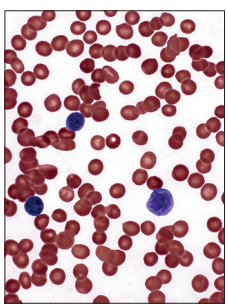
Polycythaemia vera, ruxolitinib, and hydroxyurea: where do we go now?



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The myeloproliferative neoplasms, polycythaemia vera, essential thrombocytosis, and primary myelofibrosis are unique clonal haemopoietic stem-cell disorders because they share gain-of-function driver mutations in the *JAK2*, *MPL*, and *CALR* genes. These mutations directly or indirectly activate JAK2, the cognate tyrosine kinase of the erythropoietin and thrombopoietin receptors. Unlike in most haematological malignancies, however, constitutive JAK2 activation in the myeloproliferative neoplasms increases the production of morphologically and functionally normal circulating red blood cells, granulocytes, and platelets.

The *JAK2* Val617Phe mutation is the commonest myeloproliferative neoplasm mutation, and the pan-myelopathy polycythaemia vera is the commonest myeloproliferative neoplasm because it is the ultimate phenotypic consequence of the *JAK2* Val617Phe mutation. Unsurprisingly, control of unregulated normal blood cell production in polycythaemia vera has been a source of frustration to physicians since the discovery of the disease, because phlebotomy alone represents a temporary and incomplete remedy. Radioactive phosphorus was the first successful polycythaemia vera therapy, producing a durable haematological remission in 95% of patients and eradicating splenomegaly in 74% of patients,[1] but with the same disadvantages of leukaemogenicity and failure to improve survival, which also plagues the use of chemotherapy in polycythaemia vera.[2] In *The Lancet Haematology*, Jean-Jacques Kiladjian and colleagues report the 5-year safety and efficacy data of the phase 3 RESPONSE trial,[3] the first trial of targeted therapy with ruxolitinib for patients with polycythaemia vera who are splenomegaly-resistant or intolerant to hydroxyurea compared with best available therapy (most often hydroxyurea).[4]

The RESPONSE trial involved 222 patients (110 randomly assigned to ruxolitinib and 112 to best available therapy). At 5 years, among the 22·7% patients given ruxolitinib who were primary responders (phlebotomy-independence and ≥35% spleen volume reduction) compared with 0·9% for best available therapy, 74% (95% CI 51–88) of patients were able to maintain the response; the probability of maintaining a complete haematological remission (23·6% of responders) was 55% (95% CI 32–73). 73% (60–83) of patients maintained haematocrit control without phlebotomy (66 [60%] patients given ruxolitinib compared with 21 [19%] of those given best available therapy); and 72% (34–91) maintained at least a 35% spleen volume reduction (98 [89%] in the ruxolitinib group compared with 55 [49%] given best available therapy).[3] Complete molecular remissions were rare and changes in the neutrophil *JAK2* Val617Phe allele burden were modest. There was no increase in the number of adverse events and no new adverse events; anaemia was more common with ruxolitinib and thrombocytopenia was more common with best available therapy. Infections, except for herpes zoster, were lower with ruxolitinib as was the rate of thromboembolic events (1·2 *vs* 8·2 per 100 patient-years) than with best available therapy. Patients on best available therapy who crossed over to ruxolitinib obtained its benefits as well. Thus, as in the COMFORT trials for primary myelofibrosis, ruxolitinib's effects in polycythaemia vera were durable and superior to best available therapy (usually chemotherapy), which for primary myelofibrosis was no better than placebo.[5]

On the basis of the RESPONSE trial results, ruxolitinib was approved as second-line therapy for polycythaemia vera in patients who are resistant to or intolerant of hydroxyurea. However, I believe that the clinical validity of this decision is questionable. First, a randomised clinical trial has shown that chemotherapy per se does not improve survival in polycythaemia vera and is leukaemogenic.[2] For further information, a reading list is provided in the appendix. Second, the contention that reducing the leucocyte and platelet counts to normal in polycythaemia vera has been shown to be erroneous.[6] Third, there is no evidence that hydroxyurea independently prevents arterial or venous thrombosis.[7] Finally, there has never been a randomised controlled trial to establish that hydroxyurea is a first-line therapy for polycythaemia vera. The recommendation was made based on a non-randomised observational trial.

See Online for appendix

Importantly, the design of the RESPONSE trial omitted an assessment of tumour burden, an essential variable

intrinsic to the staging of haematological malignancies, which in the myeloproliferative neoplasms is the *JAK2* Val617Phe variant allele fraction. This omission is important as so few patients reached the trial's primary and secondary endpoints, presumably because ruxolitinib (and hydroxyurea), in contrast to interferon, do not affect the involved haemopoietic stem cell. Polycythaemia vera is not a monolithic disease; some patients with polycythaemia vera maintain a variant allele fraction less than 50% with only heterozygous *JAK2* Val617Phe haemopoietic stem cells, but others, due to uniparental disomy,[8] acquire homozygous *JAK2* Val617Phe haemopoietic stem cells, which can become clonally dominant. It is probable that clonally dominant polycythaemia vera would be less responsive to ruxolitinib and the true measure of this would not be the neutrophil *JAK2* Val617Phe variant allele fraction, but the CD34-positive haemopoietic stem cell *JAK2* Val617Phe variant allele fraction,[9] which was not measured. Additionally, stratifying patients according to sex would have been useful since sex differences exist in polycythaemia vera.[10] Moreover, given the poor results with hydroxyurea, if the purpose of the RESPONSE trial was to establish a first-line therapy in polycythaemia vera, ruxolitinib, which like hydroxyurea is a supportive therapy, should have been compared with phlebotomy alone in patients with polycythaemia vera who are treatment-naive. Finally, since polycythaemia vera arises in a haemopoietic stem cell and all current first-line therapies are supportive, failure of any of these is an indication for the use of pegylated interferon, which specifically targets the involved haemopoietic stem cells.

I declare no competing interests.

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1 Lawrence JH, Berlin NI, Huff RL. The nature and treatment of polycythemia; studies on 263 patients. *Medicine (Baltimore)* 1953; **32:** 323–88.
2 Berk PD, Goldberg JD, Silverstein MN, et al. Increased incidence of acute leukemia in polycythemia vera associated with chlorambucil therapy. *N Engl J Med* 1981; **304:** 441–47.
3 Kiladjian J-J, Zachee P, Hino M, et al. Long-term efficacy and safety of ruxolitinib versus best available therapy in polycythaemia vera (RESPONSE): 5-year follow up of a phase 3 study. *Lancet Haematol* 2020; published online Jan 23. https://doi.org/10.1016/S2352-3026(19)30207-8.
4 Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med* 2015; **372:** 426–35.
5 Mesa RA, Kiladjian JJ, Verstovsek S, et al. Comparison of placebo and best available therapy for the treatment of myelofibrosis in the phase 3 COMFORT studies. *Haematologica* 2014; **99:** 292–98.
6 Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. *Blood* 2013; **121:** 4778–81.
7 Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med* 2005; **353:** 33–45.
8 Kralovics R, Guan Y, Prchal JT. Acquired uniparental disomy of chromosome 9p is a frequent stem cell defect in polycythemia vera. *Exp Hematol* 2002; **30:** 229–36.
9 Moliterno AR, Williams DM, Rogers O, Isaacs MA, Spivak JL. Phenotypic variability within the JAK2 V617F-positive MPD: roles of progenitor cell and neutrophil allele burdens. *Exp Hematol* 2008; **36:** 1480–86.
10 Stein BL, Rademaker A, Spivak JL, Moliterno AR. Gender and vascular complications in the JAK2 V617F-positive myeloproliferative neoplasms. *Thrombosis* 2011; **2011:** 874146.