Do All Patients With Polycythemia Vera or Essential Thrombocythemia Need Cytoreduction?

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Abstract

Polycythemia vera (PV) and essential thrombocythemia (ET) are Philadelphia chromosome–negative chronic myeloproliferative neoplasms (MPNs), characterized by expansion of normal blood counts, bleeding, thrombosis, and the potential for transformation to myelofibrosis (MF) or acute myeloid leukemia (AML). The primary goals of treatment for MPNs are to reduce the risk of thrombosis, alleviate systemic symptom burden (eg, fatigue, pruritus, microvascular symptoms, and symptomatic splenomegaly), and to prevent transformation to MF/AML. Preventing transformation is clearly important, but not expected with current therapies. Currently, cytoreduction is advised based on vascular risk assessments, which include age and thrombosis history, as well as molecular profile in ET. Traditionally, cytoreduction has been advised only in patients with high vascular risk. Recently, a large prospective study evaluated the safety and efficacy of cytoreduction in patients with ET with less-than-high-risk vascular profiles. A larger question in the MPN field is whether cytoreduction is advisable for all patients with ET and PV, regardless of risk. This article reviews existing data on cytoreduction, evaluating hydroxyurea, interferons, and ruxolitinib in ET and PV. This review evaluates whether evidence supports a more liberal strategy of cytoreduction for all patients with ET and PV.

Polycythemia vera (PV) and essential thrombocythemia (ET) are Philadelphia chromosome–negative chronic myeloproliferative neoplasms (MPNs), characterized by expansion of normal blood counts, bleeding, thrombosis, and the potential for transformation to myelofibrosis (MF) or acute myeloid leukemia (AML). In 2005, the discovery of molecular abnormalities associated with PV and ET were instrumental in understanding the pathophysiologic and clinical manifestations of these disorders.[1] *JAK2* activating mutations (V617F) are present in >95% of patients with PV[2] (2%–3% have *JAK2* exon 12 mutations)[3] and approximately 60% of patients with ET.[4,5] Calreticulin (*CALR)* mutations have been identified in 25% to 30% of patients with ET,[6] filling a prior diagnostic gap, and a small proportion

(≈5%) have *MPL* mutations.[7] Therefore, during the past decade, the "molecular biology era"[8] has revolutionized clinical diagnosis and the approach to monitoring and prognostication, and has provided molecular targets for drug development in both PV and ET.

The primary goals of treatment for MPNs are to reduce the risk of thrombosis and alleviate systemic symptom burden (eg, fatigue, pruritus, microvascular symptoms, symptomatic splenomegaly).[9] Although hematologists hope to modify disease biology and prevent transformation to MF/AML,[9] this is not expected with current therapies. Cytoreduction is typically prescribed for patients with ET or PV who have a high risk for vascular complications. Hydroxyurea is the most commonly used first-line therapy for cytoreduction, whereas pegylated interferon (PEG-IFN) is also considered as a

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frontline therapy, but is used less commonly in the United States. Ruxolitinib is a second-line option for PV.[10,11] Until recently, studies evaluating the efficacy and safety of cytoreduction therapy in patients with ET have only been performed in those with high-risk features. At the 2017 American Society of Hematology (ASH) annual meeting, results of the PT-1 trial were reported, which is a prospective open-label randomized trial evaluating cytoreduction therapy in patients with intermediate-risk ET.[12] This contemporary trial prompted this review, with the goal of presenting existing data for cytoreductive therapy in PV/ET and discussing whether cytoreduction should be advised in all patients with PV or ET, regardless of risk classification.

Risk Assessment

ET and PV are chronic illnesses, with a reported 15-year survival rate of approximately 80% in ET and a 10-year projected survival rate nearing 75% in PV.[13,14] This degree of longevity makes it difficult to prove in a clinical trial setting whether therapy can extend survival or significantly alter the natural history of the disease. Although progression is a concern, vascular risk has a stronger influence on a physician's therapeutic decision-making.[15] There are multifactorial contributions toward MPN-associated thrombosis, including age and thrombosis history, sex, cardiovascular risk, mutation type and burden, inflammatory stress, and other contributors.[16] However, risk classification is still conventional and somewhat generic. High-risk PV is defined by age >60 years and/or a history of thrombosis.[17] In ET, the revised IPSET-thrombosis (International Prognostic Score of Thrombosis for Essential Thrombocythemia) model[18] stratifies patients into 4 risk categories using the following parameters: history of thrombosis, age >60 years, and *JAK2* V617F mutational status. Very-low-risk patients have no adverse features, low-risk patients have a *JAK2* V617F mutation only, intermediate-risk patients have advanced age only, and high-risk patients have a thrombosis history or presence of both *JAK2* V617F and advanced age.[18]

Standard Treatment

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) are now available to guide the management of PV and ET.[10] Regardless of risk, all patients with PV should be managed with low-dose aspirin,[19] which offers a 60% reduction in risk for nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes (relative risk [RR], 0.40; 95% CI, 0.18–0.91; P=.03), without increasing the risk of major bleeding.[19] Phlebotomy with a goal hematocrit of <45% is also evidence-based; more intensive treatment (target hematocrit <45%) resulted in a significant risk reduction of the combined primary end point of cardiovascular death and major thrombosis compared with less intensive treatment (hazard ratio [HR] in the higher hematocrit group (45%–50%), 3.91; P=.007).[20]

Although aspirin is recommended for ET in the presence of microvascular disturbances or vascular symptoms,[9,10] no randomized controlled trials have confirmed the antithrombotic value of low-dose aspirin in ET. Aspirin has been reported to be beneficial in *JAK2* V617F–positive low-risk ET[21] and has been shown to alleviate microvascular disturbances associated with ET.[22] In *CALR*-mutated ET, however, aspirin may increase bleeding risk without reducing the risk for thrombosis.[23] In a large meta-analysis regarding antithrombotic therapy in ET, findings were inconsistent and imprecise among 24 observational studies.[24] The reported RR for thrombosis with antiplatelet therapy ranged from 0.26 to 3.48 (median, 0.74) compared with no therapy, with certainty of evidence being rated low or very low for all outcomes.[24]

Cytoreduction

Guidelines advise that patients with high-risk PV should receive cytoreduction therapy to minimize their risk of thrombosis.[10] Cytoreduction may also be prescribed for patients who are intolerant of phlebotomy and/or have progressive or symptomatic splenomegaly, severe symptoms, platelet count >1,500 x 10^9/L, and/or progressive leukocytosis.[9] Although hydroxyurea is currently considered a first-line cytoreductive therapy, use is based on consensus recommendations and only a scarce evidence base (Table 1).[25–29] Hydroxyurea emerged as the preferred cytoreductive therapy based more on Polycythemia Vera Study Group (PVSG) studies showing efficacy, compared with 51 historical controls (ie, patients

Table 1. PV Studies Evaluating the Effect of Cytoreductive Therapy on Thrombotic Risk

Study/Organization	Study Population	N	Intervention	Comparator	Findings
PVSG[25]	No prior myelosuppressive therapy 9.8% of men and 5.9% of women aged >70 y 35.8% with prior thrombosis	51 Median FU: 8.6 y	Hydroxyurea (30 mg/kg/d followed by 15 mg/kg/d)	Phlebotomy	No significant difference in OS or incidence of AML Incidence of thrombosis was higher in the phlebotomy group (32.8% vs 9.8%)
French Polycythemia Study Group[26,27]	Age <65 y, not previously treated 75% with no vascular risk 15% with moderate vascular risk 11% with high vascular risk	285 Median FU: 16 y	Hydroxyurea (25 mg/kg/d, followed by low-dose maintenance)	Pipobroman (1.2 mg/kg/d, followed by low-dose maintenance)	No difference in vascular events between the 2 arms Median OS was 20.3 y in hydroxyurea arm vs 15.4 y in pipobroman arm (P=.008) Transformation to AML/MDS was higher in the pipobroman arm (P=.004) Cumulative incidence of MF was similar in both arms (P=.02)
PV cohort of ECLAP study[28]	PV cohort from the ECLAP[10] study, who had received only phlebotomy or hydroxyurea to maintain HCT <45% as per ECLAP protocol Median age at diagnosis was 64.5 ± 12.2 y 28.8% had history of prior thrombotic event	1,042 Median FU: 30–35 mo	Hydroxyurea (initially 0.5–1.0 g/d followed by dose reduction based on weekly blood counts)	Phlebotomy (initially 250–500 cm³ of blood removed until target HCT reached)	Incidence of fatal/nonfatal CV events was lower in the hydroxyurea group (5.8 vs 3.0 per 100 person-years; P=.002) The excess of mortality and total CV events in patients treated with phlebotomy was restricted to the high-risk group and was significantly higher in those who did not reach the HCT target of <45% (P=.000)
Retrospective study[48]	Patients with PV with previous arterial and/or venous thrombosis	235	Cytoreduction for secondary prophylaxis	None	Cytoreduction halved the incidence of rethrombosis

Abbreviations: AML, acute myeloid leukemia; CV, cardiovascular; ECLAP, European Collaborative Low-dose Aspirin; FU, follow-up; HCT, hematocrit; MDS, myelodysplastic syndromes; MF, myelofibrosis; OS, overall survival; PV, polycythemia vera; PVSG, Polycythemia Vera Study Group.

from other studies who only received phlebotomy). Its safety was considered to be comparable to that of phlebotomy (rate of AML was higher in the hydroxyurea arm [5.9% vs 1.5%], but not statistically different) and superior to other cytoreductives, such as radiophosphorus and chlorambucil, which were leukemogenic[25] (Table 1). The association between hydroxyurea and secondary leukemia is controversial, and causality has been difficult to prove. Large studies have not associated hydroxyurea with AML when used alone, but rather when used sequentially with other chemotherapies.[30,31] Another large retrospective study implicated hydroxyurea when used with pipobroman, but not when used alone.[17] A Swedish population-based study did not observe any association between any cumulative dose level of hydroxyurea and AML transformation.[32]

Although safer than radiophosphorus, chlorambucil, and pipobroman, hydroxyurea historically has not outperformed other cytoreductives with regard to thrombosis risk. In one randomized trial with long-term follow-up of 285 patients with PV aged <65 years, no difference was seen in vascular events (thrombosis or hemorrhage) between the hydroxyurea and pipobroman arms (P=.61).[26] Although the median overall survival (OS) was higher in the hydroxyurea treatment arm in the intention-to-treat population (20.3 vs 15.4 years for pipobroman; P=.008), hydroxyurea was likely favored for safety rather than efficacy. The cumulative incidence of progression to AML/myelodysplastic syndromes (MDS) was significantly higher in the pipobroman arm (P=.004). Still, in this study, rates of AML/MDS in the hydroxyurea arm at 10, 15, and 20 years were 6.6%, 16.5%, and 24.2%, respectively; whether this follows the natural history of PV or is a signal of concern about long exposures to hydroxyurea is unclear.[26]

Hydroxyurea has not been previously studied in low-risk patients. More recently, a propensity score matching analysis using a cohort of patients with PV from the ECLAP (European Collaborative Low-dose Aspirin) study[19,33] showed an advantage in the hydroxyurea group over the phlebotomy group with respect to incidence of fatal/nonfatal cardiovascular events (5.8 vs 3.0 per 100 person-years; P=.002).[28]

However, efficacy could not be demonstrated in a low-risk population.

Rather, the efficacy of cytoreduction for PV in preventing thrombosis has largely been extrapolated from studies involving patients with ET.[34,35] In 114 patients with high-risk ET who were randomized to hydroxyurea versus observation, hydroxyurea was effective in preventing thrombosis (P=.003).[34] In another randomized controlled trial of patients with high-risk ET who were given low-dose aspirin plus either anagrelide or hydroxyurea, the low-dose aspirin plus hydroxyurea group had a reduced risk of arterial and venous thrombosis compared with the anagrelide plus aspirin group (P<.01).[35] More recently, results of the ANAHYDRET trial, in which previously untreated patients with high-risk ET were randomized to either anagrelide or hydroxyurea, showed that anagrelide was noninferior to hydroxyurea after a 36-month observation period and there were no significant differences between the groups in incidences of thromboses or bleeding events.[36] Given these data, society guidelines differ: NCCN[10] offers hydroxyurea, interferon (IFN), and anagrelide as first-line options for cytoreduction, whereas the European LeukemiaNet (ELN) offers anagrelide as a second-line option in ET.[9] Anagrelide shortages have been reported in the past, which have limited its prescription as first-line cytoreduction therapy.

IFN therapy has also been shown to effectively control myeloproliferation. Patients with newly diagnosed and previously treated PV and ET who receive IFN therapy have been shown to experience high hematologic responses, and some patients also develop molecular responses.[37] Nonetheless, in addition to intolerance, insurance approval in the United States can often be a barrier to IFN use as frontline therapy. Enthusiasm for its use was renewed by a phase II multicenter study of PEG-IFN-alfa in 40 previously untreated patients with PV, demonstrating that 94.6% experienced complete hematologic response (CHR) at 12 months.[38] The intrigue is also based on demonstrations of anticlonal activity, including complete molecular responses (CMRs) in a minority of patients. IFN therapy in patients with previously treated PV or ET was shown to achieve CHR in 76% and 77%, respectively, after a median follow-up of 82.5 months, as well as CMR in a small fraction (30%).[39] In addition to hematologic and molecular responses, case series have demonstrated histologic responses to IFN

treatment with complete normalization of bone marrow at therapy discontinuation.[40] Controlled studies comparing the effects of IFN therapy versus hydroxyurea in PV are not yet published but have been presented. One phase III randomized controlled trial from the Myeloproliferative Disorders Research Consortium (MPD-RC 112) is studying use of PEG-IFN-alfa versus hydroxyurea in patients with high-risk PV or ET. Interim analysis did not show a clear difference in the primary end point of CHR between the groups (33% vs 28%; P=.60), suggesting that hydroxyurea and PEG-IFN have similar efficacy.[41] Although CHR rates were lower in this study, it is important to note that the full cohort was not yet analyzed when these results were reported, and there may be a time dependence of best response.[37] Additional long-term data and detailed analysis regarding thrombosis event rates are not yet published.

Ruxolitinib, a *JAK1/2* inhibitor, is approved only as second-line therapy in patients with PV who are either intolerant of or have an inadequate response to hydroxyurea. In this setting, ruxolitinib was shown to be superior to standard therapy in controlling hematocrit, reducing splenomegaly, and alleviating symptoms.[42] In a phase III randomized open-label study, phlebotomy-dependent patients with hydroxyurea-resistant/intolerant PV and splenomegaly were assigned to receive ruxolitinib or standard therapy. The primary end point of both hematocrit control and at least a 35% reduction in spleen volume at week 32 was achieved in 21% of patients in the ruxolitinib group versus 1% of those in the standard-therapy group (P<.001). CHR was achieved in 24% of patients treated with ruxolitinib versus 9% of those treated with standard therapy (P=.003). Overall, this study suggested that ruxolitinib was superior to standard therapy in patients with PV for whom hydroxyurea treatment failed.[42] Similar data support second-line use in a hydroxyurea-resistant/intolerant PV population without significant splenomegaly (RESPONSE-2).[43]

Regarding ET, ruxolitinib was compared with best available therapy in a randomized phase II trial of patients resistant or intolerant to hydroxycarbamide (MAJIC-ET).[44] This trial was spurred by the results of an open-label phase II study of patients with PV and ET who were refractory and/or intolerant to hydroxyurea and treated with ruxolitinib, which showed that these patients could achieve a durable and clinically meaningful reduction in plate-

let and WBC counts as well as improvement in ET-related symptoms with ruxolitinib treatment.[45] In the MAJIC-ET trial, however, no difference was seen in CHR within 1 year (46.6% vs 44.2%; *P*=.40), and rates of thrombosis, hemorrhage, and transformation at 2 years were not significantly different. In addition, molecular response was uncommon.[44] Therefore, ruxolitinib is not advised as a second-line therapy for patients with ET.

Should Cytoreduction be Prescribed for All, Regardless of Risk?

Until recently, no randomized studies have evaluated the efficacy and safety of cytoreductive therapy in patients with ET without high-risk features. At the 2017 ASH annual meeting, results were reported of the PT-1 prospective open-label randomized trial evaluating 382 patients with intermediate-risk ET, which compared treatment with hydroxycarbamide plus aspirin versus aspirin alone.[12] Eligible patients were aged 40 to 59 years and lacked the following features: current or prior platelet count >1,000 x 10^9/L, previous thrombosis or embolism, hemorrhage due to ET, and hypertension or diabetes requiring therapy (ie, cardiovascular risk factors). The composite primary end point (time from randomization to arterial or venous thrombosis, serious hemorrhage, or death from vascular causes) was not significantly different between the groups during a median follow-up of 73 months (HR, 0.98; 95% CI, 0.43–2.27; *P*=1.0).[12] In addition, no difference in OS was seen between the arms or in the composite end point of rate of transformation to MF, AML, myelodysplasia, or PV.

Overall, a low event rate is not surprising, because included patients would now fit into very-low-risk or low-risk categories by the revised IPSET-thrombosis classification. These results suggest that patients with ET without high-risk features should not be treated with hydroxyurea, unless another indication for cytoreduction is evident. In other words, with regard to hydroxycarbamide/hydroxyurea, there is no clear upfront benefit in ET in the absence of high-risk features.

No similar contemporary studies in PV exist to guide or dissuade the use of hydroxyurea in patients with traditionally lower-risk PV. IFN-alfa–based therapies, which have been used for treatment of MPNs for decades, are now being compared with hydroxy-urea, with the goal of establishing evidence-based frontline cytoreductive therapy in PV. The PROUD-PV trial was the first phase III trial to assess efficacy, safety, and tolerability of a novel mono-pegylated IFN-alfa, ropeginterferon alfa-2b (ropeg).[46] A total of 257 patients with PV who were either treatment-naïve or had been previously treated with hydroxyurea (but were neither intolerant nor complete responders) were randomized to receive ropeg or hydroxyurea. The median age of included patients was 58 years. This median age and inclusion of treatment-naïve patients implies a lower-risk patient population, but the proportion with lower-risk PV was not explicitly stated. Preliminary pooled analysis at 12 months showed a CHR in 45% of patients, decreased need for phlebotomy at 3 months from 86% to 6%, and molecular response in 37% of patients.[46] After 12 months, patients rolled over to the CONTI-PV study; 89% of the ropeg group and 68% of the hydroxyurea arm continued. At the 24-month efficacy analysis, treatment with ropeg achieved a CHR of 70.5% versus 49.3% in the hydroxyurea group (*P*=.0101).[45] In addition, 69.9% of patients in the ropeg arm achieved a partial molecular response versus 28.6% in the hydroxyurea arm (*P*=.0046). The incidence of treatment-related adverse events was comparable in both arms (70.1% and 77.2%, respectively).[47]

These data show the safety and efficacy of ropeg in not only achieving a durable hematologic response in PV but also significantly reducing *JAK2*-mutant allele burden. Interestingly, in the first report of PROUD-PV,[45] the likelihood of achieving a molecular response was lower in patients with a longer history of PV prior to study entry and in those previously treated with hydroxyurea. This suggests an impact from early initiation of therapy.[48] Again, it is important to note that patients were not stratified by vascular risk in either the PROUD-PV or CONTI-PV studies.

Conclusions

Treatment for ET and PV is aimed at reducing thrombotic risk, alleviating symptom burden, and reducing the risk of disease transformation. Currently, therapies are guided by stratification according to thrombotic risk. Unfortunately, risk classification is imperfect and lacks precision. Progress is needed to identify patients at risk of either undertreatment or overtreatment. Cytoreduction therapy

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Interferons	Hydroxyurea	Ruxolitinib
Benefits - Control of myeloproliferation - Reduction in thrombosis risk? - Anticlonal activity Concerns - Impact on short-term QoL - Long-term tolerability Patient selection - Early in disease course - Preserved fitness/limited comorbidities - Modest if any splenomegaly - Absence of additional nondriver mutations	Benefits - Control of myeloproliferation - Reduction in thrombosis risk (high-risk ET) Concerns - Mucocutaneous toxicity, skin cancer risk, myelosuppression Patient selection - High-risk ET and PV - Caution in those aged ≤40 y - Lower-risk patients with symptomatic thrombocytosis, intolerance of phlebotomy, progressive leukocytosis, uncontrolled symptoms/splenomegaly	Benefits - Reduction in phlebotomy needs - Reduction in spleen size - Improvement in symptom burden Concerns - Infection, weight gain, cholesterol change, skin cancer risk, myelosuppression Patient selection - Later disease course - Moderate to high symptom burden - Hydroxyurea resistant or intolerant PV
Compelling data for early use	*No compelling data to advise in low-risk patients without indications*	*Data only support use as a second-line agent in PV; no frontline data or support for use in ET*

Figure 1. Currently used cytoreductives in ET and PV: benefits, risks, patient selection, and candidacy for up-front use. Abbreviations: ET, essential thrombocythemia; PV, polycythemia vera; QoL, quality of life.

has been established in high-risk ET, and there is consensus toward its use in patients with high-risk PV. This review discusses the current positioning of cytoreductives for the treatment of ET and PV (Figure 1). In low-risk patients, treatment is reactive; in other words, cytoreduction is prescribed in response to changing symptoms or risk classification. An important question is whether the treatment paradigm should shift toward treating ET and PV early in the disease course, and independent from risk grouping. Based on data from PT-1, hydroxyurea is not justified in patients without high-risk features, particularly with regard to those with ET.[12] Lack of data and concerns about long-term safety also temper enthusiasm for its use in low-risk PV. Promising data suggest that the novel IFN, ropeg, may be more efficacious in PV for achieving hematologic and molecular responses compared with hydroxyurea, particularly with early initiation of therapy.[47] Finally, there has been a decade of interest in using PEG-IFN in ET and PV, and randomized trials are underway.[41] Although also used in salvage settings, the best re-

sponses may be obtained early in the disease course. Molecular responses suggestive of anticlonal activity have been reported regardless of driver mutational status, but have been less effective with additional nondriver somatic mutations.[37] With regard to the question posed by this review, we cannot currently recommend cytoreduction for all patients with ET and PV, regardless of risk. The most commonly used cytoreductive, hydroxyurea, has an evidence base for use in high-risk ET, but prospective studies do not support its use in otherwise low-risk patients. Ruxolitinib can be offered in hydroxyurea-resistant/intolerant PV, but not as frontline therapy and not in ET. Among the currently available cytoreductives, long-acting IFNs would be the best candidates if early initiation of therapy is to be considered (Figure 1). With time, if high-quality clinical trials can prove that cytoreductives, such as IFNs, can modify the natural history of the disease, regardless of risk, with acceptable long-term safety and cost, a paradigm shift in ET/PV management will be upon us.

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