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Research Article

Epidemiology and Molecular Genetics of Acute Leukemia in a Major Industrial Center of Western Siberia

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ABSTRACT

The rationale for the present study is explained by the lack of published data on the pattern of incidence rate of acute leukemia with detailed characteristics of molecular genetic criteria of this diagnosis in the subjects of Siberian Federal District (SFD). Complex retrospective analysis of the data, obtained within the ten-year monitoring (2007 – 2017), revealed the incidence rate of different forms of acute leukemia in Novosibirsk, which is a major industrial center of Western Siberia with the population of more than 1 million people.

The aim of the present study was to evaluate the different variants of acute myeloid and lymphoid leukemia incidence rate according to the classification of the WHO in Novosibirsk for the period of 2007 – 2017. The main

method of the study was descriptive epidemiology by the local registers for estimation of general incidence rate and pattern of the hematologic malignancies.

The authors identified the relation between recurrent variants of acute leukemia according to the genetic and molecular biological criteria of the WHO classification. The significance of molecular genetic studies results (FISH and microarray) was shown for the evaluation of the disease prognosis and treatment outcome.

Total acute leukemia incidence rate was identified in Novosibirsk. It was equal to 2.7 cases per 100 thousand of adult population: acute myeloid leukemia (AML) – 2.0:100 thousand of adult population, acute lymphoid leukemia (ALL) (including the cases of undifferentiated and biphenotypic acute leukemia) – 0.7:100 thousand of adult population per year, which, in general, agrees with the morbidity rate in the European part of the country. Besides, the authors showed that marker genetic aberrations were identified in 25% of acute leukemia cases: at AML in 70.6% and at ALL in 29.4% of cases. Widespread genetic abnormalities in patients with AML primarily included variants with mutations of *NPM1* (29.2%) and *CEBPA* gene (16.7%), in patients with ALL – the variant with Ph-chromosome - t(9:22)(q34;q 11.2) and expression of chimeric gene *BCR-ABL1* (1.6%), hyperdiploid (32.6%) and hypodiploid (27.9%) variants prevailed.

The present article can be useful for planning of therapeutic needs of the population, diagnostics of acute leukemia, correction of economic calculations for hematologic service supply with pharmacologic antitumor drugs and reagents.

Key words: epidemiology of acute leukemia in Western Siberia, molecular biology, molecular genetics, flow immunocytofluorimetry of lymphoid and myeloid leukemia, microarray, immunocytochemistry, incidence rate of aberrant leukemia variants

INTRODUCTION

Novosibirsk is the third largest city in Russia. It is the largest industrial center in Western Siberia that occupies more than 500 square kilometers with the population of 1 million 602.9 thousand people in the beginning of 2017. The city is situated in unfavorable geo climatic zone with severely continental climate, hard frosts in winter time and sharp temperature fluctuations (average yearly air temperature -1.3ºC) [1]. Assessment of oncohematological morbidity in a major city is relevant because it reflects oncologic morbidity status in general, which is a highly significant social problem of modern healthcare. Acute leukemia is the most important indicating nosological entity among hematological malignancies.

Acute leukemia is the most malignant form of hemoblastosis. Based on deep understanding of tumor cells biochemistry and pathogenetic mechanisms of tumor growth, the scientists developed the technology of programmed therapy for malignant neoblastic tumors and maintenance treatment. These changes in therapeutic and diagnostic approaches positively influenced on the disease outcome, survival rate and patients quality of life. Acute leukemia became indicator nosology as regards to the quality of hematological clinics healthcare service in the whole world. A number of international conferences and forums were dedicated to the discussion and approval of the new WHO classification, treatment standards and complication preventive measures for myeloablative chemotherapeutic plans. Recently, the researchers defined allogenic transplantation of bone marrow and peripheral stem cells as the basis of remission consolidation and therapy for residual tumor, as well as a method of biological modelling of immune reaction transplant against leukemia *in vivo* [2].

Further improvement of tumor progression and therapy efficiency prediction was associated with verification of molecular genetic abnormalities in the genome of tumor blast cell, which revealed high heterogeneity of the present nosology. This led to changes in the WHO classification of acute leukemia and identification of special variants associated with a complex of immunophenotypic, cytogenetic and molecular genetic markers [3]. Close association between tumor variant and peculiarities of clinical picture, efficiency of conventional protocols of treatment and disease

outcome prognosis was proved. Implementation of diagnostic technologies of immunophenotype assay and genome of blast cells at acute leukemia, including immunofluorimetry, fluorescent in situ hybridization (FISH) microarray and other molecular biological tests was important for the development of regional hematological centers. Presently, completeness of data on epidemiology of hemoblastosis is provided not only by clinical and cytochemical characteristics of acute leukemia, but also by a wide range of immunophenotypic, cytogenetic and molecular genetic features [4].

It is established that descriptive epidemiologic studies can be useful for specification of tumor etiology, identification of population risk groups, actualization of new diagnostics technologies, treatment and prognosis of the disease outcome [5,6,7].

The authors indicate on the limitations of the regional registers data as compared to clinical studies data, like the lack of centralized reference check of tumor morphological type. Nevertheless, the majority of researchers admit that the hemoblastosis incidence rate, calculated by the population registers data, is accurate as a model of development and tumor progression of oncohematological diseases within certain territories and, thus, represent valuable object of the study [8-11]. Besides, in some countries there was positive experience of local registers data use for verification of epidemiology of noncontagious diseases [15].

There is lack of published data on the pattern of acute leukemia incidence with detailed characteristics of the specified aspects in the majority of regions, in subjects of Siberian Federal District and in Russia in general, which defined the aim and tasks of the present study.

The aim of the study was to evaluate different variants of acute myeloid and lymphoid leukemia incidence rate according to the WHO classification in Novosibirsk for the period of 2007 – 2017.

The tasks of the study:

1. To provide epidemiological characteristics of the population with acute leukemia in Novosibirsk for the period of 2007-2017.
2. To investigate the incidence rate of certain acute myeloid and acute lymphoid leukemia variants as regards to persistent genetic abnormalities, immunophenotypic characteristics and the WHO classification criteria (revision of 2008).
3. To evaluate prognostic significance of chimeric genes expression profile for acute leukemia development and therapy efficiency.

MATERIALS AND METHODS

Acute leukemia prevalence study results were obtained by the method of observational descriptive epidemiology. The data was taken from the local cancer registers of patients diagnosed with acute leukemia.

Incidence rate per 100 thousand people in the region was calculated by the formula of primary disease incidence (the incidence of primary diagnosed disease / average annual population that live in the specified region) x 100 thousand.

The pattern of acute leukemia by variants, according to the WHO classification, was identified by the formula (number of single cases of the disease variant / total disease cases) x 100.

The data on incidences of primary diagnosed acute leukemia was provided by the information system of the municipal hematological center. It was compared with the records of the database of insurance medical companies and the compulsory medical insurance fund [16].

Retrospective study of the primary documentation (medical histories, patient records, statements, cytogenetic laboratory data, results of immunophenotypic and molecular genetic assays of hemoblastosis) of the patients registered by the municipal hematological service of Novosibirsk during the period from 2007 to 2017.

Along with routine parameters, the authors accounted the results of FISH-assay, immunochemical diagnostics, flow immunofluorimetry and microarray of key genetic aberrations in tumor cells.

Cytogenetic study of bone marrow was performed by conventional method. The study of tumor blast cells by the method of fluorescent

in situ hybridization (FISH) was performed with locus-specific (LSI) DNA probes Cytocell (Great Britain). The analysis of images and hybridization signals count were performed with microscope Nikon 90i (Japan) and software package Lucia (Czech Republic).

The study of surface proteins was performed by the method of flow cytometry with flow cytometer FC500 (Beckman Coulter) by the standard protocol of lysis and blood and bone marrow staining. The authors used monoclonal antibodies (Beckman Coulter). The study of surface and intracellular proteins was performed by the method of immunocytochemistry according to the standard protocol of staining by direct visualization using Ultra Vision Quanto Detection System and ready-to-use monoclonal antibodies (Thermo Scientific).

Test-systems (matrix molecular gene array) "LK-BIOCHIP", developed by the Institute of molecular biology named after V.A. Engelgarth of the Russian Academy of Sciences (Moscow), were used for microarray of bone marrow and peripheral blood RNA. Oligonucleotides, complementary to the mRNA sequential regions that express chimeric genes AML/ETO, E2A/PBX, BCR/ABL, PML/RARA, CBFB/MYH11, TEL/AML, MLL (total) as a result of chromosome aberrations t(8;21), t(1;19), t(9;22), t(15;17), inv16, t(12;21), were immobilized on the surface of microarrays.

The authors analyzed primary records of 410 patients with acute leukemia. The analyzed group included only adult patients aged from 22 to 72. Average age was 48.4 ± 24.0 years old, 36.3% (n=149) of males and 63.7% (n=261) of females.

The diagnosis and variant of acute leukemia was specified according to the criteria of the WHO and FAB classifications [3]. According to the WHO recommendations, diagnostically significant threshold of blast cells in bone marrow was taken as 20% and more [3,4,5].

RESULTS AND DISCUSSION

Among 410 patients, acute myeloblastic leukemia (AML) was registered in 80.2% (n=328), acute lymphoblastic leukemia (ALL) – in 17.3% (n=82), undifferentiated and biphenotypic variants – in 2.5% (n=11).

The calculated registered acute leukemia incidence rate in Novosibirsk was equal to 2.7 cases per 100 thousand of adult population. Incidence rate of acute myeloblastic leukemia was 2.0 per 100 thousand of adult population, acute lymphoblastic leukemia (including undifferentiated and biphenotypic acute leukemia) – 0.7 per 100 thousands of adult population per year.

The pattern of AML by clinical cytomorphological and cytochemical features was organized according to the criteria of FAB classification. In 328 patients with AML, M0-variant was registered in 20 patients (6.2%), M1 – in 65 patients (19.8%); M2 – in 144 patients (44.2%); M3 – in 13 patients (3.9%); M4 – in 67 patients (20.3%); M5 – in 6 patients (1.8%); M6 – in 3.8 patients (1.3%).

Immunophenotyping with monoclonal antibodies (methods of flow immunofluorimetry and immunocytochemistry by bone marrow samples) allowed the authors to identify immunophenotypic variants of ALL according to the classification of EGIL (1995-2012). Totally, there were 82 patients with acute lymphoblastic leukemia in the studied category. B-linear variants of ALL were registered in 52.1% of patients (n=43) in this group, T-linear – in 26.3% of patients (n=22). Biphenotypic, expressing lymphoid and a number of myeloid markers were identified in 15.9% of patients (n= 13). Undifferentiated variants with the lack of expression of linear differentiation specific molecular markers were observed in 5.7% of patients (n= 4).

Patients with ALL, characterized by immunophenotype of early B-linear variant (proB), was registered in 11.3% of all the patients with ALL (n=9), common variant – in 20.1% of patients (n=17), preB-ALL – in 11.3% of ALL cases (n=9). «Mature» B-cells immunophenotype was observed in 9.4% of patients (n=8).

In the group of patients with T-cell immunophenotype of blast cells, the earliest proT-ALL variant was met in 11.3% (n=9), thymic (preT)ALL – in 1.8% of patients (n=2),

«mature» T-cell phenotype of lymphoblast – in 11 patients (13.2%) [2,3].

The analysis of genetic and molecular genetic studies revealed specific variants of AL based on the WHO classification [3].

Cytogenetic and molecular genetic (in situ hybridization and microarray) studies of tumor blast cells in peripheral blood and bone marrow revealed different genetic disorders in 277 patients (67.6%). Normal karyotype was observed in 96 patients (23.5%). It was not possible to obtain metaphases for cytogenetic assay in 36 patients (8.8%).

Complex abnormalities, represented by combinations of cytogenetically verified severe gene disorders (inversions, translocations, etc) and chimeric genes that comply with the criteria of persistent variants of AML and ALL, specified by the WHO classification, were identified in 102 patients (25% from all the cases with genetic abnormalities). In 42.6% of patients (n=175) other aberrations, not associated with the WHO variants of acute leukemia, were registered. In some cases (n=21) complex genetic abnormalities, that included several marker genes, were observed.

In 102 patients with genetic aberrations in blast cells, AML was registered in 70.6% of patients (n=72) and ALL – in 29.4% (n=43).

Among all the studied patients with AML, the variant, associated with translocation t(8:21) (q22:q22) and chimeric gene *RUNX1-RUNX1T1 (AML/ETO),* was identified in 14 patients (18.1%). The aberration, represented by inversion inv(16)(p 13.1q22) or translocation t(16:t6)(p 13.1;q22) with abnormal *CBFB-MYH11* gene expression, was registered in 5 patients with AML (6.8%). Promyelocytic variant of AML (M3 by FAB classification) with translocation t(15:17) (q22:q 12) and abnormal *PML-RARA* gene was identified in 6 patients (8.4%). AML with translocation t(9;11)(p22:q23) and *MLLT3-MLL* gene was observed in 3 patients (4.2%). Persistent combination of oncogenetic event t(6:9)(p23 :q34) with formation of *DEK-NUP214* was identified in 2 patients (2.8%). Myeloblasts with inv(3)(q2 1q26.2) or t(3;3)(q2 1;q26.2) with FISH-features of *RPN1 ·EVI1* gene were observed in 6 patients with AML (8.3%). Rare megakaryoblastic type of AML with t(1;22)(p13;q13) and *RBM15-MKL 1* was registered in 3 patients (4.2%). High incidence rate of AML variant with mutations of *NPM1* was found in 21 patients (29.2%), more often it was found in combinations with other associated aberrations, although it should be mentioned that the incidence rate was lower as compared to the published data [3]. Second in the incidence rate was the abnormality associated with mutation events in the *CEBPA* gene of tumor myeloblasts (n=12, 16.7%). These abnormalities are significant for evaluation of AML antitumor therapy efficiency, which is confirmed by other published data [20,21].

Some patients with ALL had persistent variants with repeated aberrations that comply with complex markers of the WHO classification. Thus, in 43 patients from this category, 18.6% of patients (n=8) had ALL variant with Ph-chromosome t(9:22)(q34;q 11.2) with expression of chimeric gene *BCR-ABL 1*. One patient with ALL had rare (met in less than 1% of cases) variant with t(v:11q23) and rearranged *MLL* gene. Two patients had a variant with t(12:2 1)(p13;q22) and expression of *TEL-AMLl (ETV6--RUNX1)* gene. Hyperdiploid variant was identified in 14 patients (32.6%), hypodiploid – in 12 patients (27.9%). ALL variant with translocation t(5; 14)(q31;q32) and chimeric gene *IL3-IGH* was found in 4 patients (10.2%). Minor ALL variant with t(1;19) (q23:P13.3) and *E2A-PBX1(TCF3-PBXI)* gene was diagnosed in 3 patients, which was 6.9% from the total amount of patients with ALL with expression of persistently reaping molecular genetic markers.

CONCLUSION

The present study results showed that, in general, acute leukemia incidence rate in Novosibirsk agreed with the rate, observed in the European part of the country [18]. Immunophenotypic and molecular genetic characteristics of acute leukemia allows the specialists to perform differentiated diagnostics of these tumors and identify the variants that differ by the disease outcome prognosis and

therapy efficiency according to the criteria of the WHO [3]. Complete genetic abnormalities picture is obtained by the complex of diagnostic methods that includes routine examinations, cytogenic assays, flow immunocytofluorimetry, FISH-assay as well as microarray diagnostics. The obtained data contribute to the evaluation of the disease outcome prognosis and resistance of tumor blasts to cytostatic polychemotherapy in all the age groups [10,11,12]. Establishment of genetic profile by several methods improves the precision of tumor cells molecular genetic characteristics identification and reveals a wide range of clinically significant genetic abnormalities for specification of prognosis and treatment plan for patients with blastic forms of hemoblastosis [17,18,19].

1. Acute leukemia incidence rate in Novosibirsk was 2.7 cases per 100 thousand adult population: acute myeloid leukemia (AML) – 2.0 per 100 thousand of adult population, acute lymphoid leukemia (ALL) (including the cases of undifferentiated and biphenotypic acute leukemia) – 0.7 per 100 thousand of adult population per year.
2. According to the criteria of FAB classification, AML variants M1 (19.8%), M2 (44.2%) and M4 (20.3%) prevailed.
3. Immunophenotypic pattern of ALL in adults revealed the prevalence of B-linear variants (52.1%) over T-cell variants (26.3%, n=22). Biphenotypic subtypes of acute leukemia were registered in 15.9%, undifferentiated – in 5.7%. Common B-variant (20.1%) prevailed among B-cell ALL variants, “mature” T-cell phenotype of lymphoblasts – among T-cell variants (13.2%).
4. Genetic aberrations are met in 25% of acute leukemia cases: in 70.6% of AML cases and in 29.4% of ALL cases. In patients with AML, variants with mutations of *NPM1* (29.2%) and *CEBPA* gene (16.7%) prevailed. In patients with ALL, the variant with Ph-chromosome - t(9:22)(q34;q 11.2) and expression of chimeric gene *BCR-ABL 1* (18.6%), hyperdiploid (32.6%) and hypodiploid variants (27.9%) prevailed.

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