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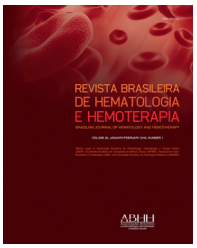

Review article

Primary myelofibrosis: current therapeutic options

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ABSTRACT

Primary myelofibrosis is a Philadelphia-negative myeloproliferative neoplasm characterized by clonal myeloid expansion, followed by progressive fibrous connective tissue deposition in the bone marrow, resulting in bone marrow failure. Clonal evolution can also occur, with an increased risk of transformation to acute myeloid leukemia. In addition, disabling constitutional symptoms secondary to the high circulating levels of proinflammatory cytokines and hepatosplenomegaly frequently impair quality of life. Herein the main current treatment options for primary myelofibrosis patients are discussed, contemplating disease-modifying therapeutics in addition to palliative measures, in an individualized patient-based approach.

Overview

Primary myelofibrosis (PMF) is a Philadelphia-negative myeloproliferative neoplasm (MPN) with a predominant proliferation of megakaryocytes and granulocytes in the bone marrow characterized by an initial proliferative phase, followed by a reactive deposition of fibrous connective tissue in the terminal phase.[1] Bone marrow failure, thromboembolic events and transformation to acute myeloid leukemia (AML) are the main causes of morbi-mortality in PMF, but additional symptoms secondary to hepatosplenomegaly and abnormal blood counts frequently impair quality of life.[1,2] The high circulating levels of proinflammatory cytokines also result in disabling constitutional symptoms (fatigue, weight loss, night sweats, fever, pruritus, arthralgias, myalgias).[2] Hence, the decision regarding the best treatment combination in PMF must be individualized, taking the symptoms, risks and life expectation of each patient into account. Despite the recent advances in the development of targeted therapies, allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative option available for PMF. Evidence on the main therapeutic options for PMF will be discussed in this article.

Molecular characterization

Although no molecular lesion can specifically identify PMF, some recurrent mutations are found and are helpful in the diagnosis and the prognostic stratification of PMF patients. *JAK2* (*Janus kinase 2*), *MPL* (*thrombopoietin receptor*) and *CALR* (*calreticulin*) genes frequently harbor somatic mutations in PMF, which induce the constitutive activation of the JAK-STAT, PI3K and ERK pathways in a ligand-independent way, leading to increased myeloid proliferation. Approximately 50–60% of PMF patients exhibit the $JAK2^{V617F}$ mutation.[3–5] A gain-of-function mutation in *MPL* ($MPL^{W515K/L}$), which encodes the

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Table 1 – Risk stratification of primary myelofibrosis patients according to the Dynamic International Prognostic Scoring System (DIPSS) and the age-adjusted DIPSS (aaDIPSS)[16]

	DIPSS			aaDIPPS		
	Value			Value		
	0	1	2	0	1	2
Age (years)	≤65	>65		–	–	–
White blood cell count ($\times 10^9$/L)	≤25	>25		≤25	>25	
Hemoglobin (g/dL)	≥10		<10	≥10		<10
Peripheral blood blasts (%)	<1	≥1		<1		≥1
Constitutional symptoms[a]	No	Yes		No	Yes	
	Risk category	Score	Survival[b]	Risk category	Score	Survival[b]
	Low	0	not reached	Low	0	Not reached
	Intermediate 1	1 or 2	14.2	Intermediate 1	1 or 2	9.8
	Intermediate 2	3 or 4	4	Intermediate 2	3 or 4	4.8
	High	5 or 6	1.5	High	>4	2.3

[a] 10% weight loss in six months, night sweats, unexplained fever higher than 37.5 °C.
[b] Median, years.

thrombopoietin receptor and is a key factor for growth and survival of megakaryocytes, has been reported in up to 5% of PMF cases.[6,7] *MPL* mutations may occur concurrently with the JAK2^{V617F} mutation.[8] Approximately 60–80% of *JAK2* and *MPL* wild type patients harbor *CALR* mutations.[9,10] Additional mutations in epigenetic regulators, such as *TET2*,[11] *ASXL1*,[12] *DNMT3A*,[13] *IDH1/2*,[14] have been described in MPN patients at variable frequencies and their prognostic value has been object of studies.[15]

Risk stratification

Adequate risk stratification in PMF is essential to establish the most suitable treatment for a particular patient, taking the risk-benefit of each approach into account. In this sense, the Dynamic International Prognostic Scoring System (DIPSS) for PMF is widely used in the clinical practice. DIPSS is a dynamic prognostic model that considers modifications in the risk profile after diagnosis and can predict prognosis at different stages of the disease (Table 1).[16] The age-adjusted DIPSS is a variation specifically developed for younger patients (age <65 years), comprising the group that is most commonly suitable for intensive therapies such as allo-HSCT (Table 1).[16]

Treatment options

Hydroxyurea

Hydroxyurea (HU) is a non-alkylating antineoplastic agent used for cytoreduction in myeloproliferative neoplasms. Although there are few well designed studies evaluating HU benefits in myelofibrosis patients, hydroxyurea is frequently used to attenuate hyperproliferative manifestations related to PMF.[17] In a group of 40 PMF patients, Martinez-Trillos et al. showed significant response rates, with reductions in constitutional symptoms (55%), symptomatic splenomegaly (45%), thrombocytosis (40%) and leukocytosis (28%); accentuation of anemia was the most common adverse event, and was observed in almost half of the patients.[17] When HU resistance/refractoriness is documented in the PMF proliferative phase, switching from HU to a molecular targeted therapy (i.e., JAK1/2 inhibitor) should promptly be considered.[18] The criteria for resistance and refractoriness to HU in PMF patients have previously been defined by the European LeukemiaNet consensus.[18]

Support therapy

Anemia

Anemia is a frequent manifestation of PMF[19] that might be caused by different interacting factors, such as bone marrow insufficiency (fibrosis), hypersplenism, bleeding, iron deficiency, vitamin B12 or folate deficiency, or autoimmune hemolysis.[20,21] Moreover, specific PMF treatment with cytoreductive drugs (HU)[17] and JAK1/2 inhibitors[22] can lead to, or increase, anemia in these patients. Besides correcting the potentially reversible causes of anemia, some other therapeutic possibilities might be considered when anemia is a disabling symptom. Some of them are discussed below.

a. Androgens

Androgens have been used to treat anemia in PMF with variable response rates; most of the studies described results observed in small cohorts. Danazol, a semisynthetic attenuated androgen that has fewer side effects, results in an anemia response rate of 30–57% depending on the adopted response criteria.[21,23,24] In a cohort of 50 patients with PMF, Cervantes et al.[21] described a 30% response rate [defined by transfusion cessation in transfusion-dependent patients or an increase in hemoglobin (Hb) >2 g/dL in patients without transfusion requirements], with a median duration of anemia response of 14 months. Androgens should not be used in patients with prostatic symptoms, prostate cancer or moderate to advanced hepatic disease.

b. Erythropoiesis-stimulating agents

Although recombinant human erythropoietin (EPO) has been widely used for the treatment of anemia of a variety of