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Management of elderly patients with chronic myeloproliferative hemopathies

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Abstract

Background: Chronic myeloproliferative hemopathies (CMPH) as a whole are the most common chronic leukemias in the elderly in the structure of morbidity by hematological malignancies with primary bone marrow involvement, being characterized in the advanced stages by a severe, recurrent evolution and unfavorable prognosis, with negative socio-economic impact.
Material and methods: A clinical, analytical, and descriptive study was carried out along with the narrative review of the international literature on the subject. The study enrolled 91 elderly patients with different phases of chronic myeloid leukemia (CML), primary myelofibrosis (PMF) and polycythemia vera (PV), who were followed up and treated at the Institute of Oncology in the period of 1995–2020. According to the impact score, 25 relevant primary sources were identified and selected having a scientific, reproducible and transparent approach to the relevant subject, followed by data extraction and analysis.
Results: The overall one- and 5-year survival in patients aged greater than or equal to 60 years old treated with tyrosine kinase inhibitors (TKIs) was 97.6 and 79%, being lower as compared with the same indices in the totality of CML. In elderly PV patients the overall 5-and 10-year survival made up 93.5% and 76.4%, being lesser than registered in all patients with PV. As reported in the recent references, a significant rate of patients with CMPH underwent reduced working hours, discontinued employment, and medical disability: PMF – 38%, 35%, 33%, and PV – 33%, 28%, and 15%, respectively.
Conclusions: The long-term treatment results in elderly patients with CMPH fail compared to those in the CMPH totality, due to the development of age-related diseases and vascular accidents caused by leuko- and thrombocytosis.
Key words: myeloproliferative hemopathies, myeloid leukemia, myelofibrosis, polycythemia vera, elderly patients.

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Introduction

Chronic myeloproliferative hemopathies (CMPH) as a whole are the most common chronic leukemias in the elderlies in the structure of morbidity by hematological malignancies with primary bone marrow involvement, being characterized in the advanced stages by a severe, recurrent evolution and unfavorable prognosis, with negative socio-economic impact [1-5, 7]. Chronic myeloid leukemia (CML), primary myelofibrosis (PMF) and polycythemia vera (PV) are considered the most common CMPH. CML is a clonal neoplastic pathology of the hematopoietic system, which results from the malignant transformation of the pluripotent stem cell, while maintaining the ability of differentiation into all cell lines [6-9]. CML morbidity increases with age, with a maximum incidence between 35 and 65 years (median age – 53 years), that indicates the predominant involvement of the workable population. CML morbidity varies between 1.0-2.0 cases per 100000 of population. The clinico-evolutional and hematologic patterns of CML comprise splenomegaly, myeloid hyperplasia of the bone marrow, hypercatabolic symptoms and progression to the acute leukemia in the majority of cases. PMF represents a chronic myeloproliferative neoplasm, which derives from the clonal myeloid prolifetaion as a result of malignant transformation of stem cell. The disease is manifested by splenomegaly, bone marrow fibrosis, anemia, extramedullary hematopoiesis, tendency to cachexia and blastic transformation. According to the majority of references, the incidence of PMF constitutes 0.7-1 case per 100000 of population [1, 3, 4]. In 67% of cases PMF is diagnosed in persons over 54 years old. PV is a clonal trilineage proliferation of the malignized hematopoietic stem cell, being characterized by blood hyperviscosity and increased risk of thromboses. The estimated incidence of PV per 100000 of population ranges from 0.4 to 2.8 cases in Europe and from 0.8 to 1.3 cases in the USA. The reported age median encompasses 65-70 years. The bone marrow is hypercellular and exhibits hyperplasia of myeloid, erythroid, and megakaryocyte lineages. Erithrocyte formation is predominantly increased. The symptoms and signs of PV can be attributed in large part to the expanded total blood volume and to the slowing blood flow as a result

of increased blood viscosity. The latent thrombogenic status occurs. Arterial hypertension commonly develops. PV and PMF are considered orphan diseases in the USA because they affect less than 200000 people regardless of the observation period [10]. Marketology researches have shown that in 2003 the prevalence per 100000 population of PV was 22 and PMF – 19. The development and increased prevalence of CMPH in the elderlies correlates with the demographic aging process in the USA and the European Union [11], in which the rate of the population over 80 years old will triple with predictability between 2011 and 2060.

Patients across all CMPH experience a marked disease burden in terms of symptoms and negative effects on quality of life, productivity, and daily living activities. It is important to have an updated and appropriate understanding of these burdens from a financial standpoint in order to improve the health and life quality of patients with CMPH. Predominantly late diagnosis, increased degree of disability, morbidity and mortality indices in the age categories greater than or equal to 60 years [2, 11] identify CMPH as an actual problem of public health and clinical hematology.

Material and methods

A clinical, analytical and descriptive study was carried out along with a narrative review of the international literature regarding this subject. The study enrolled 91 elderly patients with different phases of chronic myeloid leukemia (CML), primary myelofibrosis (PMF) and polycythemia vera (PV), who were followed up and treated at the PMSI Institute of Oncology in the period of 1995 – 2020. The following research methods were used: epidemiological, descriptive, comparative, clinical-analytical, and cohort statistics [12]. The type of CMPH was identified according to the Revised 2017 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues [13-15]. The diagnosis was confirmed via histopathological, cytological, cytogenetic and molecular examinations of the bone marrow and peripheral blood [1, 5, 6, 8, 9, 15, 16]. The quantitative real-time PCR was used to detemine the expression of the BCR-ABL chimeric gene p210 and p190 transcripts while proceeding CML diagnosis. Five transcription products (b2a2, b3a2, b2a3, b3a3 and e1a2) were analyzed by using the quantitative PCR test [8]. The quantitative detection of JAK2 V617F mutation served as a major criterion in the diagnostically unasserted cases of PV and PMF. CML patients underwent TKI single-agent chemotherapy. The first-line treatment of PMF and PV patients included a single-agent conventional chemotherapy with busulfan and hydroxycarbamide. The research data collection was carried out by analyzing information provided by the international scientific sources and official statistics related to the above mentioned nosological entities. More than 50 reference bibliographic sources have been studied. According to the impact score, 25 relevant primary sources were identified and selected with a scientific, reproducible and transparent approach regarding this relevant subject, followed by data extraction and analysis. To minimize the error, a copy of the data extraction sheet was initially obtained, listing all the elements that should be extracted from the primary studies. When doing the qualitative research, a narrative synthesis of data has been performed.

Results and discussion

Thirty-four (37.3%) patients with PMF, 26 (28.6%) – with CML and 31 (34.1%) – with PV were diagnosed in the elderly age groups and followed up by our study. The prefibrotic stage of PMF was confirmed in 15 (44.1%) cases, fibrotic stage – in 21 (55.9%). The diagnosis of CML was made in 24 (92.3%) patients in chronic phase and in 2 (7.7%) patients in accelerated phase. In all cases PV was diagnosed in the erythremic stage: II A – in 27 (87.1%) patients, IIB – in 4 (12.9%). The age group of 60-69 years was more numerous in CML (22 cases, or 84.6%), accounting for 25 (80.6%) cases in PV and 25 (73.5%) cases in PMF. The duration of the disease from the time of onset of the initial clinical symptoms to diagnosis ranged in PMF between 1.4-7 months (on average – 3.7±0.63 months), in CML between 1.5-12 months (on average – 2.1±0.37 months) and in PV between 1-7 months (on average – 3.8±0.54 months). The clinical onset and addressability of patients with CML and PMF did not differ significantly, most patients (over 90%) being consulted by a family doctor because of the presenting complaints such as fatigue, heaviness and then pain in the left hypochondrium or in the left hemiabdomen. Most patients with PV (21 persons or 67.7%) went to the territorial healthcare institutions for medical assistance, complaining of steady hypertension or so-called "astheno-vegetative" syndrome. In 3 (9.7%) cases the diagnosis of PV was made, following a treatment for myocardial infarction within the cardiology wards. Two (6.5%) patients diagnosed with ischemic stroke were hospitalized at the neurology wards for emergency medical care; the diagnosis of PV was further confirmed.

According to the references updates, the mean life span of CML patients under the conventional chemotherapy ranges between 4-5 years, exceeding 10 years in 30% of them. Although the allogeneic hematopoietic stem cell transplantation is considered in many instances as the most efficient treatment option, with a potential of complete recovery, especially in cases refractory to TKIs, it remains currently inapplicable in the elderly CML patients [9, 16, 17]. Regardless the age, recombinant interferon α (IFN α-2b) preserves its role as a valid treatment option in chronic phase of CML, committing to the achievement of complete hematologic response in 81% of cases [18]. Under the treatment with IFN α-2b the major cytogenetic response may be obtained in 40% and complete cytogenetic response in 25% of CML patients. The overall 5-year survival of patients treated with IFN α-2b is rated at 57%, being superior to that one in patients managed with conventional chemotherapy (42%). This present study showed no significant difference in the rate of complete clinical-hematological (92.3% vs

92.8%) and complete molecular response (23.1% vs 24.7%) under TKIs medication between elderly patients and total number 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 all CML patients (98.5% and 87%, correspondingly). IFN α-2b was used in rare cases of resistance to conventional chemotherapy and TKIs, showing a partial response.

A combination of chemotherapy and phlebotomies was used in all 31 patients with PV that led to a clinical-hematological remission. The response duration ranged from 3 to 9 months (on average – 5.8 months). The disease relapsed in all cases of plethoric syndrome and thrombocytosis, which required the resumption of induction chemotherapy with busulfan and hydroxycarbamide, followed by regaining remissions. Fatal cases associated with the treatment and thromboembolic complications did not occur. The over one-year overall survival in elderly patients constituted 100%, over 5 years – 93.5% and over 10 years – 76.4%, thus exhibiting a lower rate than those registered in all PV patients (over one year – 100%, 5 years – 98.6%, 10 years – 85.9%). Although the relapse rate was lower in patients treated with busulfan as compared to those managed with hydroxycarbamide, there was no significant difference in the overall survival of the elderly patients undergoing chemotherapy with these antineoplastic agents.

The recent literature sources consider single-agent chemotherapy with hydroxycarbamide as the first-line treatment option in the elderly with PMF, associated with splenomegaly and thrombocytosis. Thalidomide or lenalidomide in combination with prednisolone, danazol may be administered in cases with marked symptoms, especially in those with splenomegaly and anemia. The patients with intermediary-2 risk, especially those with prognostically unfavorable mutations ASXL1, SRSF2 and aged ≥ 65 years old, should be administered treatment with JAK kinase inhibitors (ruxolitinib, etc.). In most studies the mean survival rate is estimated to 3.5-5 years, ranging from 1 year in some patients to even decades in others. According to the international literature data, the survival rate in PMF (on average – 5.9 years) is still lower compared to the same indicator in other Ph-negative CMPH like PV (on average – 13.5 years) and ET (on average – 19.8 years) [19]. This study reported on the rate of clinical -hematological responses (73.5%) and survival rate under busulfan and hydroxycarbamide treatment in patients with PMF, which were also lower than in PV and CML. The 5-year overall survival of elderly PMF patients, constituted 67% and proved to be lower, if compared to the mean 5.9-year survival in all PMF patients, thus showing similar data as reported by other relevant studies. [20-22]. Only three PMF patients, diagnosed in 2001, 2007 and 2009 respectively, are being followed up. Generally, this suggested that new therapies may be recommended in CMPH at any age without absolute contraindications. An individual precise therapy should be mandatorily considered for every patient [17, 23]. In PMF and PV cases, refractory or intolerant to hydroxycarbamide, COMFORT and RESPONSE studies showed the rate of 41.9-62% of disease control under the treatment with JAK inhibitors, as compared with the best available therapy (0-19%). For these reasons, an accurate definition of diagnosis and prognostication is required. Precision in CMPH definition and prognostication is decisively useful for a customized therapeutic approach [17].

In order to assess the financial burden of CMPH on public health, the narrative review of the international experience was performed. A study on financial burden of CMPH on patients was carried out in the USA in 2014 [24]. The subjects who were diagnosed before 2013, aged between 16-65 old at the time of diagnosis were eligible for this analysis (PMF – 85, PV – 172). Almost all patients (99%) had health insurance, primarily group commercial insurance through an employer (PMF – 46%, PV – 53%) and Medicare (PMF – 40%, PV – 34%). The mean 2013 household incomes of patients with PMF and PV were similar to each other ($79800, and $80200, respectively) and slightly higher than the total 2013 USA mean household income of $75839. A significant rate of patients in each CMPH group reported that their disease led to reduced work hours, discontinued employment, and medical disability: PMF – 38%, 35%, 33%, and PV – 33%, 28%, and 15%, respectively. Patients' demographic features, such as age and health insurance status, were similar among patients who reported CMPH-associated effects on employment and patients who did not report these within each CMPH case. In each CMPH group, the mean percentage household income loss in patients with reduced work hours, discontinued employment, and medical disability were: PMF – 16%, 18%, 28%, and PV – 15%, 24%, 17%, respectively, compared with patients who did not experience any effects of their CMPH on employment. Discontinued employment and medical disability, especially in elderly patients, tended to have a greater negative impact compared with reduced work hours across CMPH [24, 25].

Conclusions

The long-term treatment results in elderly patients with CMPH fail compared to those of overall CMPH cases, because of the development of age-related diseases and vascular accidents due to leuko- and thrombocytosis. The slow onset, gradual increase of hemoglobin, erythrocyte count and blood viscosity along with inappropriate oncologic vigilance of primary care doctors may lead to the occurrence of thrombotic and vascular complications in the elderly PV patients. The targeted treatment with TKIs remains a therapeutic option of choice for CML patients aged over 60 years old. In the elderly PV patients, no significant difference was revealed in short- and long-term outcomes of chemotherapy with busulfan and hydroxycarbamide in combination with phlebotomy, thus providing better overall results than those used in PMF patients. The review of the literature shows that the patients with CMPH, especially the elderly ones, may suffer a considerable unfavorable impact of their employment status, which in turn may be associ-

ated with a reduced annual household income. Prevention or backtracking discrete aspects of CMPH, that negatively impact individual productiveness, may be considered as an important factor in the management of these diseases.

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Authors' contribution
VM conceptualized the study, designed the research and drafted the first manuscript; VS conducted the laboratory work and revised the manuscript critically; LC conducted the management work and revised the manuscript critically; LM collected and interpreted the data, and revised the manuscript critically; DC collected the data. All the authors revised and approved the final version of the manuscript.

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Ethics approval and consent to participate
The research was approve by the Research Ethic Board of *Nicolae Testemitanu* State University of Medicine and Pharmacy (protocol No 9 of September 21, 2015).

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