Solid Tumors in Multiple Myeloma

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The frequency of solid tumors was evaluated in 628 consecutive patients with multiple myeloma who had been treated with various melphalan-prednisone combinations. Among those patients who lived at least 2 months, the incidence and diversity of second tumors were similar to those in normal persons of the same age and duration at risk. The diagnosis was usually made within 2 years after the start of chemotherapy for the myeloma. Long-term melphalan therapy did not seem to contribute to the pathogenesis of second solid tumors in patients with multiple myeloma.

CONSIDERABLE ATTENTION has been focused on the occurrence of second malignancies in patients receiving alkylating agents for multiple myeloma (1-4). Numerous patients treated with melphalan have developed acute leukemia (1, 2), with an incidence more than 100 times that predicted for age-matched normal persons (5). Most investigators have implicated the carcinogenic properties of alkylating agents as the major cause (1, 2, 5). Patients with myeloma have also been described who developed additional solid tumors (3, 4, 6-9), but the frequency has been disputed (6, 8), and the relation to antineoplastic agents was unclear. To define the role of chemotherapy in the pathogenesis of solid tumors, we evaluated the frequency of cancers other than leukemia in a large number of patients with myeloma treated with various melphalan-prednisone combinations. In contrast to the very high incidence of acute leukemia (5), the frequency of solid tumors was similar to that found in age-matched normal persons.

Materials and Methods

The records of 628 consecutive patients with multiple myeloma treated at six Southwest Oncology Group institutions were evaluated for second malignancies. The age and sex characteristics of this study group were similar to those of patients in a population-based tumor registry (FLANNERY JT: Personal communication on the occurrence of multiple myeloma from 1965 through 1974 from the Connecticut Tumor Registry). All patients received intermittent courses of melphalan and prednisone, with or without added procarbazine, cyclophosphamide, carmustine (BCNU), or doxorubicin (Adriamycin®) according to specific treatment protocols (10, 11). Treatment courses were started between September 1965 and September 1974, and all patients were followed until November 1977, by which time more than 80% had died. Palliative radiotherapy to symptomatic bone lesions was also given when indicated.

Histologic confirmation of an additional cancer was present in all but three of the 19 patients found to have a solid tumor. In these three patients, the laboratory evidence for a second cancer was considered unequivocal; one had bronchogenic carcinoma, a second prostatic carcinoma, and a third colonic carcinoma. Five patients were also included in whom there was autopsy evidence of a second cancer, of whom three also had clear signs during life of an additional cancer. Two groups of patients were excluded from the analysis because their solid tumors were recognized before or concurrently with their myeloma. The first group consisted of nine patients with tumors recognized more than 2 months before the diagnosis of myeloma; a second group included seven patients in whom another cancer was recognized within 2 months of the diagnosis of myeloma. Because the major purpose of this study was to evaluate the role of melphalan-prednisone chemotherapy on the pathogenesis of second cancers, these patients were excluded from the analysis.

The patient-years-at-risk technique described by Watson (12) was used to evaluate the frequency of second cancers in our patient population. For the whole group and for patients in each age decade, the number of patients with a solid tumor was defined as a percentage of the total number of patient-years of observation of multiple myeloma. These frequencies of cancer in our patients with myeloma were compared with the rates reported in normal subjects of the same age by the Connecticut Tumor Registry. In addition, the predicted and observed numbers of patients were compared for four different cancers that were expected to effect at least one patient. All comparisons were made using the chi-square technique after assuming that the infrequent cancers appeared during the period of observation according to a Poisson distribution.

Results

Among the 628 patients with multiple myeloma, 595 lived for at least 2 months and could be evaluated for an oncogenic risk from melphalan. Nineteen patients developed a solid tumor at least 2 months after the start of chemotherapy (Table 1) for an overall frequency of 3.2%. The clinical features of all 595 myeloma patients at risk were similar in terms of age, race, protein type, response rate, and median survival time to those of 19 patients who developed a second cancer ($P > 0.2$). However, 16 of the 19 patients with cancer were male (84%) compared with 58% of the total population ($P < 0.05$).

For each 100 patient-years of life among patients with myeloma, the mean number of solid tumors was 1.5. This figure was similar to the predicted annual incidence of cancer among age-matched normal persons in Connecticut (1%). The frequencies at each age decade were also similar to the incidences reported in normal persons ($P > 0.2$). For each of four anatomic regions in which at least one patient was expected to develop cancer and in which at least one patient was observed to have developed cancer, the number of patients observed was similar to that predicted ($P > 0.4$); this applied to carcinomas of the breast, colon, lung, and prostate (Table 2). One patient had Kaposi's sarcoma, and none developed chronic leukemia or lymphoma.

The intervals between the treatment for multiple myeloma and the diagnosis of the solid tumor were evaluated (Table 1). Seventy percent of the second tumors were recognized within the first 2 years after treatment started for the myeloma. The annual frequency of second cancers among those still alive was constant between 0.7% and

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Table 1. Patients with Myeloma and Second Solid Tumors at Least Two Months After the Start of Chemotherapy

Patient	Age	Sex	Protein Type	Second Cancer*	Treatment†	Time To Second Cancer	Survival with Myeloma
	yrs					*months*	
1	51	M	IgG	Stomach	MPPr	2	6
2	63	M	IgAK	Kaposi's sarcoma	MP	4	14
3	79	M	L only	Hepatoma	MP	4	4‡
4	64	M	K only	Prostate	MAP	10	42
5	56	M	L only	Colon	MP	12	20
6	76	M	IgGK	Rectum	MP (XRT)	12	12‡
7	64	M	L only	Bronchus	MP	14	14‡
8	68	M	L only	Astrocytoma	MAP	14	18
9	71	M	L only	Rectum	MCP	15	40
10	60	M	IgGK	Prostate	MPPr (XRT)	15	68
11	66	M	IgGK	Kidney	MPPr (XRT)	15	15‡
12	70	F	IgG	Bladder	MP	21	24
13	68	F	IgA	Breast	MPPr	21	24
14	49	M	IgAL	Unknown primary	MPPr (XRT)	26	95
15	53	F	IgGK	Breast	MPPr	38	70
16	55	M	K only	Melanoma	MPPr (XRT)	40	52
17	60	M	IgGK	Prostate	MAP	41	54
18	70	M	IgG	Colon	MPPr (XRT)	57	58
19	61	M	IgAL	Bronchus	MPPr	69	69‡

* Site of origin of carcinoma unless indicated otherwise.
† M = melphalan, P = prednisone, Pr = procarbazine, C = cyclophosphamide, A = doxorubicin, XRT = radiotherapy to painful bone lesions.
‡ Second cancer confirmed at autopsy.

1.5% for each successive year of observation.

Discussion

The incidence of second solid tumors in patients treated for multiple myeloma was similar to that reported during a similar time period among normal persons of the same age. Each of the major types of cancer also had an incidence similar to that expected: In contrast, 13 of 476 patients with multiple myeloma followed at the same institutions developed acute myelocytic leukemia for an incidence (2.7%) more than 100 times higher than found in normal persons of the same age (5).

More than two thirds of our patients developed their nonhematopoietic cancers within 2 years after the recognition of their myeloma, later tumors developing at a low and constant annual rate similar to that found in normal persons of comparable age. These observations were consistent with the coincidental occurrence of solid tumors during a short average life span. In contrast, more than 2 years of chemotherapy had been given to all but one of 13 patients who developed acute leukemia with a median latency of 42 months from the start of chemotherapy (5). These findings suggested that long-term melphalan had no important role in the pathogenesis of solid tumors, as it seemed to have in the development of acute leukemia. Although solid tumors caused the death of 32% of the myeloma patients with a second malignancy, all patients who developed acute leukemia died from this disease

Table 2. Observed and Predicted Number of Patients with Solid Tumor in Multiple Myeloma

	Patients at Different Ages (in Years)			Patients with Solid Tumor	
	49 to 59	60 to 69	70 to 79	Total Observed	Total Predicted*
	←		*no.*		→
Bladder			1	1	0.6
Brain		1		1	0.2
Breast	1	1		2	1.1
Colon	1		1	2	1.4
Female genital				0	0.9
Head and neck				0	0.6
Kidney		1		1	0.2
Liver and pancreas			1	1	0.6
Lung		2		2	1.5
Melanoma	1			1	0.2
Prostate		3		3	1.1
Rectum			2	2	0.7
Sarcoma		1		1	0.2
Stomach and esophagus	1			1	0.7
Unknown primary	1			1	No data available
Total	5	9	5	19	12

* Predicted number of patients who would develop a solid tumor for 1270 patient-years of life with myeloma using data from the Connecticut Tumor Registry. The total predicted includes other uncommon solid tumor types not present in our patients.

while their myeloma was in remission (5).

Our evaluation of a large population of patients with myeloma confirms the studies of Berg (6), who also failed to detect an increased incidence of second solid tumors among 207 patients with myeloma. Kyle (7) reported that deaths from other cancers occurred in only 2% of 535 patients with multiple myeloma. These independent studies conflicted with the report of Weitzel (8), who found 11 unrelated solid tumors among 57 patients with malignant plasma cell disorders evaluated at autopsy and who suggested a pathogenetic relation. By confining the analysis to autopsied patients, many persons with asymptomatic cancer may have been included in whom the diagnosis was not suspected during life. More likely, Weitzel's small sample size did not reflect a representative population of patients with myeloma.

Only one patient with Kaposi's sarcoma was identified in our large series. An association between myeloma and Kaposi's sarcoma has been suggested, because several patients have been described with both diseases (9). Because 31% of male patients with Kaposi's sarcoma died from a second tumor, a cause-and-effect relation has been proposed. In view of the low incidence among our patients, any relation between these two diseases seemed to be coincidental.

Patients with another abnormality of B-cell proliferation, namely congenital Bruton-type agammaglobulinemia, have an increased incidence of acute lymphocytic leukemia but not of other cancers (13). More than 80% of our patients with myeloma had moderate or marked degrees of hypogammaglobulinemia in at least one major immunoglobulin component. Most patients with myeloma also have evidence of depressed cell-mediated immunity. Aside from an increased frequency of leukemia, lymphoreticular neoplasms, and skin cancer, diseases with depressed immunity do not appear to have a markedly increased incidence of other solid tumors (6, 13). Because the frequency of most solid tumors was not higher than in normal persons of comparable age, the acquired immune deficiencies that occurred with multiple myeloma were not considered to be a major factor in the pathogenesis of second cancers.

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References

1. KYLE RA, PIERRE RV, BAYRD ED: Multiple myeloma and acute myelomonocytic leukemia. *N Engl J Med* 283:1121-1125, 1970
2. ROSNER F, GRÜNWALD H: Multiple myeloma terminating in acute leukemia. Report of 12 cases and review of the literature. *Am J Med* 57:927-939, 1974
3. BELL R, SULLIVAN JR, FONE DJ, HURLEY TH: Carcinoma of the breast. Occurrence after treatment with melphalan for multiple myeloma. *JAMA* 236:1609-1610, 1976
4. ROBINS SM, CHOPRA D: Multiple myeloma and multiple neoplasms. *JAMA* 236:1609, 1976
5. GONZALEZ F, TRUJILLO JM, ALEXANIAN R: Acute leukemia in multiple myeloma. *Ann Intern Med* 86:440-443, 1977
6. BERG JW: The incidence of multiple primary cancers. I. Development of further cancers in patients with lymphomas, leukemias and myeloma. *J Nat Cancer Inst* 38:741-752, 1967
7. KYLE RA: Multiple myeloma. Review of 869 cases. *Mayo Clin Proc* 50:29-40, 1975
8. WEITZEL RA: Carcinoma coexistent with malignant disorders of plasma cells. *Cancer* 11:546-549, 1958
9. O'BRIEN PH, BRASFIELD RD: Kaposi's sarcoma. *Cancer* 19:1497-1502, 1966
10. Remission maintenance therapy for multiple myeloma. Southwest Oncology Group Study. *Arch Intern Med* 135:147-152, 1975
11. ALEXANIAN R, SALMON S, BONNET J, GEHAN E, HAUT A, WEICK J: Combination therapy for multiple myeloma. *Cancer* 40:2765-2771, 1977
12. WATSON TA: Incidence of multiple cancer. *Cancer* 6:365-371, 1953
13. GOOD RA, FINSTAD J, GATTI RA: Bulwarks of the bodily defense, in *Infectious Agents and Host Reactions,* edited by MUDD S. Philadelphia, W.B. Saunders Co., 1970, pp. 76-114

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