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JAK2V617F MUTATIONS IN MYELOID MALIGNANCIES: SINGLE CENTER EXPERIENCE

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Abstract: Recently, V617F mutation in JAK2 tyrosine kinase gene was established as a marker of myeloproliferation, useful for proving clonality and securing diagnosis in a considerable proportion of the myeloproliferative neoplasms (MPN) The discovery presents a major breakthrough in the understanding of the pathogenesis of the MPN. Moreover, some studies suggest a possible role of the JAK2V617F mutation in the pathogenesis of some specific acute myeloid leukemia (AML) subtypes.

To further improve the understanding of the role of JAK2V617F mutations in the pathogenesis and the clinical course of the myeloid malignancies we screened 192 patients with various MPN and AML for the mutations and analyzed the possible association between JAK2V617F mutations and the clinical features of MPNs patients.

The frequency of V617F JAK2 mutation was analyzed by theallele-specific PCR assay.

Out of 153 cases with known or suspected diagnoses of MPNs, 100 (65.3%) were positive for the JAK2V617F mutation and 53 (34.7%) were negative. In 39 AML cases the mutant allele V617F was not expressed.

Correlations of the clinical features at diagnosis and long-term prognosis between the two JAK2-V617F different MPNs groups revealed comparability regarding all tested parameters except for the incidence of thrombotic history. Patients with the mutation had significantly higher incidence of thrombotic complication (38.5%), compared to the group without the mutation (19.2%) ($P < 0.005$).

Our results confirmed the diagnostic significance of JAK2V617F mutation in MPNs and supported the notion that patients with the mutation should be classified in a new entity of MPNs.

Key words: JAK2V617F mutations, Myeloid Malignancies**,** allele-specific polymerase chain reaction (AS-PCR), myeloproliferative neoplasms, AML.

Introduction

Myeloid malignancies comprise acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPN). All three groups present clonal disorders that are characterized by acquired somatic mutations in hematopoetic progenitors [1–4].

Recent advances in the understanding of the genetic basis of myeloid malignancies have revealed important insights into the pathogenesis of AML and MPN and have guided to the development of novel therapeutic approaches [1, 4, 5].

MPNs are distinguished by the presence of variable degrees of differentiation and effective hematopoieisis. Traditionally, they are divided into "classic" and "atypical subcategories" of MPN. The former group include chronic myelogenous leukemia, polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) [2].

In 2005, several groups reported a single, acquired point mutation in the Janus kinase 2 (JAK2) genes in the majority of patients with BCR-ABL-negative myeloproliferative disorders. The mutation was detected in more than 95% of patients with PV, in 50% to 60% of patients both with ET and PMF and in a small minority of patients with others subcategories of atypical MPNs, myelodysplasia and AML [6–12]. Further studies established the activating V617F mutation in JAK2 tyrosine kinase gene as a marker of myeloproliferation, useful for proving clonality and securing diagnosis in a considerable proportion of patients with MPN [13–15]. Subsequently, the presence of a JAK2V617F mutation was adopted as a major diagnostic criterion according to the revised World Health Organization (WHO) diagnostic criteria for PV and considered as a clonal marker in ET and PMF [16, 17].

The mutation was additionally detected in a significant number of cases with secondary AML following a preceding MDS [18, 19]. Also, it was reported in de novo AML in lower frequencies, but the number of analyzed cases was limited [19–22]. Therefore, no conclusive results were obtained regarding the contribution of this genetic lesion in the pathogenesis of AML.

Furthermore, despite of the fact that identification of the JAK2V617F mutation stands as a molecular substantiation of the concept of the myeloproli-

ferative disorders, many questions remain regarding the molecular basis PV, ET and PMF, and the role of the JAK2V617F allele in the MPNs pathogenesis [1, 4]. The explanation that a single JAK2V617F allele yields three related, but clinically distinct MPNs phenotypes stays unknown. Also, the current evidence is inconclusive regarding the prognostic relevance of the JAK2V617F in MPNs [23–28].

To further improve the understanding of the role of JAK2V617F mutations in the pathogenesis and the clinical course of the myeloid malignancies we screened 192 patients with various MPN and AML for the mutations and analyzed the possible association between JAK2V617F mutation and the clinical features of MPNs patients.

Materials and methods

In the period of one year (June 2007-June 2008), a total of 192 adult (> 15 years) patients, diagnosed and followed at the University Clinic of Hematology-Skopje were tested for the presence of the JAK2V617F mutations. The study group consisted of 153 patients with MPNs plus 39 patients with AMLs who were consecutively admitted at the Clinic of Hematology-Skopje from January through June 2008. The diagnoses of MPNs were made according to the World Health Organization diagnostic criteria, 52 patients were diagnosed as PRV, 76 as ET, 9 as MF and 16 were classified as atypical MPNs [2]. The median follow up of the patients was 5.7 years.

The diagnosis of AMLs was made by standard morphological examinations and cytochemical analyses of bone marrow smears according to the criteria established by the FAB Cooperative Study Group and confirmed by immunophenotyping of bone marrow aspirates and/or peripheral blood samples following the criteria of the European Group for the Immunological Classification of Leukemia's (EGIL) and the British Committee for Standards in Hematology (BCSH) [29, 30]. Additionally, we analyzed the AML samples for the presence of the fusion transcripts AML1-ETO, PML-RARα and CBFβ-MYH11 of the recurrent cytogenetics abnormalities t(8,21), t(15,17), inv16, t(16,16) by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) assay [31].

JAK2v617F mutations analyses were performed on the granulocyte fraction of peripheral blood in MPNs cases and on mononuclear cells on bone marrow in AML cases. Mononuclear cells and peripheral blood granulocytes preparation, DNA isolation, and cDNA synthesis were performed at the Center for biomolecular sciences, Immunology and Pharmacogenetics, Faculty of Pharmacy-Skopje, according to standard procedures.

Peripheral blood granulocytes and/or mononuclear cells were separated by differential centrifugation over a Histopaque-1077 (Sigma-Aldrich) and pro-

cessed for DNA isolation with the QIAmp DNA mini blood Kit (Qiagen) according to the instructions of the manufacturer. The JAK2 V617F polymorphism was detected with allele-specific polymerase chain reaction (AS-PCR) using the following primers: forward (specific) 5'-AGC ATT TGG TTT TAA ATT ATG GAG TAT ATT-3'; forward (internal control) 5'-ATC TAT AGT CAT GCT GAA AGT AGG AGA AAG-3' ; reverse 5'-CTG AAT AGT CCT ACA GTG TTT TCA GTT TCA-3'. One μM of the common reverse primer and 0.5 μM of the two forward primers in a 25-μl total reaction volume were used. Eighty ng of DNA was amplified in a 35-cycle AS-PCR reaction at an annealing temperature of 58°C. The first forward primer is specific for the mutant allele and contains an intentional mismatch at the third nucleotide from the 3' end to improve specificity (giving a 203-bp product); the second amplifies a 364-bp product from both mutant and wild-type alleles and serves as an internal control (6, 7). The PCR fragments were separated by electrophoresis on 2% agarose gel and visualized with ethidium bromide staining (Figure 1).

Clinical data from the patients were collected according to the protocol that was used at Harvard myeloproliferative disorders study, approved by the Dana-Farber Cancer Institute Institutional review Board. All included patients have signed written informed consent [7, 15].

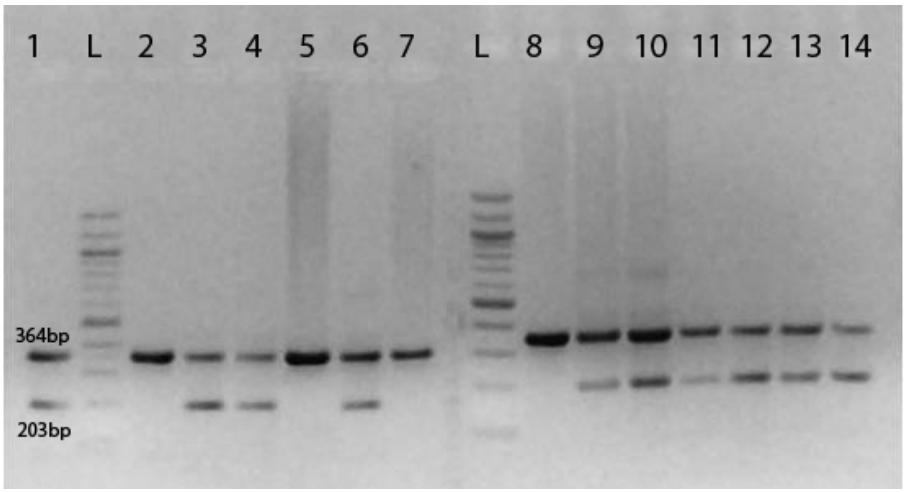

Figure 1 – Gel electrophoresis of AS-PCR assay for detecting JAK2V617F mutation

Слика 1 – Слика од гел електрофореза на алела специфична полимераза верижна реакција за детекција на JAK2V617F мутацијата

Representative results: Track number 6 is the positive control (mutant JAK2V617F allele is the lower band); track number 7 is the negative control (wild type JAK2); tracks 1–5 and 8–14 are patients, of which 1, 3, 4, 9–14 are positive for the mutant allele. L = 100bp DNA Ladder (New England Biolabs)

Statistical comparison between categorical variables was performed by chi-squared statistics or Fisher's exact tests. Statistical analyses were performed using the SigmaStat 3.1 program (Systat Software Inc., Richmond, CA).

Results

In the period of one year, between June 2007 and July 2008, of the 153 cases with known or suspected diagnoses of MPNs, 100 (65.3%) were positive for the JAK2V617F mutation by the AS-PCR assay and 53 (34.7%) were negative. Some of the representative results are shown in Figure 1.

Using the AS-PCR assay we found that the JAK2 V617F mutation was present in 46 (88.4%) of patients with PV, 44 (59.2%) with ET, 6 (66.6%) with PMF and in 3 (18.7%) with atypical MPNs.

Table 1 – Табела 1

Characteristics associated with the JAK2V617F mutation
Карактеристики асоцирани со JAK2V617F мутацијата

Characteristic	JAK2V617F mutation Present	JAK2V617F mutation Absent	P Value
Diagnosis-no. (%)*			0.001
Polycythemia vera	46 (88.4)	6 (11.6)	
Essential thrombocythemia	44 (59.2)	32 (40.8)	
Idiopatic myelofibrosis	6 (66.6)	3 (33.4)	
Atypical MPN	3 (18.7)	13 (81.3)	
Age-years			0.001
Median	51	59	
Range	(17–79)	(18–83)	
Sex-no. (%)			n.s.
Male	49 (49)	28 (52.8)	
Female	51 (51)	25 (47.2)	
Hemorrhage-no. (%)			n.s
Yes			
No			
Thromboembolic events-no. (%)			< 0.005
Yes	38 (38)	11 (20.8)	
No	62 (62)	42 (79.2)	
Disease transformation-no. (%)			n.s
Yes	1 (1)	2 (3.8)	
No	99 (99)	51 (96.2)	
Acute leukemia			n.s
Yes	0	0	
No	100 (100)	53 (100)	

*Percentages are of all patients with each diagnosis

Possible associations between the V617F mutation and the clinical and laboratory features of the MPNs patients were analyzed retrospectively. The clinical characteristics of the 153 MPNs patients included in our study, according to their JAK2V617F mutation status are detailed in Table 1.

Correlations of the clinical features at diagnosis and long-term prognosis, including the incidence of thrombo-hemorrhagic events, disease transformation in different MPNs entities or acute leukemia of the patients between the two JAK2-V617F different MPNs groups revealed comparability regarding all tested parameters except for the incidence of thrombotic history. Significantly, more patients with a mutation had a higher incidence of thrombotic complication (38.5%), compared with in the group without mutation (19.2%) ($P < 0.005$).

Also, in the period of six months, between January and July 2008, 39 consecutive patients were diagnosed as AML at the Clinic of Hematology-Skopje. According to FAB criteria, the AMLs were classified as M0 (n = 4), M1 (n = 6), M2 (n = 13), M3 (n = 4), M4 (n = 8), M5 (n = 3) and one case as AML-M6. The JAK2V617F mutation was not detected in any of the AML cases, using AS-PCR assay.

Discussion

Our results confirmed the diagnostic significance of JAK2V617F mutation in MPNs, although a small disparity of the incidence of JAK2V617F mutation in different MPNs entities in our population compared to expected literature based frequency of JAK2V617F was observed [14, 16, 17).

The cardinal features of the three main MPN are increased red-cell mass in PV, a high platelet count in ET and bone marrow fibrosis in PMF. These three disorders share many characteristics, including marrow hypercellularity, a tendency to thrombosis and hemorrhage, and a risk of leukemic transformation in the long term [3]. The current evidences regarding the prognostic relevance of the JAK2V617F in MPNs is unconvincing and limited. In PV, because of the small number of described mutation negative cases, valid assessment is not possible [15].

Evaluation of the clinical data in our study revealed significant correlations between the presence of the V617F mutation and the frequency of thrombotic complications in MPNs patients [23–26, 32–34]. With regard to the risk of thrombosis, results from the literature are conflicting. The largest relevant study in ET suggested that V617F was associated with venous but not with arterial events [23]. Also, an increased prevalence of thrombotic episodes has been reported in V617F positive PMF patients [26]. In contrast, two other relatively

large studies of ET and one of PMF showed that the overall risk of thrombosis was not affected by the presence of the mutation [24, 25]. Our analyses showed an apparent association of the mutations with thrombotic events, both venous and artherial. In eight of our patient acute myocardial infraction and in two others abdominal venous thrombosis preceded the diagnosis of MPNs. Those findings imply that low-dose aspirin prevention should be included in the initial treatment of V617F positive MPNs patients.

Investigators which reported an increased risk of thrombosis in mutated MPN patients suggest a possible biological continuum between ET and PRV [32–34].

Furthermore, the increase of the JAK2V617F mutation rate from ET to PMF and to PV suggests that these disorders overlap or represent a continuum. This is in line with the difficult discrimination of the various MPNs with respect to the clinical course and cytomorphology [35, 36].

Altough our results confirmed the diagnostic significance of JAK2V617F mutation in MPNs, we observed a disparity of the incidence of JAK2V617F mutation in different MPDs entities in our population compared to expected literature-based frequency of JAK2V617F. Therefore, we support the notion that patient that carry the JAK2V617F mutation should be classified in a new distinct entity of MPNs distinct by a specific diagnostic approach. We believe that this concept will be very soon additionally validated by the emerging specific target therapy [37].

To date, analyses of AML patients have shown that the JAK2V617F mutation is not a common event in the pathogenesis of AML and predominantly occurs in patients with a preceding myeloproliferative disorders. However, these studies did not include a significant number of specific subtypes of de novo AML [18, 19]. Some studies indicate a possible pathogenic role of the JAK2V617F mutation in t(8,21) and trisomy 8 AML.

We did not detect the JAK2V617F mutation in any of our AML patients. Also, we did not find any AML case positive for the genetic abnormalities AML1–ETO [20, 22].

Our findings are not surprising, if we take into considerations that the number of cases studied for different AML subtypes in our group was too small to reach any statistical validation.

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Резиме

JAK2V617F МУТАЦИЈА КАЈ МИЕЛОИДНИ МАЛИГНИ БОЛЕСТИ: ИСКУСТВА НА ЕДЕН ЦЕНТАР

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Неодамна откриената асоцијација помеѓу активационата V617F мутација во JAK2 киназниот ген и миелоидните малигни болести придонесе за расветлување на нивната патогенеза, го потврди клоналното потекло на оваа група болести и овозможи прецизна дијагноза на голем број хронични миелопролиферативни неоплазми (МПН). Некои студии укажуваат и на можната улога на JAK2V617F мутацијата во патогенезата на одредени подтипови на акутна миелобластна леукемија (АМЛ).

Цел на нашата студија е да придонесеме во разбирањето на улогата на JAK2V617F мутацијата во патогенезата и клиничкиот тек на миелоидните малигни болести преку тестирање на серија од 192 пациенти со дијагностицирани и суспектни МПН и АМЛ за JAK2V617F мутацијата и анализирање на можната асоцијација помеѓу истата и клиничките карактеристики на

МПН. Фреквенцијата на JAK2V617F мутацијата ја анализиравме со алел-специфична-полимераза верижна реакција.

Кај 100 (65,3%) пациенти од вкупно 153 тестирани случаи на МПН беше детектирана JAK2V617F мутацијата. Од 39 АМЛ примероци, ниту еден не го експримираше мутантниот V617F алел. Направената корелацијата на иницијалните клинички карактеристики и прогнозата на болеста помеѓу двете групи на МПН, поделени врз основа на позитивитетот за JAK2V617F мутацијата покажа дека групите се компарабилни за сите параметри, освен во поглед на тромботичните компликации. Сигнификантно поголем број на пациенти носители на мутацијата имаат висока инциденца на тромботични компликации 38,5% споредено со 19,2% во групата без мутација ($P < 0.005$).

Нашите резултати ја потврдија значајната улога на JAK2V617F мутацијата во дијагнозата на МПН и го поддржуваат ставот дека пациентите кои ја носат оваа мутација треба да се класифицираат во нов ентитет на МПН.

Клучни зборови: мутации на JAK2V617F, миелоидни малигни болсести, алел-специфична полимераза верижна реакција, миелопролиферативни неоплазми, АМЛ.

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