RESEARCH ARTICLE

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Epidemiological Features of Acute Myeloid Leukemia in Five Regions of the Republic of Kazakhstan: Population Study

Rinat Aitbekov[1,2]*, Maira Murzakhmetova[1], Gulzhan Zhamanbayeva[1], Nazgul Zhaparkulova[1], Haimantika Seel[1]

Abstract

Objective: The aim of the study was to assess the main epidemiological characteristics of AML (morbidity, survival, distribution by AML variants and age groups) in 5 regions participating in the study. **Methods:** This stat study was conducted on patients diagnosed with acute myeloid leukemia in 5 regions of Kazakhstan, from January 2017 to December 2020. Compared with self-assessment of acute myeloid leukemia using a questionnaire, postoperative histopathology in patients with suspected acute myeloid leukemia. The questionnaire, compiled by artificial intelligence, is grouped into categories "risk" and "no risk". Statistical processing and analysis of data was carried out using the analytical package SAS 9.4. Methods of reporting statistics, standardization of morbidity were used. **Result:** According to the standardized morbidity indicators obtained (from 1.39 to 2.43 per 100 thousand population), we can say that the registered incidence of AML remains low. This value practically does not differ from the incidence of AML (2.71) according to the Kazakhstan Cancer Registry for 2016 and is significantly lower than the data of European and American registries (4-5 cases per 100 thousand inhabitants per year). **Conclusion:** This study identified specific areas with a high risk of acute myeloid leukemia in Eastern Kazakhstan, as well as spatial inequality in their distribution with the formation of this disease. These results can be useful in developing any strategy for responding to a high risk of cancer in specific areas.

Keywords: blood cancer- medical online register- acute myeloid leukemia- acute leukemia.

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Introduction

Acute leukemia are not only the most malignant forms of hemoblastosis, but also nosology, in relation to which modern medicine has made the most significant breakthrough in terms of increasing the effectiveness of treatment. Based on an in-depth study of the biochemistry of tumor cells, the disclosure of pathogenetic mechanisms of tumor progression, technologies for program therapy of malignant blast neoplasia were developed, and maintenance therapy was developed. These truly revolutionary changes in therapeutic and diagnostic approaches have not been slow to affect the effectiveness of therapy, survival, and quality of life of patients (Parkin et al., 2005). Acute leukemia has become an indicator nosology in relation to the quality of work of hematology clinics around the world. At international forums, new WHO (World Health Organization) regulations were discussed and adopted-classifications, treatment standards and algorithms for preventing complications of myeloablative chemotherapeutic programs. In recent years, allogeneic transplantation of bone marrow and peripheral stem cells has been identified as the basis for the consolidation of remission with a means of combating residual tumor disease as a method of biological modeling in vivo of the immune response graft against leukemia (Siegel et al., 2014).

Further progress in predicting tumor progression and the effectiveness of therapy was associated with the verification of molecular genetic anomalies in the genome of the tumor blast cell, which revealed the extreme heterogeneity of this nosology. This position was reflected in the revisions of the WHO classification of acute leukemias, the allocation of special variants associated with a complex of immunophenotypic, cytogenetic and molecular genetic markers. To date, a close association of the tumor variant with the features of the clinical course, the effectiveness of standard treatment protocols and the prognosis of the disease has been proven.

The main methods of studying morbidity according to sample studies of individual groups are epidemiological studies. Medical registers are the main data collection tools for population studies, including in oncohematology (Visser et al, 2012). The information included in the register is used to assess the main epidemiological characteristics, such as morbidity, prevalence, treatment

*[1]Al-Farabi Kazakh National University, Faculty of Biology and Biotechnology, Almaty, Kazakhstan. [2]Ben-Gurion University of the Negev, Beer Sheva, Israel. *For Correspondence: rinat_ait@mail.ru*

outcome, survival (Turgunova et al., 2006). Given the almost complete lack of information on the basic epidemiological characteristics of acute myeloid leukemia (AML) in the Republic of Kazakhstan, it was necessary to conduct an active prospective epidemiological study and create an appropriate register for this nosology (State Statistics Service from Kazakhstan: https://stat.gov.kz).

There are several foreign registries that contain a system of registration and monitoring of patients with acute leukemia (AML), for example, the registry of the American National Cancer Institute (US National Cancer Institute SEER/www.seer.cancer.gov) (American Cancer Society), the Swedish Registry AL (Swedish Acute Leukemia Registry Group/www.symptoma.com), French Registry of Hematological Diseases (HD) (Registredes Hemopathies Malignesde Cote d'Or, France/www.epidemiologie-france.aviesan), Korean Cancer Registry (KCR) (The Korea Central Cancer Registry/www.iacr.com).

The first qualitative registration of patients to improve medical management is associated with the name of Boston surgeon Ernest Amory Codman (E.A. Codman, 1869-1940). In 1920, E.A. Codman created the first registry of bone sarcoma cancer. And only a few decades later registers began to develop in the USA, Scandinavia, Great Britain and other countries (Heilmeier et al., 2017).

Although the main purpose of registers is to assess demographic and epidemiological characteristics, such as morbidity and mortality, they can provide information for public services of health organizations, medical research institutes. This information can be used to develop new treatment protocols and prevention programs. To ensure reliable data, registers should be based on the territorial principle and cover a large percentage of the population, which naturally reduces the influence of patient selection when included in the register on the results of assessing basic statistical characteristics and relevant conclusions Nurgaziev t al., 2018).

In many works in the field of population hematology, there are references to the Swedish AML register, which contains data on adult patients who have been diagnosed with AML since 1997. This register, in addition to basic demographic indicators about the patient, includes dynamic data on the functional status, intensive treatment, the presence and time of remission, relapse, bone marrow transplantation, the patient's life status and the date of his death, if it occurred. In the period from 1997 to 2006 The Swedish registry contained information about 3,899 oncohematological patients. There were 3318 (85.1%) patients with acute myeloid leukemia (AML) aged 60 to 79 years (median age 71 years), of which 113 (3.4%) patients with acute promyelocytic leukemia (APL); 472 (12.1%) patients with acute lymphoblastic leukemia (ALL) aged 36 up to 69 years of age (median age 54 years); 109 (2.8%) had an undifferentiated/unclassified form of AML. The duration of observation of patients was 6 years.

The Survival, Epidemiology and End Results (SEER) register used by the American National Cancer Institute records data from 1973 from 17 states of America with a total population of about 80 million people. In the USA, almost 18,000 adults are diagnosed with AML every year, while more than 12,000 (66.6%) have a myeloid variant of the disease. According to estimated indicators, the incidence of AML in the USA is 5-6 cases per 100 thousand adults per year. More than 10,000 (55.5%) AML patients die annually, which is about 2% in the structure of mortality from all human malignant diseases. According to the SEER register, the incidence of AML among men in the USA (3-4 cases per 100 thousand people) is higher than in Sweden, and is noticeably higher in men over 50 and women over 75 (Turgunova, 2006).

Korean Cancer Registry and Korean Hematology Society (www.iacr.com) jointly conducted a study of the incidence of oncohematological diseases established in the period from 1999 to 2008. 8006 cases of HD (hematological diseases) have been registered in the entire population, including children. The incidence rate of AML in children under 15 years was from 1 to 1.4 per 100 thousand population, after 15 years – from 1.8 to 15 per 100 thousand population, higher mainly in males. The incidence rate of ALL under 15 years varied from 2.5 to 2.8 per 100 thousand. in the population, in subsequent age groups up to 80 years, these values ranged from 0.5 to 2.6, also higher in men. The standardized incidence rates of AML in men were 5.6, in women 4.1 per 100 thousand population (Park et al., 2012).

The first specialized registry of hematological malignant neoplasms (MN) in France (Registry des Hemopathies Malignes de Cote d'Or; www.epidemiologie-france.aviesan) was created in 1980 in the Cote d'Or district in Burgundy. Registration of all new cases of HD was conducted continuously and for more than 25 years collected data in a population of about 500,000 inhabitants. In the period from 01.01.1980 to 31.12.2004, 5086 cases of myeloid neoplasms were registered. Myeloid tumors accounted for 1,549 (30.5%) out of 5,086 cases, of which 468 (30%) were AML patients. Standardized indicators of the incidence of AML did not differ significantly by gender: 2.8 for men and 2.2 for women per 100 thousand inhabitants per year. The median age was 69.7 years (with a spread from 2 to 98 years). The frequency of AML increased with age in all subgroups, especially after 55-59 years (Veliz et al., 2012).

It seems important and relevant to develop procedures for registering AML cases and regulations for lifelong monitoring of AML patients, an appropriate information structure, data collection and storage tools. The information collected in the framework of this study will make it possible to take a step towards creating a permanent state (national) register of AML. In addition to passive registration and monitoring of the condition of AML patients, the register is also useful as a source of information for planning new clinical trials, which will allow managing the process of including patients in clinical trials and evaluating the clinical and population effect of the very fact of patients' participation in clinical trials. The results and conclusions of the statistical analysis of the AML register data may be of practical importance for the general management tasks of the specialized hematology service of the Republic of Kazakhstan.

Material and Methods

The study involved hematology clinics in 5 regions of the Republic of Kazakhstan – Almaty, Karaganda, Akmola, Zhambyl, East Kazakhstan regions (Figure 1). The criteria for selection for participation in the study of the above subjects was the completeness of coverage of the population. In these regions, the diagnosis of AML is carried out in one or two centers, which makes it possible to fully consider new cases of AML that have arisen in residents of these regions. The selected centers were previously participants in many

Data on a patient with a confirmed diagnosis of AML is entered into the register. The diagnosis and variant of AML are established based on generally accepted criteria. To enter information about the patient into the database, it is necessary to sign the informed consent of the patient to be included in the study. The data in the register is entered by the hematologist responsible for maintaining the AML register at the patient's place of residence. The information in the AML register is based on the data of medical documentation (the card of an outpatient patient, the card of a patient in a round-the-clock hospital). The information collected during registration includes full name, date of birth, gender, address, diagnosis, leukemia variant, classification of AML (WHO, ICD), date of diagnosis.

To collect registration data and monitor the status of AML patients, an appropriate information structure and a web-based data collection system were developed. Since 01.04.20, registration of new cases of AML has started in 5 regional centers. Regularly (at least once every six months) enter information about the current life status of the patient, the date of the last contact, and if the patient died, the date and cause of death.

The work is carried out under the auspices of the National Hematology Society (NHS) based on the Institute of Radiology and Oncology of Almaty, in the scientific and clinical Department of Chemotherapy of hemoblastoses and depressions of hematopoiesis and with a group of information and analytical department, with the technical support of the Al-Farabi Kazakh National University. The research topic was approved at the meeting of the Department of Biophysics, Biomedicine and Neuroscience. Researchers from regional centers conducted registration of all primary cases of AML. Approximately every 3 months (at least once every six months), regional executors, if possible, contacted registered patients and entered monitoring data into the register database. The responsible executors of the project from the NHS (Almaty) coordinated the data entry process, monitored the correctness and completeness of the entered data. Research planning, development of protocols and information structure, intermediate stages of data control, statistical analysis were carried out jointly with the support of the information and analytical department.

Statistical processing and analysis of data was carried out using the analytical package SAS 9.4. Methods of reporting statistics, standardization of morbidity were used. The statistical analysis was carried out jointly with the scientific supervisor, Doctor of Biological Sciences, Professor M.K.Murzakhmetova.

Demographic data were taken from the website of the Bureau of National Statistics of the Agency for Strategic Planning and Reforms Republic of Kazakhstan (https://stat.gov.kz) based on the materials of the population census of the Republic of Kazakhstan (State Statistics Service. https://stat.gov.kz).

To compare the obtained data on morbidity with data from other countries, a process of standardization or normalization of morbidity was carried out – a common demographic technique that allows comparing this indicator in populations with different sex and age distributions or analyzing its dynamics in the same population over time if the sex and age proportions change significantly. This is a routine demographic procedure in which, before summing up, the number of reported cases in each age stratum is multiplied by a coefficient equal to the ratio of the proportion of this stratum in the WHO standard population to the proportion of this age stratum in the study population. Normalization of the initial morbidity to the standard population is a procedure that allows taking into account and excluding national demographic deviations when comparing morbidity rates in different countries.

Results

For 3.8 years of the study (from 01.01.17 to 31.12.20), 334 patients from 5 regions of the Republic of Kazakhstan with a total adult population of 4,707,178 people were included in the register. Information on all cases of AML entered in the register is reflected in Table 1.

61 cases of primary AML were registered in the Zhambl region, 86 in East Kazakhstan, 61 in the Karaganda region, 53 in the Akmola region, 73 in the Almaty region (see Table 1). 40 (65.6%) patients from the Karaganda region and 6 (11.3%) from the Akmola region did not an AML option was specified. These patients were excluded from the estimates of the distribution of patients by AML variants. However, the general analysis of morbidity and its sex and age structure included all the initially registered cases of AML In 2 (2.7%) patients from the Almaty region, an undifferentiated variant of AML was found.

The number of registered cases was: AML 215 (64.4%), AL 54 (16.1%), APL 17 (5%), undifferentiated AL 2 (0.6%), unverified AL 46 (13.7%).

The median age in the cohort of patients with AML was 59 years (from 17 to 85 years), ALL was 37 years (from 16 to 80 years), APL was 51 years (from 27 to 79 years); in the cohort of patients with an unverified variant of OL, the median was 56 years (from 22 years to 81 years). The total number of registered cases of OL with laboratory verification of the diagnosis was 288.

Approximately the same number of registered cases of AML was recorded in Zhambyl (45) and Akmola regions (39), slightly more cases were in East Kazakhstan (62) and Almaty regions (52). The largest number of oil was registered in the East Kazakhstan region (20) and Almaty region (16). In other regions, cases of ALL from 3 to 11 were recorded. The number of unverified cases of AML

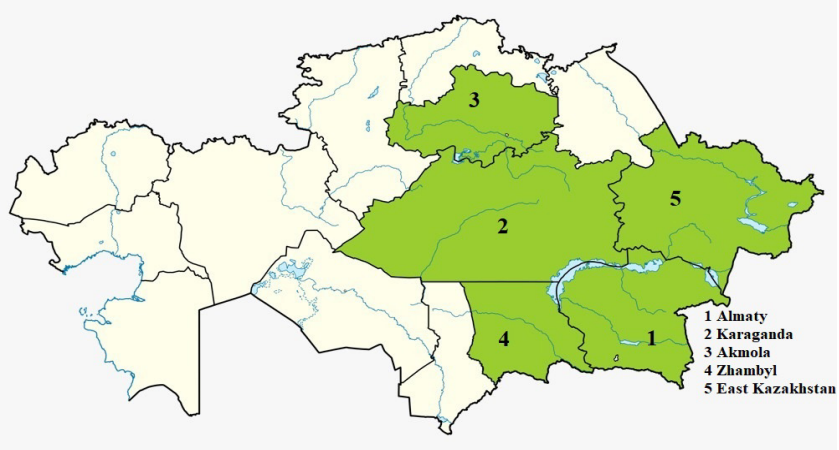

Figure 1. Hematology Clinics of the Republic of Kazakhstan. [Source: Kazakh Institute of oncology and radiology]

Table 1. Distribution of AML Patients by Regions of the Republic of Kazakhstan

Region	Diagnosis				Total number of AML cases	The number of the adult population of the region
	AML	ALL	APL	AML unverified		
Zhambl	45	11	5	-	61	876,187
East Kazakhstan	62	20	4	-	86	1,150,074
Karaganda	17	3	1	40	61	1,006,719
Akmola	39	4	4	6	53	951,262
Almaty	52	16	3	2	73	722,936
Total AML	215	54	17	48	334	4,707,178

Table 2. Distribution of Patients in the AML Registry by Age and Gender

Age	Women	Men	Total
15-19	3 (0,1%)	4 (1.2%)	7 (2.1%)
20-39	36 (11%)	34 (10.1%)	70 (21.1%)
40-59	71 (22%)	52 (15.3%)	123 (37%)
60-79	69 (21%)	59 (17.1%)	128 (38%)
80 and older	6 (1,9%)	-	6 (1.8%)
Total AML	185	149	334

remains high (in 46 patients), which is 13.7% of all initially registered AML patients (Akmola and Karaganda regions). Data on the verification of the AML variant from the Karaganda region were received untimely and the next stage of the analytical presentation and discussion will be presented later.

Demographic analysis of the collected data showed that among the registered AML patients there were more women – 185 (55.4%) than men – 149 (44.6%). The median age of patients in the entire AML group was 57 years (from 16 to 85 years). The distribution by gender and age is presented in Table 2. Starting from the age of 40, the number of women in the age groups from 40 to 59 and from 60 to 79 years prevails over the number of men. The "balance" between women and men is observed at the age of 20 to 39 years.

Data on the initial (non-standardized) morbidity are presented in Table 3. Of the 5 regions presented, the highest incidence rate was detected in the Almaty region (2.44 per 100 thousand population per year) and the East Kazakhstan region (1.8 per 100 thousand population per year). In Almaty and Zhambyl regions, the non-standardized incidence rate in men is higher than in women.

Discussion

The incidence rates of AML turned out to be slightly

Table 3. Non-Standardized and Standardized Morbidity in the Pilot Regions of the Republic of Kazakhstan

Region	Population, thousand people			Number of reported cases			Duration of registration, years	Non-standardized indicator, per 100 thousand people per year			WHO standardized indicator
	total	men	women	total	men	women		total	men	women	
East Kazakhstan	1150	518	631	86	36	50	3.7	2.02	1.87	2.13	1.79
Almaty	723	326	397	73	40	33	3.7	2.72	3.3	2.24	2.43
Karaganda	1007	449	557	61	23	38	3.1	1.97	1.66	2.21	1.75
Zhambyl	876	395	481	61	30	31	3.4	2,00	2.18	1.85	1.73
Akmola	951	428	523	53	20	33	3.6	1.51	1.26	1.71	1.39

lower than expected. To study the possible causes, it was necessary to check the version that the reduced incidence rates can be explained by the demographic feature of the Kazakh population, namely, a reduced proportion of older age groups.

For comparison with data from other countries, the initial incidence had to be standardized for the WHO population. Morbidity after the standardization process has not actually changed, even decreased slightly (see Table 3). Consequently, the hypothesis of demographic causes of low recorded morbidity is not confirmed.

Based on the standardized morbidity indicators obtained, we can say that the registered incidence of AML remains quite low. This value practically does not differ from the incidence of AML according to Kazakhstani statistics in 2019. (2.71) and significantly lower than the data of European and American registers (4-5 cases per 100 thousand inhabitants per year).

Despite the difficulties of the project, the following positive aspects and achievements can be noted. During the first years of work, a systematic, systematic input of information was established in the selected pilot regions, which allowed us to assess the incidence in the studied regions.

Thus, based on the age characteristics of patients recorded in the AML registry, it can be concluded that at the time of diagnosis of AML, patients in the Republic of Kazakhstan are somewhat younger than AML patients from European registries (AML - 59 years versus 71 years, ALL – 37 years versus 54 years). As in many foreign countries, a significant proportion of unidentified AML variants (13.7%) remains a problem. This clearly indicates a low detection, registration, and differential diagnosis of AML cases in older age groups, which explains the reduced recorded total incidence of AML in the regions of the Republic of Kazakhstan. Due to the remoteness of medical institutions, some newly ill patients, especially the elderly, are not hospitalized in specialized medical institutions, and if they are hospitalized, they are not given the full range of examinations necessary for correct and timely diagnosis.

Among the organizational problems of the AML register itself, the problems of completeness and quality of the data entered should be noted: incomplete filling of individual patient records, late receipt, and deletion of monitoring data, which limits the depth and reliability of the analysis of the register data.

The obtained indicators of standardized morbidity (from 1.4 to 2.4) are close to the indicators of morbidity according to Kazakh statistics (2.71), but lower than the indicators of European and American registers. This discrepancy can be explained by a significantly reduced activity of registration and primary diagnosis of AML in older age groups.

In conclusion, it is necessary to continue systematic research work within the AML register with further inclusion of more regions of the Republic of Kazakhstan, expansion of the information collected to obtain more reliable information on morbidity, identification of possible age and regional characteristics, the effect of inclusion of patients in multicenter clinical trials, survival analysis.

Author Contribution Statement

RA contributed to literature search, data collection, performed the data analyses and writing of the manuscript. MM contributed to the development of the study, data collection and review of the manuscript. GZ contributed to the development of the study and the review of the manuscript. NZ and HS contributed to the literature search and manuscript review.

All the authors contributed to the critical revision of the manuscript and approved the final submitted version.

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Conflict of interest statement

The authors report no conflicts of interest in this work.

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