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Ruxolitinib in the Treatment of Resistant Essential Thrombocytosis

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Description

Essential thrombocytemia (ET) is a myeloproliferative neoplasm, which are a group that feature clonal proliferation of myeloid cells. Other entities in this group include Polycythemia Vera and Myelofibrosis. There is recognized association between MPNs and somatic mutations of JAK2V617F, CALR or MPL genes. Their driving influence on cell proliferation has been a milestone development in diagnostic process as well as potential new avenue for treatment. Specifically for ET, in more than 90% of cases a mutation of one of the above genes can be. The risks of ET include thrombosis, transformation to myelofibrosis or acute myeloid leukaemia. The cornerstone of treatment is to stratify the patients into thrombotic risk at diagnosis. High risk individuals are either >60yrs of age or had an ET related thrombotic or haemorrhagic event or platelets >1500 x 109/l. Treatment of high risk individuals include aspirin, Hydroxycarbamide (or interferon in the young) as first line therapy to maintain the platelet count. This 55 year old gentleman of afro-Caribbean background and previous medical history of T2DM presented to our haematology department in early 2021 following admission with COVID pneumonitis. He was referred due to poorly controlled ET with a platelet count of 1200 x 109/l.

He was currently on 2g Hydroxycarbamide and 25mg Ruxolitinib. He was originally diagnosed over 10 years prior in another country. After retrieval of his original notes it was clear that the patients have refractory disease and was currently on a trial receiving Ruxolitinib. When he first was diagnosed with ET he received peg interferon that was titrated up to 135mcg. The patient struggled with gastrointestinal side effects and his platelets. He was switched to Anagrelide and that was stopped due to palpitations and the finding of a prolonging QT. He was then switched to Hydroxycarbamide and this was titrated up to 2grams/day. His platelet count went up consistently greater than 1000 x109/l. The case was proving difficult and therefore he was started on the JAK2v617F inhibitor Ruxolitinib 25mg twice a day. Shortly afterwards the patient travelled for work reasons and was admitted under our care. Given the history and lack of therapeutic options we repeated the bone marrow biopsy which was consistent with the known ET and had no excess reticulin. At first we re-trialled low dose (90mcg) of pegylated interferon alpha keeping both the Ruxolitinib, Hydroxycarbamide and aspirin going. After 48 hours the platelet count reduced to 823 x 109/l. At this stage the patient was initially reluctant to increase the peg interferon to a higher dose of 135mcg due to previous side effects. Interestingly at 135mcg the patient had no gastrointestinal upset and quickly the platelets fell to 422 x 109/l.

Haematology Guidelines

The Hydroxycarbamide was weaned off as it failed to exhibit beneficial effect. This case demonstrated that both Ruxolitinib and peg interferon used as single agents had no effect. When used in combination their effect was synergistic. Interestingly the previously poor tolerated peg-interferon side effects disappeared when combined with the Ruxolitinib. Based on British Society of Haematology guidelines Hydroxycarbamide remains a backbone of cytoreductive treatment. Its role in leukemogenesis remains uncertain. Other agents include previously mentioned INF and Anagrelide. Older drugs like Busulphan and radioactive phosphorous are rarely used because of the leukaemia risk especially in younger patients. Interferon Alpha inhibits TPO dependant megakaryocytic growth. Its use was originally limited by high rate of intolerable side effects such as fatigue, GI upset, affective disorders and lung and liver damage, which resulted in up to 20% drop out rate. Introduction of Pegylated preparations, which allowed once weekly administration improved tolerability with approx. 92% compliance and comparable long-term outcomes. JAK inhibitors are primarily based on benzo imidazole core. Other agents with that structure display antihelmetic and antifungal properties.

Ruxolitinib was the first drug in this class, originally approved by the FDA in 2011 and has been used in myelofibrosis for years as a single agent. Recently guidance has approved its use in Polycythaemia Vera for those refractory to Hydroxycarbamide. Sorensen et al. In their phase II single arm study explored use of Ruxolitinib in PV and pMF patients previously refractory or intolerant of INF-alpha2. Between 32-44% of patients have achieved complete or partial remission. Additionally combination treatment had improved response time, peripheral blood counts and marrow cellularity as well as decreased JAK2 allele burden. Given similar cellular signaling pathway involved in aetiopathogenesis of both PV and ET, it is logical to assume that combination treatment could be efficacious in ET. However there is no published trial evidence to support its routine use. We would propose that given recognized molecular association between JAK-stat pathway and ET, as well other described cases of synergistic effect between PEG- Interferon and Ruxolitinib, a clinical trial to ascertain the combination efficacy would be warranted. With an immunosuppressive regimen that includes rATG, patients can rapidly show evidence of symptomatic and cardiac structural improvement.

Myocardial Inflammation

Early endomyocardial biopsy can help clarify the diagnosis and guide management for a rapidly deteriorating patient where myocardial inflammation is highly suspected. Further research is needed to better understand timing of therapy and optimal immunosuppressive regimens. Past medical history of hypertension, hyperlipidaemia and prostate cancer status post total prostatectomy, presented with progressive chest pain and shortness of breath for two weeks. The chest pain was intermittent, substernal and radiating to his shoulders. Associated symptoms included palpitations, diaphoresis, and one episode of loss of consciousness. He has no family history of cardiac disease. An echocardiogram showed severe left ventricular (LV) dysfunction, grade 3 diastolic dysfunction, mild right ventricular systolic dysfunction severe LVH septal wall thickness of 2.3cm and

posterior wall thickness. After stabilization of his ventricular arrhythmias, a right and left heart catheterization were performed which showed non-obstructive coronary disease and elevated filling pressures (right atrium pressure (RA) 21mmHg, right ventricular pressure (RV) 50/12mmHg, pulmonary artery pressure 50/30mmHg, pulmonary capillary wedge pressure (PCWP) 35mmHg, cardiac output 4.7L/min, cardiac index. Based on his acute onset of heart failure, ventricular arrhythmias, underlying conduction abnormalities, severe LVH and no obstructive coronaries, his clinical picture was concerning for a myocardial inflammatory process, such as GCM. Other considerations included infiltrative diseases like amyloidosis and cardiac sarcoidosis. Incomplete right bundle branch block and LVH. Given his rapid deterioration and concern for fulminant myocarditis, a bedside endomyocardial biopsy was obtained and he was empirically treated with 1g methylprednisolone. His biopsy results were significant for active GCM.