FOCUS ON POLYCYTHAEMIA VERA

At the recent MPN Expert Forum held in Kuching, Dr Chew Lee Ping (Consultant Haematologist, Sarawak General Hospital) and Dr Yong Kar Ying (Clinical Haematologist Hospital Miri Sarawak) shared their expert opinion on treating hydroxyurea (HU) resistance/intolerance in Polycythaemia Vera (PV) patients, where real-life patients were managed successfully.

Overview of PV

Healthy haematopoietic stem cells (HSCs) differentiate into various cells: platelets, red blood cells (RBCs), and white blood cells (WBCs).[1] Myeloproliferative neoplasms (MPNs) are a group of blood disorders in which the pluripotent HSCs produce excess numbers of one or more cells of the myeloid lineage.[2,3] PV is one of the classic types of MPN – characterized by excess production of RBCs which may cause fatigue and pruritis.[4]

The 2016 WHO Diagnostic Criteria for PV requires evidence of erythrocytosis **(Figure 1).**[5] The median age of diagnosis is 60 years, with the average 15-year survival rate of 65%.[6,7] PV patients have an average 5% risk of progression to acute myeloid leukaemia. About 10% of PV runs the risk of progression to post-PV myelofibrosis,[8] and subsequently 12 to 31% of post-PV MF patients developing AML.[9] The 3-year survival of post MPN AML is only 6 to 11%.[10]

The therapeutic goal of PV is comprehensive disease control

Historically, there have been no curative drug therapies for PV.[11] While RopegIFN, a type of pegylated interferon (PEG-IFN), may have curative potential in some patients via reduction of *JAK2* allele burden, long term data is still required.[12] For now, the goal of PV treatment remains comprehensive disease control which includes reducing the risk of thrombotic and haemorrhagic events, managing debilitating symptoms and minimizing risk of progression.[13-17]

PV Management Guidelines

Management of PV differs according to the guidelines, however HU and IFN are considered as first line cytoreductive therapies. Jakavi® (ruxolitinib) is also prominently recommended in all current PV management guidelines. The European LeukemiaNet 2018 guidelines recommend HU or IFN-alpha as first line therapy and Jakavi as second line cytoreductive therapy when HU resistance or intolerance arises. HU intolerance/resistance is defined in **Table 1.** IFN-alpha is preferred in young patients in need of long-term treatment.[18]

Table 1: Criteria for HU intolerance/resistance[19]

HU Intolerance / Resistance

Criteria of clinical resistance and intolerance to HU in PV based on the European LeukemiaNet consensus

Type	Criteria
Resistance	
1	Need for phlebotomy to keep Hct <45% after 3 months of ≥2 g/day of HU, **OR**
2	Uncontrolled myeloproliferation, ie, platelet count >400×10^9/L AND white blood cell count >10x10^9/L after 3 months of ≥2 g/day of HU, **OR**
3	Failure to reduce massive* splenomegaly by more than 50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly after 3 months of ≥2 g/day of HU, **OR**
Intolerance	
1	Absolute neutrophil count <1.0x10^9/L at the lowest dose of HU required to achieve a complete or partial clinico-hematological response, **OR**
2	Platelet count <100x10^9/L at the lowest dose of HU required to achieve a complete or partial clinico-hematological response, **OR**
3	Hb <100 g/L at the lowest dose of HU required to achieve a complete or partial clinico-hematological response, **OR**
4	Presence of leg ulcers or other unacceptable HU-related nonhematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of hydroxyurea.

Figure 1: WHO 2016 Requirements for PV Diagnosis[5]

A PV diagnosis requires either:
- All 3 major criteria

OR
- The first 2 major criteria and 1 minor criteria

1 Evidence of elevated RBCs (erythrocytosis)

Hb:
- >16.5 g/dL in men
- >16.0 g/dL in women

OR

Hct:
- >49% in men
- >48% in women

OR

Increased RBC mass

2 Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis)

- Including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)

3 Presence of JAK2 mutation

JAK2 V617F or *JAK2* exon 12 mutation

Major criterion

Minor criterion

1 Subnormal serum EPO level

Case 1
By Dr Chew Lee Ping

Patient is a 69-year-old male, an ex-smoker of 30 pack-years weighing 76 kg. He has hypertension with blood pressure (BP): 156/92 mmHg, hyperlipidaemia and benign prostatic hyperplasia. He was on amlodipine, atorvastatin and tamsulosin. He presented with chest tightness in 2016 and a multi-slice computed tomography revealed minor coronary artery disease. On examination, his lungs were clear, echocardiogram (ECG) and heart function was normal. There were no palpable liver or spleen. He was diagnosed with PV and laboratory readings showing haemoglobin (Hb)=20.4 g/dL; haematocrit (Hct)=58%, WBC =12x10^9/L, platelet (Plt)=414,000/uL, *JAK2V617V* positive and erythropoietin was 1 mmol/L.

He complained of body itchiness and feeling "heavy". His itch was relieved with venesection, which was done monthly since 2016. Additionally, he was prescribed with aspirin 75 mg OD and HU 500 mg OD. HU caused patient's nails to become black. He also had on and off mouth and ankle ulcers with lengthy heal time. In March 2021, patient was started on a trial drug. While receiving trial drug, HU was reduced to 500 mg 3 times/wk and anagrelide 0.5 mg BD was added.

In August 2021, his trial drug came to an end and HU treatment was resumed to 500 mg OD with anagrelide. Again, patient complained of itch and recurrent mouth ulcers and was subsequently diagnosed with HU intolerance. In December 2022, patient was started on Jakavi® (ruxolitinib, Novartis) 10 mg BD. By April 2023, there was a marked improvement seen in WBC, Hb, Hct and Plt counts. After treatment with Jakavi, patient's WBC=8.2x10^9/L from an initial 25.8x10^9/L. Hct=37.4% from an initial 50.2% **(Figure 2).** Hb=12.1 g/dL from 15.2 g/dL. Plt=208,000/uL from 1,349,000/uL. His appetite has improved, gained 2 kg in 4 months, rash has disappeared and anagrelide was stopped after 5 months.

Case 2
By Dr Yong Kar Ying

A 45-year-old patient, ex-smoker with no known medical illness, presented in 2018 with left-sided body weakness, which lasted for 15 minutes. He denied headache, chest pain, shortness of breath, blurring of vision, pruritis, abdominal pain and constitutional symptoms. At presentation, he was overweight with BMI of 26 kg/m^2 and appeared flushed. He had raised blood pressure with reading of 150/80 mmHg. Cerebrovascular and cardiovascular examination were unremarkable. Abdominal examination demonstrated palpable liver (3 cm below the right costal margin) and spleen (tip of spleen). He had no palpable lymphadenopathy. Chest X-ray, ECG and CT brain were normal. Molecular study revealed presence of *JAK2V617V* mutation.

He was diagnosed with transient ischaemic attack (ABCD^2 score of 4 points, moderate risk), hypertension and high-risk PV. At diagnosis, his blood readings were Hb=18.2 g/dL, Hct=58.2%, WBC=26.6x10^9/L, Plt=481x10^9/L and his MPN-10 score was 5 **(Figure 3).**

Venesection was performed and he was commenced on HU 1g OD, aspirin 75 mg ON and perindopril 4 mg OD. However, PV was inadequately controlled in spite of the prescription, and he underwent 2 venesections in 2018 and 2 more in 2018. Moreover, he could not tolerate higher dose of HU due to mucocutaneous adverse event. Hence, in May 2020, he was diagnosed as HU-resistance/intolerance and was switched to Jakavi® (ruxolitinib, Novartis). As of August 2022, his laboratory profile was Hct=46.8%, WBC=8.19x10^9/L and Hb=14.7 g/dL.

After switching to Jakavi® (ruxolitinib, Novartis), he was well with no active complaint. He has no more palpable liver and spleen. Laboratory parameters showed acceptable blood results with Hb=14.6 g/dL, Hct=46.6%, WBC=7.60x10^9/L, and Plt=280x10^9/L. MPN-10 score had reduced to 0.

Figure 2: Progression of blood parameters over time of Patient 1.

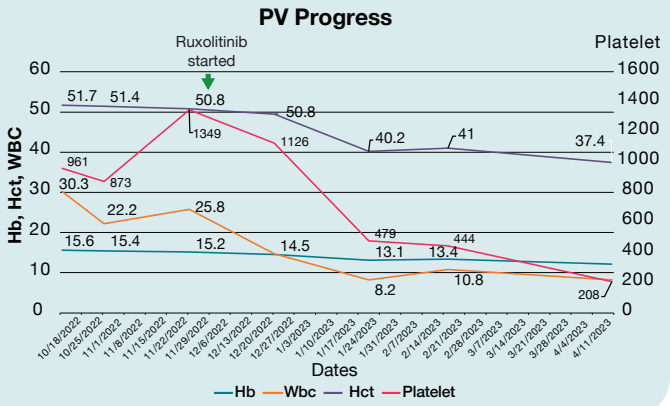
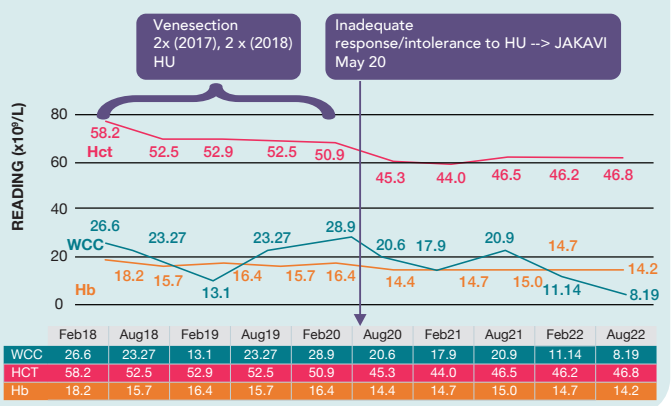


Figure 3: Progression of blood parameters over time of patient 2.



	Feb18	Aug18	Feb19	Aug19	Feb20	Aug20	Feb21	Aug21	Feb22	Aug22
WCC	26.6	23.27	13.1	23.27	28.9	20.6	17.9	20.9	11.14	8.19
HCT	58.2	52.5	52.9	52.5	50.9	45.3	44.0	46.5	46.2	46.8
Hb	18.2	15.7	16.4	15.7	16.4	14.4	14.7	15.0	14.7	14.2

Key Takeaways:

1. PV is a type of MPN which is characterized by excess production of RBCs which may cause fatigue and pruritus.[4]
2. Symptom burden in PV is considerable, even in HU-treated patients.[20]
3. HU is recommended as first line treatment for PV but many PV patients will develop resistance to or intolerance of treatment with HU.[21]
4. Jakavi significantly improves symptoms and reduces HCT vs BAT, including HU[22] and reduced the risk of death by 72% vs BAT[23].

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RESPONSE	Provides enduring response, regardless of HU intolerance / resistance[1]
CONTROL	Significantly improves symptoms and reduces HCT vs BAT, including HU[1]
SURVIVAL	JAKAVI reduced the risk of death by 72% vs BAT[2]
SAFETY	Safety profile established in 184 patients with PV[3]

BAT, best available therapy; **HU,** hydroxyurea; **PV,** polycythaemia vera; **HCT,** haematocrit.

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