INFORMATION BRIEF (RAPID REVIEW)

PEGYLATED INTERFERON ALPHA-2A IN THE TREATMENT OF MYELOPROLIFERATIVE NEOPLASM

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008/2023

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Rapid Review
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SUGGESTED CITATION: Nurul NMH and Izzuna MMG. [redacted] in the treatment of myeloproliferative neoplasm. Information Brief. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2023. 8 p. Report No.: 008/2023

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

TITLE: Usage of [redacted] (Peginterferon alpha-2a) in the Treatment of Myeloproliferative Neoplasm

PURPOSE

The regime is currently not listed under the 13th Schedule of Private Healthcare Facilities and Services (Private Hospitals and Other Private Healthcare Facilities) (Amendment) Order 2013. This review is to provide scientific evidence on the effectiveness and safety of pegylated interferon alpha-2a for patients with myeloproliferative neoplasm. Hence, this review was conducted upon request by the Director Medical Practice Division, MOH.

BACKGROUND

Myeloproliferative neoplasm (MPN) is a group of clonal haematopoietic stem cell disorders that were characterised by an increase in the proliferation of one or more myeloid lineages in the bone marrow.[1,2] In 2016, World Health Organization (WHO) has updated the classification and diagnostic criteria of MPN by recognising four main subgroups of MPN, which are:[1]

i. Chronic Myeloid Leukemia (CML)
ii. Classical Philadelphia-negative MPNs that includes polycythaemia vera (PV), essential thrombocythaemia (ET), primary myelofibrosis (PMF);
iii. Non classical Philadelphia-negative MPNs that includes chronic neutrophilic leukemia and chronic eosinophilic leukemia
iv. Unclassifiable (MPN-U) which is an MPN that does not fulfil the diagnostic criteria for other MPN groups.

According to Nurgat & Lawrence (2022), the incidence rates for PV, ET and PMF are 0.84, 1.03 and 0.47 per 100,000 population respectively internationally.[2] The primary objective in the management of myeloproliferative neoplasm, particularly in PV and ET is to prevent thrombotic events.[2]

In Malaysia, a retrospective registry of MPN recorded 1010 cases from 11 participating institutions throughout Malaysia between 2009 to 2015 with Chinese had a comparatively high weighted incidence proportion (43.2%), followed by Indians (23.8%), Malays (15.8%), and other ethnic groups (17.2%), according to the ethnic distribution with adjusted population in 2016.[3] There were different classification of MPN reported comprises of 40.4% of ET (n=408), 38.1% of PV (n=385), 9.2% of PMF (n=93), 3.1% of hypereosinophilic syndrome (HES) (n=31), and 7.9% of unclassifiable MPN (MPN-U) (n=80).[3]

The interferons (IFNs) are series of cytokines generated by mammalian immune system when it is triggered by viral, bacterial and other antigens.[4] These types of IFNs are produced by recombinant technology.[4] The modification of IFNs α–2a with polyethylene glycol (PEG) has therapeutic advantages including increase in half-life due to decreased renal and cellular clearance, improved proteolysis protection, and a decrease in toxicity.[4] In Malaysia, other than Pegasys®, there are two other interferons registered with Drug Control Authority (DCA) which are interferon beta-1a and interferon beta 1b.[5,6] Both are indicated for patients with multiple sclerosis (MS).[5,6]

Based on the National Comprehensive Cancer Network (NCCN) Guidelines on the management of MPN, pegylated interferon alpha-2a was recommended in clinical trial or under certain circumstances for patients with symptomatic low-risk myelofibrosis and as an alternative for younger patients or in pregnant patients in the early management of high-risk PV and ET.[13] It is also considered in treating symptomatic low-risk PV as an option to younger patients and pregnant patients upon evaluation of the symptoms for any indication for the initiation of cytoreductive therapy.[13]

EVIDENCE SUMMARY

The systematic search found **three** relevant articles (one Rapid Review Report and two randomised controlled trials) related t[redacted] in the treatment of myeloproliferative neoplasms from the scientific databases such as Medline, EBM Reviews via OVID, PubMed and from general search engines up to 24 March 2023 using the following search terms: *myeloproliferative disorders / or myeloproliferative neoplasm, peginterferon alfa 2a, pegasys, interferon alpha-2.*

EFFICACY/ EFFECTIVENESS

A Canada's Drug and Health Technology Agency (CADTH) Rapid Response Report published in 2020 focused on the effectiveness of pegylated interferon alpha 2a in patients with myeloproliferative disorders. The report concluded that the body of evidence was limited.[5] Two studies (randomised controlled study and non-randomised study) included in the report were of moderate quality. In the RCT, there were no significant differences in complete haematologic or cytogenic response were detected amongst four treatment groups of patients with chronic myeloid leukaemia (CML). The treatment groups in this study were imatinib plus peginterferon alfa-2a, imatinib plus cytarabine, imatinib 400mg and imatinib 600mg. It was reported that there were significant greater rates of major and superior molecular response with combination of imatinib and peginterferon alfa-2a. However, the combination caused significantly higher rate of grade 3-4 neutropaenia and thrombocytopaenia. In the non-randomised study, the treatment groups in this study were peginterferon alpha alfa-2a, ruxolitinib and hydroxyurea ± anagrelide. Among patients with polycythaemia vera (PV) and myelofibrosis (MF), it was found that there were no significant differences in both partial and complete response amongst three treatment groups. However, in patients with essential thrombocythaemia (ET), there was significantly greater rate of complete response for patients treated with peginterferon alfa-2a compared to ruxolitinib and hydroxyurea ± anagrelide. Patients treated with peginterferon alfa-2a and hydroxyurea ± anagrelide shown significantly less improvement in quality of life compared to ruxolitinib. The study was underpowered due to the small sample sizes within each disorder (i.e., N = 23 [PV], 56 [ET], and 46 [MF]). [8]

An extension of the French SPIRIT RCT study, a Phase III RCT study by Guilhot et al. (2020) as mentioned in CADTH Rapid Response Report involving 787 patients was conducted in France. The study focused on the survival outcomes between imatinib (IM) 400mg, IM 600mg, IM 400mg + cytarabine (AraC) and IM 400mg + pegylated interferon alpha2a (PegIFN-α2a) for the treatment of chronic myeloid leukaemia (CML). In this

second step of the study, the primary endpoint was overall survival (OS), whilst the secondary endpoints were progression-free survival (PFS) included events such as accelerated phase, blast crisis and death; the cumulative incidence of progression, event-free survival (EFS), cumulative incidence of unfavourable CML events and molecular response over 15 years including the cumulative incidence of MR4. They found that the collective OS at the final follow up (16.7 years) was 82%. While, at 15 years, the OS and PFS among all the treatment were similar as seen in Table 1. For the IM 400, IM 600, IM+AraC, and IM+PegIFN-α2a arms, respectively, the cumulative incidence of progression accounting for competing events was 6% (95% CI: 3 to 10), 8% (95% CI: 5 to 13), 5% (95% CI: 3 to 10), and 4% (95% CI: 2 to 7) (p=0.4092). For the IM 400 mg, IM 600 mg, IM+AraC, and IM+PegIFN-α2a arms, respectively, the cumulative incidence of unfavourable CML events at 15 years was 52% (95% CI:45 to 59%), 50% (95% CI:42 to 57%), 51% (95% CI:43 to 59%), and 48% (95% CI:40 to 56%) (p=0.5860). Major molecular response (MMR) rates were considerably higher in the IM+ PegIFN-α2a arm compared to the IM 400mg arm, 68% (129/189) versus 46% (86/189), and in the IM600 mg arm, 68% (129/189) versus 53% (79/148), respectively, with p=0.0001 and p=0.0053. The earlier greater rate of molecular response with the IM + PegIFN-α2a combination did not result in better survival and PFS for this arm. [9]

Table 1: Long term outcomes on overall survival (OS), progression free survival (PFS) and event-free survival (EFS) over 15 years[8]

	IM 400 mg N = 223	IM 600 mg N = 171	IM + ArC N = 172	IM + PeglFN-α2a N = 221	*P-value overall adjusted* on Sokal score
OS % (95% Cl)					
1 year	99 (96-100)	98 (95-99)	99 (96-100)	99 (96-100)	
5 years	95 (91-97)	94 (89-97)	91 (86-95)	95 (91-97)	0.4299
10 years	90 (86-94)	90 (84-93)	85 (79-90)	89 (84-93)	0.4554
15 years	85 (78-90)	83 (75-88)	80 (73-85)	82 (75-87)	
PFS % (95% Cl)					
1 year	97 (94-98)	98 (93-99)	98 (95-99)	98 (95-99)	
5 years	93 (89-96)	94 (89-96)	91 (85-94)	93 (88-95)	0.4487
10 years	89 (84-93)	89 (82-92)	84 (80-89)	87 (82-91)	0.5166
15 years	84 (77-89)	87 (82-91)	79 (72-84)	79 (72-85)	
EFS % (95% Cl)					
1 year	91 (87-94)	91 (85-94)	94 (89-96)	90 (86-94)	
5 years	59 (52-65)	63 (55-69)	62 (55-69)	66 (59-72)	0.9533
10 years	46 (39-53)	48 (41-56)	47 (40-55)	48 (41-54)	0.9301
15 years	40 (33-47)	43 (35-50)	44 (36-52)	39 (32-47)	

A randomised phase 3 trial by Mascarenhas et al (2022) involving 168 patients with chronic polycythaemia vera (PV) and essential thrombocythaemia (ET) was conducted in North America and Europe to evaluate effectiveness of hydroxyurea (HU) and pegylated IFN-α (PEG) in high-risk, treatment-naïve patients with PV/ET with primary endpoint was complete response (CR) at 12 months.[8] The response of HU and PEG were shown in

Table 2 at interval 12, 24 and 36 months. Although no significant difference observed in the effectiveness of both agents during the first 12 months, PEG showed increased CR compared to HU at 24 and 36 months as PEG therapy takes longer to achieve its full clinical potential.[8] Sixty-five percent patients with PV receiving PEG achieved better haematocrit control at 12 months. Within the same duration, platelet control was reported similar for both arms with patients with ET. Free of major thrombotic event, major haemorrhagic complications, progression to MF and acute leukaemia or death were defined as an overall complication-free survival. At 24 months, the cumulative incidence of thrombosis for HU and PEG was 2% (95% CI, 0.3-13) and 2% (95% CI, 0.3-15), respectively. The authors concluded that both agents were effective in normalising blood counts and reducing the thrombotic events with high-risk ET/PV patients.[10]

Table 2: Response outcomes between hydroxyurea (HU) and pegylated interferon alpha2a (PegIFN-α2a) at 12, 24 and 36 months[8]

	HU (n = 86), %	PEG (n = 82), %	Difference in proportions for combined ET/PV, 95% CI (PEG-HU)	Rate ratio (95% CI)
12 months				
Complete response	32 (37)	29 (35)	-2%	0.95
ET	19 (45)	17 (44)	(-16 to 13)	(0.64, 1.42)
PV	13 (30)	12 (28)		
Overall response	60 (70)	64 (78)	8%	1.12
ET	30 (71)	27 (69)	(—5 to 21)	(0.93, 1.34)
PV	30 (68)	37 (86)		
24 months	(n = 54)*	(n = 52)*		
Complete response	11 (20)	15 (29)	9%	1.42
ET	6 (25)	9 (38)	(-9 to 26)	(0.72, 2.79)
PV	5 (17)	7 (25)		
Overall response	22 (41)	31 (60)	19%	1.46
ET	8 (33)	14 (58)	(1 to 37)	(1.00, 2.16)
PV	14 (47)	17 (61)		
36 months	(n = 30)†	(n = 27)†		
Complete response	5 (17)	9 (33)	17%	2
ET	2 (17)	4 (40)	(-8 to 40)	(0.76, 5.23)
PV	3 (17)	5 (29)		
Overall response	14 (47)	16 (59)	13%	1.27
ET	4 (33)	6 (60)	(-15 to 38)	(0.77, 2.08)
PV	10 (56)	10 (59)		

Overall response rate = complete + partial response

*n=106 patients (HU: 54, PEG: 52) who had opportunity to receive treatment of 24 mo.

†n=57 patients (HU: 30, PEG: 27) who had the opportunity to receive treatment of 36 mo.

SAFETY

As of today, [redacted]Peginterferon α-2a) is registered by Malaysia's Drug Control Authority (DCA) as two doses, i.e. [redacted] and [redacted] for the indication of Chronic Hepatitis B and C.[11] United States Food and Drug Administration (US FDA) has approved [redacted] as 180mcg/ml in a vial and 180mcg/0.5ml in a prefilled syringe for the indication of Chronic Hepatitis B and C.[12] It was also authorised for use in the European Union as 180mcg/ml solution for injection for chronic Hepatitis B in both adults and children from 3 years old,

and chronic Hepatitis C in adults and children from 5 years old.[14] It is not authorised for myeloproliferative neoplasms.

Guilhot et al (2020) reported that there was no late serious toxicity observed during the follow up. Grade 3/4 neutropaenia and thrombocytopaenia occurred were reported in 31% and 14% for patients as the combination of IM and PegIFN-α2a. Other than that, skin rashes were often observed for patients taking IM and PegIFN-α2a than IM 400mg. Based on Table 3, there were 120 deaths reported, in which 33 deaths were reported to the patients receiving the combination of imatinib and pegylated interferon alpha2a (PegIFN-α2a).[9]

Table 3: Causes of death[9]

	IM 400 mg (*n*)	IM 600 mg (*n*)	IM + AraC (*n*)	IM + PegIFN-α2 (*n*)	Total
Progression to AP/BC	6	10	6	3	25
Second malignancies	6	7	9	9	31
Infection	2	0	0	6	8
Vascular events	4	3	3	4	14
Allo BMT	4	2	4	2	12
Suicide	0	0	3	1	4
Others	5	5	8	8	26
Totals (*n*)	**27**	**27**	**33**	**33**	**120**

AP: accelerated phase, BC: blast crisis, Allo BMT: allogeneic bone marrow transplantation

According to Mascarenhas et al (2022), it was difficult to distinguish the effects of thrombotic and progressive episodes in either arm due to small number of cases.[10] It was reported there were 60% of patients experienced Grade 3 or higher adverse effects which accounted for 46% (38) patients receiving PEG and 28% (22) for HU. Patients receiving pegylated IFN-α (PEG) experienced common adverse effects such as flu-like symptoms, injection site reaction, peripheral sensory neuropathy, and blurred vision whereas mucositis and anorexia were commonly found among patients treated with HU.[10]

COST-EFFECTIVENESS

There was no retrievable evidence on the cost-effectiveness of peginterferon alfa-2a therapy in the treatment on myeloproliferative neoplasm. However, the price ranged from RM780.50/pre-filled syringe for 135mcg/0.5ml and RM903.60 for 180mcg/0.5ml.[7] Based on the treatment plan for PV and ET, the range of dose is between 45mcg to 180mcg weekly for 12 months, which costs approximately RM43,373.00.[10]

CONCLUSION

Based on the review, there was limited evidence retrieved on pegylated interferon alpha-2a in the treatment of myeloproliferative neoplasm. The limited evidence showed the combination of PegIFN-α2a and imatinib did not significantly improved CML patients' survival when compared to imatinib alone. PegIFN-α2a also showed no significant difference when compared to hydroxyurea. There was no retrievable evidence on the cost effectiveness of pegylated interferon alpha2a (PegIFN-α2a).

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23rd August 2023