# Acute Leukemia in Multiple Myeloma

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Of 476 patients with multiple myeloma treated during a 9-year period, 11 developed acute myelogenous leukemia or sideroblastic anemia. In all, the myeloma was in remission from chemotherapy with melphalan-prednisone combinations that had been continued for a median duration of 3 years. The incidence of acute leukemia or sideroblastic anemia was about 100 times higher than found in normal individuals of the same age. In all patients studied, major cytogenetic abnormalities were present, with hypodiploidy and evidence of chromosomal damage being noted most frequently. The frequency and nature of the chromosome changes were attributed to effects resulting from the prolonged drug therapy. These findings supported the long-term follow-up of selected patients with myeloma without any chemotherapy when marked degrees of remission followed the initial treatment courses.

IMPROVED TREATMENTS have prolonged the survival of many patients with multiple myeloma (1, 2). However, acute leukemia has caused the death of some (3-5) and a refractory sideroblastic anemia has sometimes preceded the development of leukemia (6, 7). This report defines the incidence of these complications in a large number of patients with multiple myeloma who received melphalan. Of 476 patients treated during a 9-year span, six developed acute leukemia and five others had a sideroblastic anemia without leukemia. The second marrow diseases were always associated with major cytogenetic changes and occurred about 100 times more frequently than was observed in normal subjects of similar age.

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## Materials and Methods

Between January 1965 and December 1973, 476 consecutive patients with multiple myeloma received chemotherapy at six Southwest Oncology Group institutions according to specific treatment protocols. All received intermittent courses of melphalan and prednisone with or without added vincristine, or procarbazine, or both (1,2). The clinical response was evaluated from criteria previously defined and based on niarkcd, sustained declines in myeloma protein production rate to less than 25% of the pretreatment value (2). Except for 34 patients followed without chemotherapy during remission, all patients received intermittent courses of a melphalan-prednisone or carmustine prednisone combination until relapse or death (2).

The diagnosis of acute leukemia required the presence of more than 20% myeloblasts in the bone marrow. Sideroblastic anemia was defined by the presence in the marrow of marked erythroid hyperplasia and dysplasia with ringed sideroblasts constituting more than 40% of the erythrocyte precursors. All had markedly elevated, but ineffective, erythropoiesis (8). Cytogenetic studies were done on bone marrow specimens only after the onset of unexplained leukemia or anemia using pro-

**Table 1. Patients with Myeloma and Acute Leukemia or Sideroblastic Anemia***

| Patient | Acute Leukemia | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Age, *yrs* | 58 | 65 | 18 | 59 | 52 | |
| Sex | F | M | F | M | M | |
| Protein Type | L only | L only | IgGl | L only | IgG? | |
| Treatment | MPPr Radiotherapy | MP | MP | MP Radiotherapy | MPPr | |
| Survival from diagnosis, *months* | | | | | | |
| Myeloma | 32 | 73 | 45 | 58 | 27 | |
| Anemia | 2 | 2 | 8 | 4 | 2 | |
| Cytogenetics | | | | | | |
| Bone marrow† | ND | ND | 60% 44 to 45<br>15% Polyploid<br>25% Normal Diploid | 85% 43 to 45<br>15% Polyploid Chromosomal damage | ND | |
| Metaphases analyzed, *no.* | | | 40 | 25 | | |

* M = melphalan; P = prednisone; Pr = procarbazine; V = vincristine; BCNU = bischloroethylnitrosourea; Chromosomal damage = breaks, dicentrics, and so forth; ND = not done.
† Chromosome no. as indicated.

between 1969 and 1974 were used to define the predicted ...dence of acute leukemia and sideroblastic anemia in our ...ents with multiple myeloma*. The frequency of leukemia ... total patient-years of life at each age decade for our ... patients with myeloma was compared with the annual in... in a normal population. For example, among 300 ...ent-years of life for 164 patients aged 60 to 69, three pa... developed acute leukemia in comparison with the pre... number of 0.02 derived from the Connecticut frequency. ... calculation was made separately for each age decade and ...esults added in reaching the total predicted incidence for ...atients.

### Results

Among 476 patients with myeloma who were evaluated, ...developed acute leukemia and five had a sideroblastic ...emia without evidence of leukemia. The clinical and ...oratory findings for these patients are summarized on ...ble 1. All had achieved a remission by virtue of a greater ...an 75% reduction in myeloma protein production rate.

The age distribution (median, 65 years) and duration ... treatment were similar to that of other responding ...ients who had not developed acute leukemia or sidero...stic anemia. Eight of the patients were male; none had ... immunoglobulin A myeloma protein and the light-chain ...pe was lambda in all five with only Bence Jones proteins. ...hen the second marrow disorder was recognized, chemo...rapy for myeloma had been given for 3 to 68 months ...edian, 38 months); localized radiotherapy for the relief ... bone pain due to pathologic compression fractures in ...e spine had been given to three patients. The first ...oratory abnormality suggesting a new bone marrow ...order always consisted of a decline in hemoglobin to ...s than 8 g/dl from a level of greater than 10 g/dl ...ring remission; seven patients also had a decline in plate... count to less than 80 000/$\mu l^3$. When it developed, ...te leukemia was myelocytic or monocytic in type and from the occurrence of severe anemia was 7 months for all patients. In none of the four patients with sideroblastic anemia who had died was a repeat marrow sample examined during the 4 to 12 months of life subsequent to development of the disorder.

All six patients with adequate chromosome studies showed major abnormalities (Table 1). Hypodiploidy was always present with a chromosome number varying between 43 and 45; hyperdiploidy was found in two patients; polyploidy and chromosomal damage (breaks, dicentrics, and so forth) were noted frequently. There was usually marked variability in the nature of the cytogenetic abnormalities among different cells from the same patient. Marker chromosomes resembling long D and long A chromosomes were noted in three patients. There was no distinction in the cytogenetic pattern between the patients with acute leukemia and those with sideroblastic anemia.

The frequency of leukemia or sideroblastic anemia in our patients was compared with the predicted rate reported from normal human beings of the same age. Accrued were 991 patient-years of survival with six occurrences of acute leukemia and five of sideroblastic anemia. The frequency of these diseases in our patients was compared with the predicted incidence derived from the frequency in normal individuals reported by the Connecticut Tumor Registry. Because the detection of one patient with acute leukemia or sideroblastic anemia required about 10 times the number of patient-years that we observed, the presence of 11 patients in our population indicated an incidence of about 100 times higher than predicted.

### Discussion

Six patients with acute leukemia and five with a refractory sideroblastic anemia were identified among a group of 476 consecutive patients with myeloma treated at six cooperating institutions. Except for one patient, all had received chemotherapy for myeloma for at least 2 years

*Personal communication on the incidence of acute leukemia from ... through 1974 from the Connecticut Tumor Registry, J. T. Flannery, ...or

Table 1. (Continued)

| | Sideroblastic Anemia | | | | |
|---|---|---|---|---|---|
| | 7 | 8 | 9 | 10 | 11 |
| | 62 | 85 | 42 M | 74 M | 43 M |
| | L only MPPr BCNU | IgGl MP | IgGl MPPrV | IgGl MPPrV BCNU | L only MPPrV |
| | 49 | 55 | 48 | 36 | 73+ |
| | 8 | 12 | 6 | 7 | 6+ |
| | 45, XY, −C Normal Diploid | 50% 42 to 45<br>30% 47 to 51<br>10% Pseudodiploid<br>10% Polyploid<br>Chromosomal damage | 25% 45 to 46<br>70% 46 to 47<br>5% Normal Diploid<br>Chromosomal damage | ND | 100% 45, XY, −C<br>Chromosomal damage |
| | 21 | 25 | 25 | | 25 |

before the second bone marrow disease became evident. The occurrence of unexplained pancytopenia, particularly a fall in hemoglobin to less than 8 g/dl, provided the first clue to a new bone marrow disorder. After isolated reports of acute leukemia in myeloma patients (3), Kyle (4) first described the relation between the alkylating-agent treatment and the occurrence of acute leukemia as a clinical entity. Subsequently, acute myelogenous leukemia or a refractory sideroblastic anemia has been described in more than *60* patients with multiple myeloma (5-7, 10). Most patients had received many months of chemotherapy for myeloma, and an oncogenic effect from this treatment has usually been suggested as a cause. Yet, three patients have been described with a myelomonocytic leukemia occurring simultaneously with multiple myeloma and without any previous drug exposure (11, 12). As in one of our patients, in whom acute leukemia was recognized 3 months atter the diagnosis of myeloma, chemotherapy was clearly not a prerequisite for this complication. The rare occurrence of both diseases may have represented a coincidence, or else one disorder may have predisposed some patients to the second disease.

All six of our patients with adequate cytogenetic studies had hypodiploidy with major chromosome alterations. Hyperdiploidy. marker chromosomes, and evidence of chromosome damage were also present. Most chromosome groups showed abnormalities but there was considerable variability in the nature of the deviation even among cells from the same patient. The unusual degree of aneuploidy and other changes noted in our patients was similar to that reported in other patients with acute leukemia (13) or sideroblastic anemia (7, 14) after chemotherapy for multiple myeloma. Similar cytogenetic findings have been described in other patients with cancer who developed acute myeloid leukemia after prolonged treatment with alkylating agents (15). In contrast, spontaneous acute leukemia in adults has been associated with normal cytogenetics in about 60% of patients (16) and a hypodiploid karyotype has been confirmed in about *25%* of another group (9). Thus, the frequency and extent of the chromosome changes in our series and that of others (6, 13, 14) were most unusual for patients with acute leukemia or idiopathic sideroblastic anemia: for example, marker chromosomes were found in three of our six patients in comparison with a *20%* incidence in patients with spontaneous acute leukemia. Thus, the chromosome anomalies in patients with acute leukemia or sideroblastic anemia that followed treatment for myeloma most likely resulted from the alkylating-agent chemotherapy.

Acute leukemia has been described many years after the institution of radiotherapy or chemotherapy, or both, for other solid tumors (10, 17). Yet, the precise incidence of this complication has not been ascertained because the number of patients at risk in the various series was unknown. Among a clearly defined group of patients with multiple myeloma, 11 patients were identified with acute leukemia or sideroblastic anemia among 476 patients with *991* patient-years of exposure. The incidence of acute leukemia and sideroblastic anemia was about 100 times higher than that observed in normal subjects of similar age. Even. this frequency may have been underestimated because bone marrow examinations were not conducted in all myeloma patients who developed an unexplained pancytopenia.

The survival of patients with myeloma who were in remission and were then followed without chemotherapy was similar to that of patients receiving indefinite courses of melphalan-prednisone (2). There was an increased incidence of certain infections in patients maintained on chemotherapy for prolonged periods (2), and second remissions usually occurred with the resumption of melphalan-prednisone during relapse. Two percent of all patients and *6%* of those responding patients alive after 2 years developed acute leukemia or sideroblastic anemia. Despite the low incidence, this complication provided additional justification for the long-term follow-up without any chemotherapy of selected patients with myeloma. This applied mainly to those responding patients with long durations of unmaintained remission, such as those with dit. appearance of their monoclonal component after chemotherapy.

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