Interferons are cytokines with immunomodulatory properties that have been used in the treatment of myeloproliferative neoplasms (MPNs) for decades. However, their widespread use has been hampered by their adverse effect profile and difficulty with administration. Recently there has been a resurgence of interest in the use of interferons in MPNs given the development of pegylated formulations with improved tolerability. Currently, treatments for polycythemia vera (PV) and essential thrombocythemia (ET) are targeted toward decreasing the risk of thrombotic complications, because there are no approved therapies that are known to modify disease. However, recent data on interferons in MPNs have suggested the potential for disease-modifying activity, including the achievement of molecular remission and sustained clinical response. This development has led to the question of whether interferons should move forward as the preferred frontline cytoreductive agent for ET and PV, and challenges the criteria currently used to initiate therapy. We review randomized controlled trial data evaluating interferon’s efficacy and tolerability in patients with ET and PV. We then consider the data in the context of interferon’s known advantages and disadvantages to address whether interferons should be the first choice for cytoreductive treatment in patients with ET and PV.

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Polycythemia vera (PV) and essential thrombocythemia (ET) are chronic myeloproliferative neoplasms (MPNs) characterized by the expansion of mature hematopoietic cells. Although both diseases have an increased risk of transformation to acute leukemia and progression to myelofibrosis (MF), the major causes of morbidity and mortality in PV and ET are cardiovascular complications.1 Treatments in PV and ET are therefore directed at reducing the risk of thrombosis and at the palliation of symptoms. Currently, there are also no available therapies that are known to modify the disease and reduce the risk of progression to acute myeloid leukemia (AML) or MF.

Interferons are a group of cytokines with immunomodulatory properties and were the first immune therapies used in the treatment of cancers, including hematologic malignancies. Use of standard interferon alfa-2b for MPN treatment has been limited by its difficulty in administration and adverse effect profile. There has been a recent resurgence of interest in interferons for MPNs given the development of pegylated formulations, including pegylated interferon alfa-2a (Pegasys), pegylated interferon alfa-2b (PegIntron), and ropeginterferon alfa-2b (Besremi). The main difference between pegylated interferon alfa-2a and pegylated interferon alfa-2b is the structure of the polyethylene glycol chain, with a branched versus a linear polyethylene glycol chain, respectively, attached to the interferon. This affects the half-life, volume of distribution, and absorption of the 2 drugs, resulting in different dosing schemes. Both pegylated interferon alfa-2a and pegylated interferon alfa-2b have multiple pegylation sites and therefore multiple isomers. In contrast, ropeginterferon is a monopegylated interferon consisting of only one isomer. The pegylated formulations allow for less frequent administration, leading to improved tolerability. Recent data have also shown that interferons have preferential activity against the hematopoietic stem cell clone,2,3 with the induction of molecular responses and even remissions in some treated patients.4,5 This finding suggests a potential for disease modification that has not yet been shown in any other available treatments, including hydroxyurea and JAK inhibitors. In addition, although hydroxyurea is generally thought to be safe, there is still controversy over its long-term risks and leukemogenic potential.6

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Interferons therefore provide an appealing alternative to traditional cytotoxic therapy. A disease-modifying drug would also force researchers and clinicians to reevaluate the role of earlier intervention in lower-risk patients with PV and ET, who have traditionally been observed using a “watchful waiting” approach. This review considers interferon’s place in MPN therapies in the context of current treatment guidelines and evaluated the recent trial data indicating its efficacy and tolerability. Given these data, we discuss the advantages and disadvantages of interferons in the treatment of MPNs, answering the question of whether interferons are ready to be considered as the first choice for cytoreductive treatment in patients with PV and ET.

**Current Guidelines for the Treatment of MPNs**

The treatment of patients with PV and ET is based on risk stratification for thrombosis. Commonly used risk stratification models include the Revised International Prognostic Score of Thrombosis for ET and the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Myeloproliferative Neoplasms. Patients who are at high risk for thrombosis are older (aged >60 years) and have a prior history of arterial or venous thrombosis. In patients with ET, the JAK2 mutation also confers additional thrombotic risk. Cardiovascular risk factors can be considered as well when evaluating a patient’s overall risk for thrombosis. In addition to aspirin and the maintenance of a hematocrit (Hct) <45% in PV, cytoreduction with hydroxyurea has resulted in improved thrombosis-free survival in high-risk patients with ET. Expert consensus guidelines therefore recommend the initiation of cytoreduction in patients with ET and PV who are considered at high risk for thrombosis.

The most commonly used cytoreductive agent is hydroxyurea, an oral ribonucleotide reductase inhibitor that is inexpensive, generally well tolerated, and easy to administer. However, there is concern for long-term leukemogenicity with hydroxyurea in MPNs. Studying the leukemogenic effects of hydroxyurea is complicated by the lack of prospective studies and the confounding fact that patients requiring cytoreduction are older (aged >60 years), with more aggressive disease in those needing higher doses. Population studies have not clearly shown a link between prior hydroxyurea use and progression to AML, and hydroxyurea has not been associated with TP53 mutations in MPNs, a potential mechanism of leukemic transformation. However, a separate study of 357 patients with ET found a small increased risk of AML progression with prior hydroxyurea use, often associated with 17p deletions. Overall, if hydroxyurea has an impact on AML progression, then the risk increment is likely small, although this still bears consideration, especially in younger patients with ET and PV. In the NCCN Guidelines and the European LeukemiaNet (ELN) guidelines, hydroxyurea and pegylated interferon alfa-2a are listed as the preferred first-line cytoreductive therapy options for certain patients with PV. NCCN notes that pegylated interferon alfa-2a can be considered for younger or pregnant patients in need of cytoreductive therapy or for those in need of cytoreductive therapy who defer hydroxyurea or ruxolitinib to alf%C3%A2b. In patients with ET, hydroxyurea is listed as the preferred cytoreductive therapy in high-risk patients. Cytoreduction is a recommended option in certain patients with symptomatic low-risk disease.

**Trial Data Evaluating Pegylated Interferon in Patients With MPN**

Comparative analysis between hydroxyurea and interferons has not been undertaken until recently, with the advent of several randomized controlled trials directly comparing hydroxyurea and pegylated interferons in patients with ET and PV (Table 1). The MPN Research Consortium (MPN-RC) 112 trial randomized high-risk patients with ET and PV to first-line treatment using either pegylated interferon alfa-2a (n = 86) or hydroxyurea (n = 82). The primary endpoint was complete response rates at 12 months by ELN criteria, as defined by a platelet count <400 × 10^9/L, Hct <45% in the absence of phlebotomy, WBC count <10 × 10^9/L, and resolution of splenomegaly and disease-related symptoms. The 12-month complete and overall response rate by ELN/International Working Group-MPN Research and Treatment criteria was 35% and 78% for patients treated with pegylated interferon and 32% and 70% for those treated with hydroxyurea, respectively. Complete and overall responses at 36 months were 33% and 59% for pegylated interferon and 41% and 47% for hydroxyurea, respectively. Bone marrow morphologic responses were unexpectedly high in the hydroxyurea group, possibly related to hydroxyurea-related myelosuppression, and occurred in 23% of patients treated with hydroxyurea compared with 5% of those treated with pegylated interferon. The median greatest change from baseline JAK2 V617F variant allele fractions (VAF) was −10.7% in the pegylated interferon arm and −5.3% in the hydroxyurea arm. Interestingly, JAK2 V617F VAFs consistently declined to month 48 in patients treated with pegylated interferon but increased after month 12 in patients treated with hydroxyurea. There were no differences in thrombosis or progression rates between the 2 arms, but event rates were overall low.

The Low-Dose Interferon Alpha Versus Hydroxyurea in Treatment of Chronic Myeloid Neoplasms (DALIAH) trial also randomized adult patients with MPN with ET, PV, MF, or prefibrotic MF to receive hydroxyurea, pegylated interferon alfa-2a (Pegasys), or pegylated interferon alfa-2b (PegIntron). This study enrolled both treatment-naïve and previously treated patients with MPN.
Patients aged >60 years were randomized 1:1:1 to hydroxyurea or pegylated interferon alfa-2a or pegylated interferon alfa-2b, whereas those aged ≤60 years were randomized 1:1 to pegylated interferon alfa-2a or pegylated interferon alfa-2b. Clinicohematologic response rates were evaluated using ELN 2009 criteria. The 2-year complete hematologic response (CHR) rate was 21% versus 26% in the hydroxyurea and interferon arms, respectively. Decreases in V617F VAFs were significantly more likely in patients treated with interferon, and median JAK2 V617F VAF declines were also greater in these patients compared with those treated with hydroxyurea. CHRs were also significantly associated with decreases in JAK2 VAF in patients treated with interferon. Changes in CALR VAFs were more heterogenous with interferon treatment. Like the results of the MPN-RC 112 trial, response rates between hydroxyurea and pegylated interferon were similar, although the mutation-specific response patterns to pegylated interferon in the DALIAH study are intriguing. These data indicated that both pegylated interferon and hydroxyurea in high-risk patients with ET and PV are effective treatments. However, it remains to be seen whether mutant clonal burden continues to decline over time and whether this translates to clinically meaningful outcomes. It also remains to be seen whether patients can remain on long-term treatment to derive these benefits, because discontinuation rates with pegylated interferon were high in the MPN-RC 112 and DALIAH trials.

Ropeginterferon alfa-2b is a monopegylated interferon alfa with an extended half-life, allowing for every-other-week dosing and monthly maintenance. The non-inferiority phase III Pegylated Interferon Alpha-2b Versus Hydroxyurea in Polycythemia Vera (PROUD-PV) trial and its extension study, CONTINUATION-PV, randomized 257 patients with PV to ropeginterferon or hydroxyurea. Patients were eligible if they had <3 years of cytoreduction previously and had a need for cytoreduction. The primary endpoint in PROUD-PV was CHR with improvement in splenomegaly, and in CONTINUATION-PV the co-primary endpoints were CHR with improvement in splenomegaly and improved disease burden. However, few patients in the study had baseline splenomegaly, and the reported CHR rates at 12 months were 62% for hydroxyurea and 75% for ropeginterferon. In CONTINUATION-PV, significantly improved CHRs were seen with ropeginterferon by 24 months (71% vs 49%; \( P = .011 \)) and 36 months (71% vs 51%; \( P = .012 \)). This is consistent with the observation that hematologic responses with interferons tend to deepen with time. Similarly, by 24 months, patients treated with ropeginterferon had clearly increased molecular responses compared with those treated with hydroxyurea (68% vs 33%; \( P = .001 \)). Ropeginterferon is now approved for the treatment of adults with PV in both the United States and Europe, making it the first interferon developed specifically for MPNs.

These trials have focused on higher-risk patients who have an indication for cytoreduction. However, there has been increasing interest in initiating cytoreduction earlier (i.e., in low-risk patients), especially if this can alter the disease course to decrease long-term complications and progression. Current consensus guidelines have recommended phlebotomy to maintain an Hct <45% in low-risk patients with PV. However, it is unclear whether phlebotomy can consistently maintain these goals and whether cytoreductive drugs may further reduce the risk of vascular complications. These uncertainties led to the Ropeginterferon

### Table 1. Summary of Randomized Clinical Trials Evaluating Pegylated Interferon and Ropeginterferon in Patients With MPN

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Phase</th>
<th>Patients</th>
<th>Trial Arms</th>
<th>CHR</th>
<th>Molecular Response</th>
<th>Discontinuation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN Comparator</td>
<td></td>
<td>IFN Comparator</td>
<td>IFN Comparator</td>
</tr>
<tr>
<td>DALIAH (^{20})</td>
<td>III</td>
<td>Untreated</td>
<td>Pegylated IFN vs HU</td>
<td>21% (2-y)</td>
<td>16% (18-mo)</td>
<td>30%/38(^{a}) 8%</td>
</tr>
<tr>
<td>MPN-RC 112 (^{22})</td>
<td>III</td>
<td>High-risk</td>
<td>Pegylated IFN vs HU</td>
<td>35% (1-y)</td>
<td>– 10.7(^{b})</td>
<td>15% 10%</td>
</tr>
<tr>
<td>PROUD-PV</td>
<td>III</td>
<td>PV with</td>
<td>Ropeginterferon vs HU</td>
<td>43% (1-y)</td>
<td>34% (1-y)</td>
<td>8% 4%</td>
</tr>
<tr>
<td>CONTINUATION-PV (^{22})</td>
<td></td>
<td>&lt;3 y of</td>
<td></td>
<td>48% (2-y)</td>
<td>33% (2-y)</td>
<td>8% 4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cytoreduction</td>
<td></td>
<td>54% (3-y)</td>
<td>52% (3-y)</td>
<td>8% 4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n=257)</td>
<td></td>
<td>54% (4-y)</td>
<td>50% (4-y)</td>
<td>8% 4%</td>
</tr>
<tr>
<td>Low-PV (^{23})</td>
<td>II</td>
<td>Low-risk</td>
<td>Ropeginterferon vs phlebotomy</td>
<td>84(^{c}) (1-y)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: CHR, complete hematologic response; ET, erythrocythemia; HU, hydroxyurea; IFN, interferon; MPN, myeloproliferative neoplasm; NR, not reported; PV, polycythemia vera.

\(^a\)Discontinuation rates with pegylated interferon alfa-2a/2b.

\(^b\)Median decrease in JAK2 V617F allele burden.

\(^c\)Primary endpoint of Low-PV study was the percentage of patients meeting the hematocrit goal of <45% for 12 months.
Alfa-2b in Low-Risk Patients With PV (Low-PV) study, a randomized phase III trial evaluating ropeginterferon versus phlebotomy alone in patients with PV who were considered low-risk according to the NCCN Guidelines or ELN guidelines. Interim analysis at 12 months showed that 84% of patients treated with ropeginterferon met the primary endpoint of an Hct goal <45% in the absence of progressive disease, compared with 60% in the standard therapy arm, and the trial was stopped early due to efficacy. Patients treated with ropeginterferon also showed lower white blood cell and platelet counts, greater reduction in splenomegaly, and greater reductions in JAK2 V617F allelic burden. Whether these results will translate into clinically meaningful endpoints such as decreased thrombotic events or improved leukemia-free or MF-free survival remains to be seen.

Advantages and Disadvantages of Interferon Therapy

The results of these randomized controlled trials provide important information regarding the clinical use of interferons compared with other standard therapies. In terms of hematologic response rates, efficacy seems to be similar between pegylated interferon and hydroxyurea. In contrast to pegylated interferon, long-term responses seem to be improved in ropeginterferon compared with hydroxyurea, although differences in endpoints (complete responses in the MPN-RC 112 trial vs CHRIs in the PROUD-PV trial) complicate direct comparisons. A meta-analysis of clinical trials, which includes both retrospective and prospective studies, showed overall response rates of 81% with pegylated and nonpegylated interferon alfa, with discontinuation rates of 6.5% to 8.8%. However, improved hematologic response rates must be balanced against interferon’s adverse effects and cost, especially because hydroxyurea is a generally well-tolerated and inexpensive medication that is given as a pill. Pegylated interferon does have an improved adverse effect profile compared with standard interferon, but the discontinuation rates seen with the MPN-RC 112 and DALIAH trials are still high. Both trials reported higher rates of grade 3 and 4 adverse effects compared with hydroxyurea, and 40% discontinuation rates by 24 months were seen in the DALIAH study, with the most common reason being treatment toxicity. Certain adverse effects from interferons warrant consideration, including neuropsychiatric effects such as depression, liver function test abnormalities, and autoimmune adverse effects including hypothyroidism, hepatitis, or vasculitis. Ropeginterferon seems to be better tolerated than pegylated interferon, with an 8% discontinuation rate in the PROUD-PV study, which may contribute to its better responses when compared with pegylated interferon, in that more patients are able to stay on therapy. A separate study evaluating the efficacy and safety of ropeginterferon in older patients (aged >60 years) with PV found similar hematologic and molecular responses and similar rates of adverse events. However, interferon’s distinct adverse effect profile will limit its use in certain patient populations.

However, symptom burden remains substantial even among responders. In a post hoc analysis of the MPN-RC 112 trial and the single-arm phase II MPN-RC 111 trial, a clinically significant improvement in symptom burden as defined by a >50% decrease in MPN symptom assessment form scores at 12 months was seen in only 32% and 19% of complete responders treated with pegylated interferon in the MPN-RC 111 and MPN-RC 112 trials, respectively. Similarly, 19% of complete responders treated with hydroxyurea in the MPN-RC 112 study saw a significant improvement in symptom burden by 12 months. Patients with high but not low baseline symptom burden saw significant improvements in symptom scores with treatment, although given that many patients had low baseline symptom scores within the cohort, the overall percentage of symptom responders was low. Because systemic symptoms are an important feature of chronic MPNs, this finding underscores that the benefits of any treatments in MPNs must also consider other variables besides the normalization of laboratory values. Interferons may increase symptom burden because of adverse effects from treatment, and the challenge is finding the patient who will not only benefit from interferon therapy but also have a low toxicity burden.

This situation may be partially ameliorated by the possibility of treatment holidays, stopping therapy early, or further decreasing the frequency of drug administration. Unlike with hydroxyurea or JAK inhibitors, there is some evidence that patients can discontinue interferon therapy and still experience a sustained hematologic response. In a retrospective analysis of patients with MPN treated with interferon who either remained on therapy or who stopped therapy after achieving a CHR, there were no differences in overall or event-free survival. Multivariate analysis of factors associated with continued CHR despite interferon discontinuation included driver mutation VAF <10% and achievement of CHR for 24 months before discontinuation. Even if patients are unable to achieve a full discontinuation of therapy, in practice they often can receive less-frequent dosing of pegylated interferon and still achieve hematologic responses, and the FDA label for ropeginterferon allows for dosing to every 4 weeks if it occurs with sustained responses. This unique aspect of interferon therapy is appealing in a chronic disease such as MPN, and further investigation is needed to understand the duration of treatment holidays and which patient groups are the best candidates for early discontinuation.

The sustained benefits of interferons even in the absence of active treatment suggest either a sustained cytoreductive effect or a potential for disease modification. The effect on disease burden and the implication of disease
modification may justify interferon’s use as a first-line cytoreductive agent even at the expense of increased adverse effects or cost. A retrospective study has shown that patients with PV treated with interferons had improved overall, MF-free, and leukemia-free survival compared with those treated with hydroxyurea or phlebotomy. However, the study was limited by the increased likelihood of patients on interferon to be younger and White, and have lower-risk disease by ELN criteria. In addition, improved MF-free survival is confounded by the fact that interferons are also often discontinued in patients progressing to MF. Therefore, the best data showing interferon’s efficacy should come from randomized controlled trials, but these data are still unavailable. Results of the MPN-RC 112 trial showed no differences in thrombosis-free or progression-free survival, although the low event rates indicate the difficulty in evaluating these outcomes in MPN clinical trials. However, the possibility of disease modification is hinted at by the molecular responses reported in some studies. The PROUD-PV and CONTINUATION-PV studies showed that by 3 and 4 years of treatment, significantly more patients with PV treated with roprogeintereron will have a molecular response compared with those treated with hydroxyurea. In contrast, 18-month molecular responses reported in abstract form for the DALLIAH trial were not different between patients treated with pegylated interferon (23%) and those treated with hydroxyurea (16%), although molecular response definitions varied between trials, which may account for some of these discrepancies. However, genomic profiling of patient samples did show greater declines in JAK2 VAFs with pegylated interferon treatment compared with hydroxyurea treatment. The MPN-RC 112 study also found greater reductions in JAK2 V617F VAFs with pegylated interferon, with sustained decreases past month 48 compared with increases in patients treated with hydroxyurea after month 12. Although these data are encouraging, molecular responses have not necessarily translated into bone marrow histopathologic responses, and vice versa. Ultimately, it is difficult to define early surrogates of “disease modification,” and we do not yet know whether declines in mutation VAFs will translate into lower event rates.

Conclusions: Can Interferons Be Considered for Frontline Cytoreduction?

Interferons are a promising treatment strategy in MPNs and offer a significant advantage compared with hydroxyurea, namely in their potential for disease modification. Improved molecular remissions, especially with ropegintereron, and the possibility of sustained responses even after discontinuation, are all arguments for their use as a first-line cytoreductive agent. However, this must be balanced against the adverse effect profile and tolerability, and it is still unclear whether long-term treatment using interferons can result in improvements in meaningful clinical outcomes, such as thrombosis-free or MF-free survival, or enhanced quality of life. Pegylated interferon and ropegintereron are also considerably more expensive than hydroxyurea, leading to a larger question of whether these drugs are cost-effective as a whole. Currently, there are still many unknowns regarding interferon use in MPN and its mechanism of action. There is heterogeneity in responses with interferon that is at least partly dependent on mutational status. Some patients may be at higher molecular risk and warrant cytoreductive therapy; for instance, those with higher JAK2 V617F VAFs, which may portend higher thrombotic risk. One can envision a clinical scenario in which therapies for MPNs including interferon are recommended based on the genetic profile of a patient along with the patient’s comorbidities, symptoms, and other risk factors.

For these reasons, it is still too early to definitively recommend interferons over hydroxyurea in MPNs or to recommend cytoreductive therapy with interferons over watchful waiting in all low-risk patients. With longer follow-up from randomized controlled trials, new data from studies evaluating combination therapies or other novel agents, and greater preclinical study of interferon’s mechanism of action in MPNs, it is inevitable that guidelines for cytoreductive therapy will change. For now, however, our recommendations are consistent with current expert consensus guidelines in which hydroxyurea and peginterferon alfa-2a are among the recommended options for cytoreductive therapy in certain patients. Ultimately, the choice of agents is personalized, although we favor interferon’s use in younger patient populations. Interferon may be a decades-old drug, but the renewed investigation into its use has the potential to completely alter how we approach therapy in MPNs.

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