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MANAGEMENT OF PATIENTS WITH CHRONIC MYELOID LEUKEMIA – AN ACTUAL ISSUE OF ONCOLOGY AND PUBLIC HEALTH

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Abstract

Objectives: The aims of the study were to identify and evaluate the epidemiological aspects and management options in chronic myeloid leukemia (CML).

Methods: We performed the analytical, cohort and prospective-retrospective study of 134 patients with CML, who were treated and followed up in the Institute of Oncology from Moldova between 2005–2021. The quantitative reverse transcription polymerase chain reaction (RT-PCR) was accomplished in order to determine the expression of the BCR-ABL p210 and p190 transcripts. Tyrosine kinase inhibitors (TKIs) were used as a front-line therapy in the newly diagnosed CML patients and in the cases of resistance to non-TKIs chemotherapy and interferon-α.

Results: The diagnosis of CML was established in chronic phase in 122 (91,04 ± 2,32%) patients, in the accelerated and acute phases – in 12 (8,96 ± 2,03%). BCR-ABL p210 transcript range was 21.84–100% IS. Under the first-line TKIs therapy, the complete molecular response was obtained in 24.3% of cases. No significant differences were registered in the rate of complete hematologic response (92.3% vs 92.8%) and complete molecular response (23.8% vs 24.7%) under the TKIs medication between the elderly patients and the whole cohort of CML patients. The overall one- and 5-year survival in elderly patients treated with TKI was 97.6 and 79%, being comparable with the respective parameters in the totality of CML patients (98.5% and 87%, correspondingly).

Conclusions: The treatment with TKIs remains a curative option of choice for CML patients regardless of the age, gender and CML phase.

Keywords: chronic myeloid leukemia, diagnosis, management, tyrosine kinase inhibitors, survival.

Introduction:

Chronic myeloid leukemia (CML) is a clonal neoplastic disease of the hematopoietic system, which results from the malignant transformation of the pluripotent stem cell, maintaining the ability of differentiation up to all cell lines, severe and recurrent evolution in the advanced phases, with unfavorable prognosis and negative socio-economic impact [1,2,3,4,5,]. CML was presumably described and recognized as a distinctive nosological entity by Craigie D. in 1845 [6, 7]. According to the up-to-date bibliographic references, CML is characterized by the uncontrolled multiplication of myeloid cell series, with the circulating and total granulocyte overload, and comprises 15 - 20% of all cases of leukemia in adults, being the most common chronic myeloproliferative neoplasm [1, 4, 5, 8-11]. CML morbidity increases with age, with a maximum incidence between 45 and 60 years, which indicates the

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predominant involvement of a workable population [11, 12]. Patients with the accelerated and acute phases of CML experience a marked disease burden in terms of symptoms and negative effects on quality of life, productivity, and daily living activities [13, 14]. The increased incidence rates in the working-age population, commonly late diagnosis of CML in the current epidemiological context and the significant level of disability in the advanced stages of the disease may be considered as a charging subject of hematologic oncology and public health, which argued the need to study its epidemiological, diagnosis and management aspects.

The objectives of the study were to identify and evaluate the epidemiological, diagnosis issues and management options in CML.

Materials and methods:

We performed the analytical, cohort and prospective-retrospective study of 134 patients with CML, who were treated and followed up at the Institute of Oncology from the Republic of Moldova between 2005–2021. The type of hematologic malignancy was identified according to the Revised 2018 WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues. During the karyotyping examination in each patient there were analyzed at least 20 metaphase plates of the bone marrow (BM) cells, obtained in direct and nictemeral cultures without stimulation. Molecular-cytogenetic research was performed using the FISH interface method on the BM samples [15, 16]. The abnormal mixed signal, detected in the nuclei, indicated the presence of translocation t(9; 22)(q34; q11). The quantitative reverse transcription polymerase chain reaction (RT-PCR) was accomplished in order to determine the expression of the BCR-ABL p210 and p190 transcripts [15, 16, 31]. Five transcription products (b2a2, b3a2, b2a3, b3a3 si e1a2) were analyzed by the usage of the quantitative PCR test. The follow-up and study were completed at the comprehensive cancer center. The study was related to the ambulatory and hospitalized care. Tyrosine kinase inhibitors (TKIs) were used as a front-line therapy in the newly diagnosed CML patients and in the cases of resistance to non-TKIs chemotherapy and interferon-α. TKIs were provided on a regular basis within the frame of the Max Access Solutions program. In Discussion the article summarized and systematized the primary studies, dedicated to the diagnostic and management issues of CML. In order to achieve the formulated objectives, the scientific medical publications were searched via GoogleSearch, PubMed, Z-library, NCIB, Medscape, Hinari database, by the keywords: “chronic myeloid leukemia”, “incidence”, “diagnosis” , “survival”, “mortality”, “management”. Thirty-seven relevant primary sources were identified and selected, according to the significance of the impact score, with the scientific, reproducible and transparent approach to the subject under discussion, with the subsequent data extraction, evaluation and interpretation. Intending to minimize errors, a copy of the data extraction sheet was initially produced, sharing all the elements to be extracted from the primary studies [17]. In order to diversify the conclusions, the results of the international studies were supplemented by the research data from the Republic of Moldova.

Results:

In the Republic of Moldova the incidence of CML did not display any trend (Figure 1), matching that one in the countries from Western Europe and North America.

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The diagnosis of CML was established in chronic phase in 122 (91,04 ± 2,32%) patients, in the accelerated and acute phases – in 12 (8,96 ± 2,03%). The patients' age ranged between 14-81 years old. The median age was 51.4 ± 2.13 years. Within the whole CML cohort structure, the age groups of 40 - 49 (28.4 ± 4.89%) and 50 - 59 (19.7 ± 4.31%) years proved to be more numerous (P<0.05), being attributed to the workable population categories. The age ranged from 25 to 60 years in the majority of CML patients (65.3%) included in the study, that reconfirmed the recent references data on the predominant involvement of the workable population [2, 4, 5, 18].

There were 78 (58.2%) males and 56 (41.8%) females. The male/female ratio was 1.4:1. The duration of the disease from the onset of the initial clinical symptoms to diagnosis varied between 1.5-12 months (median – 2.1±0.37 months). In most cases (72.3 ± 5.07%) the diagnosis was established within the first 3 months after the onset of CML, followed by the diagnosis of the disease in the period of 3-5 months (18.1 ± 4.20% of cases).

The rate of Ph-chromosome-positive BM cells ranged from 20 to 100%. The study of the karyotype identified the following examples of ISCN diagnosis: 46, XX, t (9; 22) (q34; q11) [20] and 46, XY, t (9; 22) (q34; q11). In the absolute majority of cases (72.7%) the Ph chromosome was detected in over 70% of the BM cellular elements.

BCR-ABL p210 transcript range was 21.84–100% IS. In most cases (69.8%) the chimeric BCR-ABL gene transcripts were identified in over 65% of peripheral blood (PB) cells. Multiplex PCR detected the transcription product in the major region (M-bcr).

Under the first-line TKIs therapy, the complete molecular response was obtained in 24.3% of cases. No significant differences were registered in the rate of complete hematologic response (92.3% vs 92.8%) and complete molecular response (23.8% vs 24.7%) under the TKIs medication between the elderly patients and the whole cohort of CML patients (P>0.05). The overall one- and 5-year survival in elderly patients treated with TKI was 97.6 and 79%, being comparable with the respective parameters in the totality of CML patients (98.5% and 87%, correspondingly). Interferon α-2b was used as a second-line treatment option in cases of resistance to conventional chemotherapy and TKIs, with obtaining complete hematologic and partial molecular responses. All generations of TKIs were twice-yearly supplied by The Max Foundation under Max Access Solutions program on a basis of the regular Inventory Reports.

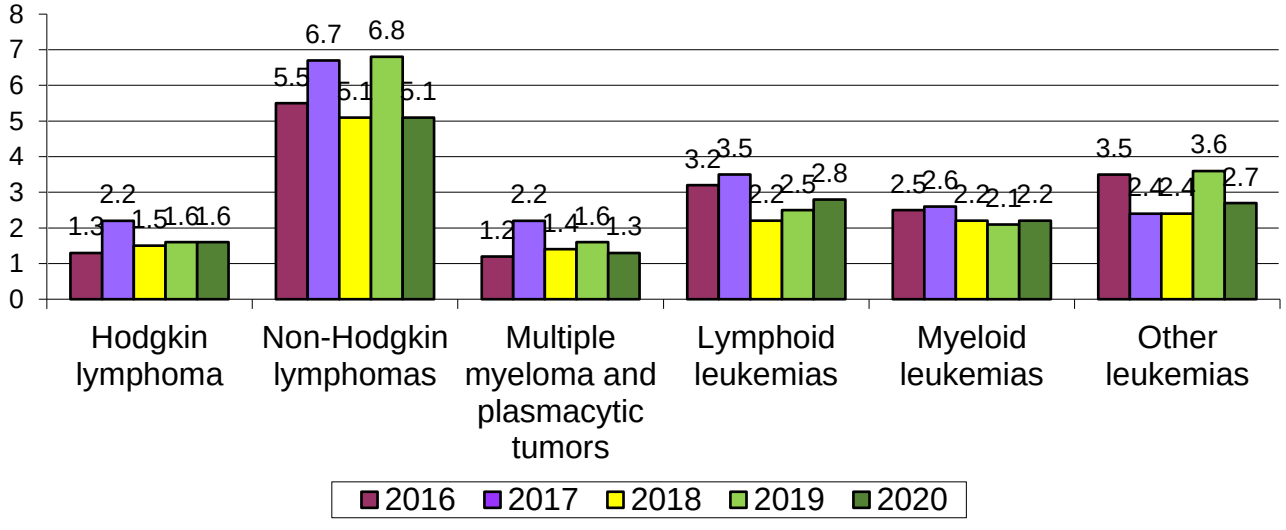

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Figure 1. The incidence of hematologic malignancies per 100000 of population in the Republic of Moldova.

In the absolute majority of CML patients (80%) treated initially with conventional chemotherapy, only the minor cytogenetic response was obtained (Ph-chromosome 60 - 100%), which was confirmed by the cytogenetic examination of the BM while preparing and processing the applications for Max Access Solutions program.

Relapse-free survival at 36 months in patients treated with TKIs (79%) was higher ($P<0.05$) than in the group of patients receiving conventional chemotherapy and / or immunotherapy (18.5%), that favored significantly the increase of the life expectancy.

Discussion:

Herewith, the discussion of epidemiological patterns and diagnosis management of CML is provided by the comparative narrative analysis of the contemporary bibliographical sources. The epidemiological and management issues of CML are descibed ambiguously by the bibliographical references and continue to trigger both scientific and practical interest. The data from summarized epidemiological studies assume the detection of CML at any age, with an average of 50 years at the time of diagnosis. The results of the published studies showed that approximately 2.5% of cases with CML were attributed to the age group under 20 years [5, 14, 18], 7.4% - to the age group between 20 - 34 years and 33% - to the age groups under 40 years, that denoted the ponderable rate of young patients [6, 13, 19]. The incidence of CML varied between 0.8 - 2.0 cases per 100000 of population. In the majority of pubished studies CML predominantly affected males, with the male:female ratio of 1.3-1.7:1. The National Institutes of Health estimated the number of cases diagnosed *de novo* in the United States at 8950 and the number of deaths from this disease at 1080 in 2017. The total number of patients diagnosed with CML increased annually by 2% during 2007-2016, and the total number of deaths decreased annually by 1% during the years 2008-2017 [13]. The 5-year survival rate years increased from 22% in the mid-70s to 90% currently in patients undergoing continuous chemotherapy with 1st generation TKIs [20].

Globally, in 2016 leukemias caused 10.2 million DALYs (disability-adjusted life-years), exceeding the respective index for malignant lymphomas (6.8 million DALYs) [22]. Between 1990-2017, the CML incidence decreased by 34.9% in quintiles with high social-demographic index (SDI), increasing by over 60% in quintiles with low, medium-small and medium SDI. Developing countries, thus, continue to bear the heavy burden of CML mainly due to their reduced access to the treatment with TKIs [14, 21]. It is summarized about the relationship between the epidemiological trends of CML and age, gender, that has an impact on policy-makers [23]. Aging, directly proportional to the reduction of hematopoietic stem cell function, is considered an essential factor associated with leukemogenesis [22, 23]. The survival of patients with CML is age-related and serves as a key factor in the selection of treatment options [16, 28]. Quintiles with higher SDI and an aging population showed a more significant proportion of patients over 70 years of age. Males formed a higher risk group for developing CML as compared to females, and the male:female ratio ranged from 1.2 to 1.7 [21, 25]. It is evoked, such as higher overall survival, the hormonal status of females, genetic and environmental factors could have an impact on the age distribution of patients with CML [26,

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27]. At the same time, in 2017 the DALYs rate in women in quintiles with low SDI exceeded the respective indicator in males. Epidemiological studies found in females from the low-income countries a tendency of mortality increase due to the inadequate early screening and treatment [26, 27, 28].

According to contemporary clinical guidelines and recommendations, morphological, cytogenetic (standard, FISH) and molecular-genetic examinations of the PB and BM have become indispensable steps of diagnostic management regardless of the clinical-evolutionary phase of CML [29]. Translocation t(9;22)(q34;q11) proved to be the main cytogenetic marker of CML. This chromosomal aberration provides a definitive diagnosis and has to be determined by the conventional cytogenetic examination or FISH during the patient follow-up for the objective evaluation of cytogenetic response to the treatment with TKIs [8, 30]. In the published studies, the rate of Ph-chromosome-positive BM cells ranged from 20 to 100% [15, 19]. In the absolute majority of cases (72.7%) Ph-chromosome was detected in over 70% of the BM cellular elements and could ensure a quick and reliable diagnosis. Beyond simple mutual translocation between chromosomes 9 and 22, approximately 5-10% of CML cases may have other types of Ph-translocations. These simple types involve one or more chromosomes in addition to 9 and 22, with chromosome 22 always changing. At the same time, 30-50% of chromosomal types in CML represent fused genes that can be detected only by molecular techniques such as FISH or PCR [31, 32, 33]. It is worth noting that the clonal evolution of CML into the acceleration phase may be associated with the appearance of additional chromosomal aberrations, especially trisomia 8, isochromosome 17 and Ph-chromosome duplicate [11]. These cytogenetic aberrations are considered as diagnostic criteria for the acceleration phase and should be applied in the differential diagnosis with chronic phase and acute leukemia.

Identification of the chimeric BCR-ABL fusion gene and transcripts p210, p190 and p230 with tyrosine kinase activity profiles CML at the molecular level. The p210 protein - the major transcription product (M-bcr) - is found in most patients with CML, being responsible for the classic CML phenotype. The p190 protein is formed following the rearrangement of m-bcr region, reflects the production of e1a2 transcript. It is less frequently determined in CML and denotes an unfavorable evolution of the disease, commonly with resistance to chemotherapy. The transcription product p230 is rarely identified in μ-bcr region, being associated with slow disease progression.

In addition to fast diagnosis, FISH and PCR proved to be able to detect rare BCR-ABL gene variants and breakpoints that go unnoticed by conventional cytogenetics, with higher specificity and sensitivity. These techniques are more sensitive and important not only for the diagnosis and evaluation of the response to treatment, but also for the differentiation from the other chronic myeloproliferative neoplasms. The authors summarized that FISH should be recommended for diagnosis in cases where the Ph-chromosome was not detectable by classical cytogenetics [33, 34]. Quantitative real-time PCR (RQ-PCR) or RT-PCR served as methods of choice for both accurate diagnosis and determination of minimal residual disease after the BM transplantation due to their superior sensitivity, allowing early diagnosis of the disease relapse and being more effective in determining the response to treatment as compared to classical methods [34]. If the BM cells cannot be obtained, the cytogenetic examination of the

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banded chromosomes may be replaced by the FISH on interphases of the PB cell, using dual color fusion probes that allow the detection of BCR-ABL+ nuclei and uncommon translocation variants [35].

Qualitative RT-PCR is performed on RNA extracted from the BM or freshly collected PB cells. By the RT-PCR quantitative determination of the chimeric BCR-ABL p210 gene in the PB cells, the published studies highlighted its large variations: 21.84 - 100% IS [5, 18, 36], that matched our observations. Multiplex PCR, as a rule, detects the transcription product in the major region (M-bcr). The analyzed studies unveiled the expression of BCR-ABL chimeric gene transcripts in over 65% of the BM cellular elements in most cases (69.8%). One study mentioned a phenomenal aspect of molecular diagnosis, as RT-PCR with a sensitivity of 10-8 identifies BCR-ABL1 chimerism in 25-30% of apparently healthy adults [11]. It is hypothesized that BCR-ABL1 may not be the only genetic aberration required for the development of CML. PB can be used for BCR-ABL monitoring, rather than BM. The guidelines of the European Leukemia Network (ELN) and the National Cancer Care Network (NCCN) include frequent monitoring as an option to track response. Both guidelines call for every 3-month PB PCR testing for BCRABL1 [2, 3]. Treatment decision-making, including changing TKIs in cases of resistance, or discontinuation of TKIs after a durable deep response, are based on the BCR-ABL1 monitoring [1,16].

Last but not least, The Max Foundation, under the umbrella of Max Access Solutions (MAS), managed the entire end-to-end TKIs supply chain into cancer treatment centers, while boosting the interactions with local stakeholders and providing hands-on, local patients support [37]. More than 280 reference medical centers specialized in hematology-oncology were included in this international program, including the Institute of Oncology from Moldova. Since its launch, TKIs were provided to more than 10,000 patients in more than 80 countries who had no other access to these efficient and well-tolerated drugs. Humanitarian donations of costly life-saving medications contributed greatly to the reduction of care inequities. The settlement of cooperation with developers of TKIs for CML treatment enables The Max Foundation to respond to health care providers' requests for 2nd and 3rd line therapy in many of the low-income countries.

Conclusions:

1. CML is characterized by the predominant involvement of the workable age categories and male gender.

2. Despite the declining overall trend of the age-standardized DALYs at the expense of high SDI quintiles, the CML burden remains stable due to the growing population in developing countries and the aging population in developed countries.

3. Diagnostic management of patients with CML includes morphological, cytogenetic and molecular-genetic investigations of the PB and BM regardless of the phase of clinical evolution, with FISH and RT-PCR as confirmative resolutive options.

4. FISH is recommended to be included in the diagnosis management pathway of patients in cases where the classical cytogenetic examination does not detect Ph-chromosome or additional chromosomal aberrations, especially in the acceleration and acute phases of CML.

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5. The treatment with TKIs remains the management option of choice for CML patients regardless of the age, gender and CML phase.

6. Developing countries continue to bear the heavy burden of CML, which is mostly contributed by their reduced access to the treatment with TKIs.

7. The Max Access Solutions program proved to be the innovative, equitable and efficient approach to the cancer care access and management.

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CONFLICT OF INTERESTS:

The author has no conflict of interests to declare.

ETHICAL APPROVAL:

The research protocol No 9 was approved on September 21, 2015 by the Research Ethic Board of State University of Medicine and Pharmacy "Nicolae Testemitanu".