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Janus kinase inhibitors in myeloproliferative neoplasms

Clinical applications

SUMMARY

Hyperactive Janus kinase 2 signalling is a key molecular event in polycythaemia, essential thrombocythaemia and myelofibrosis. This is associated with the V617F mutation in the Janus kinase 2 gene of many patients with myeloproliferative disease.

Ruxolitinib is the first Janus kinase inhibitor to be licensed in Australia for the treatment of myelofibrosis.

Ruxolitinib can cause rapid and sustained splenic shrinkage in up to 42% of patients with higher risk myelofibrosis, however it does not change the risk of leukaemic transformation.

Treatment with ruxolitinib can be limited by significant anaemia.

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Introduction

It has long been known that the myeloproliferative neoplasms – essential thrombocythaemia, polycythaemia vera and myelofibrosis – share clinical and pathological features. In 2005, a mutation in the Janus kinase 2 gene (V617F mutation) was discovered in more than 95% of patients with polycythaemia vera and approximately 50% of those with essential thrombocythaemia and primary myelofibrosis.[1-4] Chronic myeloid leukaemia, another myeloproliferative neoplasm, is associated with the presence of a different mutation – the Philadelphia chromosome (BCR-ABL translocation).

The V617F mutation makes the Janus kinase continuously active. As a result, polycythaemia, thrombocythaemia and leukocytosis can develop independently from growth factor regulation. Patients without the mutation also display hyperactive Janus kinase signalling.[5]

Janus kinase inhibitors

Several Janus kinase inhibitors are in clinical trials for myelofibrosis, polycythaemia vera and essential thrombocythaemia. These include ruxolitinib, pacritinib and momelotinib.

Ruxolitinib

Ruxolitinib recently became the first approved Janus kinase inhibitor in Australia for myelofibrosis. It has completed phase III testing and is currently being evaluated in expanded clinical settings including in patients with myelofibrosis and thrombocytopenia (starting platelet count 50–100 x 10^9/L), and in other myeloproliferative neoplasms. It is also being assessed in combination with other therapies.

Two randomised phase III trials of ruxolitinib – COMFORT-I and COMFORT-II – were completed in patients with higher risk myelofibrosis, including those with primary or secondary myelofibrosis, irrespective of whether they had the V617F mutation.[6,7] Splenomegaly is a common cause of disability in patients with myelofibrosis. The primary end point of the studies was a 35% reduction in splenic volume on magnetic resonance imaging.

Outcomes from both studies were remarkably similar. In COMFORT-I, patients with myelofibrosis received oral ruxolitinib 15 or 20 mg twice a day (155 patients) or placebo (154 patients). The starting dose was dependent on the patients' baseline platelet count. After 24 weeks, a 35% reduction in spleen size was achieved in 41.9% of ruxolitinib-treated patients versus 0.7% of placebo-treated patients ($p<0.001$). COMFORT-II compared ruxolitinib with best available therapy (2:1 ratio). After 48 weeks, 28% of the ruxolitinib-treated patients met the primary end point versus 0% in the best available therapy group ($p<0.001$).

In both studies, 97% of patients experienced some degree of splenic shrinkage with ruxolitinib therapy. Responses were rapid and sustained and were irrespective of the type of myelofibrosis (primary vs post-polycythaemia vera or post-essential thrombocythaemia), mutation status, initial spleen size or baseline symptoms. Patients on ruxolitinib had an improved quality of life and reversal of disease-related weight loss. Ruxolitinib was effective in patients with

the wild-type Janus kinase 2 gene as well as those with the V617F mutation.

At the latest update, both studies showed an improvement in overall survival with ruxolitinib therapy, with hazard ratios of 0.58 (confidence interval (CI) 0.36–0.95) in COMFORT-I[8] and 0.51 (CI 0.26–0.99) in COMFORT-II[9]. It is likely that the improvement in survival was due to the relief of disease-related symptoms (such as splenic pain, poor appetite and immobility), rather than modification of the underlying disease. In particular, the risk of leukaemic transformation is not reduced. This is unlike the situation with chronic myeloid leukaemia, where treatment with tyrosine kinase inhibitors such as imatinib substantially alters the natural history of the disease, and markedly reduces the risk of progression to acute leukaemia.

The efficacy of ruxolitinib in patients with lower risk disease has not been assessed in randomised trials.

Adverse reactions

The major toxicities of ruxolitinib were anaemia and thrombocytopenia, and to a lesser extent minor bruising (grade 1–2), dizziness, headache and diarrhoea.[6,7] Significant anaemia (haemoglobin <80 g/L) and thrombocytopenia (<50 x 10^9/L) occurred in 40–52% and 10–16% of patients respectively. Experience outside the trials (conference abstracts) suggests that the efficacy and adverse effect profile of ruxolitinib in the real world is similar to that of the COMFORT studies.

Polycythaemia vera and essential thrombocythaemia

Ruxolitinib was studied in a phase II study of patients with either polycythaemia vera (n=34) or essential thrombocythaemia (n=39) who were resistant or intolerant to hydroxyurea therapy.[10,11] In patients with polycythaemia vera, 97% reached their target haematocrit (≤0.45) without phlebotomy, and 61% of patients with splenomegaly had at least a 50% reduction in palpable spleen length. Importantly, most patients experienced a reduction or complete resolution of polycythaemia vera-associated symptoms including pruritus, night sweats and bone pain. For patients with essential thrombocythaemia, 82% had reduced platelets (<600 x 10^9/L) and in 49% the platelet count reduced to normal. Phase III studies of ruxolitinib in polycythaemia vera have completed recruitment.

Conclusion

Janus kinase 2 inhibitors have shown activity in the relief of symptoms associated with myeloproliferative neoplasms and splenomegaly. However, they do not substantially alter the natural history of the disease. Current research aims to develop combination therapies which also inhibit alternative cellular targets. ◁

Conflict of interest: none declared

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