Models of Philadelphia-negative Chronic Myeloproliferative Neoplasms

Subjects: Hematology

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Philadelphia-negative chronic myeloproliferative neoplasms (MPNs) represent a group of hematological disorders that are traditionally considered as indistinct slow progressing conditions. Many of the discoveries on the pathogenesis of MPNs are due to in vivo and in vitro models that have made it possible to reproduce this type of pathology more and more faithfully.

myeloproliferative neoplasms | polycythemia vera | idiopathic myelofibrosis

1. Introduction

The term Philadelphia-negative chronic myeloproliferative neoplasms (MPNs) refer to a heterogeneous group of hematological disorders which originate from the neoplastic transformation of a pluripotent stem cell and are associated with myeloproliferation, extramedullary hematopoiesis, splenomegaly and, in due course, bone marrow fibrosis (MF). According to the WHO 2016 classification, MPNs can be divided into Polycythemia Vera (PV), Essential Trombocythemia (ET) and idiopathic (primary) Myelofibrosis (IMF) in the prefibrotic and overt form [1]. For over two decades, MPNs have been considered as indistinctly slow-progressing conditions [2][3]. However, recent clinical evidence highlighted a subset of cases [4] with a rapid evolution towards myelofibrotic bone marrow failure, placing interest in developing personalized prognosticators and timely therapeutic strategies against this evolution, correlating latest advances in MPNs' molecular profiling with differences in clinical outcomes [5][6].

In fact, alongside MPNs' driver gene mutations (JAK2, CALR, MPL), molecular profiling identified other gene mutations, involving for example DNA methylation (TET2, DNMT3A, IDH1/2), histone modification (ASXL1, EZH2), RNA splicing (U2AF1, SRSF2, SF3B1), DNA repair (TP53) and signal transduction (NRAS, CBL). These mutations can coexist with or without driver gene mutations, affecting the evolution and prognosis of MPNs [5][6].

On this basis, different groups developed several prognostic scores, mainly based on clinical, laboratory and molecular parameters, with less emphasis on morphological and immunophenotypic data [7]. Given the improvements and advances in MPN molecular profiling, the newer models included JAK2, CALR and MPL mutation status in addition to the IPSS parameters, so that the prognostic prediction in IMF patients can be improved [4]. Furthermore, novel insights were supported by a deep analysis of genomic subsets with different clinical prognoses [5]. Recent publications have introduced new prognostic models for PMF, respectively MIPSS70 (mutation-enhanced international prognostic scoring system for transplant-age patients) [6], MIPSS70+ version 2.0

(karyotype-enhanced MIPSS70) and GIPSS (genetically-inspired prognostic scoring system) [8][9]. As the previous models, other ones have been recently introduced for both ET and PV, namely MIPSS-ET and MIPSS-PV, underlining the prognostic importance of spliceosome gene mutations [10].

In opposition to this, all these predictive models do not consider other parameters as morphological or phenotypical features, with the exception of BM fibrosis grade in the MIPPS70 model (**Table 1**).

Table 1. List of prognostic scores of MPNs from the oldest to the most recent ones and with their respective genetic and/or clinical variables, the subclassification in risk groups and the respective median survival.

Prognostic Model and Risk Factors (Weight)	Risk Groups and Median Survival
IPSS	
Hemoglobin < 10 g/dL (1 point)	Low risk: 0 point (135 months)
Leukocytes > 25 × 10^9/L (1 point)	Intermediate risk-1:1 point (95 months)
Age > 65 years (1 point)	Intermediate risk-2:2 points (48 months)
Circulating blast ≥ 1% (1 point)	High risk: ≥3 points (27 months)
Constitutional symptoms (1 point)	
DIPSS. Same variables as IPSS, apart from:	
Hemoglobin < 10 g/dL (2 points)	
	Low risk: 0 point (not reached)
	Intermediate risk-1:1–2 points (14.2 yrs)
	Intermediate risk-2:3–4 points (4 yrs)
	High risk: 5–6 points (1.5 yrs)
DIPSS+. Same variables of DIPSS, apart from:	
Unfavorable karyotype (1 point)	Low risk: 0 point (185 months)
Red cell transfusion need (1 point)	Intermediate risk-1:1 point (78 months)
Hemoglobin < 10 g/dL (1 point)	Intermediate risk-2:2–3 points (35 months)

Prognostic Model and Risk Factors (Weight)		Risk Groups and Median Survival
Platelet < 100 × 10^9/L (1 point)		High risk: 4–6 points (16 months)
Prognostic model and risk factors (weight)		**Risk groups and median survival**
MIPSS70. Same variables as DIPSS+, apart from:		
Genetic variables	Clinical variables	
One high molecular risk (HMR) mutation (1 point)	Marrow fibrosis grade ≥ 2 (1 point)	Low risk: 0–1 point (not reached)
≥2 HMR mutations (2 points)	Leukocytes > 25 × 10^9/L (2 points)	Intermediate risk: 2–4 (6.3 yr)
Type 1/like CALR absent (1 point)	Platelet < 100 × 10^9/L (2 points)	High risk: ≥5 (3.1 yr)
	Circulating blast ≥ 2% (1 point)	
MIPSS70+ version 2.0		
Genetic variables	Clinical variables	
VHR karyotype (4 points)	Severe anemia (2 points)	Very low risk: 0 point (not reached)
Unfavorable karyotype (3 points)	Moderate anemia (1 point)	Low risk: 1–2 (16.4 yr)
≥2 HMR mutations (3 points)	Circulating blasts ≥ 2% (1 point)	Intermediate-1 risk: 3–4 (7.7 yr)
One HMR mutation (2 points)	Constitutional symptoms (2 points)	High risk: 5–8 (4.1 yr)
Type 1/like CALR absent (2 points)		Very high risk: ≥9 (1.8 yr)
GIPSS. Based on a genetic-only risk factors model.		
VHR karyotype (2 points)		Low risk: 0 point (26.4 yr)
Unfavorable karyotype (1 point)		Intermediate-1 risk: 1 point (8 yr)
Type 1/like CALR absent (1 point)		Intermediate-2 risk: 2 points (4.2 yr)
ASXL1 mutation (1 point)		High risk: ≥3 points (2 yr)

2. MPNs’ Molecular Landscape, In Vivo and In Vitro Models and Possible Novel Therapeutic Strategies

Prognostic Model and Risk Factors (Weight)	Risk Groups and Median Survival
SRSF2 mutation (1 point)	
U2AF1^{Q157} mutation (1 point)	

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3. GATA-1 Low Models

Specific abnormalities in the megakaryocyte seem to play a central role in the bone marrow fibrotic evolution but also in the induction of myeloproliferation [4][11][12][13].

The thrombopoietin-treated (TPO-high) model and the GATA-1 low model are two murine models of MPN used to evaluate the megakaryocyte lineage in the MPNs pathogenesis and evolution [11][14]. The first model develops a myeloproliferative disorder mimicking human myelofibrosis, characterized by leukocytosis, anemia, thrombocytosis, splenomegaly, extramedullary hematopoiesis, fibrosis and osteosclerosis. This model is very useful for evaluating some pathogenetic mechanisms associated with fibrosis development, such as the role of transforming growth factor-beta1 (TGF-β1). The second model consists of the virtual abolishment of GATA-1 expression in megakaryocytes, while the protein continues to be expressed in erythroid cells, although at significantly lower levels [14]. These mice develop a progressive myeloproliferative disorder that has many features of myelofibrosis after 1 year of life and reduced levels of GATA-1 have also been demonstrated in the megakaryocytes of patients with IMF [14][15]. Moreover, mice with a MK-specific deficiency of the transcription factor-encoding gene GATA1 show elevated numbers of immature MK in the BM.

4. Lysyl Oxidases Models

It was also demonstrated that GATA1 (low) mutation was associated with low ploidy megakaryocytes with an extensive matrix of fibers due to the overexpression of lysis oxidase (LOX) [16]. Lysyl oxidases (LOXs) have been demonstrated to be important in this process by cross-linking collagens and elastins through deamination of lysins and hydroxylysins, resulting in a stiffer extracellular matrix (ECM) consistency [17]. Lysyl oxidases are expressed in immature megakaryocytes and downregulated in mature megakaryocytes, but upregulated in MF patient megakaryocytes and in murine models of MF [16][18]. Lysyl oxidase inhibition has shown efficacy in Gata1low and JAK2V617F mouse models of MF [19][20]. However, a novel phase 2 study of simtuzumab, a monoclonal inhibitor of LOX2, did not reduce bone fibrosis in patients with MF [21]. It was also demonstrated that the inhibition of LOX via the administration of β-aminopropionitrile could stop the progression of the myelofibrosis [22]. This last model is particularly used as a preclinical model for drug testing.

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