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Mini-review

Cytogenetic and molecular aspects of Philadelphia negative chronic myeloproliferative disorders: Clinical implications

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Abstract

Chronic myeloproliferative disorders (CMPD) are clonal disorders of the hematopoietic stem cell. The myeloid lineage shows increased proliferation with effective maturation, while peripheral leukocytosis, thrombocytosis or elevated red blood cell mass are found. In Philadelphia negative CMPD recurrent cytogenetic abnormalities occur, but no specific abnormality has been defined to date. The spectrum of cytogenetic aberrations is heterogeneous ranging from numerical gains and losses to structural changes including unbalanced translocations. The most common chromosomal abnormalities are 20q−, 13q−, 12p−, +8, +9, partial duplication of 1q, balanced translocations involving 8p11 and gains in 9p. Cytogenetic analysis of CMPD by conventional or molecular techniques has an important role in establishing the diagnosis of a malignant disease, adding also more information for disease outcome. Molecular studies may detect the possible role of candidate genes implicated in the neoplastic process, addressing new molecular target therapies. FIP1L1/PDGFRα rearrangements, as well as alterations of PDGFRβ or FGFR1 gene have been found to be associated with specific types of CMPD. Recently, a novel somatic mutation, JAK2V617F, has been reported in most of the polycythemia vera (PV) patients, as well as in a lower percentage in essential thrombocythemia (ET) or idiopathic myelofibrosis (IMF) patients. This finding represents the most important advance in understanding of the molecular mechanisms underlined the pathogenesis of CMPD, contributing to the classification and management of patients.

Keywords: Chronic myeloproliferative disorders; Cytogenetics; Chromosomal abnormalities; Molecular changes; JAK2 mutation; Clinical implications

1. Introduction

Chronic myeloproliferative disorders (CMPD) are clonal disorders of the hematopoietic stem cell. The myeloid lineage shows increased proliferation with effective maturation, while peripheral leukocytosis, thrombocytosis or elevated red blood cell mass are found. In 1951 Dameshek [1] grouped five clinically and pathophysiologically related disorders and termed them myeloproliferative diseases. This group of disorders included chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), idiopathic myelofibrosis (IMF) and erythroleukemia. Today, erythroleukemia

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is considered a specific type of acute myeloid leukemia. Furthermore, CML is now considered a separate entity defined by the t(9;22)(q34;q11), which results in the production of the BCR/ABL fusion protein. An overlap is often seen between distinct categories of CMPD with progression from one disease to another. CMPD share also a tendency to progress to bone marrow fibrosis or transform into acute leukemia. Although the established classification systems use more or less strict criteria, from a clinical standpoint, differentiation between the different types of CMPD and reactive disorders often present difficulties, especially in cases of thrombocytosis or fibrosis. Furthermore, cases that cannot be clearly defined are regarded as CMPD unclassifiable, while some cases show features of both myeloproliferative and myelodysplastic syndrome, such as chronic myelomonocytic leukemia (CMML) proliferative type. Also, the idiopathic hypereosinophilic syndrome (HES) and the systemic mastocytosis are today subsumed as CMPD [2–12].

In Philadelphia negative CMPD recurrent cytogenetic abnormalities occur, but specific patterns of chromosomal aberrations have so far not been detected. However, certain molecular changes have been recently found to be associated with specific types of CMPD. Thus, FIP1L1/PDGFRα rearrangements characterize the eosinophilic disorders, while recurrent JAK2 mutations have been constantly found in classic myeloproliferative disorders (PV, ET, and IMF). These molecular findings add new information on disease pathogenesis addressing new molecular target therapies [3,12–22].

2. Classification

The most established classification criteria of CMPDs are those of the Polycythemia Vera Study Group (PVSG) and of the World Health Organization (WHO) [2,6–8,23]. The WHO published a new classification for hematopoietic and lymphoid neoplasms [23]. A basic principle of the WHO system is that the classification should utilize not only morphologic findings, but also genetic, immunophenotypic, biologic and clinical features to define specific disease entities. The WHO classification of CMPDs includes guidelines of the Polycythemia Vera Study Group, but there are some significant differences. The WHO classification of CMPDs recognizes seven entities.

a. Chronic myelogenous leukemia t(9;22) (q34;q11), BCR/ABL positive.
b. Chronic neutrophilic leukemia with the recommendation that the possibility of an underlying disease be carefully excluded. In fact, there are well characterized cases of chronic neutrophilic leukemia, for which cytogenetic or molecular genetic studies have confirmed clonarity of the neutrophil lineage.
c. Chronic eosinophilic leukemia (CEL)/hypereosinophilic syndrome (HES). The diagnosis of CEL or HES can be made only after a number of diseases known to be associated with eosinophilia have been excluded, whereas the finding of a clonal myeloid abnormality would support the diagnosis of CEL.
d. Polycythemia vera.
e. Chronic idiopathic myelofibrosis.
f. Essential thrombocythemia.
g. CMPDs unclassifiable.

The WHO classification also recognizes the myelodysplastic/myeloproliferative (MDS/MPD) category, which includes myeloid disorders with both dysplastic and proliferative features at the time of initial diagnosis, and that are difficult to assign to either the myelodysplastic or myeloproliferative category. In this group of disorders the chronic myelomonocytic leukemia (CMML) is included. To date, no specific cytogenetic or molecular differences between patients with predominantly MDS or MPD characteristics have been reported. According to WHO classification, mastocytosis includes a heterogeneous group of diseases characterized by abnormal growth and accumulation of mast cells in one or more organ systems. Data suggested, that most variants of systemic mastocytosis are clonal with the presence of a somatic mutation of KIT, the protooncogene that encodes the tyrosine kinase receptor for stem cell factor [23,24].

Recently, Tefferi [14] proposed a simplified and yet more comprehensive classification system in order to distinguish molecularly characterized, as well as clinicopathologically defined specific disease entities. According to this classification, the term ‘‘molecularly defined’’ is referred to a specific mutation that has been shown to promote either growth factor independent cell proliferation or cause the disease phenotype in animal models. Thus, Tefferi classified the CMPD as follows: