Appropriate management of polycythaemia vera with cytoreductive drug therapy: European LeukemiaNet 2021 recommendations

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Polycythaemia vera is associated with a reduced quality of life, a high rate of vascular events, and an intrinsic risk of disease evolution. The results of several randomised trials for the treatment of this disorder are now available, and both a new ropegylated formulation of interferon alfa-2b (ropeginterferon alfa-2b; 2018) and ruxolitinib (2015) have been approved in Europe. European LeukemiaNet (ELN) investigators have therefore deemed it appropriate to provide recommendations for the use of these drugs in clinical practice. An expert panel of 14 senior haematologists from ELN centres that had actively participated in previous ELN projects or relevant randomised trials, chaired by a member of the ELN Steering Committee, developed a list of clinical questions, and a methodologist established three patient, intervention, comparator, outcome (PICO) questions and systematically reviewed the evidence. Recommendations were approved by six Delphi consensus rounds and two virtual meetings (on Jan 26, 2021, and June 24, 2021). The expert panel recommended that patients with polycythaemia vera who are younger than 60 years and have not had previous thrombotic events should start cytoreductive drug therapy if at least one of the following criteria are fulfilled: strictly defined intolerance to phlebotomy, symptomatic progressive splenomegaly, persistent leukocytosis (>15×10⁹ white blood cells per L), progressive leukocytosis (at least 100% increase if baseline count is <10×10⁹ cells per L or at least 50% increase if baseline count is >10×10⁹ cells per L), extreme thrombocytosis (>1500×10⁹ platelets per L), inadequate haematocrit control requiring phlebotomies, persistently high cardiovascular risk, and persistently high symptom burden. Recombinant interferon alfa, either in the form of ropeginterferon alfa-2b or pegylated interferon alfa-2a, is the recommended cytoreductive treatment for these patients. The expert panel suggested that either interferon alfa or ruxolitinib should be considered for patients who are being treated with hydroxyurea but require a therapy change.

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Introduction

Polycythaemia vera is a clonal disorder of haematopoietic stem cells that is characterised by mutations in exon 14 or exon 12 of *JAK2* and is phenotypically associated with one or more of erythrocytosis, systemic symptoms, major thrombosis, and microvascular symptoms.[1] Polycythaemia vera impairs both patients' quality of life and their lifespan, mainly because of an increased rate of vascular events and transformation to myelofibrosis, myelodysplastic syndrome, or acute myeloid leukaemia.[2–5] Infections and secondary malignancies are also major concerns in patients with these conditions.[6,7]

In 2018, the European LeukemiaNet (ELN) provided consensus recommendations for the management of chronic myeloproliferative neoplasms,[8] but there are still many unmet needs for the satisfactory management of patients with these conditions. For example, patients with polycythaemia vera who are younger than 60 years and have no previous vascular events, who are conventionally defined as being at low risk, are generally treated with phlebotomy and low-dose aspirin; however, the risk of vascular events for these patients remains greater than currently accepted thresholds for primary cardiovascular prevention.[9,10] Furthermore, some patients who are conventionally defined as being at low risk can have a diminished quality of life, which persists even after optimal haematocrit control is reached through phlebotomy treatment.[2] Despite this diminished quality of life, intervention with cytoreductive drugs, such as hydroxyurea, is discouraged in patients at low risk owing to a supposed risk associated with long-term use, which, although largely uncertain, could outweigh the possible benefits. For many decades, hydroxyurea has been a mainstay of therapy; however, the potential therapeutic options for polycythaemia vera have now expanded beyond hydroxyurea, with the approval of ropeginterferon alfa-2b and the JAK1/JAK2 inhibitor ruxolitinib. On the basis of the results of one randomised trial, it has been suggested that treatment with a recombinant interferon alfa could result in operational cure in a fraction of patients with polycythaemia vera,[11] and that ruxolitinib might be useful for patients whose condition is resistant or refractory to hydroxyurea treatment.

In January, 2021, the ELN promoted an international project to update the clinical indications for the use of cytoreductive drugs in the treatment of polycythaemia vera. The expert panel, the chair, and the methodologist were asked to grant the highest quality of recommendations by adhering to standard methods for developing clinical practice guidelines—namely the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.[12] This method enables a transparent and explicit management of evidence and consensus, its application being limited only in instances

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See Online for appendix

of scarce availability of scientific literature. This Review reports the 2021 evidence-based and consensus-based ELN recommendations for the use of cytoreductive drugs in patients with polycythaemia vera.

Methods

An expert panel of 14 haematologists from seven countries (Austria, France, Germany, Italy, Spain, the UK, and the USA) was convened and guided by a chair (TB) and a methodologist (MM). The panellists were selected from the ELN centres that had actively participated in previous ELN projects (eg, Working Party 9, devoted to myeloproliferative neoplasms) or relevant randomised trials.[13–19] RTS (Weill Cornell Medicine, New York, NY, USA) was invited to join the expert panel owing to his internationally recognised experience in this field. Five relevant disciplines were represented among the panellists: clinical haematology, experimental haematology, pharmacology, internal medicine, and epidemiology.

Three clinical questions—what benefits should be expected from cytoreductive drugs compared with phlebotomy in patients with low-risk polycythaemia vera, which cytoreductive drugs should be preferred in patients with low-risk disease, and what benefits should be expected from changing the cytoreductive drug in patients with polycythaemia vera treated with hydroxyurea—were translated into patient, intervention, comparator, outcome (PICO) questions and clinical recommendations were produced by a GRADE process. Critical outcomes (ie, disease transformation, vascular events, and symptoms) and important outcomes (ie, haematocrit control, haematological response, frequency of phlebotomy, quality of life, and secondary neoplasms) were ranked according to international landmark analyses as detailed in the appendix (p 2). The expert panel also considered two questions—which patients with low-risk polycythaemia vera might benefit from cytoreductive drugs, and which patients with polycythaemia vera who are treated with hydroxyurea should receive a different cytoreductive drug—aimed at identifying which patients were in need of starting or changing cytoreductive drug therapy; a structured consensus process was applied to these questions using a plain Delphi method.[20] Six Delphi rounds and two virtual meetings (on Jan 26, 2021, and June 24, 2021) enabled the expert panel to complete the consensus process.

No external support was received for this project.

Search strategy and selection criteria

References were identified through searches of the Embase database on March 20, 2021, and June 8, 2021. Five main queries were built to retrieve landmark analyses, randomised clinical trials and meta-analyses, and retrospective or prospective studies reporting patients treated with an interferon or with ruxolitinib. The results were limited to studies written in English and published within the past 10 years. Quality of the evidence for each outcome was rated according to the Grading of Recommendations Assessment, Development and Evaluation (known as GRADE) method. The quality of supporting evidence was rated as high if based on randomised trials that were not downgraded for indirectness or biases. Quality of the evidence was graded moderate if data from randomised trials reported limitations or when evidence was mostly retrieved from non-comparative studies. Evidence was graded low quality if data from longitudinal studies were not consistent or were indirect. Evidence was graded very low quality in case of severe limitations in the available longitudinal studies. Specific queries and retrieved references are detailed in the appendix (pp 8–13).

Results

What benefits should be expected from cytoreductive drugs over phlebotomy in patients with low-risk polycythaemia vera?

The expert panel agreed that the use of cytoreductive drugs in addition to phlebotomy for the treatment of patients with low-risk polycythaemia vera should be weighted upon three critical outcomes: vascular events, disease transformation, and disease-related symptoms.

First, cytoreductive drugs are expected to reduce vascular events in all patients with polycythaemia vera, including those classified as low-risk, who nonetheless have a thrombotic risk greater than that of the general population.[4,21,22] Cytoreduction can reduce the risk of vascular events by normalising blood counts and by maintaining a steady haematocrit value, whereas patients who receive phlebotomy-only treatment maintain a therapeutic haematocrit value in only 30–50% of cases.[9,13,21] The PVSG 01 study[23] reported fewer vascular events in patients randomised to alkylating agents than in patients who received phlebotomy-only treatment, and subsequent longitudinal studies (ECLAP and PVSG-08) confirmed that hydroxyurea prevented approximately two thrombotic events in 100 patient years in the overall population with polycythaemia vera.[22,24,25] More recently, the ongoing Low-PV study[13] compared treatment with ropeginterferon alfa-2b with phlebotomy-only treatment. To date, the poor follow-up, small sample size, and low rates of vascular events have prevented a robust comparison between the treatment groups. Based on these considerations, the indirect evidence supporting the use of cytoreductive drugs over phlebotomy-only treatment was deemed to be of moderate quality.

Second, a role for cytoreductive drugs in delaying the intrinsic propensity of polycythaemia vera to transform into myelofibrosis is supported by some longitudinal studies that reported improved myelofibrosis-free survival in patients treated with either hydroxyurea or with interferon alfa.[22,24,26] Based on the design of these studies, the evidence supporting the use of cytoreductive drugs over phlebotomy-only treatment was of moderate quality. Polycythaemia vera also shows a natural

propensity to transform into acute leukaemia; such transformation was not significantly increased by treatment with hydroxyurea in the PVSG-08 and ECLAP studies.[22–24] Whether treatment with the newly approved drugs, ruxolitinib and ropeginterferon alfa-2b, has a positive or negative influence on this outcome is still being investigated; however, no specific assessment was done in this Review owing to the rarity of the events and the consequent low power of the existing studies.

Finally, cytoreductive drugs could improve symptoms related to polycythaemia vera. This effect was shown in the Low-PV trial,[13] in which symptomatic improvement was documented in a higher proportion of patients who received ropeginterferon alfa-2b than those in the phlebotomy-only treatment group. This evidence was of moderate quality.

Most of the available clinical trials[13,18,22,27–42] enrolled patients with high-risk polycythaemia vera and usually targeted haematological response as the primary endpoint (appendix p 4). Therefore, the quality of evidence supporting critical outcomes in patients with low-risk disease was moderate (table 1). As a consequence, the expert panel decided not to recommend cytoreductive drugs in all patients with low-risk polycythaemia vera, but only in subgroups of patients for whom a high benefit-to-risk ratio is specifically expected owing to clinically significant improvement in one of the outcomes (panel 1).

	Favours cytoreductive drug therapy?	Quality of evidence
Disease transformation*	Yes†	Moderate[22,26,35,37]
Vascular events*	Yes	Moderate[36,37,38]
Symptoms*	Yes	Moderate[13,33,37,42]
Haematocrit control and haematological response	Yes	High[22,37,42]
Phlebotomy frequency	Yes	High[13]
Quality of life	Yes	Very low[27-34]
Adverse events	No	High[36,38,41]
Secondary malignancies	Yes and no‡	Low[18,39,40]
Overall survival	Yes	Very low[22,26]
Molecular response	Yes	High[22,36,37,42]

PICO question 1: should all patients with polycythaemia vera younger than 60 years and with no history of previous vascular events (P) receive cytoreductive drugs (interferon alfa or hydroxyurea; I) in addition to phlebotomy and antiplatelet therapy (*vs* phlebotomy and antiplatelet therapy without cytoreductive drugs; C) to minimise vascular events, disease transformation, disease-related symptoms, or other non-desirable important outcomes (O)? PICO=patient, intervention, comparator, outcome. *Critical outcome, namely the most relevant outcomes, as selected from landmark analyses (see Methods). †No relevant risk of bias was retrieved for the retrospective studies that reported outcomes of large patient cohorts after very long follow-ups and adopting propensity score or multivariate analysis for adjusting potential biases. Partial risk of bias was estimated in the randomised study, due to lack of study blinding. The overall body of evidence was consistent and a large effect size of cytoreduction with recombinant interferon was reported in one study.[26] Moreover, indirectness was not judged to be serious because subgroup analysis for patients at low risk was provided[22,26] and because the risk of transformation does not depend on the thrombotic risk class.[26] The quality of evidence supporting an advantage of cytoreductive drugs (specifically recombinant interferon) was judged to be moderate for this outcome. ‡Increased skin secondary malignancies reported for hydroxyurea but not for interferon alfa.

Table 1: **Synthetic evidence-to-decision table for PICO question 1 regarding cytoreductive drugs versus phlebotomy in patients with low-risk polycythaemia vera**

Which patients with low-risk polycythaemia vera might benefit from cytoreductive drugs?

The expert panel selected clinical subgroups of patients with low-risk polycythaemia vera who need cytoreductive drugs to ameliorate specific critical outcomes (panel 1). The expert panel considered the thrombotic risk, and agreed that patients with low-risk disease might benefit from cytoreductive drugs if one or more of leukocytosis, poor haematocrit control from phlebotomy-only treatment, and a high cardiovascular risk are present. The predictive value of leukocytosis in patients with polycythaemia vera has been consistently shown by meta-analyses of retrospective studies.[43] The thrombotic hazard did not differ for different leukocyte trajectories in a large retrospective study;[44] however, 29 thrombotic events were reported in 295 patients with leukocytosis compared with five events in 93 patients without leukocytosis. Furthermore, the results of this study could not be applied to the addressed patient population—patients with low-risk disease who were not receiving cytoreductive drugs—because 295 (78%) of 378 patients were receiving cytoreductive drugs during the observation period. Given the lack of a clear cutoff value for the number of white blood cells, the expert panel decided to adopt different leukocyte thresholds for persistently increased counts and progressive leukocytosis. Poor haematocrit control is a risk factor for thrombosis, as shown in the CytoPV randomised clinical trial;[45] patients with a median haematocrit value of 45% or higher incurred a significantly greater risk of vascular events and death (hazard ratio [HR] 3·91, 95% CI 1·45–10·53, p=0·007). Individual cardiovascular risk factors proved predictive of thrombotic events,[46] but the evidence was not sufficiently robust to differentiate the risk in patients with polycythaemia vera from the risk for the general population; therefore, the expert panel adopted the risk classification of the European Society of Cardiology as a benchmark for baseline assessment of vascular risk (appendix pp 5–6).

Symptoms were the second critical outcome considered. Patients with poor tolerance to phlebotomy, symptomatic progressive splenomegaly, a high overall symptom burden, or severe itching were all considered to have inadequately controlled disease. For these patients, cytoreductive drugs could reduce the need for phlebotomy, relieve symptoms, and reduce splenomegaly; such occurrences have been reported in randomised trials, including those recruiting patients with low-risk disease.[13,15,33] Symptoms are expected to significantly improve after treatment with cytoreductive drugs, particularly for patients with severe symptoms at baseline, as reported by the MPN-RC 111 and MPN-RC 112 trials.[33]

***Panel 1*: Recommendations for cytoreductive drug therapy in patients with low-risk polycythaemia vera**

In patients with low thrombotic risk (younger than 60 years and without previous vascular events), cytoreductive drugs should be considered only in specific clinical subgroups (consensus, 85%; strength of the recommendation, weak negative).

Cytoreductive drugs are recommended in patients reporting:

- A poor tolerance to phlebotomy, strictly defined as recurrent episodes of post-phlebotomy syncope despite appropriate preventive interventions or blood phobia leading to avoidance behaviour despite counselling, or severe difficulties in venous access (consensus: 100%)
- Symptomatic progressive splenomegaly (increase by >5 cm in the past year), provided that transformation to myelofibrosis has been ruled out (consensus: 85%)
- Persistent leukocytosis (leukocyte count >20 × 10^9 cells per L confirmed at 3 months (without therapy; consensus: 85%)

Cytoreductive drugs should be considered in patients reporting:

- Progressive (at least 100% increase if baseline count is <10 × 10^9 cells per L or at least 50% increase if baseline count is >10 × 10^9 cells per L) and persistent (leukocyte count >15 × 10^9 cells per L confirmed at 3 months) leukocytosis (consensus: 80%)
- Extreme thrombocytosis (>1500 × 10^9 platelets per L), bleeding manifestations related to the disease irrespective of the platelet count, or both (consensus: 85%)
- Inadequate haematocrit control with phlebotomies—ie, a need for at least six phlebotomies per year for at least 2 years in the maintenance phase after reaching haematocrit concentrations below 45% in the induction phase (consensus: 80%)

A trial of cytoreductive drugs can be considered:

- In patients reporting a high symptom burden (total symptom score ≥20) or severe itching (itching score ≥5) that are not ameliorated by phlebotomy, antiplatelet therapy, or antihistamines (consensus: 93%)
- On an individual basis in patients reporting a relevant cardiovascular risk (appendix p 4), provided that primary prevention strategies have been implemented (appendix p 5; consensus: 85%)

In treatment-naive patients with polycythaemia vera who are younger than 60 years and have had no previous vascular events but need cytoreductive drug therapy, the first cytoreductive drug to be considered should be ropeginterferon alfa-2b or pegylated interferon alfa-2a, unless clinically contraindicated (consensus: 85%; strength of the recommendation: weak in favour of interferon alfa).

A specific recommendation was devoted to preventing clinically relevant bleeding. Severe acquired von Willebrand factor syndrome (ie, von Willebrand factor activity of <30%) is reported in myeloproliferative neoplasms, especially in patients with very high platelet counts. Although there is no direct supporting evidence, the expert panel decided that cytoreductive drugs should be considered for patients with extremely high platelet counts (>1500 × 10^9 platelets per L), as previously reported in the 2018 ELN recommendations,[8] and in patients with symptomatic acquired von Willebrand factor syndrome or bleedings related to polycythaemia vera itself.

The appendix (p 7) shows the list of clinical subgroups and the target outcomes for each. Subgroups reporting a consensus of greater than 75% were selected after the first consensus round and eventually refined. Two of the selected subgroups, younger patients and patients with a high *JAK2*^{V617F} allele (1849G→T) burden, were subsequently discarded because indirect evidence was deemed insufficient to support the initiation of cytoreductive drug therapy in the low-risk group.

Which cytoreductive drugs should be preferred in low-risk patients?

For patients with polycythaemia vera who require cytoreductive drug therapy, either hydroxyurea or interferon alfa are currently recommended.[8] The two treatments have been prospectively compared in three randomised trials (PROUD-CONTI,[15] MPN-RC-112,[18] and DALIAH[47]); however, only a few patients with low-risk disease were enrolled into these studies, and hydroxyurea was not offered to younger patients in the DALIAH trial. These three trials differed in terms of study duration, the interferon molecule used for treatment, and treatment tolerability. Nevertheless, mid-term trial results reported that haematocrit levels of less than 45% were maintained without the need for phlebotomy in 82% of patients in the ropeginterferon alfa-2b arm in the fifth year of treatment, which was significantly higher than the rate of 63% observed in the control group (hydroxyurea treatment; p=0·01). The rate of molecular response at 5 years was also significantly higher among patients treated with ropeginterferon alfa-2b than in the control arm (69% *vs* 22%; RR 3·2 [2·1–4·9]; p<0·0001).

In addition to randomised trials, high-quality retrospective studies and meta-analyses were also assessed for evidence relating to disease transformation, vascular events, secondary malignancies, and life expectancy. A large retrospective study in the USA found that treatment with interferon alfa resulted in a 19% absolute risk reduction of transformation to myelofibrosis, a 14% absolute risk reduction (p=0·021) of thromboembolic events, a 9% risk reduction of post-polycythemia vera myelofibrosis per year of treatment (HR 0·91, p<0·001; table 2), and a 6% mortality risk reduction per year of treatment (HR 0·94, p=0·012), independent of other risk

factors, by multivariate analysis, compared with phlebotomy.[26] A population-based study indicated a four-fold reduced risk of secondary malignancies for interferon alfa treatment compared with hydroxyurea treatment.[52] In two meta-analyses that evaluated the rate of vascular events in 1457 patients with polycythaemia vera treated with either pegylated or non-pegylated interferon alfa, the results indicated a very low rate of thrombosis of 0·2–0·4 events per 100 patient years.[36,38]

In summary, high-quality evidence (table 2)[2,15,26,36–38,53–56] supports the use of interferon alfa rather than hydroxyurea to attain haematocrit control and a molecular response, and moderate-quality evidence suggests that treatment with interferon alfa delays or reduces the risk of disease transformation into myelofibrosis and secondary malignancies compared with hydroxyurea. Therefore, the expert panel recommended either pegylated or non-pegylated interferon alfa as cytoreductive drug therapy in patients younger than 60 years with polycythaemia vera, especially because their potentially longer lifespan might be associated with a higher cumulative incidence of secondary malignancies and myelofibrosis (panel 1). Conversely, hydroxyurea was confirmed to be the mainstay cytoreductive drug for individuals older than 60 years.[8]

The discontinuation rate due to adverse events in patients treated with ropeginterferon alfa-2b was low.[13,15] This drug is the only interferon alfa formulation currently approved in Europe and the USA for patients with polycythaemia vera; however, because it is not available worldwide, the expert panel recommendations included the use of any of the pegylated interferon alfa formulations available (panel 1).

	Favours interferon alfa over hydroxyurea?	Quality of evidence
Disease transformation*	Yes	Moderate[22,24,48,49]
Vascular events*	Yes	Moderate[26,50]
Symptoms*	Yes, for itching and night sweats	Moderate[2,15,37]
Haematocrit control	Yes	High[37]
Phlebotomy frequency	Yes	High[51]
Haematological response	Yes	High[36]
Quality of life	No	Moderate[2]
Adverse events	No	Moderate[36,37]
Secondary malignancies	Yes†	Low[52]
Molecular response	Yes	High[37]
Overall survival	Yes	Low[26]

PICO question 2: should patients with polycythaemia vera who are younger 60 years, naive to cytoreductive drug treatment, and with no history of previous vascular events but in need of cytoreductive drug therapy (P), preferably be treated with interferon alfa (I) rather than hydroxyurea (C) to minimise vascular events, disease transformation, and disease-related symptoms or other non-desirable important outcomes (O)? PICO=patient, intervention, comparator, outcome. *Critical outcome, namely the most relevant outcomes, as selected from landmark analyses (see Methods). †Increased skin secondary malignancies reported for hydroxyurea but not for interferon alfa.

Table 2: **Synthetic evidence-to-decision table for PICO question 2 regarding cytoreductive drugs in patients with low-risk polycythaemia vera**

Which patients with polycythaemia vera who are treated with hydroxyurea should receive a different cytoreductive drug?

In clinical practice, about 10–15% of patients with polycythaemia vera who are treated with hydroxyurea develop an intolerance to the drug,[57,58] which prompts a therapeutic shift. The occurrence of secondary skin malignancies after treatment with either hydroxyurea or ruxolitinib, but not after treatment with interferon alfa, is of particular concern. In addition to intolerance, many patients with polycythaemia vera who are treated with hydroxyurea do not show a partial or complete response.[48,49,57] 60 (40%) of the 149 patients enrolled in the RESPONSE-2 trial,[16] 102 (46%) of the 222 patients enrolled in the RESPONSE trial,[14] and a variable proportion (depending on definition) of patients enrolled in the PROUD-CONTI, MAJIC,[17] and RELIEF trials (appendix p 4) were classified as suboptimal responders to hydroxyurea. Based on the overall body of direct and indirect evidence available, clinically relevant amelioration was reported after treatment with ruxolitinib, interferon alfa, or both, in terms of the following outcomes.

Two meta-analyses detected a clinically and statistically significant reduction in the rate of vascular events, from 5·51 events per 100 patient years to 3·09 events per 100 patient years, in patients receiving ruxolitinib rather than the best available therapy.[50,51]

In the RESPONSE trial, at week 32, a total of 36 (49%) of 74 patients in the ruxolitinib group and 4 (5%) of 81 patients in the standard-therapy group had at least a 50% reduction in the 14-item MPN-SAF total symptom score. In the RESPONSE-2 trial, 29 (45%) of 64 patients in the ruxolitinib group had at least a 50% reduction in the MPN-SAF total symptom score, compared with 5 (23%) of 22 patients receiving the best available treatment. In the MAJIC trial, mean MPN-10 total symptom scores (itching, fatigue, night sweats, early satiety, weight loss, bone pain, inactivity, and concentration; all $p<0·05$) during the first 12 months were all significantly lower for patients treated with ruxolitinib compared with patients who received the best available therapy. Subgroup analysis of RESPONSE trials for patients intolerant to hydroxyurea was not available; however, the quality of supporting evidence was judged to be high, because of the large and consistent efficacy reported by different studies. In terms of patients' quality of life, assessed by the EQ-5D score, a trend to an overall improvement was suggested for patients who were randomly assigned to ropeginterferon alfa-2b compared with those assigned to hydroxyurea in the PROUD-CONTI trial. However, detailed symptom scales and subgroup analysis of patients who were pretreated with hydroxyurea (and were not intolerant to

this drug) were not available. Therefore, the quality of supporting evidence for this critical outcome was judged to be moderate.

Haematocrit control was optimal for 5 years in 59% of patients randomly assigned to ropeginterferon alfa-2b compared with 17% of patients assigned to hydroxyurea in the PROUD-CONTI trial (relative risk 3·52; 95% CI 2·13–5·81).[37] However, only 82 (32%) of 254 patients enrolled in the PROUD trial had received previous treatment with hydroxyurea, therefore the quality of supporting evidence was judged moderate. More patients reached the target haematocrit values with ruxolitinib treatment (53–68%) than with the best available therapy (20%), and haematocrit control was partially durable, being maintained in 16 of 74 patients assigned to ruxolitinib in the RESPONSE-2 trial at week 260.[16] The quality of supporting evidence was therefore judged to be moderate.

In the PROUD-CONTI trial, 69% of patients assigned to ropeginterferon alfa-2b showed a molecular response at 5 years, with a reported mean absolute decline in *JAK2*^{V617F} allele burden from 37·3% to 7·3%, compared with no decline in those assigned to hydroxyurea (from 38·1% to 42·6%; p<0·0001).[37] Furthermore, 27 (41%) of 66 patients with a baseline *JAK2*^{V617F} allele burden of greater than 10% who were treated with ropeginterferon alfa-2b for 5 years reached an operational cure, which was defined as a *JAK2*^{V617F} allele burden lower than 10%, a complete haematological response maintained for at least 2 years, and no disease progression, thromboembolic events, or worsening of symptoms.[11] A meta-analysis of 37 studies, which included both pegylated and non-pegylated interferon alfa, confirmed that 204 (45%) of 451 patients who received these treatments showed a molecular response. The mean maximal reduction in *JAK2*^{V617F} allele burden was –35·9% (SD 29·7%) during ruxolitinib treatment in the RESPONSE trial, and a molecular response was seen in 57 (53%) of 107 patients.[59] However, these results should be interpreted with caution because the mean baseline allele burden was different in the three analysed trials (37% in PROUD-CONTI, 76% in RESPONSE, and 76% in RESPONSE-2) probably because of the high proportion (209 [56%] of 371) of patients intolerant to hydroxyurea who were enrolled in the RESPONSE trial. Consequently, the quality of the supporting evidence for this outcome was judged to be high for interferon alfa and moderate for ruxolitinib.

Lower rates of transformation to myelofibrosis in the ropeginterferon alfa-2b and ruxolitinib treatment groups than in the hydroxyurea group were reported in the PROUD-CONTI (0·2 per 100 patient years *vs* 1·0 per 100 patient years), RESPONSE-2 (0 per 100 patient years *vs* 1·9 per 100 patient years), and MAJIC trials. These findings suggest a possible protective effect of these treatments, despite heterogeneous disease durations for the patients enrolled in the trials. A shift in therapy from hydroxyurea to either interferon alfa or ruxolitinib resulted in inconsistent trends in other outcomes.

In the PROUD-CONTI trial, similar rates of adverse events were reported in patients treated with ropeginterferon alfa-2b (4·2 per 100 patient years) and with hydroxyurea (6·6 per 100 patient years). Therapy discontinuation was also similar for the two treatments (2·2 cases per 100 patient years for ropeginterferon alfa-2b *vs* 2·8 cases per 100 patient years for hydroxyurea). Cumulative discontinuation rates of about 16% were reported in both the PROUD-CONTI trial (17% of patients treated with ropeginterferon alfa-2b) and the RESPONSE and RESPONSE-2 trials (15% of patients treated with ruxolitinib). However, an increased risk of herpes zoster infection was documented only in the ruxolitinib group of the RESPONSE trial (3·8 events per 100 patient years *vs* no events for best available treatment), and propensity-adjusted retrospective studies reported a higher risk of recurrent infections after treatment with ruxolitinib than with best available treatment.[7] By contrast, interferon alfa has not, to our knowledge, been associated with an increased risk of infection in any randomised trial or meta-analysis. Besides randomised trials, safety outcomes of interferon alfa were also collected from meta-analyses and large real-life retrospective studies. Grade 3–4 adverse events associated with interferon alfa treatment occurred in 178 (18%) of 998 patients and were the major cause of therapy discontinuation—mostly as a result of cytopenias or neuropsychiatric, endocrine, or autoimmune disorders. Patients who are considered for interferon alfa treatment should therefore be screened for subclinical thyroid dysfunction and for autoimmune and psychiatric disorders.[41]

Regarding secondary malignancies, higher rates were consistently reported in the ruxolitinib group than in the best available treatment group in both the RESPONSE (7·0 per 100 patient years *vs* 4·1 per 100 patient years) and the RESPONSE-2 (2·7 per 100 patient years *vs* 1·9 per 100 patient years) trials. A higher risk of non-melanoma skin cancers was associated with ruxolitinib exposure than for phlebotomy or interferon exposure in case-control studies.[13] In patients treated with interferon alfa, the incidence of secondary malignancies was similar to or lower than that in the overall polycythaemia vera population, both in case-control and randomised trials.[13,15,37]

On the basis of the moderate-quality evidence (table 3),[8,14–17,19,26,36–38,40,41,50–52,60–63] the expert panel recommended considering a therapeutic shift in patients who are intolerant to hydroxyurea (panel 2).

To define inadequate clinical response to hydroxyurea, the expert panel selected patient subgroups who did not reach the benchmark threshold in critical outcomes (appendix p 6). The panel deemed that a therapeutic shift should be considered for patients who report a high and persistent symptom burden despite moderate-to-high

doses of hydroxyurea (higher than 1500 mg per day, which is believed to be the highest dose commonly used in treating polycythaemia vera).[49] Symptomatic splenomegaly and microvascular symptoms also were deemed relevant for considering a therapeutic shift to improve quality of life in patients treated with hydroxyurea; the operational definitions for these outcomes were taken from clinical trial eligibility criteria and previous ELN guidelines.[8,53] The third benchmarked outcome, thrombotic or bleeding events, suggested a therapeutic shift to interferon alfa or ruxolitinib in patients treated with hydroxyurea who have one or more of high platelet counts, progressive and persistent leukocytosis, or inadequate haematocrit control. The higher risk of disease transformation in patients treated with hydroxyurea who have progressive leukocyte counts or increased spleen size reinforced the decision to examine these patient subgroups.

To our knowledge, ruxolitinib and interferon alfa have not been compared therapeutically, and the number of patients who had previously been treated with hydroxyurea differed between the PROUD-CONTI trial and both the RESPONSE and RESPONSE-2 trials (appendix p 4). An indirect post-hoc analysis compared 26 patients who were treated with interferon alfa in the best available treatment group of the RESPONSE and the RESPONSE-2 trials (21 with pegylated interferon alfa, five with non-pegylated interferon alfa, and none with ropeginterferon alfa-2b) with 184 patients who were treated with ruxolitinib. Haematocrit control was reached in five of 26 patients and symptom relief in one of 11 patients who were treated with an interferon alfa. These values are lower than those reported in the RESPONSE and the RESPONSE-2 trials (haematocrit control in 113 [67%] of 168 patients and symptom control in 65 [47%] of 138 patients), but no propensity-match was applied and most of the patients had advanced polycythaemia vera and were treated with non-pegylated interferon alfa.[65] A propensity-matched analysis of 31 patients with polycythaemia vera who were treated with ruxolitinib compared with 14 patients who were not treated with ruxolitinib reported an HR for secondary malignancies of 10·8 (95% CI 2·54–45·92) in patients treated with ruxolitinib.[7] For the stated reasons, the expert panel decided not to provide specific recommendations for interferon alfa or ruxolitinib in this clinical setting, but rather to allow clinicians to tailor cytoreductive drug therapy for patients who have previously been treated with hydroxyurea according to clinical features, such as symptom burden and haematological or bone marrow findings, symptomatic splenomegaly, or patient preference. In particular, patients who have previously been treated with hydroxyurea and have clinically relevant splenomegaly—which is uncommon in patients with polycythaemia vera before transformation to myelofibrosis—were deemed more suitable for treatment with ruxolitinib than with interferon alfa, on the basis of the favourable outcomes reported by the RESPONSE trial and the few patients with splenomegaly in the PROUD-CONTI trial. Nevertheless, 102 (46%) of 222 patients enrolled in the control group of RESPONSE and 60 (40%) of 149 in RESPONSE-2 had an inadequate response to hydroxyurea but still continued treatment with it, which could affect the results.

	Favoured shift to interferon alfa?	Quality of evidence	Favoured shift to ruxolitinib?	Quality of evidence
Disease transformation*	Yes	Moderate[26,37]	Yes	Low†[14,17]
Vascular events*	Yes	Low[36-38]	Yes	Moderate[50,51,60]
Symptoms*	Yes	Moderate[45]	Yes	High[17,19]
Haematocrit control	Yes	Moderate[37,38]	Yes	Moderate[14,16,60]
Phlebotomy frequency	Yes	High[37,38]	Yes	High[14]
Haematological response	Yes	Moderate[36,38]	Yes	High[16]
Quality of life	Yes	Moderate[15]	Yes	High[32,61]
Adverse effects	No	High[7,37,41,62]	No	High[7,41,62,63]
Secondary malignancies	Yes	Moderate[8,37,40,48]	No	Moderate[8,14,16,38,48]
Molecular response	Yes	High[15,37]	Yes	Moderate[14,16]
Overall survival	Yes	Low[26,37]	Yes	Low[16,64]

PICO question 3: should all patients with polycythaemia vera who are receiving hydroxyurea (P) move to another cytoreductive drug (interferon alfa or ruxolitinib; I) rather than continuing hydroxyurea (C) to minimise vascular events, disease transformation, and symptoms or other non-desirable important outcomes (O)? PICO=patient, intervention, comparator, outcome. *Critical outcome, namely the most relevant outcomes, as selected from landmark analyses (see Methods). †The quality of evidence was downgraded for lack of significance and for severe inconsistency between the RESPONSE-2 trial and the RESPONSE trial: the RESPONSE trial reported more transformation events in the ruxolitinib arm than in the best-avaliable therapy arm (2·1 per 100 patient years *vs* 0·0 per 100 patient years).

***Table 3*: Synthetic evidence-to-decision table for PICO question 3 regarding a shift to different cytoreductive drugs in patients with polycythaemia vera receiving hydroxyurea**

Discussion

Although polycythaemia vera is a rare disorder, two new drugs have recently been approved that considerably expand the scope of its treatment. However, innovation needs to be accurately guided to avoid inappropriate clinical pathways. For this reason, the ELN promptly elaborated clinical practice recommendations, adopting the GRADE framework for the core clinical questions relating to these new drugs, thereby permitting explicit recommendations on the basis of limited evidence and on expert consensus. Moreover, unambiguous subgroups of patients with low-risk polycythaemia vera were selected for consideration for cytoreductive drug therapy; each subgroup had a high risk of undesirable critical outcomes (ie, symptoms, phlebotomies, thromboses, bleedings, or transformation to myelofibrosis). As a result of these recommendations, some patients with low-risk polycythaemia vera are not suitable candidates for phlebotomy-only treatment and antiplatelet therapy but should be assessed for cytoreductive drug therapy, preferably with ropeginterferon alfa-2b or pegylated interferon alfa. While waiting for more robust evidence that supports the role of molecular response and clonal

Panel 2: **Recommendations for second-line cytoreductive drug therapy in patients with polycythaemia vera**

Patients with polycythaemia vera who are receiving hydroxyurea are recommended to change to another cytoreductive drug if they meet at least one of the following criteria:

- Intolerance to hydroxyurea because of grade 3–4 or prolonged grade 2 non-haematological toxicity (eg, mucocutaneous manifestations, gastrointestinal symptoms, fever, or pneumonitis) at any dose (consensus: 100%; strength of the recommendation: strong. Note that the expert panel provided a strong recommendation if it was confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects)
- Intolerance to hydroxyurea because of haematological toxicity (haemoglobin <100 g/L, platelet count $<100 \times 10^9$ cells per L, or neutrophil count $<1 \times 10^9$ cells per L) at the lowest dose of hydroxyurea to achieve a response[53] (consensus: 100%; strength of the recommendation: strong)
- Development of non-melanoma skin cancers (consensus: 80%; strength of the recommendation: weak)
- Development of vascular events: either clinically relevant bleeding, venous thrombosis, or arterial thrombosis (consensus: 80%; strength of the recommendation: weak)

Patients with polycythaemia who receive hydroxyurea should be considered to change to another cytoreductive drug if they show an insufficient clinical response to hydroxyurea (at ≥1·5 g per day for at least 4 months and without reporting intolerance), as defined by at least one of the following criteria:

- Persistent disease-related symptoms: a total symptom score of at least 20 or an itching score of at least ten for at least 6 months (consensus: 92%; strength of the recommendation: strong)
- Persistent thrombocytosis: a platelet count $>1000 \times 10^9$ cells per L, microvascular symptoms, or both, persisting for more than 3 months (consensus: 92%; strength of the recommendation: weak)
- Symptomatic or progressive splenomegaly: increased in spleen size by more than 5 cm from the left costal margin in 1 year (consensus: 83%; strength of the recommendation: weak)
- Progressive (at least 100% increase if baseline count is $<10 \times 10^9$ cells per L or at least 50% increase if baseline count is $>10 \times 10^9$ cells per L) and persistent leukocytosis (leukocyte count $>15 \times 10^9$ cells per L confirmed at 3 months; consensus: 75%; strength of the recommendation: weak)
- Insufficient haematocrit control: need for six or more phlebotomies per year to keep haematocrit below 45% (consensus: 83%; strength of the recommendation: weak)

In patients treated with hydroxyurea who require a therapy change, either ruxolitinib or interferon alfa should be chosen on the basis of individual clinical features—in particular, age, spleen size, symptoms, history of skin cancers, and patient preferences (consensus: 80%; strength of recommendation: neutral).

evolution[66] in predicting long-term outcomes, these recommendations enable the prevention of long-term undesirable outcomes, especially in patients who have a long life expectancy, while concomitantly improving their quality of life. In patients older than 60 years with polycythaemia vera, the 2018 ELN recommendations to start cytoreductive drug therapy with either hydroxyurea or interferon alfa were still considered valid on the basis of the results of several clinical trials.[18,37,47]

The ELN project also provided practice recommendations for a therapeutic shift in patients on current treatment with hydroxyurea in clinically relevant doses; specific subgroups were selected on the basis of the high risk of these patients to have undesirable outcomes. Such recommendations extend those that have been previously defined and offer rational support for clinicians, who can now manage such patients with either ruxolitinib or interferon alfa.[8,67,68]

Some limitations of this project must be reported. We strove to adhere to GRADE framework but faced several difficulties. The first concerns the risk–benefit ratio between drug side-effects and desirable outcomes. In patients at low risk, most of the panellists agreed that evidence supporting the benefits of cytoreductive drug therapy on critical outcomes was not sufficient to support universal treatment; however, some experts felt that the risk–benefit balance of interferon alfa was favourable overall, and disagreed with the proposal to recommend treatment for only some patients. We believe that future results from the Low-PV trial[13] will provide more evidence supporting the use of ropeginterferon alfa-2b therapy in patients with low-risk polycythaemia vera.

A second limitation of the use of an analytical approach to produce recommendations occurs when direct published evidence is scant.[69] GRADE suggests reconsidering the eligibility of study designs, indirect

evidence, modelling, and unpublished studies. When even the latter approach is not successful, panels can transparently review their personal experience and use this to fill the evidence gaps; this approach was adopted for selecting patient subgroups.[70] However, proposed thresholds for leukocytes, phlebotomies, and platelet counts were debated among the panel members, because most of the evidence was from retrospective studies of patients treated with hydroxyurea and was therefore only partially applicable to the subset of patients with low-risk disease who were not being treated with cytoreductive drugs. Our recommendations were made after the expert panel reached a sufficient consensus; however, they recommended caution, frequently using the phrase "may be considered". The expert panel discussed the daily dose of hydroxyurea required to accurately judge clinical response as insufficient; such a dose was reached for more than 10% of patients. Moreover, this dose was very similar to the threshold dose used for assessing resistance to treatment with hydroxyurea. The panel also considered the operational definition of haematocrit control in patients treated with hydroxyurea,[71] which could vary with testing frequency. Most panellists agreed to adopt a conservative threshold of six phlebotomies per year in patients receiving hydroxyurea for recommending a change to a different cytoreductive drug. However, this issue deserves validation in longitudinal studies. Some panellists also proposed changing the definition of low risk (patients younger than 60 years and without previous thrombosis); however, for practical reasons, the standard definition was maintained.

Finally, economic outcomes were not included in the assessment of proposed treatment strategies, owing to the scarcity of health-care resource data for outpatients. Within the past 2 years, studies have shown that the yearly health-care cost to insurance schemes for patients with polycythaemia vera in the USA is US$18 966, and is 25% higher for patients who have thrombotic events.[72] Moreover, high indirect social costs are expected for patients with polycythaemia vera, as reported by landmark analyses (appendix pp 8–9). However, because only a few cost–utility assessments have been reported,[73] the economic effect of treatments could not be assessed.

Despite the limitations discussed, this project was successful in applying the GRADE framework to develop clinical recommendations for the management of polycythaemia vera.[74] Landmark analyses framed the hierarchy of the outcomes, to enable the aims of therapy to be shared with the major actors of the field, who are the patients themselves.

We expect that more evidence concerning both new and existing factors will add to our knowledge of interferon alfa and ruxolitinib, and that the present recommendations will be continually updated. In particular, we expect that additional evidence will emerge regarding secondary malignancies, infections, disease transformation, and molecular response. Moreover, the value of surrogate endpoints and biomarkers for predicting thrombosis and disease transformation will be further ascertained, including through use of artificial intelligence algorithms,[75] and clinical trial design will be improved by avoiding composite endpoints and by adopting homogeneous definitions of responsiveness to hydroxyurea.[75]

Contributors

All authors conceived the project. TB administered the project, invited the expert panel, and revised the paper. MM acted as a methodologist and planned patient, intervention, comparator, outcome (known as PICO) questions, reviewed the literature (data curation), and built and analysed Delphi questionnaires (formal analysis). MM and TB verified the underlying data. All members of the expert panel contributed to the Delphi panels by voting for, and reformulating, the recommendations, and revised the paper. All authors wrote the first draft and revised the final manuscript.

Declaration of interests

MM has received consulting fees from Gilead Sciences, speaker fees from Amgen, support for attending meetings from Takeda, and is a member of the guideline committee of the Italian Society of Hematology. AMV has received speaker fees from Novartis, AOP Health, Incyte, AbbVie, GlaxoSmithKline (GSK), and Bristol Myers Squibb (BMS); and has participated on the advisory boards of Novartis, Incyte, AOP Orphan Pharmaceuticals, AbbVie, GSK, BMS, and Roche. MG has received consulting and speaker fees, support for attending meetings, and participated on advisory boards for AOP Health, Novartis, Celgene, Amgen, AstraZeneca, CTI BioPharma, Shire, Pfizer, Roche, Janssen Pharmaceuticals, and Gilead Sciences. CH has received grants or contracts with payment to her institution from Novartis, Celgene, and Constellation Pharmaceuticals; consulting fees from Keros Therapeutics, Galecto Biotech, and Roche; speaker fees from Novartis, Celgene, CTI BioPharma, AbbVie, Gilead Sciences, Janssen Pharmaceuticals, Promedior, and Geron Corporation; support for attending meetings from Novartis and Celgene, and has participated on advisory boards for Roche, CTI Biopharma, Geron Corporation, Promedior, AbbVie, AOP Orphan Pharmaceuticals, and Galecto. SK has received research grants from AOP Health, Novartis, Janssen Pharmaceuticals, and Imago BioScience; consulting fees from Pfizer, CTI BioPharma, Sanofi, Novartis, BMS/Celgene, Incyte/ARIAD, Roche, AOP Orphan Pharmaceuticals, and Janssen Pharmaceuticals; speaker fees from Pfizer, CTI BioPharma, Sanofi, Novartis, BMS/Celgene, Incyte/ARIAD, Roche, AOP Orphan Pharmaceuticals, Janssen Pharmaceuticals, Kartos Therapeutics, and Imago BioScience; support for attending meetings from Alexion Pharmaceuticals, Novartis, BMS/Celgene, Incyte/ARIAD, AOP Orphan Pharmaceuticals, CTI BioPharma, Pfizer, Sanofi, Janssen Pharmaceuticals, Geron Corporation, Kartos Therapeutics, Sierra Oncology, Imago BioScience; has participated on advisory boards for Pfizer, CTI BioPharma, Sanofi, Novartis, BMS/Celgene, Incyte/ARIAD, Roche, AOP Orphan Pharmaceuticals, Kartos Therapeutics, and Imago BioScience; has patents planned, issued, or pending from Rheinisch-Westfalische Technische Hochschule Aachen; and has a leadership role in Deutsche Gesellschaft fur Hamatologie und Medizinische Onkologie. HG has received research grants and support for attending meetings from AOP Orphan Pharmaceuticals and Novartis; consulting fees from AOP Orphan Pharmaceuticals, Novartis, and BMS/Celgene; and speaker fees from AOP Orphan Pharmaceuticals, Novartis, BMS/Celgene, and Janssen. AÁ-L has participated on advisory boards and has received speaker fees from Novartis, AOP Orphan Pharmaceuticals, and Celgene; and has received support for attending meetings from Novartis and Pfizer. VDS has received speaker fees from AbbVie and Novartis, and participated on advisory boards of AOP Health and Novartis. PG has received speaker fees from AbbVie and Novartis, and support for attending meetings from Sanofi. FPal has received speaker fees from Novartis and Incyte; consulting fees from AOP Health, CTI BioPharma, Novartis, and Celgene/BMS; and support for attending

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