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REVIEW

Recommendations for the use of pegylated interferon-α in the treatment of classical myeloproliferative neoplasms

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Abstract

The classical myeloproliferative neoplasms (MPN) are uncommon clonal haemopoietic malignancies characterised by excessive production of mature blood cells. Clinically, they are associated with thrombosis, haemorrhage, varying degrees of constitutional disturbance and a risk of progression to myelofibrosis or acute myeloid leukaemia. Many of the disease manifestations may be ameliorated by treatment with interferon-α (IFN), but its use in Australian MPN patients has been limited due to the inconvenience of frequent injections and side-effects. The pegylated form of IFN is a long-acting preparation, which is better tolerated, and its Pharmaceutical Benefits Scheme listing is likely to lead to increased usage. We review the literature on risks and benefits of IFN treatment for MPN, suggest criteria for patient selection in each of these diseases and discuss strategies to manage the side-effects of pegylated IFN.

Introduction

Philadelphia-negative myeloproliferative neoplasms (MPN) comprise a heterogeneous group of blood cancers characterised by the accumulation of mature myeloid cells (granulocytes, erythrocytes and platelets) and include a spectrum of diseases, from essential thrombocythaemia (ET) and polycythaemia vera (PV), to the more advanced and aggressive disease of myelofibrosis, which can be either primary (PMF) or secondary to antecedent ET/PV. MPN result from acquired mutations in haemopoietic stem cells that lead to the activation of tyrosine kinase signalling. The most common genetic mutation, found in more than 95% of patients with PV, and a majority of patients with ET or PMF, is a valine to phenylalanine substitution within Janus Kinase 2 (*JAK2* V617F) leading to constitutive kinase signalling and cytokine-independent growth.[1] Other common mutations activate signalling through the thrombopoietin receptor (encoded by the *MPL* gene) or c-terminal mutations in calreticulin (*CALR*).[1] These mutations can be detected in the peripheral blood of patients with MPN at the time of diagnosis and throughout treatment.

Life expectancy in PV (median survival 14 years) and PMF (median survival 6 years), and probably also ET (median survival 20 years) is significantly worse than that of the age- and sex-matched general population.[2–4] Life-threatening complications in MPN include thrombosis, haemorrhage, progressive fibrosis leading to marrow failure and an increased risk of transformation to acute myeloid leukaemia, which is typically resistant to treatment and dramatically shortens patient survival.[5,6]

The treatment of MPN patients in Australia has been limited to anti-platelet agents and cytoreductive drugs (primarily hydroxycarbamide (HC), formerly 'hydroxyurea' and to a lesser extent anagrelide and busulfan), which largely address thrombosis risk and do not alter the disease course. More recently, ruxolitinib has been approved for MF but is not funded for patients with low-risk MF or PV/ET.

Standard interferon α-2a (IFN) (Roferon-A) has been used for more than three decades to treat MPN and is

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available on the Pharmaceutical Benefits Scheme (PBS) for MPN patients with 'excessive thrombocytosis' but has not been widely used as it requires multiple injections per week and is often poorly tolerated due to adverse effects (AE).[7] The coupling of IFN to polyethylene glycol (PEG) inhibits its proteolytic breakdown and clearance, and thereby prolongs its half-life allowing for a decreased frequency of administration and better tolerance and adherence. Recently, pegylated interferon α-2a (PEG-IFN, Pegasys) has been listed on the Australian PBS. This paper reviews the evidence for its activity in MPN, its side-effect profile and makes recommendations regarding its optimal use.

It is unclear whether safety and efficacy differ between PEG-IFN (Roche, Sydney, NSW, Australia; Pegasys) and peginterferon α-2b (Merck, Kenilworth, NJ, USA; Pegintron). Throughout this paper we have treated them as equivalent, although the PBS listing applies only to the former.

How the PBS listing of PEG-IFN eventuated

The listing of PEG-IFN (Pegasys) on the Australian PBS in 2018 is significant as the first ever consumer-instigated PBS drug listing to occur in Australia. This follows 7 years of advocacy by Nathalie Cook (one of the co-authors of this paper), who was diagnosed with PV in 2010 and subsequently became a founding member of the patient advocacy group, MPN Alliance Australia.

The normal pathway for PBS listing follows a submission from the relevant pharmaceutical company of a drug with an approved indication from the Therapeutic Goods Administration (TGA) and requires an extensive dossier outlining safety, efficacy and cost-effectiveness. High-quality data of this type may be impossible to produce for rare diseases. In this case, the responsible committee agreed that there was an unmet need for PEG-IFN therapy in MPN and requested that Roche products lodge an application to the Pharmaceutical Benefits Advisory Committee without a TGA approval for this indication.

The unusual pathway that resulted in the PBS listing of Pegasys for MPN demonstrates the Australian Government's commitment to rare 'neglected' cancers and coincides with a substantial financial commitment from the Medical Research Future Fund to support rare cancer and disease research, recognising that rare and less common cancers receive a disproportionately low share of cancer research funding despite accounting for over 50% of cancer deaths.[8]

Rationale for using PEG-IFN in MPN

Preclinical models of MPN have been developed using the driver gene mutations and have been instructive in understanding the way in which patients with MPN can respond to treatments such as IFN or targeted inhibitors of JAK2.[9,10] IFN is non-leukaemogenic and has anti-proliferative, anti-angiogenic and differentiation effects on haemopoietic progenitors and may preferentially target the malignant clone.[11] Clinical trials have shown activity of PEG-IFN in PV and ET, with normalisation of blood counts seen in the majority of patients and durable disease control.[12] Long-term treatment with PEG-IFN may induce molecular remission (disappearance of the *JAK2* V617F allele) in approximately 15% of patients.[13–15]

Data review and recommendations for PEG-IFN in PV and ET

Phase 2 clinical trials, involving over 400 PV and ET patients, have shown that PEG-IFN induces objective haematological responses in up to 80% of patients (including freedom from phlebotomy in 60% of PV patients), reduces thrombotic complications and improves pruritus.[12,16] There is a reduction in the abnormal clone in up to 65% of patients who have a measurable *JAK2* V617F mutation and complete molecular responses (undetectable *JAK2* V617F) are reported in up to 24% after 3 years of therapy.[12] Similarly, durable complete haematological response (CHR) and a reduction in the mutated *CALR* allele burden, regardless of the type of *CALR* mutation, have been noted among ET patients treated with PEG-IFN.[17] An improvement in bone marrow histopathology after PEG-IFN therapy has been reported in both PV and ET patients in small studies that have included serial bone marrow evaluations.[18]

Both haematological and molecular responses tend to be durable, and a small percentage of patients maintain CHR after cessation of the drug with follow-up of at least 2 years.[18] Disappearance of the malignant clone does not mean cure of the MPN, and relapse can rapidly occur after PEG-IFN discontinuation. Furthermore, mutations in genes other than *JAK2* may persist in molecular remission.[12] Larger, randomised studies are required to determine whether molecular responses have any impact on the rate of transformation and survival.

Several phase 3 clinical trials comparing PEG-IFN to HC are ongoing, and these trials should help define the role of PEG-IFN in MPN treatment. The MPD-RC 112 randomised trial is comparing PEG-IFN (Pegasys) to HC in treatment-naïve patients with high-risk PV/ET.[19] An interim analysis (12-month data) did not show a difference in the primary endpoint of CHR between HC

and PEG-IFN. Grade 3 AE were more common in patients receiving PEG-IFN (16/36, 44%) than HC (5/36, 14%). Within the first 6 months, the improvement in symptom burden was greater with PEG-IFN than HC, but with longer duration of therapy this advantage dissipated as patient-reported toxicities of PEG-IFN increased over time.[20]

The MPD-RC 111 trial is evaluating responses to PEG-IFN in patients with high-risk ET/PV refractory to or intolerant of HC.[21] The interim results of this study reported that PEG-IFN achieved a 12-month overall response rate of 69 and 60% in ET and PV, respectively. The presence of a *CALR* mutation in ET patients was associated with superior CHR rates. PEG-IFN did not appear to decrease quality of life for those patients who are able to tolerate treatment, but the rate of treatment discontinuation was high with only 72% of patients remaining on therapy for over 12 months.

Recently, an ultra-long-acting ropeginterferon-α-2b (RoPEG-IFN) has been evaluated in clinical trials.[22] This preparation is administered once every 2 weeks but may be reduced to monthly during long-term maintenance treatment. The phase III CONTI-PV study in PV patients showed that 24 months of treatment with RoPEG-IFN achieved a high CHR rate of 70.5% and a significant reduction in the mutant *JAK2* allele burden (69.6% of patients achieved a partial molecular response) with a low rate of drug discontinuations (<10%).

The recently published revised European Leukaemia Net (ELN) management guidelines recommend either HC or PEG-IFN as first-line cytoreductive therapy for patients with PV or ET at any age. PEG-IFN is also included in their recommendations as second-line drug therapies for both PV and ET patients who are intolerant of, or have an inadequate response to, HC.[23]

Data review and recommendations for IFN in MF

There is no conclusive evidence that any therapy other than allogeneic transplantation alters the risk of progression or transformation in MF. Ruxolitinib is the best available medical therapy for symptomatic MF patients in the intermediate-2 (INT-2) and high-risk cohorts, including those with constitutional symptoms and symptomatic splenomegaly.[24] Australian PBS criteria permit its use in intermediate-1 (INT-1) risk patients with an unsatisfactory response to other therapies (primarily HC, but PEG-IFN might also be considered in this category).

Several small studies have used IFN, most often PEG-IFN, for the treatment of MF (PMF and secondary MF) and observed both clinical and histological responses. The largest such study was from France, and the outcomes of 62 patients treated with MF in a non-randomised trial were recently updated.[25] The median age of patients was 67 years, and the Dynamic International Prognostic Scoring System (DIPSS) classification was Low/INT-1/INT-2/High in 16%/37%/43%/5%, respectively. The under-representation of high-risk patients likely reflects previous experience showing poor tolerability and limited efficacy of IFN in patients with advanced disease. Responses in the same study were reported in an earlier publication.[26] Splenic responses were seen in 47% of patients, and constitutional symptoms resolved in 82%. Thrombocytosis and leukocytosis improved in around 60–80%, whereas thrombocytopenia and leukopenia improved in around 60% of evaluable patients. Anaemia improved in 72% of evaluable patients, and 39% of transfusion-dependent patients became transfusion-independent. A 50% reduction in mutant allele burden was seen in 37% of *JAK2*-positive patients who had serial quantitative tests performed. In a multivariable model, the only significant predictor of partial response (morphologic remission in peripheral blood and resolution of clinical manifestations of disease but without bone marrow histological normalisation) was palpable spleen length (optimal cut-off of <6 cm below the costal margin).[27] The median duration of PEG-IFN treatment was 39 months. A little over half of the patients who discontinued treatment did so due to disease progression. Overall survival was 70 months from diagnosis, which is not dissimilar to that of the historical DIPSS cohort, considering that the study population is dominated by intermediate risk MF.[28] Seven patients who proceeded to allogeneic stem cell transplantation after discontinuation of PEG-IFN all died, with a high rate of graft-versus-host disease. Patients who received ruxolitinib after PEG-IFN ($n = 15$) had a median survival of only 22 months, which is shorter than was observed in the ruxolitinib arms of the COMFORT (controlled myelofibrosis study with oral JAK inhibitor treatment) studies.[24,29]

In low-risk PMF where reduction in blood counts and thrombosis risk is the main aim of treatment, the choice of first-line therapy is likely to be between HC and PEG-IFN. As in ET/PV, the factors that are likely to influence this decision include convenience, toxicity profile and the perceived importance of molecular responses.

In intermediate-risk MF patients, the choice is likely to be between PEG-IFN and ruxolitinib. There is no direct comparison of PEG-IFN and ruxolitinib on which to make an evidence-based recommendation. Situations in which PEG-IFN might be preferable include patients with a high risk of infection (e.g. latent hepatitis B virus

or mycobacterial infection), and those for whom improvement of cytopenia is a major goal of treatment. Conversely, the evidence for benefit with ruxolitinib is strongest in patients with higher risk MF, bulky splenomegaly and a high symptom burden.

Dosing and administration of PEG-IFN

We recommend a low starting dose of 45 μg/week and gradual dose escalation in increments of 45 μg/week as tolerated. The 'flu-like side-effects (fever, myalgia, chills), which may occur after each injection, can be reduced by pre-medication with 1000 mg paracetamol and by administering the injection at night. Paracetamol should be continued regularly for 1–3 days until the symptoms resolve. Flu-like symptoms usually settle with repeated dosing but often recur with each dose increase; hence, the dose should only be increased once tolerability at each dose level has been confirmed.

The main goal of treatment is normalisation of elevated blood counts, which is often only achieved after several months of PEG-IFN therapy. Therefore, patients switching from an oral cytoreductive agent to PEG-IFN should ideally continue oral therapy until a CHR is achieved before gradually weaning the oral medication. Blood count control is achieved in many patients at a dose of 90 μg/week, and doses above 180 μg/week are usually poorly tolerated.[30] Once normalisation of blood counts is achieved, the dose of PEG-IFN may be tapered to the lowest dose that maintains normal blood counts. Reducing the frequency of injections to fortnightly is achievable for many patients after 1–2 years of therapy.

Despite the improved tolerability of PEG-IFN, toxicity remains a significant issue, and approximately 20% of patients in trials have discontinued PEG-IFN due to AE, with the majority of discontinuations occurring in the first year of treatment.[14,30] Table 1 lists the reported haematological and non-haematological AE from a large international cohort of MPN patients treated with PEG-IFN.[30] The most notable side-effects other than flu-like effects include fatigue, headaches, alopecia, abnormal liver function tests and immune-mediated phenomena, particularly thyroid dysfunction.[30] Fatigue is a common adverse event reported in 20–25% of patients in most series but usually improves with continuing therapy and is only infrequently the major precipitant for treatment discontinuation. Hair loss is usually manifest as thinning, which tends to reach a plateau rather than continuing to worsen. Abnormal liver function tests are usually transient and rarely lead to discontinuation. Autoimmune thyroid dysfunction (hypothyroidism and hyperthyroidism) occurs in up to 5% of patients on IFN and appears more common in women and possibly also during the first year of therapy.[31] Thyroid function tests should be performed at baseline and at least annually during treatment, although more frequent monitoring could be considered for female patients during the first year of therapy. No dose reduction is necessary in renal impairment even though approximately 40% of the total clearance is renal.[32] Patients with renal disease on haemodialysis have been excluded from most studies with PEG-IFN.[33] Appropriate patient selection, education and the support of an experienced haematology clinical team can assist in minimising discontinuation due to toxicity.

Table 1 Adverse events in 118 myeloproliferative neoplasm patients treated with PEG-IFN[17]

	Number with AE (% of total)
Haematological	
Thrombocytopenia	10 (8)
Anaemia	7 (6)
Leukopenia	7 (6)
Non-haematological	
Fatigue	24 (20)
LFT elevation	7 (6)
Skin/allergic reaction	6 (5)
Nausea	5 (4)
Mood disorder	5 (4)
Headache	3 (2.5)
Alopecia	3 (2.5)
Myalgia	3 (2.5)
Stomatitis	2 (2)
Thyroiditis	1 (<1)
Cough	1 (<1)

AE, adverse effect; LFT, liver function test; PEG-IFN, pegylated interferon-α.

A history of depression is a relative contraindication to therapy with PEG-IFN. Depression, suicidal ideation and attempted suicide have been reported during treatment and within 6 months following discontinuation.[34] Patients should be evaluated for signs or symptoms of mood disorders and, if depression develops or worsens, PEG-IFN should be discontinued and psychiatric intervention provided, as appropriate.

Monitoring response to treatment

MPN treatment response criteria have been described by the ELN; however, these are predominantly used in the clinical trial setting.[27,35] Clinically relevant assessments of response would be based on resolution of symptoms and signs and normalisation of blood counts. Table 2 details the current definitions of response in ET and PV. Effects on marrow fibrosis and histology can only be assessed by a bone marrow biopsy. Outside a clinical trial setting, there is no standard approach to follow-up histological

Table 2 European Leukaemia Net definitions of clinical and haematological responses in polycythaemia vera (PV) and essential thrombocythaemia (ET)[35]

Response grade	Response in polycythaemia vera	Response in essential thrombocythaemia
Complete response (all criteria met)	1 Ht <45% without phlebotomy 2 Platelet count ≤400 × 10^9/L 3 WBC count ≤10 × 10^9/L 4 Normal spleen size 5 No disease related symptoms†	1 Platelet count ≤400 × 10^9/L 2 WBC count ≤10 × 10^9/L 3 Normal spleen size 4 No disease related symptoms†
Partial response	1 Ht <45% without phlebotomy, or 2 Response in ≥3 other above criteria	1 Platelet count ≤600 × 10^9/L or decrease of >50% from baseline
No response	Does not satisfy partial response	Does not satisfy partial response

Response criteria should be observed for at least 12 weeks. †Absence of microvascular disturbances, pruritis, headache. Ht, haematocrit; WBC, white blood cell.

assessment. At the discretion of the treating haematologist and the patient, a repeat marrow examination could be considered after several years of haematological response, particularly in patients with MF where successful clinical response correlates with an improvement in bone marrow morphology (reduction in marrow fibrosis, cellularity and megakaryocyte density).[36] Measuring molecular response by the allele burden of *JAK2* V617F (or other mutations) is not currently standard practice in Australia. Complete response from a molecular viewpoint is defined as eradication of the pre-existing abnormality and a partial response as ≥50% decrease in allele burden.[27] Measurement could be considered after 1–2 years of PEG-IFN, especially to aid in decisions regarding dose reduction or discontinuation.

PEG-IFN in pregnancy

Only a minority of MPN cases are diagnosed in women of childbearing age. Pregnancy in patients with ET is associated with an increase in foetal (spontaneous abortion, stillbirth, intrauterine growth retardation) and maternal complications (thrombosis, haemorrhage, preeclampsia).[37] Most published experience is in ET, and expert recommendations for PV are extrapolated from the experience in ET. Current expert advice for patients with low-risk disease (no prior thrombosis or MPN-related pregnancy complications, and platelets <1500 × 10^9/L) does not recommend cytoreduction but includes low-dose aspirin and – in PV patients – phlebotomy to maintain haematocrit less than 40%.[37,38] In patients with high-risk disease, cytoreduction with IFN is recommended.[37] There has been substantial experience with conventional IFN in pregnancy, and there are emerging data with PEG-IFN, which is considered safe to use in all trimesters (category B3) as placental transfer appears unlikely. In a series of 10 pregnancies in eight women with ET treated with PEG-IFN, treatment was started before conception for patients with high-risk disease.[39] Additional therapy included aspirin and low-molecular-weight heparin. The median platelet count fell progressively throughout pregnancy from 509 × 10^9/L preconception to 285 × 10^9/L at delivery. Neither major bleeding nor thrombosis was reported, and there were no grade 3–4 AE nor drug discontinuation. Nine live births (with no infant malformations) and one miscarriage were reported.

PEG-IFN is considered safe to use during breastfeeding as the drug is excreted into breast milk in very small amounts and is not absorbed from the gastrointestinal lumen.[40]

Table 3 Recommendations for patient selection for pegylated interferon-α (PEG-IFN) treatment

ET/PV patients for whom PEG-IFN should be considered:
(patients meeting any of the following criteria)
First-line cytoreductive therapy, particularly in younger patients
Patients requiring cytoreductive therapy who are planning a pregnancy
Second-line therapy for patients with intolerance or resistance to HC
MF patients for whom PEG-IFN should be considered:
(patients meeting all of the following criteria)
Low or intermediate risk disease with proliferative features
Absence of massive splenomegaly (≤5 cm below costal margin)
Absence of marked leukopenia or thrombocytopenia
Less severe bone marrow fibrosis (MF 0–2)
Not planned for allogeneic transplantation in the next 12 months

ET, essential thrombocythaemia; HC, hydroxycarbamide; MF, myelofibrosis; PV, polycythaemia vera.

Conclusion

The therapeutic armamentarium for MPN in Australia has been expanded by the recent public funding of PEG-IFN and Table 3 summarises what we feel are reasonable indications for its use. Despite this, many unmet patient needs remain, including normalisation of life span, prevention of haematological progression and improved quality of life. PEG-IFN may make a modest contribution to addressing these unmet needs, especially in ET/PV. Major advances are likely only with the development of novel therapies with more specific disease-modifying activity.

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CLINICAL PERSPECTIVES

Multiple endocrine neoplasia: an update

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Abstract

The multiple endocrine neoplasia (MEN) syndromes include MEN1, MEN2 (formerly MEN2A), MEN3 (formerly MEN2B) and the recently identified MEN4. Clinical presentations are varied and often relate to the overproduction of specific hormones. Understanding the genetics of each syndrome assists in determining screening timelines. Treatments for each manifestation are dependent on location, risk of recurrence or malignancy, hormone excess and surgical morbidity. Multidisciplinary management should include geneticists, genetic counsellors, endocrinologists and endocrine surgeons.

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