Ruxolitinib for intermediate-2 primary myelofibrosis.

Critical appraisal on the use of ruxolitinib for treatment in adult with intermediate-2 primary myelofibrosis.

Introduction:

Patients with primary myelofibrosis are prone to develop complicated infection due to defect in their humoral immunity. In addition, patients may develop complication such as portal hypertension, splenic infarction (which may lead to nausea, vomiting and shoulder discomfort), osteosclerosis, hypertrophic osteoarthropathy, occasionally periostitis, spinal cord compression, seizures, haemoptysis and gastrointestinal (GI) tract bleeding. (6, 7, 8, 9)

In UK, Novartis holds the marketing authorisation for oral formulation. Ruxolitinib works by inhibiting Janus associated tyrosine kinase (JAK1 and JAK2) protein signalling.

Ruxolitinib (Jakavi) is licensed for the treatment of disease related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis but not recommended by NICE.(10)

The major adverse drug reaction associated with Jakavi, documented in the summary of product characterisation (SPC) at incidence greater than 10% are urinary tract infection, anaemia, thrombocytopenia, neutropenia, hypercholesterolemia, dizziness, headache, increase both alanine aminotransaminase and asparte aminotransferase, bruising , bleeding and increase blood pressure. Novartis also recorded other common side effect

patient experienced incidence between 1-10% was weight gain, flatulence and herpes zoster, whiles tuberculosis incidence was 1%.(3)

The following clinical study, COMFORT-I and COMFORT-II trails as well as primary peered review articles Verstovsek S, Masa RA, Gotlib J, et al and Harrison C, Kiladjian JJ, Al-Ali HK, et al published in The New England Journal of Medicine (NEJM) is used to address the questions below;

1. Evidence recommendation for or against the use of ruxolitinib in Mrs MN treatment
2. Pharmaceutical care plan and medication optimisation for Mrs MN.

Creditability and quality of evidence

The clinical trial from COMFORT-I was a multicentre (USA, Canada and Australia), phase III, randomised, double blind trial (large sample size, n= 309) that compared patient treatment in primary myelofibrosis with ruxolitinib (n= 155) to placebo (n= 154). All patients enrolled in the trial had intermediate-2 risk or high risk of myelofibrosis, a palpable spleen length of at least 5cm and was 18years or above. Patients excluded were those with an absolute neutrophil count of 1x 10^{9} /L or less, platelet count less than 100x 10^{9} /L. Incyte pharmaceutical funded this trial.(5)

The COMFORT-II trial, was a multicentre (Europe with UK inclusive), phase III, randomised, open label trial that compared ruxolitinib (146) with best available therapy n= 73 (hydroxycarbamide, prednisone, opoetin, lenalidomide and thalidomide). The trial was funded by Novartis pharmaceuticals. (4)

The primary outcome for both trails was the proportion of patients having a spleen volume reduction of 35% or more from baseline and assessed by MRI or CT scan. The primary efficacy outcome was measured at 24 weeks in CONFORT I and 48 weeks in COMFORT II. Also the COMFORT trail (50% of primary myelofibrosis PM) population of patients with different subtypes of myelofibrosis did not reflect the global prevalence (i. e. PM is 30 times more) data reported. In addition the trials were not powered to measure overall survival or to detect statistically significant differences between subgroups (that is sex, myelofibrosis subtype), IPSS risk category or JAK2 mutation status.(1, 2, 3, 4, 5)

Patient background verse evidence:

Mrs MN creatinine clearance (CrCl) is 60ml/ min (normal about 100-125ml/min). The UK guideline for identification, management and referral March 2006 show that, she has stage 2 mild degree of renal function. But from SPC it is unclear, how this will increase Mrs MN risk of taking ruxolitinib. I must point out that Mrs MN is overweight with a BMI of 28 and ruxolitinib common side effect is weight gain (1-10% incidence rate). Mrs MN is capable of carrying out light house or office work from her ECOG status 1. Again patient is taking clarithromycin prescribed by GP, for possible chest infection. Novartis pharmaceutical (Javaki SPC) advises to treat any infection prior to taking ruxolitinib. (3)

Mrs MN presenting complain with symptoms of anorexia, lethargy, night sweats, fever and a productive cough is a suggestive of tuberculosis (TB) infection. She is returning from holiday where risk of getting TB infection is

high. If Mrs MN is prescribed ruxolitinib, she has high chances of developing complicated TB. Base on the evolution of patient background and evidences, I will not recommend ruxolitinib treatment for Mrs MN.

Since Mrs MN will be receiving treatment for tuberculosis (isoniazid/ rifampicin) for at least 6 months, there is significant interaction between isoniazid and clarithromycin. Isoniazid will increase the level or effect of clarithromycin by affecting hepatic or intestinal enzyme CYP3A4 metabolism. Hence clarithromycin dose be reduce when taking with isoniazid and monitor closely. (4, 5, 11)

If opting for rifampicin TB treatment, rifampicin will decrease the level or effect of clarithromycin by affecting hepatic or intestinal enzyme CYP3A4 metabolism. Hence, increase the dose of clarithromycin for the duration of treating chest infection.(11)

Also, Mrs MN should be advised to recognise signs of liver disorders to discontinue treatment and seek immediate medical attention if symptoms such as vomiting, nausea, malaise and jaundice develop. (11)

References:

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