Radiation-induced leukemia is considered to be similar to the de novo disease. However, following an analysis of clinical and hematological findings in leukemia occurring in irradiated cervical cancer patients, adult Japanese atomic-bomb survivors, and spondylitics treated with x-ray, striking differences were noted. Acute leukemias in cervical cancer patients and Japanese survivors were similar in type to acute de novo leukemias in adults. Cell types among spondylitics were very dissimilar; rare forms, eg, acute erythromyelocytic leukemia (AEL) and acute megakaryocytic leukemia, were increased. Pancytopenia occurred in 25 of 35 cases and erythromelodysplastic disorders were noted in seven of 35 acute cases. The leukemias and myelodysplastic disorders closely resembled those occurring in patients treated with alkylating agents. This similarity suggests a common pathogenesis involving marrow stem cell injury and extra-medullary mediators of hematopoiesis. Investigation of early acute leukemias and myelodysplastic disorders with newer techniques may provide valuable insights into the pathogenesis of leukemia in humans.

Radiogenic Leukemia Revisited

By William C. Moloney

THE LEUKEMOGENIC effect of ionizing radiation was first described by von Jagic et al in 1911. Since then many individual case reports and small groups of leukemias attributed to radiation exposure have been reported. However, only three large series, well-studied epidemiologically and hematologically, have been published. The latter include cases among Japanese atomic-bomb survivors; leukemia occurring in British spondylitics treated with x-ray and leukemia in women with cervical cancer following radium and x-ray therapy. It is generally accepted that the types of leukemia induced by radiation are similar to the de novo disease; however, when the clinical and hematological findings from the three series mentioned above were reviewed, interesting differences were noted. These observations and their possible implications for the role of ionizing radiation in the pathogenesis of leukemia are presented in this report.

MATERIALS AND METHODS

Atomic-bomb survivors. In 1947 the US government established the Atomic Bomb Casualty Commission (ABCC), and in 1950 set up field headquarters in Hiroshima and Nagasaki. Extensive studies were carried out on survivors in order to determine the late effects of radiation. In 1975 the Japanese government assumed responsibility for these investigations under the auspices of the Radiation Effects Research Foundation (RERF). Numerous articles and reports have been published, many concerned with the incidence and dose relationship of radiation-induced leukemia. In an overall review Ichimaru et al published an article on 149 cases of definite and probable leukemias occurring from November 1945 to October 1971 among 82,000 atomic-bomb survivors and 27,000 others not in the cities at the time of bombing. All leukemias in these survivors, including 13 that occurred before October 1, 1950, were listed; other data included age at time of bombing, type of leukemia, date of onset, and estimated radiation dose. In the present analysis records on 98 of these Japanese patients over the age of 30 were reviewed. In order to obtain more detailed information on the types of leukemia and to determine whether a preleukemic stage occurred, abstracts of case histories and reports on peripheral blood and bone marrow studies along with results of autopsies were examined on the 78 Hiroshima and 20 Nagasaki survivors. To carry out a comparative analysis the following changes were made in nomenclature used by Ichimaru et al; acute stem cell leukemia (ASL) to acute unclassified leukemia (AUL), acute myelogenous leukemia (AML) to acute monocyctic leukemia (AMOL), and erythroleukemia to acute erythromyelocytic leukemia (AEL). Ichimaru et al did not identify cases of acute monocyctic leukemia (AMML) and these cases were apparently included with AMOL. It should be noted that no cases of acute progranulocytic leukemia (APL) or acute megakaryocytic leukemia were reported among these atomic-bomb survivors. As far as possible acute leukemias were reclassified according to the French, American, and British Nomenclature Committee (FAB).

Spondylitic patients treated with x-ray. A well-documented series of leukemias was reported in 1957 by Court Brown and Doll among 13,352 irradiated spondylitics. To be accepted for that study the diagnosis of spondylitis had to be confirmed, amount and duration of x-ray therapy established, and only cases occurring 12 months or more following x-ray therapy were included. In the Court Brown and Doll study, intensive efforts were made to identify and observe all cases, and detailed clinical, hematological, and pathological data were published in their monograph. In view of the changing myelopathic concepts and difficulties in classifying disorders, an attempt was made to reevaluate 57 cases from the original Court Brown and Doll series. Case histories were reviewed along with available peripheral blood and bone marrow specimens as well as postmortem results. Radiation doses were obtained from the case histories. Twelve cases were omitted for a variety of reasons, and as far as possible the leukemias and other myelopathic disorders were reclassified according to the FAB nomenclature.

Leukemia occurring in women following radiation therapy for cervical cancer. Beginning in 1960, an investigation was carried out on the incidence of leukemia and other malignancies occurring in women with cervical cancer treated with radium to the cervix and x-ray to the lower abdomen. This study was under the auspices of the International Agency for Research on Cancer (WHO) and the Radiation Epidemiology Branch, National Cancer Institute. In a recent article describing this study Boice et al reported that 182,616 patients had been enrolled in the program: of these, 82,616 had invasive cervical cancer requiring radiation therapy. At the time of the report the average period of observation was 7.6 years with a total of 603,788 women-years of follow-up. Intensive efforts were made to obtain accurate assessment of radiation dosage: average dose to the active marrow was 300 to 1,500 rads. Considerable care was taken to verify the diagnosis and type of leukemia. Due to...
excellent cooperation of the tumor registries and clinics involved in the study, clinical information along with results of blood and bone marrow examinations were obtained in over 80% of cases. When the diagnosis was in doubt, marrow specimens were submitted for central review. When slides could not be sent out of the country, opinions were obtained from local experts. As far as possible the acute leukemias were reclassified according to the FAB system.

Leukemia in adults de novo. As part of this comparative analysis a series of leukemia patients observed in the Hematology Division, Brigham and Women's Hospital, from 1969 to 1979 were reviewed. Only patients 30 years of age or older were selected for this study and individuals with a prior history of refractory anemia, multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's disease, or myeloproliferative disorders were excluded. No patient had received chemotherapy or significant radiation exposure before the onset of leukemia. There were 232 cases of acute leukemia, 94 females and 138 males, as well as 86 cases of chronic myelogenous leukemia (CML). The acute leukemias were classified according to the FAB classification.

RESULTS

CML. Among a total of 98 cases of leukemia in Japanese survivors, 37 were CML (18 females, 19 males). CML was typical hematologically and clinically. Median age was 50 with a range of 31 to 84 years. Median latent period was 11 years (range 2 to 25 years). The median radiation dose was 45 rads with a range of 1 to 443 rads. There was no estimate of dose in four cases and zero dose was recorded in four cases. It is of interest to note that of 20 leukemias in Nagasaki only three were CML, while in Hiroshima 34 of 78 cases were CML.

Among the 43 leukemias in the irradiated spondylitic patients there were eight cases of CML (seven males, one female). The average age was 45 years with a range of 30 to 64. While the small number precludes a meaningful analysis, it is noteworthy that the latent periods were considerably shorter than in the Japanese survivors or cervical cancer patients: average 3.6 years with a range of one to six years. Radiation dose was available in seven cases with an average of 1,708 rads and a range of 377 to 2,706 rads.

Of the 139 cases of leukemia in the irradiated cervical cancer patients 40 were CML. Clinical and hematological features were typical of CML. Median age was 58 (range of 41 to 83 years) and the median latent period was 9 years (range 1 to 23 years). The median dose of radiation to the bone marrow was 750 rads (range 300 to 1,500 rads).

Acute leukemias and myelodysplastic disorders. Among Japanese survivors 61 cases of acute leukemia over age 30 were reviewed (29 females and 32 males). The median age was 54 (range 30 to 78 years), the median radiation dose was 120 rads (range 1 to 900 rads). Median latent period was 17 years (range 6 to 31 years). Following my review of the clinical histories, peripheral blood, bone marrow, and postmortem findings, cases were reclassified as follows: acute granulocytic leukemia (AGL) (M1 and M2) 29, AMML (M4) seven, AMOL (M5) seven, AEL (M6) three, ALL ten, AUL five. In general the acute leukemias resembled de novo cases; pancytopenia was present in four cases; however, blast cells were found either in the peripheral blood or bone marrow. In two of the three cases of AEL, pancytopenia was present at time of diagnosis and ring sideroblasts were noted in the bone marrow.

Among the irradiated spondylitics, there were 35 cases (34 male, one female) designated as AML by Court Brown and Doll, and, in addition, two cases of aplastic anemia proven by biopsy and autopsy. Median age was 41 (range 22 to 70 years). Estimated latent period (using a mean between first and last x-ray therapy) gave a median of 3.0 and a range of 1 to 12 years. Median dose of radiation was 1,070 rads with a range of 220 to 3,525 rads. Twenty-five cases were pancytopenic at onset of the myelopathic disorder, in one case no leukocyte count was available. For all 35 cases median leukocyte count was 3,400/mm³ (range 700 to 240,000). In the peripheral blood smears leukemic cells were noted in 15, none were present in 18, and in two cases peripheral smears were not available. Following a review of the clinical histories, blood studies, bone marrow aspirates and biopsies, as well as results of postmortem examinations, the eight cases of AGL could be separated into M1 and M2 from descriptions of myeloblasts and promyelocytes in blood smears and bone marrow specimens. There were seven cases of AMOL in the Court Brown and Doll report, a diagnosis based on morphological criteria. The designation AMML was not widely used 30 years ago, but no doubt cases of this type were included in the AMOL category. A diagnosis of ALL was made in two cases and AUL in three. In three cases, while acute leukemia was apparently present, the cell type could not be established due to lack of adequate blood and marrow specimens.

An unusual feature of the hematological disorders in this series was the presence of nine patients with erythromyelocytic abnormalities in the marrow. These are included in the Court Brown and Doll report as AML–aleukemic. In two cases the marrow findings strongly suggest to this investigator a diagnosis of AEL and in two others either refractory dysmyelopoietic anemia (RDA) or refractory anemia with excessive blasts (RAEB). There were five patients who had marked erythroid proliferation associated with the presence of promyelocytes and myeloblasts; these marrow findings are consistent with a diagnosis of transition from RAEB to AML (RAEB-T).

Three other cases with an initial diagnosis of AML are of considerable interest. All three had features at bone marrow biopsy and autopsy of myelofibrosis and were termed acute myelofibrosis or myelosclerosis. In the light of recent technical developments in hematology and pathology, these cases appear to be candidates for the diagnosis of acute megakaryocytic leukemia, a diagnosis proposed in two of three cases by the pathologist who originally reviewed the postmortem material for the Court Brown and Doll report.7

The cervical cancer study provided excellent clinical and hematological information in the great majority of the 99 cases of acute leukemias. In this group the median age was 65 (range 38 to 89), latent period, median eight years (range 1 to 41). The median radiation dose was 720 rads (range 210 to 2,000 rads). After review, 52 cases were classified as AGL (M1 and M2) consisting of 37.4% of the acute leukemias, a figure similar to that found in the de novo series (see Table 1). The remaining cases consisted of APL three, AMML seven, AMOL seven, AEL three, AUL ten, ALL 16 and one...
Table 1. Classification of Leukemia in 3 Irradiated and 1 De Novo Population

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cervical Cancer</th>
<th>A-Bomb Survivors</th>
<th>Spondylitics</th>
<th>De Novo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML</td>
<td>40 (28.7)</td>
<td>37 (37.7)</td>
<td>8 (18.4)</td>
<td>86</td>
</tr>
<tr>
<td>AL/MDS</td>
<td>99</td>
<td>61</td>
<td>35</td>
<td>241</td>
</tr>
<tr>
<td>M1 + M2</td>
<td>52 (52.5)</td>
<td>29 (45.9)</td>
<td>8 (22.8)</td>
<td>101 (41.9)</td>
</tr>
<tr>
<td>M3</td>
<td>3 (3.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>13 (5.4)</td>
</tr>
<tr>
<td>M4</td>
<td>7 (7.0)</td>
<td>7 (11.6)</td>
<td>0 (0)</td>
<td>37 (15.4)</td>
</tr>
<tr>
<td>M5</td>
<td>3 (3.0)</td>
<td>3 (4.9)</td>
<td>2 (6.7)</td>
<td>11 (4.6)</td>
</tr>
<tr>
<td>M6</td>
<td>3 (3.0)</td>
<td>0 (0)</td>
<td>3 (8.3)</td>
<td>9 (3.7)</td>
</tr>
<tr>
<td>AUL</td>
<td>10 (10.0)</td>
<td>5 (8.2)</td>
<td>3 (8.3)</td>
<td>9 (3.7)</td>
</tr>
<tr>
<td>ALL</td>
<td>16 (16.0)</td>
<td>10 (16.3)</td>
<td>2 (5.7)</td>
<td>18 (7.5)</td>
</tr>
<tr>
<td>RDA</td>
<td>0</td>
<td>1 (2.8)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>RAEB</td>
<td>0</td>
<td>0 (0)</td>
<td>1 (2.8)</td>
<td>—</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>0</td>
<td>0 (0)</td>
<td>5 (14.2)</td>
<td>—</td>
</tr>
<tr>
<td>7 AML</td>
<td>0</td>
<td>3 (8.3)</td>
<td>17 (7.1)</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>139</td>
<td>98</td>
<td>43</td>
<td>327</td>
</tr>
</tbody>
</table>

Abbreviations: CML, chronic myelogenous leukemia; AL, acute leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphatic leukemia.

case of acute megakaryocytic leukemia. In two cases of AEL and one AGL, ringed sideroblasts were present in the bone marrow. In one case of AUL there was a six-month history of pancytopenia before the diagnosis of leukemia.

The distribution of types of acute leukemia in the de novo series may be noted in Table 1. Since the de novo series consisted of patients referred to the Hematology Division, Brigham and Women’s Hospital, it may not necessarily be fully representative of all de novo adult leukemias. Special studies, including histochemical stains and immunological markers, were carried out on many of the problem cases. This may account for the relatively low incidence of AUL and ALL cases in this series.

DISCUSSION

Although it is generally assumed that radiogenic leukemia is similar to the de novo disease, it is evident from the observations in this review that marked differences exist between irradiated spondylitics compared with Japanese A-bomb survivors, women irradiated for cervical cancer, and de novo acute leukemia patients. In all three series of irradiated patients CML was typical clinically and hematologically. However, considerably fewer cases occurred in spondylitics (8) than among Japanese survivors (37) or the cervical cancer patients (40) (Table 1). The elevated incidence in Japanese survivors involved only Hiroshima; of 37 cases, 34 occurred in Hiroshima and only three in Nagasaki. The increased incidence in Hiroshima has long been recognized, but to date no suitable explanation has been forthcoming. The average latent period of CML in spondylitics was 3.5 years compared with a median latent period of 9.0 years for cervical cancer patients and 11 years for Japanese survivors.

In all types of acute leukemia clinical and hematological features were similar in Japanese survivors, cervical cancer patients, and the de novo series. However, these three groups pose a striking contrast to acute leukemias and related disorders among irradiated spondylitics. In the latter series 25 of 35 cases, collectively classified as AML in the Court Brown and Doll report, were pancytopenic at onset and required bone marrow examination to establish a diagnosis. The spectrum of myelopathic states included nine with striking erythromelodysplastic features. The presence of a pancytopenic stage accompanied by lack of leukemic cells in the peripheral blood bears a close resemblance to features of the acute leukemias and myelodysplastic states following treatment with alkylating agents. Similar also are the unusual cell types, eg, erythroblast and acute megakaryocytic leukemia. Other shared features are the rapidly fatal course and low response to chemotherapy. Unfortunately, the leukemias among spondylitics were encountered before 1958 and no cytogenetic studies were available.

In the past 15 years there has been an increasing recognition of so-called “preleukemia” states, chiefly refractory dysmyelopoietic anemia with or without ringed sideroblasts in the bone marrow. Many studies have been carried out on both the de novo disease and those secondary to chemotherapy in order to clarify the relationship of these disorders to acute leukemia. The FAB established a classification for acute leukemias that provides a useful means of comparison for hematologists and other interested groups. The designations of RDA, RAEB, and the more controversial refractory anemia with excess blasts in RAEB-T, have provided additional descriptive terminology. Along with the newer morphological developments, the recognition of genetic and nonrandom chromosomal abnormalities in the myelodysplastic states, especially 5-, 5q-, 7-, 8+, and 13-, has added new dimensions to the diagnosis and investigation of these disorders and their relationship to AML.

To account for the unique effect of x-ray therapy in spondylitics two possibilities should be considered: (1) that patients with spondylitis have a predisposition for developing leukemia; or (2) the x-ray therapy used had special leukemogenic characteristics. Ankylosing spondylitis is an inflammatory arthritis but as far as is known carries no increased risk of malignancy. Moreover, in addition to direct injury to marrow stem cells, the possibility should be considered that spondylitics may have defective T lymphocytes or T cells that are unduly radiosensitive. X-ray therapy in spondylitics was administered in one, or more often, in a number of courses. It was delivered in relatively high dosage over large joints and the spine, areas containing major amounts of bone marrow. Furthermore, orthovoltage x-rays interacting with dense bone may release photons that can deliver high levels of ionizing radiation to local areas, especially the endosteum, stromal cells, and marrow stem cells contiguous to the endosteal lining. Recently considerable attention has been directed to the relationship of stromal cell damage and leukemogenesis. The studies by Greenberger and his co-workers on the isolation of a new factor capable of transforming normal mouse marrow cells into malignant myeloblasts is of special interest in this regard. In considering the pathogenesis of radiation-induced leukemia it is important to emphasize that the acute leukemias and myelodysplastic disorders following therapy with alkylating agents closely resemble, both clinically and hematologically, the disorders occurring in irradiated spondylitics. Since both...
modalities of therapy damage stem cells and also suppress or modify lymphocytes, which mediate hematopoiesis, it is reasonable to postulate that leukemias and myelodysplastic disorders may be caused by a combination of these effects.

In spite of intensive research for the past 70 years, the role of radiation in leukemogenesis remains an enigma. However, recent developments in the field of molecular biology, especially the discovery of oncogenes,\textsuperscript{9,20} studies on clonality and differentiation of myeloblasts such as those carried out by Fialkow,\textsuperscript{21} and the investigation of the differentiation of human myeloblasts with the use of DNA probes by Fearon et al give promise of important progress in the field of leukogenesis.\textsuperscript{22} Application of these newer techniques to the myelodysplastic disorders and early phases of leukemia second ary to radiation and alkylating agents present unique opportunities for the type of research that may lead to better understanding of the pathogenesis of leukemia in man.

ACKNOWLEDGMENT

The author is grateful to John Boice, National Cancer Institute, and Goran Engholm, International Agency for Research on Cancer, for information on the cervical cancer patients; and to T. Hoshino and M. Ichimaru for clinical and hematological records on Japanese A-bomb survivors. Thanks are extended to R. Mole, Sir Richard Doll, P. Smith and S. Darby for case histories and follow-up data on British patients with spondylitis. I am indebted to H. F. Bunn, R. I. Handin, and D. S. Rosenthal for helpful discussions and corrections of the manuscript.

REFERENCES

Radiogenic leukemia revisited

WC Moloney