Polycythemia vera and hydroxyurea resistance/intolerance: a monocentric retrospective analysis

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Abstract

Hydroxyurea (HU) resistance or intolerance occurs in 15 to 24% of patients with polycythemia vera (PV). Resistance to HU is associated with a shortened life expectancy, intolerance has no prognostic value. We assessed the occurrence of HU resistance or intolerance comparing the original (ELNo) versus the modified European Leukemia Net (ELNm) criteria as applied in recent large clinical trials including PV patients. We retrospectively analyzed 106 patients with PV treated with HU at the University Hospitals of Leuven between 1990 and 2016 for occurrence of HU resistance/intolerance when using both ELNo as ELNm. After a mean duration of treatment of 5.1 years, when applying the ELNo 20.7% of patients had shown resistance or intolerance to HU in comparison to 39.6% when using the ELNm. When using the ELNo 4.7% of patients were resistant to HU versus 23.6% when applying the ELNm. In total, 16.0% of patients were HU intolerant. This rate was identical when using both ELNo and ELNm. 20.7% of PV patients were considered as HU-resistant or intolerant when using the original ELN criteria. However, when applying the modified ELN criteria 39.6% of PV patients were resistant or intolerant to HU. In our hands, no patient received a minimum dose of 2 g HU a day, as such the ELNm seem better adapted for daily clinical use. However, the prognostic value of HU-resistance in PV, when defined by the ELNm, still needs to be confirmed.

Keywords Polycythemia vera · Hydroxyurea resistance/intolerance · Ruxolitinib · European leukemia net criteria

Introduction

PV is a myeloproliferative neoplasm characterized by clonal stem-cell proliferation of multipotent hematopoietic progenitors, leading to abnormal production of red blood cells the erythroid, megakaryocytic and myeloid lineages [1–3]. Nearly all patients with PV have an acquired mutation of *Janus Kinase 2* (*JAK2*). The *JAK2V617F* and *JAK2 exon 12* mutation have been detected in 95% and 3% of PV patients, respectively [4]. PV is associated with an increased risk of

thrombosis and progression to myelofibrosis or acute myeloid leukemia [5–7]. Patients with PV have a considerable symptom burden including pruritus and constitutional symptoms such as fatigue and night sweats [8–10]. Aggressive control of hematocrit levels with target values below 45% lowers the risk of cardiovascular death or major thrombosis [11]. Control of hematocrit can be achieved through phlebotomy and/or cytoreductive therapy. Cytoreductive therapy is recommended for high risk patients defined by the risk for thrombosis [12–16]. The first-line cytoreductive treatment of choice currently is hydroxyurea [17–19]. Inadequate response or resistance to HU occurs in 5 to 11% of PV patients and is associated with a shortened survival [20–22]. Approximately 5–13% of patients treated with HU develop unacceptable side effects such as leg ulcers, drug-induced fever, or mucocutaneous manifestations [19–21]. Intolerance to HU has no prognostic significance. A unified definition of resistance and intolerance to HU has been defined by the European LeukemiaNet (ELN) [23]. These criteria were initially defined to identify a subgroup of patients who could benefit from second-line treatment. Until recently, patients with HU resistance/intolerance had few therapeutic alternatives in some

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European countries, as interferons are not reimbursed for PV patients. Ruxolitinib, a JAK1/2 inhibitor, has been evaluated in PV patients with HU resistance and intolerance in the RESPONSE and RESPONSE-2 trials [24, 25]. These trials used a modification of the ELN criteria. Instead of the minimum dose of 2 g of HU a day as defined in the original ELN criteria (ELNo), the maximum tolerated dose was used in the modified ELN criteria (ELNm).

The objective of our current study is to examine the rate of HU resistance/intolerance of patients with PV who were treated at the University Hospitals of Leuven and to compare the frequency of HU resistance/intolerance according the ELNo versus the ELMN.

Material and methods

This study is a monocentric retrospective analysis of patients with PV treated with HU at the University Hospitals of Leuven in Leuven, Belgium, from 1990 until 2016. The study was approved by the Ethics Committee of the University Hospitals of Leuven. Informed consent was obtained from all patients for being included in the study. In all patients, the diagnosis of PV was assessed using the criteria of the World Health Organization applicable at time of diagnosis. The indication for cytoreductive treatment with HU was decided by the attending hematologist based on the clinical guidelines at that time. In all patients, when available, the main clinical data at time of diagnosis were collected including age, sex, PV-related symptoms (microvascular symptoms and pruritus), history of thrombosis or thrombosis at diagnosis and the presence of palpable splenomegaly. Hematological data at time of diagnosis such as hemoglobin level, white blood cell

count, platelet count and *JAK2* mutation status were also recorded. The duration of therapy with HU was recorded. Occurrence of resistance/intolerance was registered using both ELNo (Table 1) for HU resistance/intolerance and ELMN (Table 2), as used in the RESPONSE trials [13, 25, 26]. Instead of using a minimum dose of 2 g of HU a day, the modified ELN criteria used the maximum tolerated dose. Resistance to HU was defined as fulfilling one of the first four criteria (criterion 1–4, Table 1 and 2). Intolerance was defined as presence of unacceptable HU-related non-hematological toxicities (criterion 5, Table 1 and 2).

The initial survey included 133 patients. Twenty patients did not meet the World Health Organization criteria for PV applicable at time of diagnosis or had an unclear differential diagnosis with myelodysplasia or other myeloproliferative neoplasms such as essential thrombocytosis or primary myelofibrosis. Two patients, initially treated at another hospital, were excluded because of absence of 1 year of follow-up at our center prior to evolution to post-PV myelofibrosis (PPV-MF). Five patients were lost to follow-up. In total, 106 patients were included in this study.

Results

Patient characteristics

A total of 106 patients were included in this retrospective study. Their main clinical and hematological characteristics at time of diagnosis are shown in Table 3. Regarding anti-thrombotic therapy, 93 patients (87.7%) were treated with a low-dose aspirin, three patients (2.8%) were treated with clopidogrel without a low-dose aspirin, six patients (5.66%)

Table 1 Original ELN criteria for HU resistance/intolerance [23]

1. Need for phlebotomy to keep hematocrit < 45% after 3 months of at least 2 g/day of HU OR
2. Uncontrolled myeloproliferation, i.e., platelet count > $400 \times 10^9/L$ and white blood cell count > $10.0 \times 10^9/L$ after 3 months of at least 2 g/day of HU OR
3. Failure to reduce massive[†] splenomegaly by more than 50% as measured by palpation OR failure to completely relieve symptoms related to splenomegaly after 3 months of at least 2 g/day of HU OR
4. Absolute neutrophil count < $1.0 \times 10^9/L$ OR platelet count < $100 \times 10^9/L$ or hemoglobin < 10.0 g/dL at the lowest dose of HU required to achieve a complete or partial clinicohematological response, OR
5. Presence of leg ulcers or other unacceptable HU-related non-hematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU

HU hydroxyurea

[†] Organ extending by more than 10 cm from the costal margin

Table 2 Modified ELN criteria for HU resistance/intolerance [25, 26]

1. Need for phlebotomy to keep hematocrit < 45% after 3 months of at least 2 g/day OR a maximum tolerated dose OR
2. Uncontrolled myeloproliferation, i.e., platelet count > $400 \times 10^9/L$ And white blood cell count > $10.0 \times 10^9/L$ after 3 months of at least 2 g/day OR a maximum tolerated dose OR
3. Failure to reduce massive[†] splenomegaly by more than 50% as measured by palpation OR failure to completely relieve symptoms related to splenomegaly after 3 months of at least 2 g/day OR maximum tolerated dose OR
4. Absolute neutrophil count < $1.0 \times 10^9/L$ OR platelet count < $100 \times 10^9/L$ or hemoglobin < 10.0 g/dL at the lowest dose of HU required to achieve a complete or partial clinicohematological response, OR
5. Presence of leg ulcers or other unacceptable HU-related non-hematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU.

HU hydroxyurea

[†] Organ extending by more than 10 cm from the costal margin

Table 3 Main clinicohematological characteristics at time of diagnosis

Clinicohematological characteristics	Value
Number of patients	106
Median age, years (range)	63 (29–83)
Age above 60 years, <i>n</i> (%)	59 (55.7)
Male/female, <i>n</i>	59/47
History of thrombosis, <i>n</i> (%)	19 (22.4)
Microvascular symptoms, <i>n</i> (%)	33 (36.7)
Pruritus, <i>n</i> (%)	16 (17.6)
Thrombosis at diagnosis, <i>n</i> (%)	12 (12.9)
Palpable splenomegaly, <i>n</i> (%)	13 (14.9)
Hemoglobin, g/dL	
Male*	19.2 (15.0–23.1)
Female*	19.1 (14.9–22.9)
Hematocrit, (%)	
Male*	58.2 (35.0–70.0)
Female*	58.1 (46.5–70.7)
White blood cell count, $10^9/L^*$	11.41 (4.0–34.0)
$> 10.0 \times 10^9/L$, <i>n</i> (%)	46 (49.0)
$> 15.0 \times 10^9/L$, <i>n</i> (%)	15 (16.0)
Platelet count, $10^9/L^*$	472 (80–1152)
$> 450 \times 10^9/L$, <i>n</i> (%)	49 (52.1)
JAK2 mutation	
V617F, <i>n</i> (%)	100 (95.2)
Exon 12, <i>n</i> (%)	1 (1.0)
No mutation, <i>n</i> (%)	5 (3.8)

*Data are median (range)

received no antithrombotic therapy but anticoagulation (under form of vitamin K antagonist, direct thrombin or direct Xa inhibitor), and four patients (3.77%) received no antithrombotic nor anticoagulant therapy.

Complications

After a median follow-up of 8.2 years, a total of nine thrombotic events were registered (seven arterial, two venous). There was no major bleeding. Progression to myelofibrosis occurred in 12 patients (11.32%). The mean time of progression to myelofibrosis was 10.3 years. One patient showed evolution to AML, 19.0 years after the diagnosis. A total of 16 patients (15.09%) died. Causes of death included transformation to myelofibrosis ($n = 3$), malignancy ($n = 3$), interstitial lung disease ($n = 1$), and unknown cause of death ($n = 9$).

HU resistance/intolerance

Assessment of resistance/intolerance to HU is shown in Table 4. The median length of treatment with HU was 5.1 years with a range from 0.1 to 24.8 years. When using the original ELN criteria, 22 patients (20.7%) were resistant or intolerant, in comparison to 42 patients (39.6%) when applying the modified ELN criteria (Table 4).

Original ELN criteria (ELNo)

When using the ELNo, 5 patients (4.7%) were resistant to HU. No patient received a minimum dose of 2 g of HU a day for at

Table 4 Occurrence of HU resistance/intolerance: original versus modified ELN criteria

	Original ELN criteria	Modified ELN criteria
Total patients, <i>n</i>	106	106
Median length of treatment with HU, years*	5.1 (0.1–24.8)	5.1 (0.1–24.8)
Ongoing therapy, <i>n</i> (%)	66 (62.3)	66 (62.3)
Resistance/intolerance, <i>n</i> (%)	22 (20.7)	42 (39.6)
Resistance, <i>n</i> (%)	5 (4.7)	25 (23.6)
Hematocrit $> 45\%$, <i>n</i> (%)	0 (0.0)	18 (16.7)
Leukocyte count $> 10.0 \times 10^9/L$, <i>n</i> (%)	0 (0.0)	1 (0.9)
Platelet count $> 400 \times 10^9/L$, <i>n</i> (%)	0 (0.0)	1 (0.9)
Palpable splenomegaly, <i>n</i> (%)	0 (0.0)	0 (0.0)
Hemoglobin < 10.0 g/dL, <i>n</i> (%)	1 (0.9)	1 (0.9)
Neutrophil count $< 1.0 \times 10^9/L$, <i>n</i> (%)	0 (0.0)	0 (0.0)
Platelet count $< 100 \times 10^9/L$, <i>n</i> (%)	4 (3.8)	4 (3.8)
Intolerance, <i>n</i> (%)	17 (16.0)	17 (16.0)
Leg ulcer, <i>n</i> (%)	11 (10.4)	11 (10.4)
Fever, <i>n</i> (%)	3 (2.8)	3 (2.8)
Mucocutaneous manifestations, <i>n</i> (%)	3 (2.8)	3 (2.8)

HU hydroxyurea

*Data are median (range)

least 3 months. Therefore, no patient fulfilled criterion one to three of the ELNo (Table 1). Five patients (4.7%) had occurrence of cytopenia at the lowest dose of HU to induce response. Anemia (hemoglobin < 10.0 g/dL) and thrombocytopenia (platelet count $< 100 \times 10^9$) occurred in one (0.9%) and four patients (3.8%), respectively. No neutropenia (neutrophil count $< 1.0 \times 10^9$) was recorded.

Seventeen patients (16.0%) were intolerant to HU. Leg ulcers appeared in 11 patients (10.4%). Three patients (2.8%) had drug-induced fever. In three patients (2.8%), HU was discontinued because of mucositis.

Modified ELN criteria (ELNm)

Resistance occurred in 25 patients (23.6%) when applying the ELM. Eighteen patients (16.6%) required of phlebotomy to control hematocrit $< 45\%$. One patient (0.9%) had leukocytosis $> 10.0 \times 10^9$ /L. One patient (0.9%) had thrombocytosis $> 400 \times 10^9$ /L. No patient had palpable splenomegaly. Five patients (4.7%) developed cytopenia at the lowest dose of HU to induce response. Anemia (Hb < 10.0 g/dL) and thrombocytopenia (platelet count $< 100 \times 10^9$) occurred in one (0.9%) and four patients (3.8%), respectively. No neutropenia (neutrophil count $< 1.0 \times 10^9$) was recorded.

Discussion

In this study, we analyzed resistance/intolerance to HU in 106 patients with PV treated at the University Hospitals of Leuven between 1990 and 2016. Both the original ELN criteria and the modified ELN criteria as used in the RESPONSE trials [24, 25], were applied.

HU resistance/intolerance, as defined by the ELNo, has been analyzed in two previous studies in patients included in the Spanish Registry. One study included 261 PV patients and recorded resistance in 11.5% and intolerance in 12.6% of patients [20]. A more recent study included 890 PV patients and showed a resistance and intolerance rate of 5.7% and 10.7% respectively [21]. In these studies, the prognostic significance of HU resistance, defined by the ELNo, was shown. When applying the ELNo to our PV database, 4.7% of patients were resistant and 16.0% of patients were intolerant to HU, like the data of the Spanish Registry.

Because of its prognostic significance, it is important to identify PV patients with HU resistance as defined by the ELNo. This subgroup of patients' needs second-line therapy to achieve effective disease control. However, at our center, no patient received a minimum dose of 2 g of HU a day. As such, only patients with cytopenia at the lowest dose of HU to achieve partial or complete hematological response (criterion 4, Table 1) were resistant to HU, following the ELNo. This

high dose of HU (2 g or more a day) does not seem to be a common practice, as the median daily dose of HU in patients included in the Spanish Registry was 1000 mg (range 250–2500). The lowest possible dose is prescribed to minimize the risk of adverse effects [13, 22]. A possible explanation for not prescribing 2 g HU or more daily, is the pragmatic combined approach of low-dose HU together with sporadic intermittent phlebotomies to achieve adequate hematocrit control in some PV patients. This means that intermittent phlebotomies are accepted and tolerated by the patient, rather than further increasing the dose of HU when the need of phlebotomies appears. Keeping the low-dose HU keeps the phlebotomy-frequency low.

As such, the modified ELN criteria seem to be more appropriate for daily clinical practice. When applying the ELM, resistance and intolerance occurred in 23.6 and 16.0% of patients, respectively. Not surprisingly, the HU intolerance rate is equal between ELNo and ELM and the HU resistance rate is much higher in ELM compared to ELNo. However, the prognostic significance of HU resistance is only proven when using the ELNo and still needs to be confirmed when using the ELM. Due to relatively small number of patients in this study and the short median time of follow-up for, no conclusions can be made regarding the prognostic value of the ELM.

Intolerance to HU does not have any prognostic significance; however, it is clinically relevant. HU needs to be discontinued in this subgroup of patients who experience unacceptable side effects due to therapy with HU. These patients are also eligible for second line therapy. Both ELNo and ELM do not include worsening of PV-related symptoms such as constitutional symptoms and pruritus. However, patients with PV have an impaired quality of life due to a significant symptom burden. When HU has little effect in controlling these symptoms [22, 24, 25], this also is an indication for second-line therapy to reduce the potentially severe symptom burden of PV.

Before the advent of the JAK1/JAK2 inhibitor ruxolitinib, PV patients with HU resistance and intolerance had few therapeutic alternatives. Interferon is recommended as first- or second-line therapy in PV [14]; however, it is not licensed for treatment of PV in many European countries [15, 27].

Ruxolitinib has been evaluated in the RESPONSE and RESPONSE-2 trial [24, 25], comparing ruxolitinib versus the best available therapy in HU-resistant or HU-intolerant PV patients. As inclusion criteria, the ELM criteria were used. This modification allowed to include more patients in the clinical trials and extend the clinical indication of ruxolitinib. Although it must be noted that the prognostic significance of HU resistance has only been proven using the ELNo. HU resistance and intolerance is defined here by the ELM. Ruxolitinib was superior to standard therapy in achieving hematocrit control and in reduction of symptom burden [24, 25, 28]. In the 80-week follow-up study of the RESPONSE trial, patients treated with ruxolitinib had a lower thrombo-embolic event rate per

100 patient years (1.8 in the ruxolitinib group versus 8.2 in the best available therapy group) [29]. This suggests all patients with HU resistance/intolerance defined by the ELNm may benefit from therapy with ruxolitinib.

In conclusion, detection of HU resistance in PV patients is important because of its prognostic significance (proven when using the ELNo) and because of recent availability of more second line treatment options. In our hands, incidence of HU resistance in PV patients is 23.6% when applying the ELNm. This rate is only 4.7% with the ELNo. In our practice, no PV patient received “at least 2-g HU daily for 3 months.” As such, the ELNm seem better adapted for daily clinical use. However, the prognostic value of HU resistance in PV, when defined by the ELNm, still needs to be confirmed.

Authorship contributions All authors declare that they have participated in writing the paper and have seen and approved the final version of the paper.

Compliance with ethical standards

Conflict of interest Thomas Demuynck, Gregor Verhoef, Michel Delforge, and Peter Vandenberghe have no conflict of interest to declare. Timothy Devos did participate in an advisory board for Novartis and Gilead.

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