SCIENCE, INNOVATIONS AND EDUCATION: PROBLEMS AND PROSPECTS

Proceedings of VIII International Scientific and Practical Conference

Tokyo, Japan

9-11 March 2022

Tokyo, Japan

2022

UDC 001.1

The 8th International scientific and practical conference "Science, innovations and education: problems and prospects" (March 9-11, 2022) CPN Publishing Group, Tokyo, Japan. 2022. 227 p.

ISBN 978-4-9783419-3-8

The recommended citation for this publication is:
Ivanov I. Analysis of the phaunistic composition of Ukraine Science, innovations and education: problems and prospects. Proceedings of the 8th International scientific and practical conference. CPN Publishing Group. Tokyo, Japan. 2022. Pp. 21-27. URL: https://sci-conf.com.ua/viii-mezhdunarodnaya-nauchno-prakticheskaya-konferentsiya-science-innovations-and-education-problems-and-prospects-9-11-marta-2022-goda-tokio-yaponiya-arhiv/.

Editor
Komarytskyy M.L.
Ph.D. in Economics, Associate Professor

Collection of scientific articles published is the scientific and practical publication, which contains scientific articles of students, graduate students, Candidates and Doctors of Sciences, research workers and practitioners from Europe, Ukraine, Russia and from neighbouring coutries and beyond. The articles contain the study, reflecting the processes and changes in the structure of modern science. The collection of scientific articles is for students, postgraduate students, doctoral candidates, teachers, researchers, practitioners and people interested in the trends of modern science development.

e-mail: tokyo@sci-conf.com.ua

homepage: *https://sci-conf.com.ua*

TABLE OF CONTENTS

AGRICULTURAL SCIENCES

VETERINARY SCIENCES

MEDICAL SCIENCES

PHARMACEUTICAL SCIENCES

TECHNICAL SCIENCES

MEDICAL SCIENCES

UDC: 616.411-003.972

MOLECULAR GENETIC MARKERS OF MYELOPROLIFERATIVE Ph - NEGATIVE NEOPLASMS IN COMPARISON WITH CLINICAL AND LABORATORY DATA

Pesotskaya Lyudmila Anatolyevna
MD, Associate Professor
Schukina Elena Sergeevna
Assistant
Kochkarova Yaniljan Dzhumanyazovna
PhD student
Medvedkov Maxim Alexandrovich
Student
Dnipro State Medical University
Dnipro, Ukraine

Annotation. Based on the literature data, the frequency of occurrence of somatic mutations in the Janus-kinase genes JAK 2 (JAK2V617F), CALR - encoding protein calreticulin, MPL - thrombopoietin receptor in polycythemia vera, essential thrombocythemia, primary idiopathic myelofibrosis. Their influence on the clinic and the prognosis of the course of Ph - negative myeloproliferative neoplasms are described.

Key words. Myeloproliferative neoplasms, molecular genetic status, clinical and laboratory data.

Introduction. Myeloproliferative philadelphia-negative neoplasms (MPN) are chronic clonal diseases derived from hematopoietic stem cells, characterized by uncontrolled proliferation of differentiated myeloid cells, similar pathogenesis and clinical course [1, 2, 3]. They often develop from one clinical phenotype to another

and eventually progress to acute myeloid leukemia [4].

According to the 2016 World Health Organization (WHO) classification, MPN includes polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The 2016 revision of the WHO classification aimed to differentiate between masked PV and JAK2-mutated ET, as well as between prefibrotic/early PMF and overt PMF [2, 4, 5].

In 2005, a somatic point mutation was discovered in exon 14 of the Janus-kinase gene JAK 2 (JAK2V617F) at the level of pluripotent hematopoietic stem cells. Its presence causes independent activation JAK 2-kinases followed by cascade phosphorylation (activation) of the STAT family proteins responsible for the proliferation and differentiation of hematopoietic progenitor cells. Further studies of the molecular pathogenesis of MPN revealed other somatic mutations (CALR - coding protein calreticulin and MPL - thrombopoietin receptor) that also activate the JAK - STAT signaling pathway. Dysregulation of the JAK/STAT pathway is a unifying mechanistic feature of MPN [1, 6] . The identification of driver mutations has contributed to a greater understanding of the pathogenesis of the disease, highlighting the importance of JAK transducer and transcription activator (STAT) signaling [6]. Additional mutations in genes associated with myeloid neoplasms have also been identified with established prognostic significance, especially in PMF [2, 7]. In general, MPN develop as a result of the transformation of early precursors of hematopoiesis with impaired functioning of signaling pathways that regulate cell growth, activation, differentiation, adhesion, and apoptosis **.**

The fact that MPN is characterized by the presence of various molecular genetic markers of clonality that affect the activation of the JAK - STAT signaling pathway reflects the biological heterogeneity of the disease [8, 9], which complicates the differential diagnosis of its individual forms. Therefore, it is relevant to study the listed molecular genetic markers in comparison with the frequency of presence in various MPN nosologies and the impact on the clinical picture of the latter.

Data on the frequency of carriage of somatic mutations in a certain MPN nosology presented by various authors are mostly close, but there are also

differences. In particular, according to the results of studies [1, 7] the presence of JAK2 mutation was encountered in 94.7% of cases with PV, in 75% with ET, in 25.0% with PMF. Partially the same results were obtained [6] by the frequency of occurrence of this mutation in PV and ET. However, the authors observed a higher incidence of JAK2 mutation in IMF (82.8%).

Exon 12 mutation was found in 1.7% of patients with PV and none of patients with ET or PMF, with an overall mutation rate of 0.5% [6]. Gene mutations CALR occurred in 12% of patients with both ET and UTI. An MPL mutation was found in 0.9% of patients with ET and in 1.1% of patients with PMF, with an overall mutation rate of 0.6% [1, 6].

None of the tested mutations were detected (TN status) in 11% of patients with ET. According to other authors, TN -status is about 10-15% of the general population of patients with ET [8, 10].

In earlier studies, 50–60% of patients with ET had JAK 2 mutations [11, 12], and 15–24% of patients had CALR mutations. [13], in 5-7 % cases of MPL mutation [14]. Overall, JAK2 somatic mutations cause MPN in 50–60% of cases, and CALR mutations in 25–30% of cases [3]. CALR exon 9.0 mutations have been identified in a third of patients with JAK2-negative ET and IMF; MPL (W515K/L) mutations have not been detected [7]**.** Due to the discovery of molecular genetic (MG) markers, ET verification is possible in 79-87% of cases [15, 16]. The simultaneous occurrence of any two types of driver gene mutations was not found, but not for patients with CALR or MPL mutation [5, 6].

Features of the clinical picture of individual myeloproliferative neoplasms in comparison with MG markers are presented by the researchers as follows.

For ET in subgroups with CALR 1+ and CALR 2+, there were significantly higher platelet counts at the stage of primary diagnosis in comparison with JAK2+ and TN (mutations were not detected). Mean platelet counts were 1252×10^9/l with CALR 2 + and 1079×10^9/l with CALR 1+, and 775×10^9/l with JAK2+ and TN, respectively [1] . The platelet count in MPN patients in general with CALR mutation was statistically significantly higher than in patients with JAK2 [966 (400-2069) ×

10^9 /l versus 800 (198-3730) × 10^9 /l [6].

Thrombotic complications in ET were observed in 27.4% of the JAK2+ subgroup, 30.7% of the TN subgroup, and 18.2% of the CALR1+ subgroup. There were no thrombotic complications in the CALR2+ and MPL + subgroups, despite higher platelet counts. In general, the CALR 1+ status is characterized by the authors as prognostically the most favorable (5-year overall survival of 100%), and TN as unfavorable (5-year overall survival of 85%) [1]. The results obtained by other researchers are different. In particular, patients with CALR-mutated ET were more likely to progress to accelerated or blast phases compared with patients with JAK2 mutations. The prognostic value of CALR mutations probably differs for different subtypes of MPN [6].

The effect of JAK2 allelic load in Ph-negative MPN on the clinical picture, disease progression, and treatment outcome was established. A high proportion of the mutant JAK2 allele (mutation load > 50%) was predominantly observed in PV compared with ET [7]. PV patients are heterohomozygous versus homozygous for JAK2 mutation in early versus late stages with increased mutation load from less than 50% to 100% and disease progression. MPN with mutations in JAK2 exon 12 is a distinct benign feature in early-stage PV [17].

Although a high level of JAK2 allelic load was closely associated with a high leukocyte count in both PV and ET, some hematological parameters (hemoglobin, hematocrit, and platelet count) were independent of JAK2 mutation load [7]. According to other authors, patients with JAK2 had significantly higher numbers of not only leukocytes, but also hemoglobin levels, compared with patients with or without CALR mutation, or only a significantly higher number of leukocytes compared with patients with MPL mutation [6].

In general, Japanese MPN patients grouped by different mutation subtypes show characteristics similar to those of Western ones. Compared to JAK2 ET patients, CALR mutated ET patients were younger, had lower white blood cell counts, lower hemoglobin levels, higher platelet counts, and fewer thrombotic events. A CALR1-like mutation was the dominant subtype in patients with overt PMF.

Compared with patients with a JAK2 mutation in ET, patients with a JAK2 mutation during the development of PMF showed higher LDH levels, lower hemoglobin levels, a higher JAK2 allelic load, and a higher incidence of splenomegaly [18]. CALR mutations have been associated with lower levels leukocytes, lower bone marrow cellularity, and higher megakaryocyte counts [19].

For hypercellular thrombocythemia in the bone marrow with a CALR mutation, distinct signs are characteristic - grouped large immature dysmorphic megakaryocytes with bulky (bulging) hyperchromatic nuclei, which are not observed with JAK2 mutation in PV and ET. MPL-mutant normocellular thrombocythemia is characterized by the accumulation of giant megakaryocytes with hyperlobulated nuclei in the form of deer antlers without signs of polycythemia in the blood and bone marrow. Mutation load in myeloproliferative diseases in each of the JAK2, CALR, and MPL genes influences the degree of anemia, splenomegaly, bone marrow cellularity, and myelofibrosis [17].

Thus, JAK2 mutation is the most common cause of Ph-negative myeloproliferative neoplasms. Although experiments have shown that this mutation is associated with the expansion of myeloid blood cells and increased production of leukocytes, erythrocytes, and platelets, the transcriptional consequences of the JAK2 mutation in various bone marrow cell compartments have not yet been fully elucidated [20]. Thus, a certain mutational status in MPN has not only differential diagnostic, but also prognostic value, which requires further research.

REFERENCES

1. Zhernyakova A.A., Martynkevich I.S., Shuvaev V.A. Molecular genetic markers and manifestations of essential thrombocythemia // Clinical oncohematology. 2017;10(3):402–8.

2. Coltro G et al. Classical Philadelphia-negative myeloproliferative neoplasms (MPNs): A continuum of different disease entities //Int Rev Cell Mol Biol. 2021;365:1-69.

3. Milosevic JD Feenstra PD-L1 Overexpression Correlates with JAK2-V617F

Mutational Burden and Is Associated with 9p Uniparental Disomy in Myeloproliferative Neoplasms // American Journal of Hematology 11 Jan 2022

4. Tremblay D. History, Pathogenesis, Diagnostic Criteria, and Complications Hematol Oncol // Clin North Am. 2021 апр; 35(2):159-176

5. Rabade N et al. Molecular genetics of BCR-ABL1 negative myeloproliferative neoplasms in India // Indian J Pathol Microbiol. Apr-Jun 2018;61(2):209-213.

6. Li M Y et al. Clinical significance of JAK2、CALR and MPL gene mutations in 1 648 Philadelphia chromosome negative myeloproliferative neoplasms patients from a single center // Zhonghua Xue Ye Xue Za Zhi. 2017 Apr 14;38(4):295-300.

7. Singdong R et al. Characterization and Prognosis Significance of JAK2 (V617F), MPL, and CALR Mutations in Philadelphia-Negative Myeloproliferative Neoplasms // Asian Pac J Cancer Prev. 2016 Oct 1;17(10):4647-4653.

8. Al Assaf C, Van Obbergh F, Billiet J, et al. Analysis Of Phenotype And Outcome In Essential Thrombocythemia With CALR or JAK2 Mutations. Haemato-logica. 2015;100(7):893-7. doi: 10.3324/haematol.2014.118299.

9. Cazzola M, Kralovics R. From Janus kinase 2 to calreticulin: the clinically relevant genomic landscape of myeloproliferative neoplasms. Blood. 2014;123(24):3714-9. doi: 10.1182/blood-2014-03-530865.

10. Labastida-Mercado N, Galindo-Becerra S, Garces-Eisele J, et al. The mutation profile of JAK2, MPL and CALR in Mexican patients with Philadelphia chromosome-negative myeloproliferative neoplasms. Hematol Oncol Stem Cell Ther. 2015;8(1):16-21. doi: 10.1016/j.hemonc.2014.12.002.

11. Abdulkadyrov K.M., Shuvaev V.A., Martynkevich I.S. Modern approaches to the diagnosis and treatment of essential thrombocythemia: a review of the literature and own data. Clinical oncohematology. 2015;8(3):235-47. doi: 10.21320/2500-2139-2015-8-3-235-247.

12. Rampal R, Al-Shahrour F, Abdel-Wahab O, et al. Integrated genomic analysis illustrates the central role of JAK-STAT pathway activation in

myeloproliferative neoplasm pathogenesis. Blood. 2014;123(22):e123-33. doi: 10.1182/blood-2014-02-554634.

13. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic Mutations of Calreticulin in Myeloproliferative Neoplasms. N Engl J Med. 2013;369(25):2379-90. doi: 10.1056/nejmoa1311347.

14. Vainchenker W, Delhommeau F, Constantinescu SN, et al. New mutations and pathogenesis of myeloproliferative neoplasms. Blood. 2011 ;118(7):1723—35. doi: 10.1182/blood-2011-02-292102.

15. Lundberg P, Karow A, Nienhold R, et al. Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms. Blood. 2014;123(14):2220-8. doi: 10.1182/blood-2013-11-537167

16. Tefferi A, Barbui T. Personalized management of essential thrombocythemia—application of recent evidence to clinical practice. Leukemia. 2013;27(8):1617-20.

17. Michiels J J et al. 2016 WHO Clinical Molecular and Pathological Criteria for Classification and Staging of Myeloproliferative Neoplasms (MPN) Caused by MPN Driver Mutations in the JAK2, MPL and CALR Genes in the Context of New 2016 WHO Classification: Prognostic and Therapeutic Implications // Maedica (Bucur). 2016 Mar;11(1):5-25.

18. Misawa K et al. Mutational subtypes of JAK2 and CALR correlate with different clinical features in Japanese patients with myeloproliferative neoplasms // Int J Hematol. 2018 Jun;107(6):673-680.

19. Kim S Y et al. CALR, JAK2, and MPL mutation profiles in patients with four different subtypes of myeloproliferative neoplasms: primary myelofibrosis, essential thrombocythemia, polycythemia vera, and myeloproliferative neoplasm, unclassifiable // Am J Clin Pathol. 2015 May;143(5):635-44.

20. Van Egeren et al. Transcriptional differences between JAK2-V617F and wild-type bone marrow cells in patients with myeloproliferative neoplasms // Exp Hematol. 2021 Dec 15;S0301-472X(21)00823-7.