URN 2420: Peginterferon alfa-2 and ropeginterferon alfa-2b to treat myeloproliferative neoplasms (Myelofibrosis)

Narrative summary of papers presented for review

Two papers were presented for review by NHS England. Paper 1 is a retrospective case series[1] conducted at 17 centres in France and Belgium. Participants (n=62) were adults with primary myelofibrosis (PMF), post-essential thrombocythaemia myelofibrosis (PET-MF) and post-polycythaemia vera myelofibrosis (PPV-MF) treated with peginterferon alfa-2 (Peg-IFNa-2a) for at least six months. Paper 2 reports prospectively on the long-term outcomes of all patients included in Paper 1 (n=62) and assesses correlations with mutational patterns of driver and non-driver mutations analysed by targeted next generation sequencing in a subgroup of patients (n=49).

Paper 1: Ianotto et al 2013. Efficacy and safety of pegylated-interferon a-2a in myelofibrosis: a study by the FIM and GEM French cooperative groups

This paper reports a retrospective case series of 62 adults diagnosed with PMF (n=29), PPV-MF (n=19) or PET-MF (n=14) in accordance with the 2008 World Health Organization classification and treated with Peg-IFNa-2a for at least six months. Patients were identified from 16 centres in France and one centre in Belgium between December 2006 and January 2012. The mean age at diagnosis was 64.4 years (range 33 to 81) for the PMF group and 52.7 years (range 23 to 72) for the PPV-MF and PET-MF combined group[2] and the mean age at the initiation of Peg-IFNa-2a was 66 years (33 to 81) for the whole cohort. The female/male sex ratio was 0.72 (26 females and 36 males). Risk was assessed by the International Prognostic Scoring System (IPSS) score and 14.7% were classified as low risk, 27.9% intermediate-1 risk, 36.1% intermediate-2 risk and 21.3% high risk. Around a third of patients had been previously treated for myelofibrosis (n=42, 67.7%), with hydroxycarbamide (n=40), pipobroman (n=16), anagrelide (n=10) and/or six mercaptopurine (n=7). Data were collected from patients' files at diagnosis and every three months thereafter. The mean follow-up was 26.3 months (range 6 to 60) and the mean duration on Peg-IFNa-2a was 20.6 months (range 6 to 56). The mean doses of Peg-IFNa-2a were 107 µg/week, 90 µg/week, and 74 µg/week, at the initiation of therapy, after 12, and after 24 months, respectively. The authors stated that the use of concomitant therapies was at the discretion of each centre in accordance with local guidelines. The use of concomitant erythropoiesis-stimulating agent (ESA) was reported for patients with anaemia, with ten out of 25 patients with anaemia receiving ESA (including three after failure of Peg-IFNa-2a alone).

Paper 2: Ianotto et al 2018. Benefits and pitfalls of pegylated interferon-α2a therapy in patients with myeloproliferative neoplasm-associated myelofibrosis: a French Intergroup of Myeloproliferative neoplasms (FIM) study

This paper reports on the prospective long term follow up of Paper 1 for all patients (n=62) and also assesses correlations with mutational patterns of driver and non-driver mutations analysed by targeted next generation sequencing in a subgroup of patients (n=49). The

[1] The abstract of Paper 1 states that the study was retrospective but Paper 2 refers to Paper 1 as a prospective study.

[2] Mean age at diagnosis was not reported separately for the PPV-MF group and PET-MF group. A mean was provided for the combined group only (MF secondary to PV or ET).

median follow-up was 58 months (range 9 to 107) and the median duration on Peg-IFNa-2a was 39 months (range 6 to 107). The mean dose of Peg-IFNa-2a was not reported. Nineteen patients (30.6%) received concomitant ESA.

Effectiveness

Clinical and biological response

Ianotto et al 2013 evaluated clinical and biological responses to Peg-IFNa-2a therapy in 62 patients with myelofibrosis with mean follow-up of 26.3 months. These were reported as anaemia, transfusion dependence, leukocyte abnormalities, platelet abnormalities, splenomegaly and constitutional symptoms. Responses were assessed every three months using the 2006 International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) response criteria and were presented as complete or partial response and the time to best response.

Anaemia

Ianotto et al 2013 reported that among the 25 patients with anaemia (haemoglobin levels below 100 g/l) at baseline, 18 (72%) patients responded including 16 (64%) complete responders. The time to achieve the best response was 7.1 months. Among anaemic patients on Peg-IFNa-2a alone (n=18), nine (50%) patients responded and among anaemic patients on Peg-IFNa-2a with concomitant ESA therapy (n=7), six (86%) responded.

Transfusion dependence

Ianotto et al 2013 reported that among the 13 patients who were transfusion-dependent at baseline, five (38.5%) patients became transfusion-independent. Time to best response was six months. The authors stated that concomitant ESA did not affect outcomes in transfusion-dependent patients.

Leukocyte abnormalities

Ianotto et al 2013 reported that among the five patients with leukopaenia (not defined) at baseline, all five (100%) patients responded with all achieving complete response. Among the 32 patients with leukocytosis, 22 (68.8%), patients responded with all achieving complete response. The time to best response was 4.2 months for leukopaenia and 5.7 months for leukocytosis.

Platelet abnormalities

Ianotto et al 2013 reported that among the eight patients with thrombocytopaenia (not defined) at baseline, five (62.5%) responded, including two (25%) who achieved complete response. Among the 29 patients with thrombocytosis, 24 (82.8%) responded, with all achieving complete response. The time to best response was 4.5 months for thrombocytopaenia and 4.4 months for thrombocytosis.

Splenomegaly

Ianotto et al 2013 reported that among the 43 patients with splenomegaly (not defined) at baseline, 20 (46.5%) patients responded, with 10 (23%) achieving complete response. Complete response was observed only in patients with splenomegaly ≤5 cm below costal margin. The average time to best response was nine months. The authors reported that in responding patients, the reduction of spleen size compared with baseline ranged from 50% to 100%, with a mean reduction of 83%. Spleen size at diagnosis was found to be a predictor for partial response in a multivariate logistic model.

Constitutional symptoms

Ianotto et al 2013 reported that among the 28 patients with constitutional symptoms[3] (not defined) at baseline, 23 (82.1%) patients experienced symptom resolution, with all achieving complete response. The average time to best response was 6.3 months.

One of the included papers reported on response to Peg-IFNa-2a according to the 2006 IWG-MRT response criteria in 62 patients with myelofibrosis and mean follow-up of 26.3 months (range 6 to 60). Among anaemic patients (n=25), 72% responded (64% complete responders), with a time to best response of 7.1 months. In transfusion-dependent patients (n=13), 38.5% became transfusion-independent with a time to best response of six months. All patients with leukopaenia (n=5) responded, all achieving complete response at a time to best response of 4.2 months. Among patients with leukocytosis (n=32), 68.8% responded, all achieving complete response at a time to best response of 5.7 months. Among patients with thrombocytopaenia (n=5), 62.5% responded, with 25% of thrombocytopaenia patients achieving complete response with a time to best response of 4.5 months. Among patients with thrombocytosis (n=29), 82.8% responded, all achieving complete response with a time to best response of 4.4 months. In patients with splenomegaly (n=43), 46.5% responded (23% complete responders), with a mean spleen size reduction of 83% and a mean time to best response of nine months. Among patients with constitutional symptoms (n=28), 82.1% responded, all achieving complete response with a time to best response of 6.3 months.

Survival

Ianotto et al 2018 reported on survival outcomes in 62 patients with myelofibrosis who received Peg-IFNa-2a with median follow-up of 58 months (range 9 to 107).

The median overall survival[4] was reported to be 7.4 years from the diagnosis of myelofibrosis and the median leukaemia-free survival[5] was reported as not being reached. The 5-year actuarial survival rate was reported to be 69.4% from diagnosis and 54.8% from the start of Peg-IFNa-2a. The following factors were found to have a statistically significant impact on median overall survival: duration of Peg-IFNa-2a (30 months overall survival for less than 2 years of Peg-IFNa-2a treatment and 70 months for more than 2 years; p<0.0001), Lille score (4.5 years for high score, 5.4 years for median score and 8.9 years for low score; p=0.007), DIPSS score (4.6 years for high score, 6.9 years for intermediate 2 score, 8.9 years for intermediate 1 score and not reached for low score; p=0.027), treatment status (5.7 years for intolerance, 2.7 years for resistance and not reached for still ongoing; p<0.00001) and type of driver mutation (13.5 years for *CALR*-mutated patients and 7 years for *JAK2*-mutated patients; p<0.0001). No statistically significant differences were observed between patients with primary and secondary myelofibrosis for either median overall survival or leukaemia-free survival nor between patients who received or did not receive concomitant ESA for leukaemia-free survival.

Ianotto et al 2018 analysed 49 patients with targeted next-generation sequencing and found that 28 (57.1%) patients carried at least one additional mutation different from the driver mutation. The presence of at least one mutation was found to have a statistically significant impact on leukaemia-free survival (medians not reached; p=0.026). No statistically

[3] The authors reported that this outcome was assessed using qualitative evaluation, not the MPN Symptoms Assessment Form because a French version was not available.

[4] Overall survival was defined as the period between diagnosis of myelofibrosis or, when indicated, initiation of Peg-IFNa-2a treatment and last visit or death.

[5] Leukaemia-free survival was defined as survival without transformation to acute leukaemia.

significant differences were observed for the presence of at least one mutation on overall survival nor the presence of one high molecular risk mutation[6] on overall survival and leukaemia-free survival.

One of the included papers reported on survival outcomes in 62 patients with myelofibrosis and median follow-up of 58 months (range 9 to 107). The median overall survival was 7.4 years from diagnosis, and the median leukaemia-free survival was not reached. The 5-year actuarial survival rate was 69.4% from diagnosis and 54.8% from the start of Peg-IFNa-2a. Factors found to statistically significantly impact on median overall survival included duration of Peg-IFNa-2a treatment, Lille score, DIPSS score, treatment status (intolerance, resistance or ongoing treatment), and driver mutation type (*CALR* or *JAK2*). Having at least one additional mutation beyond the driver mutation was found to have a statistically significant impact on leukaemia-free survival, but no significant differences were found on overall survival.

Number and causes of deaths

Ianotto et al 2013 reported 15 deaths among the 62 included patients with myelofibrosis at a mean follow-up of 26.3 months (range 6 to 60), all of which were among patients who had discontinued Peg-IFNa-2a. Causes of deaths included: complications of cytopenia, secondary clonal evolution, infections and graft-versus-host disease in transplanted patients (n not reported).

Ianotto et al 2018 reported 32 deaths among the same 62 patients at a median follow-up of 58 months (range 9 to 107). Causes of death (reported in 29 patients) included: secondary malignancy (n=8) including transformation to AML (n=7) and secondary cancer (n=1), complications of myelofibrosis/cytopenia (n=7), graft-versus-host disease in transplanted patients (n=5), cardiovascular events (n=5) and infections (n=4).

Two of the included papers reported on the number and causes of deaths in patients with myelofibrosis. One paper (n=62) reported 15 deaths at a mean follow-up of 26.3 months (range 6 to 60). Causes of deaths included: complications of cytopenia, secondary clonal evolution, infections and graft-versus-host disease in transplanted patients. One paper of the same 62 patients reported 32 deaths at a median follow-up of 58 months (range 9 to 107). Causes of death included: secondary malignancy, complications of myelofibrosis/cytopenia, graft-versus-host disease in transplanted patients, cardiovascular events and infections.

Transformation to acute myeloid leukaemia

Ianotto et al 2018 reported that myelofibrosis evolved to acute myeloid leukaemia (AML) in eight (13%) of 62 patients at median follow-up of 58 months (range 9 to 107), seven of whom died. Transformation to AML occurred during Peg-IFNa-2a treatment in three patients at a median time of 1.2 years after initiation of treatment and in five patients after discontinuation of Peg-IFNa-2a at a median of 4.2 years after initiation of treatment. The authors reported that patients who received concomitant ESA (n=19) were not observed to have a greater occurrence of AML.

One of the included papers (n=62) reported that myelofibrosis evolved to AML in eight (13%) patients at a median follow-up of 58 months (range 9 to 107), seven of whom died. Transformation to AML occurred during Peg-IFNa-2a treatment in three patients

[6] High molecular risk was defined by the presence of one of the following mutations: *ASXL1*, *SRSF2*, *EZH2* or *IDH1/2*.

at a median time of 1.2 years after initiation of treatment and in five patients after discontinuation of Peg-IFNa-2a at a median of 4.2 years after initiation of treatment.

Discontinuation of treatment

Ianotto et al 2013 reported that Peg-IFNa-2a was discontinued in 28 (45.2%) of 62 patients after a mean duration of 11.7 months (range 6 to 44). Reasons for discontinuation included: adverse events (n=5), disease progression (n=11), transformation to AML (n=4) or undergoing allogeneic stem cell transplantation (ASCT; n=5). Mean follow-up was 26.3 months (range 6 to 60).

Ianotto et al 2018, a long-term follow-up of Ianotto et al 2013, reported that Peg-IFNa-2a was discontinued in 45 (72.6%) of 62 patients. Duration of Peg-IFNa-2a treatment was 20 months in patients with resistance and 12 months in those with intolerance. Reasons for discontinuation included: resistance (n=25) due to myelofibrosis progression (n=19), transformation to AML (n=3) or failure of the disease to improve (n=3); or intolerance (n=20) due to occurrence of new cytopenia (n=8), psychiatric complications (n=6), fatigue (n=2), cutaneous porphyria (n=1), type 2 diabetes mellitus (T2D; n=1) or other (n=2). Median follow-up was 58 months (range 9 to 107).

Ianotto et al 2018 also reported that of the 45 patients who stopped Peg-IFNa-2a treatment, 15 (33.3%) were given ruxolitinib, seven (15.6%) underwent ASCT and 23 (51.1%) patients were treated with different drugs or received no further medicine.

Two of the included papers reported on discontinuation of Peg-IFNa-2a treatment in patients with myelofibrosis. One paper (n=62) with mean follow-up of 26.3 months (range 6 to 60) reported that Peg-IFNa-2a was discontinued in 28 (45.2%) of patients after a mean duration of 11.7 months. Reasons for discontinuation included adverse events, disease progression, transformation to AML and undergoing ASCT. One long-term follow-up paper of the same 62 patients with a median follow-up of 58 months (range 9 to 107) reported that 45 (72.6%) discontinued treatment. Duration of Peg-IFNa-2a treatment was 20 months in patients with resistance and 12 months in those with intolerance. Reasons for discontinuation included resistance due to myelofibrosis progression, transformation to AML or failure of the disease to improve or intolerance due to occurrence of new cytopenia, psychiatric complications, fatigue, cutaneous porphyria or T2D or other.

Allele burden of driver mutations

Ianotto et al 2018 evaluated the evolution of mutant allele burdens in 27 out of 31 *JAK2*-mutated patients and four out of eight *CALR*-mutated patients. Median follow-up was 58 months (range 9 to 107). In the *JAK2*-mutated patients (n=27), the median allele burden decreased from 57.3% prior to starting Peg-IFNa-2a to 47.1% at 24 months and 29% at 36 months. More than 10% reduction in allele burden was achieved in 17 (63%) patients, more than 20% in 15 (55.6%) patients, more than 50% in 10 (37%) patients and more than 95% in four (15%) patients. The authors reported that they did not observe any difference in death or AML evolution between patients whose *JAK2* allele burden did or did not decrease. Among the four *CALR*-mutated patients, the authors reported that the allele burden remained essentially stable, with a median change from 42.4% to 46.8%. Only one patient experienced a reduction of mutant *CALR* allele burden, which decreased by 33%.

One of the included papers evaluated the evolution of allele burdens in 27 *JAK2*-mutated and four CALR-mutated patients with median follow-up of 58 months (range 9 to 107). In *JAK2*-mutated patients, the median allele burden decreased from 57.3%

before Peg-IFNa-2a treatment to 47.1% at 24 months and 29% at 36 months. No difference in death or AML progression was observed between those with or without *JAK2* allele burden reduction. In *CALR*-mutated patients, the allele burden remained stable, with only one patient showing a reduction which decreased by 33%.

Safety

Haematological adverse events

Ianotto et al 2013 reported on haematological adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3 criteria. Among the 62 patients:

- Leukopaenia was observed in six patients with grade 1–2 severity, one patient with grade 3 and none with grade 4.
- Thrombocytopaenia occurred in four patients with grade 1–2 severity, three patients with grade 3 and two patients with grade 4.
- Anaemia was reported in nine patients with grade 1–2 severity, six patients with grade 3 and one patient with grade 4.

The authors reported that grade 3–4 toxicities were mainly reported in patients who were cytopenic at baseline. Mean follow-up was 26.3 months (range 6 to 60).

One of the included papers reported on haematological adverse events in 62 patients with myelofibrosis with mean follow-up of 26.3 months (range 6 to 60). Leukopaenia was observed in seven patients (six grade 1–2 severity and one grade 3). Thrombocytopaenia occurred in nine patients (four grade 1–2, three grade 3 and two grade 4). Anaemia was reported in 16 patients (nine grade 1–2, six grade 3 and one grade 4).

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