ORIGINAL ARTICLE

Hematological malignancies in Chernobyl clean-up workers (1996-2010)

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Abstract

Background: Even 25 years after the Chernobyl catastrophe, the interpretation of the findings on leukemia risk among Chernobyl clean-up workers is still a point of much controversy. Precise diagnosis of the main types of hematopoietic malignancies according to FAB classification and new WHO classification may be helpful in estimating the relative contribution of the radiation factor to the overall incidence of such pathologies.

Methods: The data on 295 consecutive cases of malignant tumors of hematopoietic and lymphoid tissues in Chernobyl clean-up workers diagnosed from 1996 to 2010 are given in comparison with the data of 2,697 consecutive patients other than clean-up workers of the same age group. For this study, a set of complex diagnostic techniques were used, including morphology, cytochemistry of bone marrow and peripheral blood cells, immunocytochemistry (APAAP, LSAB-AP) as well as the utilization of monoclonal antibodies to lineage specific and differentiation antigens of leukocytes.

Results: All the main forms of tumors of hematopoietic and lymphoid tissues were diagnosed among clean-up workers under study in 10-25 years after the Chernobyl catastrophe including myelodysplastic syndromes (MDS), acute leukemias (ALL and AML), chronic myelogenous leukemia (CML) and other myeloproliferative neoplasms, chronic lymphocytic leukemia (B-CLL) and lymphoid neoplasms of B and T cell origin. Among 46 AML cases in clean-up workers, leukemia was preceded by MDS in seven patients. CML percentage tended to be higher in the group of patients representing clean-up workers (9.13% vs. 6.59%). B-CLL was a predominant form of hematopoietic malignancies in clean-up workers under study (26.10%). Nevertheless, the percentage of B-CLL in patients of clean-up workers group did not differ significantly from that in the non-exposed patients. The multiple myeloma percentage in our study was higher in the clean-up workers (6.46% vs. 4.00%).

Conclusions: The verified diagnosis of tumors of hematopoietic and lymphoid tissues according to the up-to-date WHO classification could be prerequisite for further molecular genetics and analytical epidemiology study of leukemias that may be related to the Chernobyl catastrophe.

Key words

Chernobyl clean-up workers, Leukemias, Cytochemistry, Immunophenotyping

1 Introduction

The Chernobyl nuclear power plant accident on April 26, 1986 remains the worst ever in the history of the nuclear industry. Cancers, and in particular leukemias seem to represent the most serious effects of the exposure to ionizing radiation. Meanwhile, the question as to whether the incidence of leukemias and malignant lymphomas among 260,807 Ukrainian clean-up workers of 1986 and 43,366 of 1987 (average doses of 14.0 cGy in 1986 and 9.0 cGy in 1987) has increased in the 25 years since the catastrophe is still a point of much controversy [1-6].

The UN Scientific Committee on Effects of Atomic Radiation (report to UN General Assembly, 2001) and Chernobyl Forum (Vienna, 2005) rejected the possibility of increasing leukemia incidence in Chernobyl clean-up workers. This point of view is inconsistent with the results of several descriptive epidemiologic studies in Ukraine, Belarus, and Russia. The recent studies of Chernobyl clean-up workers have provided evidence of the increased risk of leukemia and other hematological malignancies. In fact, a number of authors have predicted and reported the increased incidence of leukemia among clean-up workers in Russia, Belarus and Ukraine. According to Ivanov et al., the dynamics of standardized incidence ratio demonstrates a 2.5-3-fold increase in the leukemia incidence in Russian cohort of Chernobyl clean-up workers in 5-7 years after the accident [7]. Prisyazhniuk et al. stated statistically significant increment in observed-to-predicted ratio of leukemia and lymphoma incidence: 2.6 in 1990-1993 and 2.0 in 1994-1997 [8]. Kesmeniene et al. reported on 117 cases of neoplasms of lymphoid and hematopoietic tissues in Belarus, Russia and Baltic countries as of 2007 [9]. In a study of the cohort of male clean-up workers in Ukraine subjected to the external radiation exposure, the investigators at the National Cancer Institute (USA) observed a radiation-related risk of leukemia comparable to risks experienced by Japanese atomic bomb survivors with acute exposure [10].

Nevertheless, in most studies the actual incidences of hematopoietic malignancies as well as the risks of increasing incidence of leukemias were assessed according to the primary data categorized on the basis of the obsolete ICD-9 (1975) classification. The acute leukemias have been registered in total even without delineation of myeloid and lymphoid forms, to say nothing of the immunophenotypic variants. Moreover, in Belarus, Russia and Ukraine, no systematic centralized population-based cancer registry existed at the time of the accident.

The risks of radiation-induced leukemias for various biological subtypes of hematological malignancies appear to differ significantly. Only precise diagnosis of the major types of hematological malignancies among Chernobyl clean-up workers will be helpful in estimating the relative contribution of the radiation exposure to the overall incidence of such pathologies. Unfortunately, until recently only cytomorphology and several cytochemical techniques were routinely used for diagnostic purposes in the vast majority of onco-hematological clinics in Ukraine.

In 1993, the Reference Laboratory was set up as a public service in RE Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, National Academy of Sciences of Ukraine with the aim of obtaining a precise diagnosis of the haematopoietic malignancies based on cytomorphology, cytochemistry, immunophenotyping in accordance with FAB, WHO, EGIL, ICD-10 and ICD-O-2 classifications. The leukemias and lymphomas in Ukrainian patients, including Chernobyl clean-up workers and inhabitants of contaminated areas have been diagnosed at the Reference Laboratory since that time. This article deals with the analysis of tumors of hematopoietic and lymphoid tissues diagnosed in the patients of one of these two categories, namely in Chernobyl clean-up workers.

The aim of the study is to sum up the data on immunophenotypes and the percentage of the various forms and cytological variants of leukemia and lymphoma verified according to Western standards in a consecutive group of 295 Ukrainian Chernobyl clean-up workers diagnosed at the Reference Laboratory in 1996-2010 (10-25 years after Chernobyl catastrophe) and categorized according to up-to-date WHO classification. The data on Chernobyl clean-up workers are compared with that in the patients other than clean-up workers who also were diagnosed at the Reference Laboratory consecutively at the same time.

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2 Materials and methods

The complex of diagnostic techniques used included MGG staining of blood and bone marrow smears; cytochemical detection of myeloperoxidase, acid phosphatase, alkaline phosphatase, acid non-specific esterase, naphtol-AS-D-chloracetate esterase, PAS-reaction. Immunocytochemical techniques were applied (ABC-AP, APAAP) for detecting the antigens of myeloid cells (CD33, CD13, CD15, CD64, CD16, MPO), erythroid and megakaryocytic cells (CD71, CD61, CD62, CD41, CD42, glycophorin A), T-cells (CD7, CD5, CD3, CD2, CD1a, CD4, CD8, CD45RO, γδTCR), B-cells (CD19, CD20, CD22, CD10, κ, λ, μ chains), stem cell markers and commitment markers (CD34, CD38, CD45RA, HLA-DR).

All the clean-up workers referred to the Reference Laboratory within the period stated above were examined consecutively without any previous selection of cases. The radiation load of the clean-up workers under study varied from 7.5 to 25 cGy [11].

295 patients with tumors of hematopoietic and lymphoid tissues (254 males and 41 females) were distributed according to the age such as follows: 30-39 years – 14 patients, 40-49 years – 47 patients, 50-59 years – 91 patients, 60-69 years – 109 patients, and 70 years and above – 34 patients. The group of comparison included 2697 consecutive patients other than clean-up workers diagnosed at the Reference Laboratory in 1996-2005.

For statistical analysis, odds ratio (OR), 95 % confidence interval (CI) of OR, and *P* value were calculated by conventional methods [12].

3 Results

The summary of tumors of hematopoietic and lymphoid tissues in Chernobyl clean-up workers as well as non-exposed patients diagnosed at the Reference Laboratory is given in Table 1.

Table 1. Types of hematopoietic malignancies in Chernobyl clean-up workers

Type of leukemia	Absolute number of cases and percentage (in brackets)		OR (95 % CI)	*P*
	Chernobyl clean-up workers	Non-exposed patients		
Acute leukemias				
Acute lymphoblastic leukemia	17 (5.76%)	214 (7.93%)	0.7095 (0.4264 to 1.1806)	0.1865
Acute myeloid leukemia	46 (15.60%)	732 (27.14%)	0.4959 (0.3580 to 0.6869)	< 0.0001
Myeloproliferative neoplasms				
Chronic myelogenous leukemia	27 (9.13%)	178 (6.59%)	1.4257 (0.9331 to 2.1785)	0.1010
Polycythemia vera	6 (2.03%)	3 (0.11%)	18.6436 (4.6380 to 74.9433)	< 0.0001
Primary myelofibrosis	4 (1.36%)	–	n/e	
Essential thrombocythemia	10 (3.39%)	–	n/e	
Chronic eosinophylic leukemia/ Hypereosinophylic syndrome	3 (1.02%)	–	n/e	
Myelodysplastic / Myeloproliferative neoplasms				
Chronic myelomonocytic leukemia	10 (3.39%)	84 (3.11%)	1.0915 (0.5602 to 2.1265)	0.7970
Myelodysplastic syndromes	16 (5.42%)	107 (3.70%)	1.3881 (0.8092 to 2.3813)	0.2336
Mature B-cell neoplasms				
Chronic lymphocytic leukemia	77 (26.10%)	791 (29.32%)	0.8511 (0.6479 to 1.1180)	0.2466
B-cell prolymphocytic leukemia	4 (1.36%)	23 (0.85%)	1.5981 (0.5489 to 4.6529)	0.3899
Hairy cell leukemia	11 (3.73%)	118 (4.37%)	0.8465 (0.4509 to 1.5893)	0.6042
Non-Hodgkin's lymphoma in leukemization phase	35 (11.86%)	296 (10.97%)	1.0919 (0.7520 to 1.5855)	0.6440
Multiple myeloma	19 (6.46%)	108 (4.00%)	1.6503 (0.9978 to 2.7294)	0.0510
Mature T-cell neoplasms				
T-cell prolymphocytic leukemia	2 (0.68%)	3 (0.11%)	6.1297 (1.0201 to 36.8343)	0.0475
T-cell large granular lymphocytic leukemia	5 (1.69%)	3 (0.11%)	15.4828 (3.6812 to 65.1196)	0.0002
Sezary syndrome	3 (1.02%)	8 (0.29%)	3.4533 (0.9111 to 13.0887)	0.0683

n/e – not estimated

3.1 Acute lymphoblastic leukaemias (ALL)

In patients with ALL of B-cell origin, the following cytological subtypes were diagnosed:

- ALL with phenotype of stem hematopoietic cell: $CD34^+$, $CD38^+$, $HLA\text{-}DR^+$, $CD45RO^+$
- pre-pre-B-ALL: $CD19^+$, $CD22^+$, $CD20^-$, $CD10^-$, $cy\mu^-$
- common ALL: $CD19^+$, $CD22^+$, $CD20^{+/-}$, $CD10^+$, $cy\mu^-$
- pre-B-ALL: $CD19^+$, $CD22^+$, $CD20^{+/-}$, $CD10^+$, $cy\mu^+$
- B-ALL: $CD19^+$, $CD22^+$, $CD20^+$, $CD10^+$, sIg^+

ALL of T-cell origin were also subdivided into four variants:

- T1-ALL with a phenotype of subcortical thymocytes: $CD7^+$, $CD2^+$, $cyCD3^+$, $CD5^-$, $CD1a^-$, $CD4^-$, $CD8^-$
- T2-ALL with a phenotype of cortical thymocytes: $CD7^+$, $CD2^+$, $sCD3^+$, $CD5^+$ $CD1a^{+/-}$, $CD4^+$, $CD8^+$
- T3-ALL with a phenotype of medullar thymocytes: $CD7^+$, $CD2^+$, $CD3^+$, $CD5^+$, $CD1a^+$, $CD4^+$ or $CD8^+$
- T4-ALL with γδT-cell receptor: $\gamma\delta TCR^+$, $CD7^+$, $cyCD3^+$, $CD2^+$, $CD5^-$, $CD1a^-$, $CD4^-$, $CD8^-$

3.2 Acute myeloid leukemias (AML)

The series of patients with AML were classified by WHO system into such entities: AML with minimal differentiation; AML without maturation; AML with maturation; acute monoblastic and monocytic leukemia; acute myelomonocytic leukemia; acute promyelocytic leukemia; acute erythroid leukemia, acute megakaryocytic leukemia; blastic plasmacytoid dendritic cell neoplasm (BPDC). Such biological subtypes as AML with minimal differentiation, acute megakaryoblastic leukemia, acute erythroid leukemia and acute leukemias of ambiguous lineage required immunocytochemical study to be diagnosed precisely.

In most cases of AML with minimal differentiation, blast cells express CD34, CD38, CD13 and CD117 antigens and in several cases, expression of CD7 was seen. MPO was negative in blast cells by cytochemistry but the results of detection of intracytoplasmatic MPO antigens in blast cells were positive by staining with anti-MPO MoAbs.

AML without maturation was characterized by MPO-positive blasts and expression of CD13, CD33 and CD117 antigens. CD34 and HLA-DR were revealed and expression of CD7 and CD56 was registered in some patients.

AML with maturation was characterized by expression of such myeloid-associated antigens as CD13, CD33. In a fraction of blasts, expression of HLA-DR and CD34 was evident.

Acute myelomonocytic leukemia showed population of blasts expressing myeloid antigens CD13, CD33, CD15 and population of leukemic cells with markers of monocytic differentiation CD14, CD4, CD11b, CD11c. In most cases, blast cells were positive for HLA-DR and CD7.

Acute monoblastic and monocytic leukemia demonstrated acid non-specific esterase - positive blasts expressing HLA-DR, myeloid antigens CD13, CD15, CD11b, CD11c, CD68. In some cases, expression of CD7 and CD56 was found. MPO was expressed more often in acute monocytic leukemia. Acute promyelocytic leukemia was characterized by absence of HLA-DR, CD34 and CD15 expression, and weak positive reaction with MoAbs to CD117.

Acute erythroid leukemia was characterized by blast cells negative for HLA-DR, CD34 and MPO. Expression of glycophorin A was detected in cases with more differentiated leukemic cells. In two cases, expression of CD36 was

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detected that may be expressed also by monocytes and megakaryocytes. The early marker specific of the erythroid lineage is required since the cases resulting from leukemic transformation of primitive erythroid cells are underdiagnosed.

Acute megakaryoblastic leukemia is characterized by expression of CD41 (glycoprotein IIb/IIIa), CD61 (glycoprotein IIIa) and CD36. Reactions for CD34 and HLA-DR were negative.

It is worth noting that in seven AML patients, including patients with AML with minimal differentiation, acute myelomonocytic leukemia and acute erythroid leukemia (15.2% of all AML cases), leukemia was preceded by MDS. At the same time, only six (1.5%) cases of preceding MDS were found upon examination of AML patients in general population of Kyiv city and district.

3.3 Myeloproliferative neoplasms

Myeloproliferative neoplasms (chronic myelogenous leukemia, polycythaemia vera, primary myelofibrosis, essential thrombocythemia) were diagnosed in 50 clean-up workers. The relative contribution of CML to the total number of clean-up workers with leukemias and lymphomas was about 1.4-fold higher than corresponding percentage in the general population.

3.4 Mature B-cell neoplasms

Mature B-cell neoplasms comprise 49.49% of all hematopoietic malignancies in our group of clean-up workers. B-CLL (26.10%) was a predominant form under study. Immunophenotype of all B-CLL was quite typical (HLA-DR$^+$, CD19$^+$, CD20$^+$, CD22low, CD5$^+$, CD23$^+$, CD79a$^+$, sIg^{low}, CD10$^-$). B-cell prolymphocytic leukemia (B-PLL) was registered in four patients. Lymphoid cells of hairy cell leukemia were quite typical (HLA-DR$^+$, CD19$^+$, CD20$^+$, CD22$^+$, CD5$^-$, CD23$^-$, CD10$^-$, CD25$^+$, sIg^{bright}, $\kappa^+\lambda^-$).

Different types of B-cell non-Hodgkin's lymphoma (NHL) were diagnosed based on cytomorphological and immunocytochemical study of bone marrow and blood cells in 35 patients.

The following immunophenotypes of B-cell non-Hodgkin's lymphoma were identified:

- Follicular lymphoma (12 pts.): CD19$^+$, CD20$^+$, CD22$^+$, CD10$^{+/-}$, CD5$^-$, CD23$^{+/-}$, CD25$^-$, CD43$^-$, CD11c$^-$
- Lymphoplasmacytic lymphoma (5 pts.): CD19$^+$, CD20$^+$, CD22$^+$, CD10$^-$, CD5$^-$, CD23$^-$, CD25$^-$, CD38$^+$
- Mantle cell lymphoma (5 pts.): HLA-DR$^+$, CD19$^+$, CD20$^+$, CD22$^+$, CD5$^+$, CD23$^-$, CD10$^-$, Cyclin D$^+$
- Splenic marginal zone B-cell lymphoma (3 pts.): HLA-DR$^+$, CD19$^+$, CD20$^+$, CD22$^+$, CD5$^-$, CD23$^-$, CD25$^-$, CD10$^-$, CD43$^-$, sIg$^+$
- Diffuse large B-cell lymphoma (7 pts.): CD19$^+$, CD20$^+$, CD22$^+$, CD79a$^+$, CD5$^-$, CD23$^-$
- Extranodal marginal zone B-cell lymphoma of MALT type (3 pts.): CD19$^+$, CD20$^+$, CD22$^+$, CD79a$^+$, CD23$^-$, CD5$^-$, CD10$^-$, CD43$^{+/-}$

Multiple myeloma (diffuse and solitary forms) was diagnosed in 19 patients (mean age 57.9 years). In six patients (31.6%), the disease developed at the age under 50. Multiple myeloma percentage in the patients of Chernobyl clean-up worker group in our study turned out to exceed that in the patients of the general populations studied at the same period (6.46% vs. 4.00%).

3.5 Tumors from mature (peripheral) T-cells and NK-cells

Tumors from mature (peripheral) T-cells and NK-cells among clean-up workers studies were diagnosed in 10 cases with the following immunophenotypes:

–T-cell prolymphocytic leukemia (2 pts.): $CD1a^{-}$, $CD2^{+}$, $CD3^{+}$, $CD5^{+}$, $CD7^{+}$, $CD4^{+}$,$CD8^{-}$

–Sezary syndrome (3 pts.): $CD7^{+}$, $CD3^{+}$, $CD4^{+}$, $CD8^{-}$, $CD25^{-}$

– Large granular lymphocyte leukemia (LGL-leukemia)

T-cell subvariant (3 pts.): $CD3^{+}$, $CD5^{+}$, $CD2^{+}$, $CD7^{low}$, $CD4^{-}$, $CD8^{+}$, $CD56^{low}$, $CD57^{+/-}$, $CD16^{+}$, HLA-DR^{-}

NK-cell subvariant (2 pts.): $CD3^{-}$, $CD5^{-}$, $CD2^{+}$, $CD7^{+}$, $CD4^{-}$, $CD8^{+/-}$, $CD56^{low}$, $CD57^{+}$, $CD16^{+}$, HLA-DR^{low}

4 Discussion

The data on immunophenotypes and the percentage of the various forms and variants of leukemia and lymphoma in the representative group of leukaemia patients among Ukrainian Chernobyl clean-up workers examined consecutively in 1996-2010 have been presented. All the cases under study were strictly categorized according to their immunophenotypes. In principle, all the main forms of tumors of hematopoietic and lymphoid tissues including B-cell chronic lymphocytic leukemia were diagnosed in this group. While the relative contribution of radiogenic factor into the genesis of the leukemias and lymphomas under study remains uncertain, the patterns of the distribution presented for the specified forms of hematopoietic and lymphoid malignancies in the patients diagnosed among Chernobyl clean-up workers demonstrates the increased multiple myeloma rate and the tendency to the increased CML rate as compared to the group of general population. The same trend as to the increased incidence of multiple myeloma was observed in epidemiological study in the contaminated areas of Belarus [13].

The peculiar feature of AML was evident in clean-up workers under study, namely 15.2% of AML cases were preceded by MDS.

The high incidence of LGL-leukemia among clean-up workers with hematopoietic malignancies (1.69%) is of particular importance since this category of T-cell and NK-cell neoplasms has not been revealed earlier in oncohematological clinics in the Ukraine. High incidence of neutropenia due to NK or NK-like T-cell proliferative disorders was found among atomic bomb survivors in Japan [14].

In the cohort of 86,572 A-bomb survivors followed up in 1950-1990 upon the reclassification of hematopoietic malignancies according to FAB system accounting new dosimetry systems DS86 and DS02 the differential effects of radiation on major subtypes of human leukemias were shown. In particular, the incidences of multiple myeloma, ALL and CML increased more than that of other biological subtypes of leukemia [15].

In our study, B-CLL was shown to be a predominant form of hematopoietic malignancies in clean-up workers as well as the patients of general population with percentage difference being non-significant (26.10% vs. 29.32%). Until recently, B-CLL was excluded from consideration in many analyses of leukemias in association with exposure to ionizing radiation. Nevertheless, the question of B-CLL association with exposure to ionizing radiation seems to be worth of further study as several authors having challenged the accepted view that B-CLL is nonradiogenic form of cancer [16]. The delineation of specific B-CLL subtypes with different somatic mutations contributing to the genesis of the disease followed by the analysis of their incidence will undoubtedly clarify this subject. It is also noteworthy that according to the data from the Research Centre for Radiation Medicine of the National Academy of Medical Sciences of Ukraine, CLL in Chernobyl

clean-up workers develops at younger age with more advanced symptoms and more aggressive course and resistance to standard therapy [17].

Search for the molecular markers of radiation-associated leukemias is one of the principal problems in confirming the association between irradiation and leukemia. Imamura et al. demonstrated that 60% patients with MDS among atomic-bomb survivors had p53 suppressor point mutations [18]. Recently, we have obtained the data on gene expression profiling in Ukrainian B-CLL patients [19].

Data on the tumors of hematopoietic and lymphoid tissues originating in the exposed persons after Chernobyl catastrophe may be very important for the prognostic estimates of the health effects of the Fukushima disaster. According to recent data, the risk of radiation-induced hematological malignancies, especially MDS, persisted even over 50 years since the exposure [20, 21]. Therefore, much longer follow-up seems to be required for a correct estimate of such risks.

We believe that only precise diagnosis of the major types of hematological malignancies among Chernobyl clean-up workers according to the up-to-date classification with delineation of the specific biological subtypes of hematological malignancies may represent the basis for the studies of the risks of radiation leukemias in the persons having been exposed to ionizing radiation. The large massive of empirical data filed at our Reference Laboratory might be advantageous for further research aimed at elucidating the molecular mechanisms of the origin of radiation-associated leukemias.

Competing interests

The authors declare that they have no competing interests.

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