

Histologic Verification of Leukemia, Myelodysplasia, and Multiple Myeloma Diagnoses in Patients in Ukraine, 1987-1998

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Abstract

In preparation for a possible large epidemiological study of radiation-related leukemia in Chernobyl clean-up workers of Ukraine, histologic evaluation of 62 cases of leukemia and related disorders was conducted by a panel of expert hematologists and hematopathologists from the United States, France, and Ukraine. All cases were randomly selected from a surrogate population of men in the general population of 6 regions of Ukraine who were between the ages of 20 and 60 years in 1986 and were reported to have developed leukemia, myelodysplasia, or multiple myeloma between the years 1987 and 1998. The hematologists and hematopathologists on the panel were in agreement with one another and with the previously reported diagnoses and classifications of about 90% of the cases of acute and chronic leukemia in the study. These results suggest that strong reliance can be placed on the clinical diagnoses of acute and chronic forms of leukemia and multiple myeloma that have occurred in Ukrainian Chernobyl clean-up workers providing that the diagnoses are supported by records of the patients having had adequate histologic bone marrow studies. The number of cases in this study with the diagnosis of myelodysplasia, however, was too small to draw firm conclusions. *Int J Hematol.* 2002;76:55-60.

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1. Introduction

The primary objective of the study in this report was to determine the extent to which the diagnosis and classifica-

tion of leukemia in Chernobyl accident clean-up workers of Ukraine who were reported to have developed leukemia following the accident might be histologically verified by Western standards. This hematology review was an important part of a 2-year study initiated in November 1997 by the National Cancer Institute in the United States and the Research Center for Radiation Medicine (RCRM) in Ukraine to determine the feasibility of conducting a large retrospective radiation dose-related study primarily of cases of leukemia, but also of myelodysplasia (MDS) and

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multiple myeloma (MM) in Chernobyl accident clean-up workers of Ukraine, occurring between 1987 and 1998 [1]. The study consisted of a review by a highly qualified group of hematologists and hematopathologists from Ukraine and 2 Western countries of bone marrow slides and abstracted medical records from cases of randomly selected adult men in the general populations of 5 specific regions of Ukraine who were reported to have developed leukemia, MDS, or MM between the years 1987 and 1998. These men were selected for the histologic review to serve as surrogates for the Chernobyl accident clean-up workers with leukemia or one of the other disorders.

Currently there is considerable interest in demonstrating the possibility of increased leukemia in the radiation-exposed clean-up workers of the Chernobyl accident. The Chernobyl clean-up workers comprise a large population of men with radiation exposures in considerable excess of those received by the general population from fallout. Much of the interest in this group of workers is because of the uncertain influence on the extent of leukemia induction of their relatively slow rate of radiation exposure compared to the almost instantaneous exposure of the atomic bomb survivors for whom there now are well-established dose-response relationships [2]. This difference is of considerable importance in the projection of possible similar effects, not only to the general population exposed to the fallout of the Chernobyl accident, but also to nuclear power and other radiation workers throughout the world whose rates of radiation exposure are much more similar to those of the Chernobyl clean-up workers than to those of the atomic bomb survivors. It also is expected that the extent of the radiation induction of leukemia in the clean-up workers will provide a good index of the extent of any possible excess cancer burden among others exposed to radiation from the Chernobyl accident.

Several recent reports based on information derived from registries and other sources suggest that the incidence of leukemia may be increased in Chernobyl accident clean-up workers, especially for those who worked during the years 1986 and 1987 [3-8]. The results of 1 of these reports [4] have been reported to be flawed primarily on the basis of the use of an inappropriate comparison population and inclusion of cases of chronic lymphocytic leukemia (CLL), a type of leukemia that has never been demonstrated to be increased in any human radiation-exposed population [9,10]. A subsequent published report based on the same cohort of liquidators with the exclusion of CLL cases and with other modifications in methodology showed no significant correlation between leukemia risk and radiation exposure or evidence of a dose-related trend [5]. The completeness of case ascertainment in the other studies of leukemia in the Chernobyl clean-up workers is uncertain, and there is little evidence that the cases included in those reports were subjected to rigid and impartial histologic review for verification of diagnosis. A number of excellent studies relating ionizing radiation exposure to the occurrence of leukemia have recognized that histologic verification of diagnosis is an essential component of the study [11-18]. The leukemia reports of the Chernobyl clean-up workers also raise questions of whether the diagnosis and classification of leuke-

mia cases in those reports meet the currently accepted international diagnostic criteria and terminology standards that are used by hematologists in the United States and western Europe.

The present review provides valuable information about whether the diagnosis and classification of cases of leukemia and also of MDS and MM that occurred in the adult male population of Ukraine during the 10 years following the Chernobyl accident can be histologically verified in accordance with internationally accepted hematology standards. The study also provides considerable information regarding the quality of stored bone marrow slides in Ukrainian hospitals. The results of this study are very useful in the consideration of conducting future histologically verified studies of the possible retrospective radiation induction of leukemia and some related disorders in the Ukrainian Chernobyl accident clean-up workers.

2. Materials and Methods

Data recording forms were developed, and the hematology panel members were provided with a considerable amount of background information concerning the objectives of the review. During the several months prior to the hematology panel session in Kiev, in which the bone marrow slides and abstracted clinical records of the cases were reviewed, 6 regions of Ukraine were tentatively identified as suitable for a future detailed study of leukemia in the Chernobyl clean-up workers within their resident populations. With 1 exception, each of the regions selected was an oblast (roughly equivalent to a state in the United States). The exception was Kiev City, the largest metropolitan area in Ukraine.

The objectives and research plans for the hematology pilot project were described to hospital officials and physicians by one or more senior hematologists from RCRM to obtain their permission to abstract records and to borrow bone marrow slides for review by members of an international panel of expert hematologists. A small team from the RCRM in Kiev, including an epidemiologist and a hematologist, then visited appropriate hospitals and clinics in the 6 target areas to collect materials for the review.

Men aged 20 to 60 years, in the general population, who were reported to have developed leukemia, MDS, or MM between the years 1987 and 1998 in any of the 6 regions of Ukraine in the proposed study for each of 3 time periods (1987-1990, 1991-1994, and 1995-1998), were randomly selected from hospital or clinic lists of patients for whom a pretreatment bone marrow aspiration smear was known to be available. The number of cases of each type of disease requested for evaluation from each region is shown in Table 1. Whenever 2 cases of a particular type of disease were required, 1 case was selected from the early period and the other from the most recent period. Similarly, if 5 cases were required, 2 were chosen from the earliest period, 1 from the middle period, and 2 from the latest period. The purpose of this selection process was to make certain that bone marrow slides from persons who had developed one of the diseases of interest during both the early and more recent years following the Chernobyl accident were examined.

Table 1.

Cases of Hematologic Disorders Requested from 6 Regions in Ukraine for Histologic Verification (Men, Aged 20-60 Years), 1987-1998

Diagnosis	No. of Cases Requested from Each Region	Total No. of Cases Requested from All 6 Regions
Chronic myelogenous leukemia	2	12
Chronic lymphocytic leukemia	2	12
Acute leukemia (any type)	5	30
Myelodysplasia	2	12
Multiple myeloma	2	12
Total	13	78

The histologic review sessions were conducted at the RCRM by the members of the expert review panel in Kiev over a period of 4 working days. At the outset it was stressed that the major objective of the review was to determine whether the expert panel members could confirm with reasonable certainty the clinical diagnosis of leukemia for each case. Other important objectives of the review were to evaluate differences in the classification of types of leukemia that might exist between the hematologists of Ukraine and those of the Western countries, the extent to which the diagnosis of MDS and MM could be confirmed, and the quality of the bone marrow slides and abstracted clinical records. The panelists agreed at the outset of the review that the criteria for the diagnoses of acute leukemia and MDS would be in accordance with the French-American-British (FAB) system with the minimum requirement of 30% blasts in the bone marrow smear for the histologic diagnosis of acute leukemia [19,20]. The minimum number of typical plasma cells in the bone marrow smear required for the histologic diagnosis of MM was 10% [21].

Following agreement on procedures to be used, the panelists reviewed 5 cases at a time and recorded their impressions on their worksheets regarding disease diagnosis, disease classification, and the quality of histologic materials and clinical records. One member of the panel then chaired open discussions of 10 cases at a time to achieve a consensus regarding disease diagnosis and classification. The process was continued in this fashion with daily rotation of discussion chairpersons until conclusions were reached for all cases

in the study. All histologic materials were carefully returned to their hospitals of origin upon completion of the slide reviews.

3. Results

Bone marrow aspiration smears from 45 cases of leukemia, 6 cases of MDS, and 11 cases of MM were identified by a random selection process (Table 2). Selection of cases from the entire adult male general populations of the 6 target areas in Ukraine resulted in the identification, using bone marrow slides, of only 62 cases of the various types of leukemia and related disorders rather than the 78 cases proposed for evaluation in accordance with the randomized selection process (Tables 1 and 2). The study was 16 cases short of the objective number, principally because of failure to identify enough cases of myelodysplasia during the early period of 1987-1990 and the almost complete absence of cases in one region where a natural disaster has destroyed most of their archived hematology slides.

The diagnosis of leukemia was histologically confirmed by members of the panel for 38 (84%) of the previously diagnosed cases of leukemia (Table 2). Exclusion of the 1 case of chronic lymphocytic leukemia (CLL) and 2 cases of chronic myelogenous leukemia (CML), for which only poor quality slides that were inadequate for diagnosis were available, improved the confirmation rate to 90%. It also should be noted that 3 of the 4 remaining cases that were not confirmed as leukemia were reclassified as MDS. All 3 cases previously had been classified as acute myelogenous leukemia (AML). Eight of the 11 cases of MM, for which bone marrow slides were available, were confirmed by members of the panel (Table 2) by consensus. On the other hand, panel members confirmed only 3 of the 6 cases of MDS (Table 2). The low confirmation rate for the 6 cases of MDS was the result of the reclassification of 3 of these cases as AML. Concurrence rates with the consensus diagnosis of leukemia for the 2 Ukrainian panel members and the 3 panel members from the United States and France were 92% and 85%, respectively.

Panel members classified all cases of acute leukemia by FAB but, because none of the previous Ukrainian cases had been classified by FAB, comparisons for all types of leukemia

Table 2.

Histologic Confirmation of the Diagnoses of Leukemia, Myelodysplasia, and Multiple Myeloma for Ukrainian Men, Aged 20-60 Years, by International Panel Members, 1987-1998

Reported Diagnosis	No. of Cases	Total No. of Cases Confirmed	% of Total Confirmed	No. of Cases with Inadequate Histology*	% of Cases Confirmed with Adequate Histology
Acute leukemia	28	24†	86	0	86
Chronic myelogenous leukemia	9	7	78	2	100
Chronic lymphocytic leukemia	8	7	88	1	100
Myelodysplasia	6	3‡	50	0	50
Multiple myeloma	11	8	73	2	89
All disorders combined	62	49	79	5	86

*Number of cases with bone marrow slides of such poor quality that they were undiagnosable.

†Three of the 4 cases not confirmed as acute leukemia were reclassified as myelodysplasia.

‡All 3 cases not confirmed as myelodysplasia were reclassified as acute leukemia.

Table 3.

Histologic Confirmation of the Type of Leukemia by Members of an International Hematology Panel Compared to Previous Classifications by Regional Hematologists in Ukraine

Reported Type of Leukemia	No. of Cases	No. Verified for Type of Leukemia	% Verified for Type of Leukemia
Acute myelogenous	10	9*	90
Acute lymphocytic	5	4†	80
Acute, other types	9	7‡	78
Chronic myelogenous	7	7	100
Chronic lymphocytic	7	7	100
All types combined	38	34	89

*One case was reclassified as acute lymphocytic leukemia.

†One case was reclassified as acute leukemia, type uncertain.

‡Two cases were reclassified as acute myelogenous leukemia.

were made in accordance with standard International Classification of Diseases terminology. The type of leukemia previously diagnosed was verified by members of the panel for 34 (89%) of the 38 proven cases of leukemia (Table 3). All 7 of the cases diagnosed as either CML or CLL were confirmed by members of the panel (Table 3). Panel members agreed with the diagnosis of leukemia type for 20 (83%) of the 24 cases of acute leukemia. This group of cases included 9 of 10 cases of AML and 4 of the 5 cases of acute lymphocytic leukemia (ALL). Two previously unclassified cases of acute leukemia were reclassified as AML. The rate of agreement with the type of acute leukemia as determined by consensus for the Ukrainian members of the panel was 85% compared to 80% for the panel members from the United States and France. Agreement by both groups for determination of the types of chronic leukemia was more than 90%.

Bone marrow aspiration smear quality generally was quite good. In only 3 of the 45 cases, because of poor smear quality, it was not possible to establish the diagnosis of leukemia. However, only about half of the smears examined were considered to be of excellent quality, because of such factors as faded stain, excessive dilution of marrow cells, or coverslip artifact. Bone marrow smear quality had little relationship to the time of disease occurrence. Abstracted information from medical records was generally very complete and almost invariably contained important information in support of the diagnosis of the underlying hematologic disorder.

4. Discussion

The results of this study strongly suggest that for at least the past 10 years there have been close similarities regarding the histologic diagnosis and classification of the major types of leukemia among the hematologists in Ukraine, western Europe, and the United States. These findings therefore suggest that clinical records that verify completion of an adequate pretherapy bone marrow aspiration smear almost invariably reflect an accurate diagnosis and classification for the major types of leukemia. This information is of particular importance for the proposed retrospective Chernobyl clean-up worker leukemia study because, during the immediate post-Chernobyl years, patients' bone marrow slides not infre-

quently were lost or destroyed, whereas their clinical records were more often retained and maintained in a good state of preservation.

There were several reasons for initially conducting the study on adult male members of the general population rather than on the clean-up workers. The logistical problems associated with a wide geographic search in Ukraine for an adequate number of the different types of leukemia in the clean-up worker population appeared quite formidable. The selection of a cohort of Chernobyl clean-up workers for the proposed epidemiological study of leukemia was still incomplete at the time of the review, and its completion appeared to be many months ahead. It also seemed unlikely that the proposed Chernobyl clean-up worker cohort was large enough to provide enough cases of the various types of leukemia to satisfy the requirements for expert hematology panel review.

Evidence that MDS is a radiation-induced disorder is scanty but certainly is sufficient to recommend that this disease be included in any study of radiation-induced leukemia [12,22-28]. One problem with the inclusion of MDS in such studies is that the clinical presentation and morphologic characteristics of MDS and AML frequently are so similar that diagnostic differentiation between advanced MDS and AML may be extremely difficult, particularly in the absence of cytogenetic and special histochemical studies [22]. Primary MDS is a clonal stem cell disorder with a rate of progression from its most advanced form, refractory anemia with excess blasts in transformation (RAEB-t), to acute nonlymphocytic leukemia reported to be in the range of 40% to 60% [29,30]. Actuarial studies of the transition rates of certain advanced primary forms of MDS to acute nonlymphocytic leukemia are reported to be 100%, implying that the border between RAEB-t and AML is completely arbitrary [31]. The relationship between secondary MDS and AML is so close that a recommendation also has been made that MDS should not be separately identified in any study of secondary leukemia [23]. The blurring of diagnostic criteria between either MDS associated with a large number of blast cells or some secondary forms of MDS and AML also has been emphasized in the recent World Health Organization recommendations for the classification of hematologic malignancies [32].

The earliest case recorded as MDS in this series was in 1993, but there is considerable evidence that the disorder was recognized by Western hematologists a number of years before that time. Perhaps general unfamiliarity with this disorder among Ukrainian hematologists 10 to 15 years ago, along with the problem of separating many cases of MDS from AML, difficult even for many expert hematologists, accounted for the reclassification to acute leukemia of 3 of the 6 cases of MDS included in the study. In a similar fashion, if 3 of the AML cases had not been reclassified as MDS, the confirmation rate for AML would have been more than 95% (Table 2).

The number of cases of MM included in this pilot study was too small to draw strong conclusions, but the results suggest that a more extensive study of this disorder in relation to radiation exposure is quite feasible. The case for radiation induction of MM remains somewhat controversial, but there are several reasons why a radiation dose-response study of MM in the clean-up workers could be important [2,33-39].

The age distribution of the male nuclear power workers for whom studies at some nuclear power sites have shown an increased risk of radiation-induced MM is quite similar [33,34,37,38]. Although the current number of person-years for a retrospective study of MM for the population of the approximately 100,000 Ukrainian clean-up workers proposed for a future study of leukemia is moderately less than that for the nuclear power workers in the 3-country study, the estimated cumulative radiation dose for the entire cohort of clean-up workers in the proposed study is several times greater than that for the nuclear power workers. This calculation is based on an average clean-up worker radiation dose estimate of approximately 110 mGy [40]. Finally, it should be mentioned that even if the current latent period for determination of radiation-induced risk for MM in the clean-up workers is too short, or if the population of workers is too young to provide conclusive results, a study at this time should provide the groundwork for future investigations.

Overall, the information derived from this study provides strong support for acceptance of the diagnoses of the chronic and acute leukemias that have occurred in Ukrainian Chernobyl clean-up workers following the accident, providing the diagnoses were supported by bone marrow examinations. This study also suggests that the previous histologic diagnosis of cases of MM in this population has been quite reliable. Too few cases of MDS were evaluated to draw any firm conclusions, but the results suggest that most cases reported with this disorder are either correctly diagnosed MDS or cases of AML. Such information is of considerable importance as a background for the future conduct of retrospective studies of radiation dose-response relationships for the occurrence of leukemia, myelodysplasia, and MM in Chernobyl clean-up workers of Ukraine. It is likely that bone marrow slides for many of the cases will not be located at this late date, but if the clinical information and bone marrow reports are consistent, the diagnoses of leukemia and MM should be accepted.

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