Curability of Solitary Bone Plasmacytoma

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Purpose: **The effects of involved-field radiotherapy were assessed in patients with a solitary plasmacytoma of bone (SBP).**

Patients and Methods: **Forty-five consecutive patients with an SBP received megavoltage irradiation of at least 3,000 cGy. The median age was 53 years, 67% of patients showed a myeloma protein, and uninvolved immunoglobulins (Igs) were preserved in 93% of patients.**

Results: **Permanent control of presenting disease was achieved in all but two patients, but 46% of patients developed multiple myeloma. When it occurred, progression of myeloma occurred within 3 years in two thirds of the patients, suggesting that the extent of disease was understaged at diagnosis. Myeloma protein disappeared in nine patients (30%) whose disease has not yet recurred. The median survival for all patients was 13 years and the myeloma-specific survival fraction at 10 years was 53%.**

Conclusion: **In patients with an SBP, the disappearance of myeloma protein with involved-field radiotherapy predicted long-term disease-free survival and possible cure. Nonsecretory disease and persistent myeloma protein after treatment were adverse prognostic factors for which adjuvant therapy with interferon alfa should be considered.**

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A SOLITARY BONE plasmacytoma (SBP) represents the only disease feature in approximately 5% of patients with myeloma. Although local radiotherapy has usually been effective for the primary lesion, most patients have developed multiple myeloma. Thus, SBPs have been considered a manifestation of systemic disease and, therefore, incurable.[1-3] However, most series contained small numbers of patients, and criteria for identifying solitary disease varied. Some investigators included patients with more than one lesion, others included patients with high levels of myeloma protein, and some excluded patients whose disease progressed within 2 years or whose abnormal protein persisted after radiotherapy.[2,4,5] Thus, long-term results after treatment have varied significantly, and the potential for cure has remained uncertain.

This report summarizes our experience with 45 consecutive patients with a diagnosis of SBP that was established by strict criteria and who received a consistent program of intensive radiotherapy only. Chemotherapy was withheld until there was evidence of generalized disease. Results indicated a freedom-from-relapse rate of 42% at 10 years, suggesting that many patients may have been cured.

PATIENTS AND METHODS

Among 956 consecutive, previously untreated patients with histologically confirmed plasma-cell myeloma who were referred between 1966 and 1991, 45 (5%) had an SPB. After pathologic confirmation, evaluations included bone marrow aspirate, skeletal survey, and electrophoretic studies of serum and urine concentrates, including immunoelectrophoresis, immunofixation, and immunoglobulin (Ig) quantitations as such laboratory procedures became available.

Clinical Features

All patients with SPB had only one area of bone destruction, and mature plasma cells accounted for less than 5% of the cells in marrow aspirates. There were 31 males (69%), the median age was 53 years, (range, 29 to 77 years), and three patients were black. The most common disease site was a vertebra (15 patients, 33%); less frequently involved sites included the pelvis (six patients), a rib (seven patients), a scapula (five patients), and the skull (five patients). Serum myeloma protein was detected in 26 patients (range, 0.1 to 2.2 g/dL), and none of these patients showed additional Bence Jones protein. Bence Jones protein only was present in the urine of four patients (range, 0.02 to 0.7 g/d). Thirty-three percent of all patients did not have a myeloma protein, and 93% of all patients showed preservation of uninvolved Igs (IgM, > 50 mg/dL; IgA, > 95 mg/dL; and IgG, > 700 mg/dL), frequencies that were much higher than those found in patients with multiple myeloma.

Treatment

All patients were treated definitively with megavoltage irradiation. Thirty-one patients were treated at our center, and 14 were treated at other institutions according to our recommendations. The radiotherapy fields were designed to encompass all gross disease with generous margins of normal tissue. In 41 patients, treatment was delivered at a rate of 200 cGy per fraction, per 5-day week. Thirty-one of these patients received tumor doses ≥ 4,500 cGy. Radiation doses to the spinal cord did not exceed 4,000 cGy. No patient received less than 3,000 cGy; the three patients who received only 3,000 cGy were treated at a rate of 300 cGy per fraction (Table 1).

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Table 1. Relation of Radiotherapy Dose to Clinical Outcome

Dose (cGy)	Total	Myeloma Protein: No. of Patients	Myeloma Protein: Disappearance (%)	Current Status: Multiple Myeloma	Current Status: Remission ≤ 10 Years	Current Status: Remission > 10 Years
3,000-4,500	18*	10	10	12	3	3
4,600-5,500	18	13	38	8	7	3
> 5,500	9	7	45	3	2	4
Total	45	30	30	23	12	10

*Local control was not achieved in two patients.

Assessments After Treatment

When present, levels of myeloma protein were measured serially during and after treatment to identify those patients whose abnormal globulin disappeared on immunoelectrophoresis or immunofixation. Thereafter, all patients were monitored for the occurrence of bone marrow plasmacytosis, new lytic bone lesions, or progressive elevation of monoclonal globulins. Patients who developed multiple myeloma were treated on specific chemotherapy regimens in accordance with ongoing randomized trials.[6] Criteria for response to chemotherapy were a ≥ 75% reduction of serum myeloma protein production and the disappearance of Bence Jones protein from the urine. Survival curves were calculated by the life-table technique from both radiotherapy for the SPB and chemotherapy for the generalized disease; statistical differences were assessed by a Wilcoxon test.[7]

RESULTS

Local Disease Control

Permanent control of disease was achieved at the presenting sites of involvement in 43 of 45 patients. One patient showed early recurrence of a thoracic spine plasmacytoma after treatment with 4,000 cGy, and the other had a persistent sacrum mass after treatment with 4,500 cGy. The myeloma protein, present in 30 patients at diagnosis, disappeared in nine with radiotherapy (30%). None of the nine patients had a serum myeloma protein level of more than 1.0 g/dL or Bence Jones protein of more than 0.7 g/d (Table 2). Reduction of abnormal protein level was rapid, with the longest time interval to disappearance being 9 months. Of the 21 patients who had a persistent myeloma protein, the level was reduced by at least 75% in six patients.

Table 2. Correlation of Myeloma Protein Level With Outcome After Radiotherapy

Protein Level	Total	Disappearance of Myeloma Protein	Current Status: Multiple Myeloma	Current Status: Remission ≤ 10 Years	Current Status: Remission > 10 Years
Serum myeloma protein (g/dL)					
None	15	—	10	3	2
0.1-1.0	17	7*	7	5	5
1.1-2.2	9	0*	5	3	1
Only Bence Jones protein (g/d)					
0.02-0.7	4	2	1	1	2
Total	45	9	23	12	10

*$P = .02$.

Evolution of Multiple Myeloma

To date, 23 patients have developed multiple myeloma. Linear trend analyses indicated that there was no clear relation between the dose of local radiotherapy and the likelihood of long-term stability or the onset of multiple myeloma (Table 1). Among the patients who developed multiple myeloma, the median time to progression was 20 months. Sixty-eight percent of initial relapses occurred within 3 years, and only two relapses (9%) developed after 7 years. Earlier relapse was often associated with rapid tumor growth (myeloma protein doubling time, < 4 months) whereas relapse after 3 years was associated with slower tumor growth. In some patients, the evolution of multiple myeloma was so slow that the only abnormalities were new bone lesions without intervening marrow plasmacytosis or an abnormal protein. Moreover, the response rate when multiple myeloma developed was high (80%), and the subsequent survival time was long (median, 63 months). The presence, persistence, and disappearance of myeloma protein after treatment were important indicators of remission time. Myeloma protein persisted in all patients with a serum level greater than 1.0 g/dL, and most have had progression of their disease (Table 2). All nine patients who presented with myeloma protein that disappeared have remained free of disease; in contrast, 64% of patients with either persistent myeloma protein or nonsecretory disease have developed multiple myeloma ($P < .01$; Fig 1). Neither patient age nor site of presenting disease influenced the occurrence of multiple myeloma.

When SPB patients with a myeloma protein evolved to multiple myeloma, the monoclonal Ig type remained the same. Of 10 patients with nonsecretory SBP who developed multiple myeloma, the disease remained nonsecretory in only three. A monoclonal IgG appeared in the serum of two patients, and Bence Jones protein appeared in the urine of five patients.

Survival

Of the 45 patients, 26 remain alive. Of the 19 who died, 11 succumbed to multiple myeloma and eight died of other causes, three of the latter after at least 15 years. To date, 10 patients are free of disease for more than 10 years and 12 others remain in remission for less than 10 years.

The median survival time for all patients was 13 years. Figure 1 compares the actuarial survival time with the

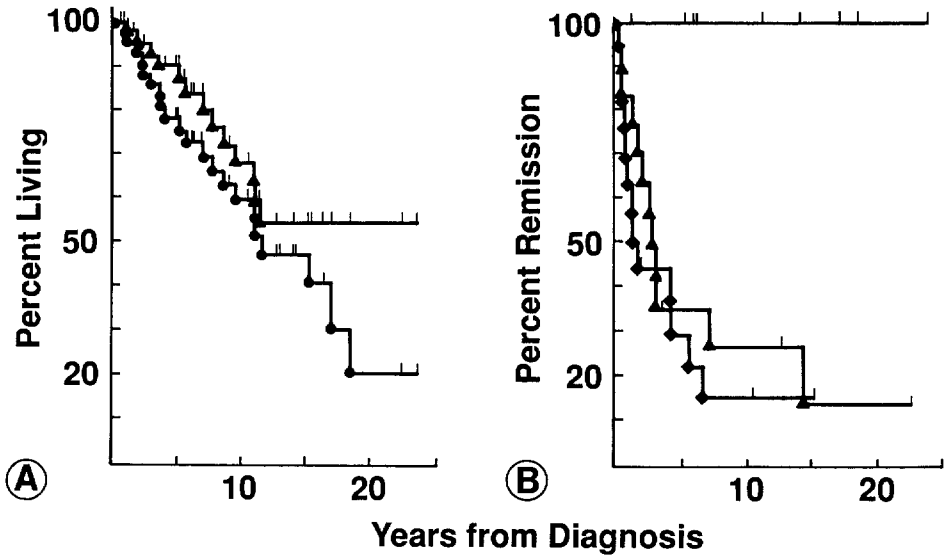

Fig 1. (A) Overall (●) or myeloma-specific (▲) survival from radiotherapy with 8 patients who died of other causes while in remission removed from the population at risk. (B) Remission time from radiotherapy for 3 categories of patients: those with a myeloma protein that disappeared with treatment (—), those with persistent protein (▲), and those with nonsecretory disease (◆).

survival time when deaths due to unrelated disease were censored. Cause-specific survival removes intercurrent deaths from the survival data and focuses on the impact of myeloma.

After 10 years, 42% of all patients have remained in remission, with only one patient developing multiple myeloma after 10 years. Remission rates were correlated with the myeloma protein status after radiotherapy (Fig 1). All nine patients who presented with a myeloma protein that disappeared with treatment remain in remission. However, only 15% of patients whose myeloma protein did not disappear or who presented with nonsecretory disease have remained in remission for longer than 10 years.

DISCUSSION

In most published series, the median age of patients with an SBP has been approximately 7 to 10 years less than that of patients with multiple myeloma.[1-3,8,9] This feature and the long-term control after radiotherapy in some patients with SBP suggested that multiple myeloma may evolve from a single lesion. Such focal lesions appear to have a greater tendency to expand locally rather than to disseminate, a property that may be regulated by specific cytokines. Thus, about 5% of our patients who had been referred with myeloma were found to have an SBP recognized after the early and fortuitous fracture of their primary lesion.

Intensive radiotherapy achieved local control of an SBP in 43 of 45 patients, 42% of all patients then remaining in a durable long-term remission. Consistent with the studies reported by Mill and Griffith,[10] we observed a clear relation between local control, disappearance of myeloma protein, and prolonged remission. This correlation was not observed by others who used less intensive radiotherapy.[8,11] In most series, only about 15% of patients have remained free of disease for more than 10 years.[2,3,11] However, our results and those reported by Frassica et al[8] are much more encouraging. Better results for some studies may be due both to a more rigorous initial staging of patients for generalized disease and the more consistent application of intensive radiotherapy to ensure local control.

The persistence of myeloma protein after radiation can serve to identify patients who are at high risk of early progression. However, approximately 15% of our patients with persistent myeloma protein have remained free of disease for more than 10 years. Thus, the disease in such patients reverted to a stable phase similar to that of a previous benign gammopathy that may have preceded the SBP.[12] Conceivably, the SBP in these patients resulted from the proliferation of an aggressive subclone that was destroyed with radiotherapy.

Multiple myeloma was recognized within 7 years in 21 of the 24 patients whose disease had disseminated. Others have reported significantly different time intervals to progression.[3,12,13] The reasons for these variations are not clear but may be due to differences in criteria for defining SBP. All of our patients had only one bone lesion, less than 5% plasma cells in bone marrow, and received intensive radiotherapy to the involved region. Adjuvant chemotherapy was not used except for progression, and all patients were included in the analysis despite the early evolution of multiple myeloma in some. Presumably, most patients who developed early progression had occult generalized disease that was not recog-

nized by standard techniques at diagnosis. We project that institutional differences in the time to progression will narrow with the routine use of newer, more sensitive procedures. During the past 4 years, we have added magnetic resonance imaging and computed tomography studies of the thoracic and lumbar spine to our staging procedures. This has demonstrated unequivocal intramedullary disease in four patients who would otherwise have been included in this study.

The depression of uninvolved Ig levels was rare among our patients with SBP, indicating that preserved values would be a useful criterion for correct staging. The diagnosis of SBP is also unlikely when myeloma protein levels exceed the highest values measured in this and other similar studies.[8] A myeloma protein was not detected in one third of our patients at presentation, a finding consistent with very low tumor load. However, most of these patients developed an abnormal protein with progressive disease. For patients who present without myeloma protein, routine immunoperoxidase or immunofluorescent studies of tissue biopsies should be performed to identify the type of myeloma protein produced and to allow a more focused search for low levels of monoclonal Ig in blood and urine at early phases of progression. Finally, preliminary results suggest that a more vigorous search for monoclonal plasma cells in the bone marrow by flow cytometry and other techniques should aid in identifying more patients with multiple myeloma.[14]

The median survival of 13 years for our patients was similar to that of other series.[2,3,8,9] In addition to a significant number of long-term remissions and possible cures, this encouraging outcome was also attributed to an indolent course with good response to chemotherapy for most patients who developed multiple myeloma. In reflecting on the options for future improvement, there are two populations of SBP to consider. Adjuvant therapy would be of no value for patients who present with a myeloma protein that disappears with radiotherapy because such patients have a high likelihood of long-term stability. In contrast, adjuvant therapy could be useful for patients with either persistent myeloma protein or nonsecretory disease who are at high risk for developing multiple myeloma. As adjuvant chemotherapy has not prevented the development of multiple myeloma[11,13,15] and may cause a treatment-related leukemia,[16] alkylating agents should be avoided. Interferon alfa has shown clinical activity in newly diagnosed disease[17] and may prolong remission time.[18] This agent seems worthy of study in selected patients who are most likely to progress after radiotherapy for SBP.

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