Localized and Indolent Myeloma

By Raymond Alexanian

Criteria were defined for recognizing 29 patients with a localized plasmacytoma of bone and 20 patients with an indolent variety of multiple myeloma in order to justify long-term follow-up without chemotherapy. All patients with indolent myeloma were asymptomatic from their low tumor mass disease, had a hemoglobin greater than 10 g/dl, and showed no more than 3 lytic bone lesions. The presence of more than 200 mg/day of Bence Jones protein was usually followed by disease progression within 2 yr. Serial assessments of myeloma protein level provided a useful index of changing tumor load and the need for chemotherapy. In patients with localized disease, radiotherapy usually reduced myeloma proteins markedly with subsequent disease control for many years, even though small serum peaks persisted. Chemotherapy for multiple myeloma was not required for a median of 8 yr in patients presenting with localized disease and of 3 yr in those with indolent myeloma. The additional survival from the start of drug treatment was similar to that of comparable patients treated promptly for overt multiple myeloma. The delay of chemotherapy until evidence of tumor progression did not affect the long-term outcome of patients with localized or indolent myeloma.

Most patients with multiple myeloma are symptomatic, show evidence of generalized disease, and require chemotherapy promptly in order to reduce the number of malignant plasma cells. In recent years, many patients without any symptoms attributable to myeloma have been diagnosed during screening tests for unrelated disorders. Other patients have local symptoms from a single plasmacytoma that usually responds well to radiotherapy for prolonged time periods. In both groups, chemotherapy for multiple myeloma can be withheld for many months or years. This report summarizes an experience with 49 patients with localized or indolent myeloma who were followed without drug therapy until there was evidence of progressive multiple myeloma. Careful disease staging at the time of diagnosis was essential in order to identify those patients who were most likely to experience prolonged clinical stability.

Methods

The records of 555 consecutive previously untreated patients with myeloma who had been referred to the University of Texas M.D. Anderson Hospital from 1965 to 1979 were evaluated. Each was assigned to one of the diagnostic categories listed in Table 1. All had evidence of plasmacytosis to more than 15% of the cellularity either in bone marrow aspirates or on tissue biopsy specimens. Ninety-one percent had overt multiple myeloma with typical clinical features and received chemotherapy with various alkylating-agent-prednisone combinations according to specific treatment protocols.2,3 Twenty-nine patients were considered to have a solitary plasmacytoma of bone with only one symptomatic area of bone destruction without evidence of bone destruction or bone marrow plasmacytosis elsewhere; all patients received at least 4000 rad of radiotherapy to the known area of disease. None received chemotherapy unless myeloma globulin levels were rising or there was an unequivocal increase in the size and/or number of lytic bone lesions.

Twenty patients were considered to have an indolent form of multiple myeloma. All were asymptomatic, had bone marrow plasmacytosis, and either a monoclonal IgG peak greater than 2.5 g/dl or an IgA peak greater than 1.0 g/dl. Most showed marked depression of normal serum immunoglobulins. By definition, none had hypercalcemia, a hemoglobin less than 10 g/dl, painful vertebral compression fractures, more than 3 lytic bone lesions, or recurrent infections that would have qualified them for chemotherapy. The diagnosis was usually established after a coincidental multichemical scan of serum revealed an elevated total protein shown by electrophoresis to be due to an abnormal globulin peak; in five patients, mild anemia was the first abnormality detected. All patients were followed without chemotherapy until the abnormal globulin level rose by at least 50%. The criteria for the diagnosis of indolent myeloma were developed gradually and then applied retrospectively. Initially, chemotherapy was withheld from all asymptomatic patients who might have qualified for an indolent course. When it became apparent that early morbidity from progressive disease developed in those with painful compression fractures, anemia, or more than 3 lytic bone lesions, the presence of any of these features indicated the need for chemotherapy in subsequent patients. Thus, a decision to treat a patient immediately with chemotherapy was never arbitrary and was not used as an unaided criterion for distinguishing indolent (untreated) from overt (treated) myeloma.

Changes in the serum globulin concentration were measured serially in all patients. Variations in myeloma tumor mass were calculated from changes in serum myeloma protein production rate using techniques described previously.2,4 In patients with small monoclonal peaks less than 2.0 g/dl, the myeloma globulin level was calculated after subtracting the amount of normal gamma globulin at the base of each monoclonal component included in the densitometer measurement.4 The clinical response to the radiotherapy or to subsequent chemotherapy was defined by a 75% reduction in serum myeloma protein production rate. Survival curves were calculated by the life-table technique both from diagnosis and from the start of chemotherapy; statistical differences were compared by a generalized Wilcoxon test.

Results

The major clinical features of patients with localized or indolent myeloma are summarized in Table 1. The median time between the first suspicion of a plasma cell dyscrasia and the evaluation at this hospit...
of those with disease (52% have required chemotherapy myeloma). Seventy-two percent of the patients in the indolent myeloma group were male in contrast to 85% of the localized myeloma patients. Seventy-two percent with localized myeloma had either hypercalcemia (>10.5 mg/dl) or azotemia (BUN > 30 mg/dl). None of the patients with localized or indolent myeloma had either hypercalcemia (>10.5 mg/dl) or azotemia (BUN > 30 mg/dl).

The frequency of the different monoclonal immunoglobulin types was evaluated in each patient group. Among the 20 patients with indolent myeloma, bone surveys revealed 1-3 lytic lesions in 3 and mild demineralization in 5 other patients. Using the criteria of Durie and Salmon, all patients with indolent myeloma were in a low tumor mass category.

Changes in the myeloma tumor mass were evaluated serially from the myeloma protein production rate and other serum markers in all patients with an abnormal serum component. Figure 1 and Table 2 distinguish two groups of patients with indolent myeloma, seven of whom showed progressive increments in tumor mass and the need for early chemotherapy within 1 yr. In retrospect, these patients were misjudged as indolent despite their initial asymptomatic status and benign clinical features. The remaining 13 patients showed very slow elevations in myeloma protein and usually did not require chemotherapy for at least 2 yr. A stable long-term course was usually recognized when unchanging serum myeloma protein concentrations persisted for at least 12 mo. All three patients with a serum monoclonal peak and excessive Bence Jones protein (0.2–1.4 g/day) doubled their myeloma

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<th>Table 1: Clinical Features of Patients With Different Variants of Myeloma*</th>
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*Each value shows percent of total unless indicated otherwise.
†Thirteen patients with localized plasmacytoma and 15 with indolent myeloma have required chemotherapy for disease progression.

The median of patients with localized disease (52 yr) was 8 yr less than that of patients with overt myeloma. Seventy-two percent of the patients with localized myeloma were male in contrast to 53% of those with overt myeloma (p = 0.07); the initial site of a localized tumor was in a vertebra, the skull, the sternum, or a scapula in more than 85% of the patients. None had a hemoglobin value of less than 13 g/dl, in comparison with 60% of those with indolent myeloma and 87% of the patients with overt myeloma. None of the patients with localized or indolent myeloma had either hypercalcemia (>10.5 mg/dl) or azotemia (BUN > 30 mg/dl).

The frequency of the different monoclonal immunoglobulin types was evaluated in each patient group (Table 1). All but 2 of the 20 patients with indolent myeloma had an IgG monoclonal peak, the median level being 3.7 g/dl; in contrast, the median value for IgG peaks in patients with overt myeloma was 5.5 g/dl. Only 3 of the 20 patients with indolent myeloma and a serum peak excreted more than 200 mg/day of Bence Jones protein, in comparison with about 45% of the patients with overt myeloma and none of the patients with a localized plasmacytoma. About one-half of the patients with a localized plasmacytoma did not have a myeloma protein in either serum or urine. Even when present, the monoclonal protein was usually of IgG type and was always 1.6 g/dl or less; 2 patients had only light chain excretion of an amount less than 500 mg/day. Of 8 patients without an abnormal protein at diagnosis of their solitary tumor who later developed generalized disease, monoclonal globulins became evident in 5 (only light chains in 3 and IgG peaks in 2). Normal IgM and IgA serum immunoglobulin levels were usually preserved in patients with a localized plasmacytoma; in contrast, marked depressions were usually present in generalized myeloma (Table 1). Among the 20 patients with indolent myeloma, bone surveys revealed 1-3 lytic lesions in 3 and mild demineralization in 5 other patients. Using the criteria of Durie and Salmon, all patients with indolent myeloma were in a low tumor mass category.

Changes in the myeloma tumor mass were evaluated serially from the myeloma protein production rate in all patients with an abnormal serum component. Figure 1 and Table 2 distinguish two groups of patients with indolent myeloma, seven of whom showed progressive increments in tumor mass and the need for early chemotherapy within 1 yr. In retrospect, these patients were misjudged as indolent despite their initial asymptomatic status and benign clinical features. The remaining 13 patients showed very slow elevations in myeloma protein and usually did not require chemotherapy for at least 2 yr. A stable long-term course was usually recognized when unchanging serum myeloma protein concentrations persisted for at least 12 mo. All three patients with a serum monoclonal peak and excessive Bence Jones protein (0.2–1.4 g/day) doubled their myeloma
protein production within 2 yr. The median duration between diagnosis and the institution of chemotherapy was 28 mo for patients presenting with indolent myeloma; following the start of chemotherapy, the median survival time was 36 mo (Fig. 2).

The effect of radiotherapy was evaluated in 14 patients with localized plasmacytoma and a serum monoclonal component. In all but 2, the reduction of myeloma protein production exceeded 75%. The abnormal peak disappeared from the electrophoretic strip in 6 patients and persisted at very low levels in 6 other patients (Fig. 3); less than a 50% reduction occurred in 2 patients who have now remained stable for more than 2 yr. Light chain excretion disappeared from the urine in 1 of the 2 patients with this abnormality. Fewer than one-half of the patients have required chemotherapy for multiple myeloma, with 5 patients still in normal health after more than 10 yr. No patient with electrophoretic and radiographic stability for more than 8 yr has yet developed multiple myeloma. The median interval between the diagnosis of a localized plasmacytoma and the start of chemotherapy for multiple myeloma was 95 mo; following the start of chemotherapy, the median survival was 44 mo (Fig. 2). The survival times from diagnosis differed markedly among the diagnostic groups (p < 0.001) (Fig. 2); survival from the start of chemotherapy was more similar, being longer for patients who had presented with a localized or indolent myeloma than for those treated for overt disease (p < 0.05).

The sensitivity of the myeloma to combination therapy with alkylating-agent–prednisone combinations was evaluated in 28 patients who had presented initially with localized or indolent disease. Seven of 13 patients with progression from a localized plasmacytoma and 5 of 15 with previous indolent disease responded in terms of a 75% reduction of myeloma protein production rate. These response rates were similar to the 57% incidence of response in patients with overt myeloma who were treated soon after diagnosis.1-3

**DISCUSSION**

Most patients with multiple myeloma have symptoms due to serious disease complications, such as...
pathologic fractures, severe anemia, or hypercalcemia. In about 5% of those referred to the M.D. Anderson Hospital, only a single area of bone destruction was evident, and the patient was considered to have a localized plasmacytoma; in another 4%, typical changes of multiple myeloma were recognized, although there were no symptoms. These frequencies may have been exaggerated by the referral of atypical patients to a major treatment center. The similarly short time interval between the suspicion of a plasma cell dyscrasia and the referral of patients in each stage did not support a selection of patients with previously diagnosed but stable disease. This report indicates that most properly staged patients with localized or indolent myeloma remain stable for a long time without chemotherapy.

Specific criteria were used to distinguish patients with localized or indolent myeloma from those with overt myeloma who required chemotherapy promptly. Patients with localized plasmacytoma had only one area of bone destruction with no evidence of other lytic lesions or bone marrow plasmacytosis; anemia, hypercalcemia, and azotemia were absent. Only one-half of the patients showed evidence of a monoclonal globulin in the serum or urine, in contrast to 96% of the patients with multiple myeloma; even when present, IgG or IgA protein peaks were always less than 1.6 g/dl and the amount of Bence Jones protein was less than 500 mg/day. These quantitative aspects have not been emphasized before and were valuable guides in confirming the localized stage of the myeloma. Presumably, the low or absent myeloma protein values resulted from the much lower plasma cell burden in patients with localized disease, calculated at about 5% of that present in patients with generalized myeloma. Normal immunoglobulin concentrations were also preserved in contrast to the low values usually present in multiple myeloma, contributing an additional criterion for the identification of patients with localized disease. The younger age of these patients has been reported previously and was attributed to the earlier and fortuitous occurrence of most of the low tumor burden in a single bone that then fractured. The predominance of males and the long survival time for most patients with a localized plasmacytoma have been described by others.

All patients with a localized plasmacytoma of bone received radiotherapy to the involved lesion and were then followed without further treatment. Most showed a marked reduction of any myeloma protein production that had been present, confirming the radiosensitivity of the lesions and the likelihood that most of the initial tumor was encompassed within the radiotherapy treatment field. In several patients, a maximum reduction of myeloma protein did not occur for several years after completion of the radiotherapy, suggesting that some of the primordial cells may have survived and/or replicated for many generations. Thus, the response to radiotherapy provided further evidence for the presence of a single tumor mass.

About 20% of the patients with localized myeloma showed evidence of multiple myeloma within the first year after diagnosis. In retrospect, these patients had probably been understaged during an early phase of proliferating multiple myeloma. In most patients, overt multiple myeloma did not develop for many years, the median time being 8 yr before the evolution of generalized disease. Serial electrophoretic studies were useful in confirming tumor progression, since the appearance or elevation of monoclonal globulins and the progressive decline of normal immunoglobulins correlated well with the development of new bone lesions and bone marrow plasmacytosis. Conversely, some patients experienced long-term clinical stability without further treatment even though small myeloma protein peaks persisted at a low and constant level. No explanation was available on the prolonged viability of a nonproliferating cell population in some patients who had presented with a major area of bone destruction due to the same tumor clone.

Multiple myeloma was diagnosed in an asymptomatic indolent phase in 20 patients. The criteria for classification also required that none had recurrent infection, painful compression fractures, or more than 3 lytic bone lesions. In essence, these patients had a low tumor mass myeloma that was recognized mainly because of unanticipated laboratory abnormalities, such as large monoclonal peaks or mild anemia. Since asymptomatic patients with higher tumor mass grades (i.e., stages II and III of Durie and Salmon) are even less common with disease morbidity that is even more imminent, chemotherapy should not be withheld in those rare asymptomatic patients with intermediate or high tumor mass disease. Also, the presence of an IgA myeloma protein or the excretion of more than 200 mg/day of Bence Jones protein favored the need for early chemotherapy. No other features were identified that predicted whether early tumor growth was likely. Of considerable importance was that patients with progressive disease were clearly distinguished from those likely to have a stable, long-term course by serial electrophoretic studies during the first year of follow-up.

This report demonstrates that some patients will present with generalized multiple myeloma and remain completely asymptomatic for several years. Of the patients considered to have indolent myeloma, most eventually required chemotherapy for progres-
sive disease, with a median time to therapy of about 3 yr for those without Bence Jones protein. When treatment was required, the response rate was similar to that of patients treated at the start for symptomatic multiple myeloma. The 3-yr median survival after the start of therapy was also similar to that found in patients treated for low tumor mass myeloma.\textsuperscript{7,11} Thus, the deferral of initial chemotherapy did not affect the long-term outcome. As long as periodic follow-up was possible and the long-term gains from withholding chemotherapy outweighed the potential risks from disease or treatment morbidity, such patients should be identified and followed without treatment. Nevertheless, major errors in patient management are possible by assuming that all asymptomatic patients have indolent disease, as well as in concluding that all patients with myeloma require prompt chemotherapy.

About 2% of patients with multiple myeloma die from acute leukemia, a complication that occurs in about 6% of responding patients living longer than 2 yr.\textsuperscript{12} Most investigators have implicated the alkylating agent treatment as a major factor in the pathogenesis of acute leukemia.\textsuperscript{12,14} Certain patient groups have now been identified where long-term follow-up without chemotherapy seems justified. These include responding patients with disappearance of myeloma proteins\textsuperscript{15} and selected asymptomatic patients in stable phases of multiple myeloma.

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**REFERENCES**

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