Initially used in patients with chronic myeloid leukemia (CML), interferon has evolved in the cancer treatment paradigm, with most studies showing the medication to be safe and effective in controlling high platelet counts and improving difficult symptoms in hard-to-treat patients with myeloproliferative neoplasms (MPNs).

“Interferon, way back when [before] imatinib (Gleevec), was used in CML in the short-acting formulation at a high dose,” said Ruben A. Mesa, MD. “This was the first evidence that it was really active in MPNs before there were targeted therapies for [patients with] CML.”

More recently, longer-acting pegylated interferons have been evaluated in phase III clinical trials: pegylated interferon alfa-2a in patients with polycythemia vera (PV) and essential thrombocythemia (ET) and ropeginterferon alfa-2b in those with high-risk PV.

In the MPN Research Consortium 112 trial, investigators compared the use of pegylated interferon alfa-2a with that of hydroxyurea (HU) therapy in patients with high-risk PV and high-risk ET. The study accrued 168 patients, 86 of whom were randomized to receive hydroxyurea, while 82 were given interferon. Participants were treated for up to 1 year with the goal to achieve a partial or complete response (CR).

Patients who achieved response continued to receive therapy for a maximum of 6 years, but the minimum follow-up was 1 year from the time the last patient was randomized. The median duration of follow-up for the trial was 89.9 weeks (range, 0-293.3 weeks) and the median treatment duration was 86.0 weeks (range, 0-287.3).

Results presented at the 2018 ASH Annual Meeting showed that at 1 year, the overall response rate (ORR) was 78% in those who received pegylated interferon alfa-2a compared with 69.8% for those who were given hydroxyurea ($P = .22$).¹ Fifty-nine patients were still on treatment at 24 months, with an ORR of 91% for those in the pegylated interferon alfa-2a arm, and 88% in the hydroxyurea arm. Of all 106 patients who were determined to be eligible to receive treatment for 24 months, the ORR was 59.6% for pegylated interferon.
alfa-2a. This consisted of a 28.9% (n = 15) partial response (PR) rate and a 30.8% (n = 16) CR rate. In the hydroxyurea arm, the ORR was 40.7%, with a 20.4% (n = 11) PR rate and a 20.4% (n = 11) CR rate.

Three-year follow-up data from the phase III PROUD/CONTI-PV trials were also presented at the 2018 ASH Annual Meeting. Here, 254 patients were randomized to receive either ropeginterferon alfa-2b or hydroxyurea in the PROUD-PV study and were then rolled over to the CONTI-PV trial after 1 year, with the option to switch from hydroxyurea to best available therapy (BAT).

Eighty-three patients in the ropeginterferon arm and 70 patients in the hydroxyurea/BAT arm completed the 36-month efficacy analysis timepoint. The mean treatment duration for the analysis was 3.8 years and median doses remained constant at 425 µg of ropeginterferon alfa-2b every 2 weeks and 1000 mg of hydroxyurea daily.

Results showed that after 3 years of treatment, maintenance of higher responder rates was shown in those who received ropeginterferon alfa-2b compared with those given hydroxyurea/BAT for complete hematological response (CHR; 70.5% vs 51.4%; \( P = .0122; \) RR, 1.38 [95% CI, 1.07-1.79]) and for CHR plus symptom improvement (52.6% vs 37.8%; \( P = .0437; \) RR, 1.42 [95% CI, 1.01-2.00]).

Compared with hydroxyurea/BAT, response rates steadily increased in the ropeginterferon alfa-2b arm over 2 years; this remained constant after 36 months. The number of adverse events (AEs) were comparable between arms at 89.8% for ropeginterferon and 90.6% for hydroxyurea, and treatment-emergent AEs at 74.8% and 78.7%, respectively. Due to the high and durable hematologic responses and the tolerability demonstrated with ropeginterferon alfa-2b, investigators concluded that this was a safe and long-term treatment option.

In an interview with OncLive, Mesa, who is the director of UT Health San Antonio MD Anderson Cancer Center, discussed the evolving role of interferon in the treatment of patients with MPNs, highlighted recent treatment advances, and shared insight on the future of treatment for these patients.

**OncLive: How has the use of interferon in patients with MPNs evolved?**

*Mesa:* In the 80s and 90s, Harriet S. Gilbert, MD, and Richard T. Silver, MD, both did studies using low doses of interferon in MPNs, particularly in PV, and demonstrated that if given in low dose—compared to what it was in CML—that it could be both tolerated and active in PV and sometimes in ET, as well.

Fast forward to now, [long-acting] pegylated interferon alfa-2a was then tried in French trials in the late 2000s, as well as some other phase II studies in the United States that showed single-agent activity in PV and in ET.
More recently, 2 formulations of long-acting pegylated interferons have been evaluated in phase III clinical trials: pegylated interferon alfa-2a in PV and ET and ropeginterferon alfa-2b in high-risk PV. Most studies demonstrated that interferon was safe; it was effective in controlling high counts and helped improve difficult symptoms. Both of those were frontline studies against hydroxyurea; they were both equivalent to hydroxyurea at the 12-month timepoint, but longer follow-up data does suggest some potential superiority of the interferons in some aspects of molecular control of the disease.

**What is the current role of interferon in the treatment of MPNs?**

The only long-acting formulation of interferon that is commercially available in the United States is pegylated interferon alfa-2a; it is currently indicated for hepatitis C [in the United States]. Therefore, when it’s used, it’s used off-label. It is in the National Comprehensive Cancer Network guidelines for the treatment of MPNs, for frontline therapy for PV; it is used as a second- or third-line therapy for [patients with] ET, and it is considered an option in myelofibrosis in patients with disrupted [platelet] counts.

**Beyond interferon, what other recent treatment advances have been made in this space?**

There is ruxolitinib (Jafaki), which is our frontline therapy for myelofibrosis and second-line for PV; it’s currently being tested as second-line therapy in a phase III study for ET. There are 3 JAK2 inhibitors, that are each trying to seek approval in myelofibrosis.

The first is pacritinib, from CTI BioPharma, which is seeking an approval to be used as treatment in individuals who have myelofibrosis with marked thrombocytopenia. There is also momelotinib from Sierra Oncology, that is looking to [build] from this phase III data to help treat anemia in patients with myelofibrosis in addition to improving splenomegaly symptoms. There is fedratinib, which is currently owned by Celgene and is trying to seek approval in ruxolitinib-failing patients with myelofibrosis.

There have been positive studies of combinations of ruxolitinib with decitabine as well as with thalidomide (Thalomid). In addition to that, I would mention idasanutlin (RG7388), which is a Nutlin inhibitor in PV. At the 2018 Annual ASH Meeting, [investigators presented] favorable preclinical data suggesting that Nutlin inhibitors would be active in PV both alone and in combination with interferon. Idasanutlin was helpful in improving the spleen, decreasing spleen size, and improving blood counts and symptoms in the spleen in patients who had failed hydroxyurea. These were phase II studies presented by Mount Sinai Health System.

**Were there any other important data presented at the 2018 ASH Annual Meeting that you wanted to highlight?**
In addition to the combinations, there were long-term data reported for both of those pegylated interferons studies. Longer-term follow-up showed benefits of ropeginterferon alfa-2b as well as the pegylated interferon alfa-2a over hydroxyurea. Finally, in terms of other novel drugs, there was longer-term information on the drug PRM-151, which is an anti-fibrosing drug which showed benefit.

**What challenges still need to be overcome in order to move the needle forward?**

We still don’t have therapies that seem to cause a deep remission in the disease. They’re all having some benefit, but the depth of the benefit is still an opportunity. Second, in myelofibrosis, there is still no approved therapy for individuals who fail ruxolitinib. Many are competing in that space, but there is no drug yet available that has received FDA approval other than ruxolitinib. As I presented at the 2018 ASH Annual Meeting during the education session, patients with advanced disease don’t have any good options and tend to have a very difficult disease to control.

**Where is the future of treatment headed?**

In the future, we’ll continue to refine combinations with a JAK inhibitor base. With those 3 other JAK inhibitors, 1 or more of them will get an approval from the FDA that might be beneficial. There will be further refinement regarding the timing and activity of stem cell transplants, so that is still an unmet need. An approval and refinement around the role of interferon will be important. At the current time, it’s still not an approved therapy and the pegylated interferon alfa-2b is not yet commercially available in the states. Many of the efforts going on with immune-based therapies and cell-based therapies have not yet been tested to any significant degree in MPNs, but that will come forward in the future as well.

**What would the clinical implications be if this generation of interferon is approved by the FDA for treatment of patients with MPNs?**

It would certainly expand their use quite a bit. It would primarily come with less usage of hydroxyurea, which as an older generic drug. It probably wouldn’t change the market that much, but it might lead to a lot of patients switching from hydroxyurea over to interferon.

**What is your take-home message?**

Although they are not common diseases, there’s quite a bit activity [in this space]. There’s a pretty deep pipeline of agents in development. Ruxolitinib has made a big impact on being approved in multiple indications in MPNs, and, building on that, in combination. But, around the lessons learned are all hopeful signs for the future.

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**References**
1. Mascarenhas J, Kosiorek HE, Prchal JT, et al. Results of the Myeloproliferative Neoplasms – Research Consortium (MPN-RC) 112 randomized trial of pegylated interferon alfa-2a (PEG) versus hydroxyurea (HU) therapy for the treatment of high risk polycythemia vera (PV) and high risk essential thrombocythemia (ET). In: Proceedings of the 2018 Annual ASH Meeting; December 1-4, 2018; San Diego, CA. Abstract