Critical Reviews in Oncology/Hematology 105 (2016) 112–117

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Second line therapies in polycythemia vera: What is the optimal strategy after hydroxyurea failure?

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Contents

ARTICLE INFO

Article history:
Received 11 April 2016
Received in revised form 6 June 2016
Accepted 16 June 2016

Keywords:
Polycythemia vera
Hydroxyurea
Interferon-a
JAK2 inhibitors

ABSTRACT

Cytoreductive therapies have traditionally been the standard treatment for older patients with polycythemia vera (PV) or those with a history of prior thrombosis. Hydroxyurea (HU) is the most frequently used cytoreductive agent in PV. However, approximately 24% of patients treated with HU will eventually develop resistance or intolerance and patients who fail HU have an increased risk of death, transformation to myelofibrosis or acute myeloid leukemia. Interferon-alpha has been used in younger PV patients and is capable of inducing a complete hematologic response and significant reductions, or even eradication, of *JAK2 V617F* mutation allele burdens in a small but notable subset of PV patients. The potential toxicities of interferon-alpha must be weighed against the disease control benefit in a case-by-case fashion. Recently JAK2 inhibitor, ruxolitinib, demonstrated significant improvement in controlling the hematocrit and splenomegaly versus best available therapy in patients with PV who failed or are intolerant to HU and currently is FDA-approved in this setting. In this review, we will discuss novel emerging therapies for PV with a special focus on the currently available and upcoming treatment options for patients who fail HU.

1. Introduction

Polycythemia Vera (PV) is a myeloproliferative neoplasm (MPN) characterized by a non-reactive increase in the number of red blood cells. The clonal proliferation in PV involves not only erythroid precursors but also to a lesser extent precursors committed to the granulocytic and megakaryocytic lineages (Tefferi et al., 2007; Vardiman et al., 2002, 2009).

Approximately 95% of patients with PV harbor a somatic mutation involving *JAK2 V617F* (James et al., 2005; Levine et al., 2005; Baxter et al., 2005; Kralovics et al., 2005a) and an additional 4% harbor mutations involving other codons in exon 12 of the *JAK2* gene (Scott et al., 2007; Passamonti et al., 2011). Several other mutations have recently been described, including mutations involving the *TET2* (Tefferi et al., 2009; Delhommeau et al., 2009) and *EZH2* (Ernst et al., 2010) genes. Most patients with PV are diagnosed incidentally while undergoing routine blood testing. In some patients the occurrence of a thrombotic event or disease-related symp-

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http://dx.doi.org/10.1016/j.critrevonc.2016.06.013
1040-8428/

toms – microvascular disturbances, pruritus, and/or headaches – leads to the diagnosis of PV (Landolfi et al., 2004; Passamonti et al., 2003). The median survival in a study cohort of 1545 PV patients was projected at 18.9 years with a trend towards worse survival in comparison with age- and sex-matched US population (Tefferi et al., 2013). When the analysis was restricted to the centers with the most mature follow-up information (n = 337) the median survival was 14.1 years and was significantly worse than that of age- and sex-matched US population (Tefferi et al., 2013). Without treatment, PV patients have 1.6 fold mortality compared to general population (Passamonti et al., 2004; Anon, 1995). The most common causes of death include thrombosis and cardiovascular mortality, progressive myelofibrosis, or transformation to acute myeloid leukemia (AML) (Passamonti et al., 2004; Cervantes et al., 2008; Alvarez-Larran et al., 2009; Najean et al., 1994). Rate estimates for thrombosis in patients with PV are high, ranging from 2.7 to 3.8 per 100 persons per year and rates of CV mortality are 1.7 per 100 persons per year (Tefferi et al., 2013). In this study, CV mortality accounted for 45% of all deaths while hematologic transformation and solid tumors accounted for 33% of all deaths (Tefferi et al., 2013). In a separate study by Tefferi and colleagues, the 10- and 15-year leukemia transformation rates were approximately 2.3%, and 5.5%, respectively (Tefferi et al., 2013). In addition to increased mortality patients with PV experience a broad range of disease related burdens including symptom burden from fatigue, splenomegaly, pruritis, thrombotic or hemorrhagic complications, a reduced quality of life from symptoms and complications, and a financial burden to the individual and society from loss of productivity, income and cumulative healthcare costs (Geyer and Mesa, 2014; Stein et al., 2014). Other complications noted in patients with untreated PV include hypertension, hyperuricemia and gout, renal stones and erythromelalgia (Spivak, 2002). These burdens and complications may be mitigated to a significant degree by risk-stratified early and effective interventions. Therefore, the goals of therapy in PV are (1) to improve disease-related symptoms, splenomegaly and complications, (2) prevent the occurrence or recurrence of thrombosis, (3) delay or prevent the progression to myelofibrosis or AML, and (4) increase survival.

2. Overview of PV therapeutic strategy

Treatment strategies for patients with PV are multimodal and include evaluation and management of cardiovascular and thrombosis risk factors, introduction of antiplatelet therapy, and when necessitated phlebotomy and cytoreduction (Vannucchi, 2014; Marchioli et al., 2005; Barbui et al., 2011a). Low dose aspirin (81–100 mg) has been shown to significantly lower the risk of nonfatal arterial and venous thromboembolic events and death from cardiovascular causes in patients with PV in a randomized study and should be used in all PV patients who can tolerate it without bleeding or gastritis (Landolfi et al., 2004, 1992). Cytoreductive therapies are reserved for patients with a high risk of thrombosis defined by age >60 years and/or history of prior thrombosis (Marchioli et al., 2005). Prior thrombosis is an especially high risk factor for recurrent thrombosis as well as a significantly increased risk of death (Marchioli et al., 2005; Barbui et al., 2011a). Although less universally practiced studies have also demonstrated the role of cytoreductive therapy in low risk PV to alleviate symptomatic splenomegaly, uncontrolled disease-related symptoms, and progressive leukocytosis or thrombocytosis (Barbui et al., 2011b). Although the optimal hemoglobin target is controversial, a recent randomized trial that compared outcomes in patients with PV who had more intensive hematocrit control <45% versus patient who had less intensive control (hematocrit 45–50%) demonstrated a significantly reduced risk of thrombosis and death from cardiovascular causes with intensive hematocrit control and it is now widely accepted that the goal is to maintain hematocrit <45% in PV patients (Marchioli et al., 2013).

Table 1
European LeukemiaNet criteria for hydroxyurea (HU) resistance or intolerance.

HU resistance	Need for phlebotomy to keep hematocrit <45% after 3 months of at least 2 g/d of HU, OR Uncontrolled myeloproliferation (ie, platelet count $<400 \times 10^9$/L AND WBC count $<10 \times 10^9$/L) after 3 months of at least 2 g/d of HU, OR Failure to reduce massive splenomegaly by >50% as measured by palpation OR failure to completely relieve symptoms related to splenomegaly after 3 months of at least 2 g/d of HU
HU intolerance	Absolute neutrophil count $<1.0 \times 10^9$/L OR platelet count $<100 \times 10^9$/L OR hemoglobin <10 g/dL at the lowest dose of HU required to achieve a complete or partial clinicohematologic response OR Presence of leg ulcers or other unacceptable HU-related nonhematologic toxicities, such as mucocutaneous manifestations, GI symptoms, pneumonitis, or fever at any dose of HU

Hydroxyurea (HU) is an oral antimetabolite that inhibits DNA synthesis and remains the first line cytoreductive therapy in patients with PV (Saban and Bujak, 2009). PV patients who receive HU achieve an overall response rate of approximately 90% (24% complete response and 66% partial response, as defined by the European LeukemiaNet [ELN] criteria (Barbui et al., 2011b)) and have less thromboembolic events. However, approximately 24% of the patients will develop either resistance (11%) or intolerance (13%) to HU over time (Barbui et al., 2011b; Finazzi et al., 2003; Alvarez-Larran et al., 2012). The ELN definition of resistance or intolerance to HU is summarized in Table 1. More importantly, resistance to HU is associated with an aggressive disease course in patients with PV: HU resistant patients have a 5.6-fold increase in death and a 6.8-fold increase in the risk of transformation to myelofibrosis or AML. Therefore, alternative therapies are needed for these patients (Alvarez-Larran et al., 2012).

In this review, we will discuss the current options that are available as second line therapies for PV patients after HU failure.

2.1. Interferon

Interferon-alpha (IFN-α), a class 2a-helical cytokine, is an important regulator of innate and adaptive immunity (Krause and Pestka, 2005). IFN-α has a wide variety of biological and molecular activities including cytotoxicity to inflammation- and tumor-promoting immune cell populations, activation of multiple proapoptotic genes and proteins, and down-regulation of several anti-apoptotic proteins (Pestka et al., 2004; Ortaldo et al., 1983). These characteristics make IFN-α an attractive therapeutic agent in patients with cancer in general and in patients with MPNs in specific.

IFN-α manifests specific activities that support its use in MPNs, including PV such as direct inhibition of bone marrow fibroblast progenitor cells and suppression of hematopoietic progenitor proliferation (Carlo-Stella et al., 1987; Castello et al., 1994; Dudley et al., 1990). In vitro studies suggest that the hematopoietic progenitors in patients with MPNs have a higher sensitivity to IFN-α than their normal counterparts (Massaro et al., 1997). A recent analysis of erythroid colonies derived from progenitors from PV patients treated with IFN-α demonstrated that IFN-α dramatically reduced the *JAK2 V617F* allele burden without affecting the *TET2* mutant allele burden. Of note, *TET2* mutations are frequent in *JAK2 V617F*-independent clones and may be responsible for the progression of PV to myelofibrosis and AML (Beer et al., 2010; Schaub et al., 2010).