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Current status of hydroxyurea in treatment of polycythemia vera

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Abstract

Hydroxyurea (HU) is a first-line pharmacotherapy drug used in high-risk patients with polycythemia vera (PV). It has a good tolerability profile, a convenient oral formulation, and a low price. With the increasing availability of other therapeutic options for PV patients, there is a need to redefine the place of HU formulations in the treatment of this condition, and to consider the current criteria for resistance and intolerance to this drug, which may help in accurate decision-making about modifying cytoreductive treatment in PV. This article presents the general characteristics of HU, its position in the therapeutic pathway of PV patients, and the modified resistance and intolerance criteria for this drug.

Keywords: polycythemia vera, hydroxyurea, hydroxyurea resistance criteria, hydroxyurea intolerance criteria, cytoreductive treatment

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Introduction

Polycythemia vera (PV) is a Philadelphia-negative myeloproliferative neoplasm with a median age at incidence of 60–65. The majority of patients are found to have a mutation in the JAK2 gene, of which 96% involve exon 14 — the V617F mutation — and 3–4% involve exon 12. Non-canonical mutations in other exons (13 or 15) are extremely rare [1, 2], but also have oncogenic potential in PV. The risk of thrombosis within 10 years of PV is more than 20%. 25% of patients develop post-PV MF (post-polycythemia vera myelofibrosis) within 20 years of disease duration, with a 20-year risk of transformation to acute myeloid leukemia (AML) or myelodysplastic neoplasm (MDN) of more than 10% [3, 4]. The risk of blastic transformation is higher in older patients with an abnormal karyotype, leukocytosis ≥15 × 10^9/L and/or previous exposure to alkylating drugs. Risk factors for progression to the fibrotic phase include a JAK2 V617F mutant allele burden >50%, the presence of features of marrow fibrosis at diagnosis, and persistent leukocytosis [5]. The main goals of PV treatment include preventing thrombotic complications, improving quality of life by reducing symptom severity, and delaying disease progression. The choice of treatment is made according to current criteria after the patient has been classified as low or high risk, taking into account the 'conventional' risk factors i.e. age and history of thrombosis. Age over 60 or a history of thrombotic episodes indicate a high risk of PV. In all patients, irrespective of risk group, it is recommended to maintain a hematocrit (Hct) value <45%, as this ensures a significantly longer overall survival (OS) than in those who fail to achieve and maintain a value below 45% [5, 6]. In low-risk patients, periodic bloodletting and low-dose acetylsalicylic acid (ASA) (75–150 mg/day) have so far been recommended.

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Cytoreductive treatment according to the 2021 European Leukemia Net recommendations [7] is required for patients with high-risk PV assessed according to the 'conventional' risk factors. It should also be considered in low-risk patients after meeting at least one additional clinical criterion: the need for frequent bloodletting (at least six per year) or poor tolerance to it; symptomatic splenomegaly; severe pruritus; persistence of constitutional symptoms; persistent or progressive leukocytosis >15 × 10^9/L; extreme thrombocytosis ≥1,500 × 10^9/L; and high cardiovascular risk (including hypertension, ischemic heart disease, diabetes) [7].

In addition to the clinical prognostic model, there is genetic risk stratification based on the identification of additional mutations using next-generation sequencing testing. In 15% of patients with PV, unfavorable mutations are present, which include: *ASXL1*, *SRSF2* and *IDH2*. Their presence is associated with poorer survival associated with progression of PV to fibrotic stage or AML [8]. The tool that most fully assesses risk in PV, combining clinical features with a molecular background, is the MIPSS-PV (mutation-enhanced international prognostic score for polycythemia vera) scale. This distinguishes the following risk factors: presence of unfavorable mutations (SRSF2), age >67 years, leukocytosis ≥15 × 10^9/L, and a positive history of thrombosis [9]. First-line cytoreductive treatment includes HU or pegylated interferon 2alpha formulations (Peg-IFNα-2a or Ropeg-IFNα-2b), which is the ELN recommended choice for patients with low-risk PV according to conventional risk factors [7]. Second-line treatment includes drug switching (HU to an IFN α-2a or IFN α-2b formulation or vice versa) or ruxolitinib, possibly busulfan acceptable for older patients (over 65) [5] or those with a limited life expectancy [10]. However, treatment with busulfan, which belongs to the alkylating group of drugs, is generally not recommended due to its myelotoxicity and leukemogenic potential. Transformation rates to AML of between 1% and 10% have been reported [11, 12]. When treated with busulfan, the patient's peripheral blood count should be monitored frequently for neutropenia and thrombocytopenia [10].

Hydroxyurea — general information

Hydroxyurea (HU), also known as hydroxycarbamide, was synthesized in 1869 [13] and its anticancer properties were discovered in 1963 [14]. HU is a cytostatic drug, active mainly in the S-phase of the cell cycle. Its mechanism of action is to inhibit the activity of ribonucleotide reductase, an enzyme that catalyzes the conversion of ribonucleotides to deoxyribonucleotides. Thus, the drug inhibits DNA synthesis and causes cell cycle arrest. The aforementioned enzyme is also involved in DNA repair processes, with which HU can interfere [15, 16]. HU is taken orally, penetrates the intestinal wall by diffusion, and has an almost 100% bioavailability. It reaches its maximum blood concentration c.60 minutes after administration. The exact metabolic pathways of HU are unknown; the drug is partly metabolized in the kidney and liver to urea. The plasma half-life is 3–4 hours; after 12 hours, c.80% is excreted in the urine, mostly unchanged, a small proportion as urea. [16, 17]. Indications for the use of HU include myeloproliferative neoplasms, the need for cytoreduction in patients with acute leukemia or myelodysplastic-myeloproliferative neoplasms, and sickle cell anemia [16]. The drug is generally well tolerated and has low toxicity at low doses. The main adverse effects include: myelosuppression (rapidly resolving after drug discontinuation), skin and mucosal symptoms (including ulceration, non-specific rash, hyperpigmentation), vascular complications, nausea, vomiting, diarrhea, pneumonia, fever, headache and dizziness. Long-term treatment with HU favors squamous cell and basal cell skin cancer [18]. The leukemogenic potential of HU has not yet been elucidated. No leukemogenic effect of HU has been found in observational studies, as has been demonstrated for pipobroman, chlorambucil and ^{32}P. However, the association of an increased risk of PV transformation to AML under HU treatment cannot be entirely excluded on the basis of such studies [19, 20]. For the progression of myeloproliferative neoplasms to AML, factors unrelated to the type of antiproliferative therapy are of the greatest importance [21].

Hydroxyurea in treatment of polycythemia vera

HU has so far been the standard first-line cytoreductive treatment for high-risk PV patients due to the proven efficacy of HU therapy in this group of patients and the favorable safety profile of the drug, bearing in mind the 20% risk of developing malignancies secondary to long-term HU therapy [22–25]. Treatment with HU shows superiority over treatment with bloodletting alone in terms of a significant reduction in the risk of thrombotic complications [24, 25]. Under HU treatment, a 90% hematological response rate (including 24% complete responses and 66% partial responses) has been observed, but a quarter of those treated fail to achieve optimal disease control due to the development of resistance or intolerance [26]. Some still require periodic phlebotomies to maintain Hct at the desired level [27]. C.20–25% of those treated discontinue therapy, usually due to a lack of or suboptimal response. Other reasons for discontinuation of HU therapy include intolerance and disease progression [26, 28, 29]. Factors significantly associated with HU resistance or intolerance are low baseline hemoglobin levels, age over 60, and splenomegaly [30]. HU resistance and intolerance are unfavorable prognostic factors for the course of PV, as they are associated with poorer survival due to an increased risk of disease progression to post-PV MF and AML. The risk of

Table I. Clinical response criteria in polycythemia vera according to European Leukemia.Net (ELN) [32]

Complete
1. Lasting ≥12 weeks resolution of physical symptoms (including splenomegaly) and great improvement in subjective symptoms (reduction of ≥10 points in MPN-SAF TSS)
2. Lasting ≥12 weeks Hct <45% (without phlebotomies), WBC <10 × 10^9/L, PLT <400 × 10^9/L
3. No progression to MF, MDN, or AML
4. Remission in bone marrow (histologically): normal cellularity, no trilineage hyperplasia, no reticulin fibrosis >1 stage
Partial
Fulfilment of 1 + 2 + 3 without 4

transformation to fibrotic stage at five and 10 years is 3% and 17% respectively in patients who have developed HU resistance or intolerance, and 1.5% and 6.7% in patients who do not meet the criteria for resistance or intolerance. Higher 5-year transformation rates have been observed in patients with failure to reduce massive splenomegaly (14% vs. 1.6%) and those developing cytopenias (10% vs. 1.6%). No simple relationship has been observed between HU resistance or intolerance and progression of PV to AML. Analysis of individual resistance/intolerance criteria shows that the development of cytopenias during HU treatment correlates with an increased risk of progression to AML (28% vs. 0.8% over five years) [31].

The ELN criteria for clinical response to PV treatment are set out in Table I.

Table II sets out the modified criteria for resistance and intolerance to hydroxyurea in patients treated with this drug for polycythemia vera.

In the absence of an optimal response to HU, or if HU is intolerant, IFN α-2a and IFN α-2b or ruxolitinib are recommended for the next line of cytoreductive treatment, and busulfan may be considered in older patients with limited life expectancy [5, 10].

Data from recent studies comparing the efficacy of PegIFN α-2a and RopegIFN α-2b administration versus HU therapy in first-line cytoreductive treatment [34, 35] suggests the need to revise recommendations for first-line cytoreductive treatment in PV patients. Interferon significantly reduces the risk of progression to MF, prolongs overall survival, and reduces the risk of death. Median MFS (myelofibrosis-free survival) is 23.8 years in PV: for rIFN-a (including recombinant IFN α-2a, recombinant IFN α-2b and PegIFN α-2a), HU and phlebotomy-only treatment (PHL-0) it is 32.5, 22.6, and 20.5 years, respectively (p <0.001). Median overall survival (OS) is 26.7 years in PV: for rIFN-a, HU and PHL-0 it is 27.7, 25.9, and 21.3 years, respectively (p <0.01). Patients in the interferon-treated group had a lower risk of developing MF and death compared to patients treated with HU and PHL-0: interferon reduced the annual risk of post-PV MF and the annual risk of death by 6% and 8%, respectively [36]. Pegylated forms of interferon PegIFN α-2a and RopegIFN α-2b are preferred in previously untreated patients aged under 60, without a history of embolic episodes or thrombosis, but who require the implementation of cytoreductive treatment, unless they have contraindications to these drugs. Pegylated interferons should be considered in patients with a need for frequent phlebotomies (>6 per year), persistent pruritus, symptomatic splenomegaly, or chronic symptoms of microvascular disorders [5]. Ruxolitinib for the treatment of PV is recommended in cases of resistance to both HU and pegylated IFN-2 α preparations, but the finding of interferon resistance is not a necessary factor for starting ruxolitinib treatment in patients with post-PV MF, or in patients suffering from refractory pruritus or with symptomatic splenomegaly [5]. The current registration of ruxolitinib allows the treatment of adult patients with PV who are resistant or intolerant to HU treatment. For this reason, in patients with treatment failure with IFN α-2a or IFN α-2b used as first-line cytoreductive therapy, HU therapy should be attempted, followed by ruxolitinib if resistance or intolerance to this drug emerges.

Data from randomized trials provides arguments for the use of ruxolitinib in cases of HU resistance or intolerance. The superiority of ruxolitinib over best available therapy (BAT) arms in which HU, pegylated IFN-2α, or HU in combination with pegylated IFN-2α was used in the majority of cases has been demonstrated in the form of higher complete response rates, better symptom control, longer progression-free survival, and a lower rate of thrombotic events [37, 38].

Summary

HU is a drug that has been widely used in clinical practice for many years, including as a cytoreductive treatment in high-risk PV patients. It is usually well tolerated, and is inexpensive and has a convenient oral formulation. The use of HU prevents thrombotic complications and prolongs overall survival compared to treatment with bloodletting. The wider availability of drugs that modify the course of PV, including reducing the burden of the mutated *JAK2 V617F* allele, such as interferons and the JAK kinase inhibitor ruxolitinib, makes it necessary to define more precisely the

Table II. Criteria for change of cytoreductive therapy in patients with polycythemia vera treated with hydroxyurea [7, 33]. A change is recommended if at least one of the following criteria from 'resistance' (inadequate clinical response) or 'intolerance' categories is met:

Resistance	Intolerance
After 3 months of treatment with a dose ≥2 g/d (or 2.5 g/d in individuals >85 kg bw): • need for phlebotomy to maintain Hct <45% **OR** • PLT >400 × 10^9/L **AND**: WBC >10 × 10^9/L **OR.** less than 50% reduction in size of spleen palpable ≥10 cm below the left costal margin **OR** No complete resolution of symptoms related to enlarged spleen **OR**	**On treatment with lowest dose of HU to achieve at least a partial clinical response*:** • ANC <1,000 × 10^9/L **OR** • PLT <100 × 10^9/L **OR** • Hb <100 g/L **OR**
ELN criteria **After 3 months of treatment with each dose of HU:** • PLT >1,000 × 10^9/L **OR** • microcirculatory symptoms **OR** • increasing leukocytosis (≥100% increase if initially WBC <10 × 10^9/L **OR ≥50%** increase if initially WBC >10 × 10^9/L) **OR** • persistent WBC >15 × 10^9/L **OR**	
After one year of HU treatment at tolerated dose: • Symptomatic or increasing splenomegaly, palpable >5 cm below the left costal margin **OR** • need ≥6 phlebotomies to maintain Hct <45% **OR**	
Increased constitutional symptoms (dose ≥1.5 g/d HU for ≥4 months): • MPN-SAF TSS ≥20 points **OR** • Skin pruritus of MPN-SAF TSS 10 severity for at least six months	**During treatment with each dose of HU**, appearance of one or more symptoms: • lower leg ulceration **OR** • non-melanotic skin cancer **OR** • skin and mucosal symptoms • vascular complications: clinically relevant bleeding, venous or arterial thrombosis • symptoms in digestive tract • pneumonia or fever • any non-hematological intolerance of HU stages 3 or 4 or prolonged toxicity of HU CTCAE stage 2

*Clinical response criteria in polycythemia vera according to ELN

eligibility criteria for each risk group and to revise current recommendations for cytoreductive treatment.

HU still remains a valuable drug for first-line cytoreductive therapy in high-risk PV patients requiring a rapid reduction in erythrocyte count and lower hematocrit. HU is not inferior in efficacy to interferons in short-term treatment, but in the long term the effects of treatment with pegylated IFN-2α preparations are superior due to longer patient survival and more effective protection against PV evolution to MF. HU also has its uses in the combination treatment of PV in the initial phase of interferon treatment, providing good control of red cell parameters.

However, this drug should no longer be the standard for chronic PV treatment. This is especially true for young adults, in whom ensuring long-term survival free of embolic complications and transformation to bone marrow fibrosis or acute myeloid leukemia is a very important therapeutic goal.

The current modified resistance and intolerance criteria for HU may be helpful in assessing the course of PV treatment with this drug and in deciding whether to change cytoreductive treatment in a timely manner and to use drugs that affect the pathogenetic mechanisms underlying the development of PV and the course of this disease.

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