protocol, when compared with other trials using similar drugs at different doses, is unexplained. Considering the conflicting results, no convincing and reproducible gain seems evident from combinations of different alkylating agents, with or without a nitrosourea.

When Adriamycin became available, the drug was evaluated in combination with other agents. No differences in response or survival were found from combinations of alkylating agents, Adriamycin, and prednisone compared with melphalan-prednisone alone. Slightly superior results were obtained, however, when more recent studies combined vincristine-Adriamycin-prednisone with either an alkylating agent or a nitrosourea.[9] Among 256 patients evaluated at our institution between 1974 and 1980, the response rate was 58 percent for patients who received combinations containing both vincristine and Adriamycin, compared with 42 percent for patients for whom one or both of these drugs were omitted.[9] The onset of remission occurred more rapidly among patients receiving the vincristine-Adriamycin combinations. Yet, the median survival time was similar at 30 months whether or not patients received vincristine and Adriamycin as part of the early treatment program.

Most patients resistant to melphalan-prednisone received Adriamycin-containing regimens later in their course, and many then achieved their first or second remission. These observations suggest that the outcome in patients without severe complications (for example, low tumor mass)

TABLE 1
TUMOR MASS STAGING OF MULTIPLE MYELOMA

High Tumor Mass—
One of the Following

Hemoglobin < 8.5 gm/100 ml without renal failure or hypoferremia

Calcium > 11.5 mg/100 ml* without bedridden status

Supporting Features Often Present:

Marrow plasmacytosis > 40 percent on flow cytometry or suspension smears in most patients

IgM < 20 mg/100 ml *or* IgA < 40 mg/100 ml *or* IgG < 400 mg/100 ml in about half the patients

Serum beta$_2$ microglobulin > 8.0 mg/liter without creatinine > 1.8 mg/100 ml in about half the patients

Low Tumor Mass—
All of the Following

Hemoglobin > 10.5 gm/100 ml, unless other factors causing anemia

+ Calcium < 11.0 mg/100 ml*

+ IgG or IgA peak < 5.0 gm/100 ml

+ Serum beta$_2$ microglobulin < 4.5 mg/liter

Supporting Features Often Present:

Marrow plasmacytosis < 20 percent on flow cytometry or suspension smears in most patients

IgM > 50 mg/100 ml *and* IgA > 100 mg/100 ml *and* IgG > 750 mg/100 ml in about half the patients

Intermediate Tumor Mass—
All Other Patients

*Corrected calcium (mg/100 ml) = serum calcium (mg/100 ml) − serum albumin (gm/100 ml) + 4.0.

may be the same when the initial treatment consists of melphalan-prednisone only, provided that vincristine-Adriamycin programs are always used later in the disease course. Unfortunately, many patients treated initially with melphalan-prednisone never receive Adriamycin later, when their disease is progressing. We favor the use of VCAP combinations as part of the initial treatment in all patients because of the higher response rate and the opportunity to stop or change therapy after the maximum tumor reduction.

Remission Maintenance

Early studies showed no advantage for maintenance therapy in patients who achieved a 75-percent reduction in tumor mass, in comparison with no treatment until relapse.[10] The median duration of unmaintained remission in more recent trials has been 14 months in those who achieved disappearance of their abnormal protein and six months in those with a persistent serum peak.[9] When relapse occurs in either group, about one half achieve a 50-percent reduction in tumor mass when therapy is resumed. In those who fail to respond by these criteria, myeloma protein either remains stable or rises slowly for many months. Thus, unmaintained remission follow-up seems appropriate for those responding patients in whom the myeloma protein has disappeared following 12 months of treatment (20 percent of the total patient population) or in whom a markedly reduced serum myeloma protein remains stable following 24 months of treatment (10 percent of the total patient population). This approach is not advisable for patients who have not responded with a reduction of 75 percent in tumor mass or for whom regular follow-up is not possible.

In previous studies, acute leukemia developed in about six percent of our responding patients treated indefinitely with alkylating agents.[11] With the elimination of procarbazine from our treatment program and the reduced use of melphalan, especially in patients followed on no therapy, this frequency has been reduced to about one to two percent in recent years.

Prognosis

No clinical features have consistently predicted response to chemotherapy. The frequency of response is similar for patients regardless of the initial tumor burden. Recently, flow cytometric measurements have indicated that patients with a high RNA content in plasma cells have a greater likelihood of response than those with a lower content.[3] The most important predictor of prolonged survival is the occurrence of response; the pretreatment tumor mass is a secondary factor. Table 2 demonstrates that longevity is determined primarily by the residual number of plasma cells after an optimal program of chemotherapy. For this reason, projections of prognosis in individual patients should be deferred until several months after the start of chemotherapy.

Resistant Multiple Myeloma

All patients who achieve remission eventually relapse if they do not die of another cause. Occasionally, the pattern of relapse may involve a rising Bence Jones protein or progressive bone lesions and soft tissue tumors even with no change in the myeloma protein level. Such occurrences often presage the development of a more aggressive disease course and may be associated with new clones apparent in flow cytometry studies. For this reason, patients in remission should be followed with periodic measurements of Bence Jones protein and bone films (lateral skull and anteroposterior pelvis) in addition to regular assessments of their abnormal globulin. The onset of relapse is followed by a median survival time of only nine months unless remission is achieved.

In the past, chemotherapy has not been very effective for patients with melphalan-resistant myeloma. Response rates were about 25 percent in patients treated with nitrosourea-Adriamycin combinations. Recent experience suggests a role for more intensive courses of glucocorticoids. Houwen et al reported responses in about 25 percent of patients with refractory myeloma who had received weekly courses of

TABLE 2
EFFECT OF TUMOR MASS AND RESPONSE ON SURVIVAL IN MULTIPLE MYELOMA
(Median Months of Survival)

	High	Intermediate	Low
All patients	22	31	45
Unresponsive*	8	15	28
Improved**	20	24	28
Responsive	32	45	58

Includes 189 patients treated with VCAP combinations from 1974 to 1981.

* < 50-percent reduction of tumor mass (excludes three percent of patients with early death within four weeks).

**50-75-percent reduction of tumor mass.

vindesine and prednisone.[12] In further trials at our institution, no patient responded to vindesine alone, but about one fourth achieved significant tumor reduction from frequent pulses of prednisone, either alone or in combination with vindesine. About one half of patients then responded when prednisone pulses were combined with vincristine and Adriamycin.[13]

These encouraging results prompted us to design a vincristine-Adriamycin-dexamethasone (VAD) regimen.[14] Dexamethasone was substituted for prednisone in a dose that provided a fourfold increase in glucocorticoid effect. Vincristine and Adriamycin were given over four days by continuous infusion to provide slowly cycling cells with prolonged exposure. About two thirds of relapsing patients and about one third of unresponsive patients achieved a 75-percent reduction in tumor mass. These results were superior to those described for any group of patients with myeloma refractory to alkylating agents.

When considered in the context of our previous experience with pulse prednisone, the results suggest that glucocorticoids provide a dose-dependent antitumor action. This finding has been overlooked for many years and should be exploited in all patients with myeloma, as well as in those with closely related lymphoma. Dexamethasone pulses alone have been especially useful in myeloma patients undergoing radiation therapy or in those severely thrombocytopenic from marked bone marrow infiltration. The future assessment of steroid receptors on plasma cells may identify those patients most likely to benefit.

New Directions

Several new approaches to the therapy of myeloma patients are currently under investigation. Based on the success of the VAD regimen for patients with refractory myeloma, higher doses of glucocorticoids should be included in the treatment of previously untreated patients. Studies are indicated that offer patients under the age of 55 in early relapse reinduction treatments with high doses of chemotherapy and au-

tologous bone marrow rescue.

Interferon has been studied extensively in clinical trials at this institution. About one fourth of previously untreated patients have achieved a 50-percent reduction in tumor mass with leukocyte interferon, either with an impure preparation from Finland or with a purified interferon prepared by recombinant DNA techniques. Only about 10 percent of patients resistant to melphalan have achieved a similar response. These results do not support a role for interferon as a single agent, but they offer promise that leukocyte or other interferons might improve the results in combination with other agents.

Hemibody irradiation as a consolidation treatment for patients in remission is under study at several institutions, but definitive results are not available. When the variables that affect remission time were controlled, no obvious gain resulted following the treatment of a small number of patients at our institution. Cisplatinum has been effective in one murine model of myeloma and warrants further investigation in patients with refractory disease. While recent trials with high-dose cytosine arabinoside or spirogermanium have not been encouraging, very high doses of melphalan have achieved some success in selected patients.[15] No consistent gain has resulted from the use of BCG or levamisole as part of an immunotherapy consolidation program.

Clinical research over the last 20 years has clarified the heterogeneity of disease features and the clinical course of patients with multiple myeloma. The physician must consider whether the patient needs any chemotherapy at all (e.g., localized or indolent myeloma), the choice of the initial therapy, the indications for no-treatment follow-up, the sequence of drug combinations for progressive disease, and then the application of selected new agents. Rigorous attention to the changing mass of the tumor from serial electrophoretic studies, the rational projection of outcome based on prognostic factors, and knowledge of improved therapies are all essential for optimal care.

References

1. Alexanian R: Localized and indolent myeloma. Blood 56:521–525, 1980.
2. Durie BGM, Salmon SE: A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 36:842–854, 1975.
3. Barlogie B, Alexanian R, Gehan E, et al: Marrow cytometry and prognosis in myeloma. J Clin Invest 72:853–861, 1983.
4. Scarffe JH, Anderson H, Palmer MK, et al: Prognostic significance of pretreatment serum beta$_2$ microglobulin levels in multiple myeloma. Eur J Cancer Clin Oncol 19:1361–1364, 1983.
5. Salmon SE: Immunoglobulin synthesis and tumor kinetics of multiple myeloma. Semin Hematol 10:135–144, 1973.
6. McLaughlin P, Alexanian R: Myeloma protein kinetics following chemotherapy. Blood 60:851–855, 1982.
7. Alexanian R, Haut A, Khan AU, et al: Treatment for multiple myeloma. Combination chemotherapy with different melphalan dose regimens. JAMA 208:1680–1685, 1969.
8. Lee BJ, Lake-Lewin D, Meyers JE: Intensive treatment of multiple myeloma, in Wiernik PH (ed): Controversies in Oncology. New York, John Wiley & Sons, 1982, pp 61–79.
9. Alexanian R, Dreicer R: Chemotherapy for multiple myeloma. Cancer 53:583–588, 1984.
10. Alexanian R, Gehan E, Haut A, et al: Unmaintained remissions in multiple myeloma. Blood 51:1005–1011, 1978.
11. Gonzalez F, Trujillo JM, Alexanian R: Acute leukemia in multiple myeloma. Ann Intern Med 86:440–443, 1977.
12. Houwen B, Ockhuizen T, Marrink J, et al: Vindesine therapy in melphalan-resistant multiple myeloma. Eur J Cancer 17:227–231, 1981.
13. Alexanian R, Yap BS, Bodey GP: Prednisone pulse therapy for refractory myeloma. Blood 62:572–577, 1983.
14. Barlogie B, Smith L, Alexanian R: Effective treatment of advanced multiple myeloma refractory to alkylating agents. N Engl J Med 310:1353–1356, 1984.
15. McElwain TJ, Powles RL: High-dose intravenous melphalan for plasma-cell leukaemia and myeloma. Lancet 2:822–824, 1983.