Journal Pre-proof

Combination Therapy with Pulmonary Vasodilatation and JAK2 Inhibition for Pulmonary Hypertension with Polycythemia Vera

Riichi Momose, Takumi Inami, MD, Kaori Takeuchi, MD, Hanako Kikuchi, MD, Ayumi Goda, MD, Takashi Kohno, MD, Kyoko Soejima, MD, Nobuyuki Takayama, MD, Toru Satoh, MD

PII: S2589-790X(22)00244-X

DOI: https://doi.org/10.1016/j.cjco.2022.11.007

Reference: CJCO 599

To appear in: *CJC Open*

Received Date: 24 August 2022

Revised Date: 5 November 2022

Accepted Date: 8 November 2022

Please cite this article as: R. Momose, T. Inami, K. Takeuchi, H. Kikuchi, A. Goda, T. Kohno, K. Soejima, N. Takayama, T. Satoh, Combination Therapy with Pulmonary Vasodilatation and JAK2 Inhibition for Pulmonary Hypertension with Polycythemia Vera, *CJC Open* (2022), doi: https://doi.org/10.1016/j.cjco.2022.11.007.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Published by Elsevier Inc. on behalf of the Canadian Cardiovascular Society.

Journal Pre-proof

Combination Therapy with Pulmonary Vasodilatation and JAK2 Inhibition for Pulmonary Hypertension with Polycythemia Vera

Riichi Momose[1)], Takumi Inami; MD, [2)], Kaori Takeuchi; MD[2)], Hanako Kikuchi; MD[2)], Ayumi Goda; MD[2)], Takashi Kohno; MD[2)], Kyoko Soejima; MD[2)], Nobuyuki Takayama; MD[3)], Toru Satoh; MD[2)]

Affiliations address:

1) Kyorin University School of Medicine, Tokyo, Japan.

2) Department of Cardiovascular Medicine, Kyorin University School of Medicine, Tokyo, Japan.

3) Department of Hematology, Kyorin University School of Medicine, Tokyo, Japan

Word count of the text: 1,178

Short title: Polycythemia with pulmonary hypertension

Corresponding author:

Takumi Inami, MD

6-20-2, Shinkawa, Mitaka, Tokyo 181-8611, Japan

Tel: +81-422-5511 Fax: +81-422-44-4137

E-mail address: tinami@ks.kyorin-u.ac.jp

Keywords: polycythemia vera, JAK2 inhibitor, pulmonary hypertension, PH-targeted drugs

Journal Pre-proof

Journal Pre-proof

Pulmonary hypertension (PH), associated with polycythemia vera (PV), can result from various conditions. Few case reports of patients with PV and PH have described drug treatment with PH-targeted drugs, and its effect remains unknown. It has been reported that ruxolitinib, a Janus kinase (JAK)1/2 inhibitor, improved PH associated with increased nitric oxide levels. We present a case of a 70-year-old female with PV and PH, for which she had multiple etiologies including cardiopulmonary comorbidities, treated with combination therapy of riociguat and macitentan and a JAK1/2 inhibitor, leading to improvement of pulmonary hemodynamics and REVEAL 2.0 risk score.

Case Report

A 70-year-old female with well-controlled polycythemia vera (PV) receiving hydroxyurea treatment (Hemoglobin:12.5 g/dl, WBC: 3500 /mcL, Platelet count: 295,000 mcL) presented with worsening dyspnea (World Health Organization functional class [WHO-FC] IV). The patient had had comorbidities such as permanent atrial fibrillation and chronic obstructive pulmonary disease (COPD), receiving an inhaled long-acting muscarinic antagonist and beta 2 agonist and long-term oxygen therapy for the last 6 months because of hypoxemia (air blood gas test; pO2: 50.7 mmHg; pCO2: 30.5 mmHg). The patient was admitted due to worsening

Journal Pre-proof

dyspnea and was diagnosed with congestive heart failure (HF) and atrial fibrillation without rapid ventricular response by clinical manifestations and imaging modalities including computed tomography which showed pulmonary edema (i.e., ground-glass opacities) due to left heart failure. Iron deficiency was not observed. Transthoracic echocardiography revealed preserved left ventricular ejection fraction (63%), severe tricuspid regurgitation, and dilatation of left atrium (left atrial volume index: 63.7 ml/m^2). Right heart catheterization (RHC) revealed the following: combined pre- and post-capillary pulmonary hypertension (PH) (mean right atrial pressure, 19 mmHg; mean pulmonary arterial pressure [mPAP], 36 mmHg; pulmonary arterial wedge pressure [PAWP], 16 mmHg; pulmonary vascular resistance [PVR], 7.9 wood units; and diastolic pressure gradient, 8 mmHg) (Figure 1). Follow-up RHC after achieving euvolemia by using diuretics on the 25th day showed a sustained increase in the mPAP (35 mmHg) and PVR (14.7 wood units) despite a decrease in the PAWP (6 mmHg), revealing a shift from combined pre- and post-capillary PH to pre-capillary PH (Table1, Figure 1, Supplemental Table S1). The severity of COPD was not proportional to that of PH (Computed tomography showed centrilobular emphysema with predominantly upper lobe involvement. There were no findings of severe bullae or fibrosis; forced expiratory volume in 1 s as a percentage of forced vital capacity, 66.8%; forced vital capacity, 104.1%; total lung capacity,

Journal Pre-proof

128.6%; diffusing capacity of lung for carbon monoxide (DLco), 30.1%; DLco corrected alveolar volume, 26.0%). Bone marrow examination revealed marked hypercellular marrow and mild fibrosis, which indicated progression to post-polycythemic myelofibrosis. Genetic analysis revealed a mutation in the Janus kinase 2 (JAK2) gene (*JAK2*V617F), a common abnormality in PV; most cases are positive for this mutation.[1] After ruling out connective tissue diseases, chronic thromboembolic pulmonary diseases by pulmonary ventilation-perfusion scan, and other systemic diseases, the patient was diagnosed with combined pre- & post- capillary PH most likely as a consequence of PV, based on studies showing both types being linked to PV.[2] Since the clinical characteristics were compatible with pulmonary arterial hypertension, monotherapy with riociguat, off-label for PV, was initiated on the 26th day. Furthermore, ruxolitinib, a JAK1/2 inhibitor, was added as a sequential combination therapy on the 53rd day because riociguat improved hemodynamic parameters such as PVR and CI but did not affect the risk score, which remained at high risk (WHO-FC IV to III; mPAP, 34 to 35 mmHg; PVR, 14.7 to 6.7 wood units; Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management [REVEAL] 2.0 score, 15 to 13 points). Since the patient remained at high risk (13 points), macitentan, off-label for PV, was further added, and the dosage of ruxolitinib was increased from 10 mg to 20 mg daily on the 109th day.

Journal Pre-proof

Combination therapy with PH-targeted drugs and ruxolitinib finally improved the REVEAL2.0 score (6 points) without worsening left-sided HF on the 263rd day (Figure 1). Oxygen requirements did not increase after the initiation of these drugs. The arterial oxygen partial pressure levels on the 11th and 263rd day were 51.4 (oxygen flow rate: 4 L/min.) and 79.2 (oxygen flow rate: 2 L/min) torr, respectively. During the 19-month follow-up after hospital discharge, no HF deterioration was observed.

Discussion

Observational studies have shown that myeloproliferative neoplasms (MPNs), including PV, are associated with PH. A recent evaluation of hemodynamic parameters among patients with PV and suspected PH revealed PH in approximately 80% of patients, pre-capillary PH in 30% of patients, and post-capillary PH in 50% of patients.[2] Due to various mechanisms of PH development in PV, such as chronic thromboembolic PH, pulmonary arteriopathy, and left HF diseases,[1] the ideal therapeutic approach among patients with PH and PV has not been established.

In a case report of a PV patient with pulmonary veno-occlusive disease (PVOD), PH-targeted drugs caused pulmonary edema.[3] In our case, oral dual therapy with riociguat and macitentan

Journal Pre-proof

was cautiously initiated after confirming the absence of PVOD-specific computed tomography imaging, such as centrilobular ground-glass opacities or intralobular septum thickening. The partial improvement of PH by pulmonary arterial hypertension-specific pharmacotherapy suggests that nitric oxide (NO) deficiency and increased endothelin activation within pulmonary vessels could partly cause PH in PV and could be a therapeutic target for these patients.

JAK1/2 inhibition could be a novel target for managing PH-associated PV. In a case series of 15 patients with MPNs and PH, ruxolitinib, a JAK1/2 inhibitor (median 10 mg [minimum, 5 mg, maximum, 20 mg]), improved PH and was associated with an increase in NO levels.[4] In a case report of an active hematopoietic state PV patient with PVOD, ruxolitinib improved hemodynamics and hematopoiesis.[3] We firstly aimed for optimal activation of NO - soluble guanylate cyclase - cyclic guanosine monophosphate (cGMP) pathway to reduce right ventricular afterload and increase cardiac output because of severely impaired pulmonary hemodynamics. Riociguat reduced PVR by half of the baseline, but the risk category remained high, and we expected that adding ruxolitinib would enhance cGMP stimulation by activating NO levels. In our case, PH did not improve with 10 mg/day of ruxolitinib but improved after a 20 mg/day dose, with the addition of macitentan. It is difficult to differentiate the effect of

Journal Pre-proof

ruxolitinib escalation from that of macitentan initiation, because both are performed nearly at the same timing. To our knowledge, there were no previous case reports using these treatments in patients with PH and PV. Although the precise mechanism of the limited effect of a JAK1/2 inhibitor on pulmonary circulation in our case remains unknown, there are several possibilities. First, our case was not hematopoietic in nature. Second, pretreatment with riociguat, which activates the downstream target of NO, might attenuate the NO-dependent effect of JAK inhibition. Because it is still uncertain that ruxolitinib had an effect vs. the PH-targeted drugs, we would suggest repeating the right heart catheterization before adding more therapy.

Due to the increased PAWP in this case, we carefully chose a therapeutic strategy considering the involvement of left ventricular diastolic dysfunction, which was common in patients with MPNs.[5] As PH-targeted drugs could worsen pulmonary hemodynamics in patients with left ventricular diastolic dysfunction, we initiated sequential therapy with two PH-targeted drugs under the euvolemic status, improving PH. As increased PAWP could be partly caused by the interaction between the right and left ventricle due to PH, we need to consider the balance between the benefits and risks expected from using PH-targeted drugs among patients with multifactorial PH.

Journal Pre-proof

In conclusion, this is the first report of sequential combination therapy with multiple PH-targeted drugs and a JAK2 inhibitor, leading to adequate improvement of pulmonary hemodynamics and risk category in patients with PV and PH.

Novel Teaching Point

- Clinical findings of pulmonary arterial hypertension, which may improve by PH-targeted drugs, could be overlooked in patients with well-controlled PV because of noticeable clinical manifestations and findings of left heart failure.

Funding Sources

The authors have no funding sources to declare.

Disclosure

The authors have no potential conflicts of interest related to any company or organization whose products or services are discussed in this article.

Journal Pre-proof

Journal Pre-proof

References

1. Adir Y, Elia D, Harari S. Pulmonary hypertension in patients with chronic myeloproliferative disorders. Eur Respir Rev. 2015;24:400-10.

2. Khan NA, Ahuja KA, Wang X, Chaisson NF. Evaluation of hemodynamic parameters among patients with myeloproliferative neoplasms suspected pulmonary hypertension. Leuk Lymphoma. 2021;62:1458-65.

3. Tachibana T, Nakayama N, Matsumura A, et al. Pulmonary hypertension associated with pulmonary veno-occlusive disease in patients with polycythemia vera. Intern Med. 2017;56:2487-92.

4. Tabarroki A, Lindner DJ, Visconte V, et al. Ruxolitinib leads to improvement of pulmonary hypertension in patients with myelofibrosis. Leukemia. 2014;28:1486-93.

5. Kim J, Krichevsky S, Xie L, et al. Incremental utility of right ventricular dysfunction in patients with myeloproliferative neoplasm-associated pulmonary hypertension. J Am Soc Echocardiogr. 2019;32:1574-85.

Journal Pre-proof

Journal Pre-proof

Figure legends

Figure 1. Clinical time-course changes in the present case. mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; PVR, pulmonary vascular resistance; PAWP, pulmonary arterial wedge pressure; RAP, right atrial pressure; DPG, diastolic pressure gradient; CI, cardiac index; RVSWi, right ventricular stroke work index; PAPi, pulmonary artery pulsatility index; 6MWD, 6-min walk distance; BNP, brain natriuretic peptide; REVEAL, Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management. Cardiac output was measured by using the indirect Fick method.

Journal Pre-proof

Journal Pre-proof

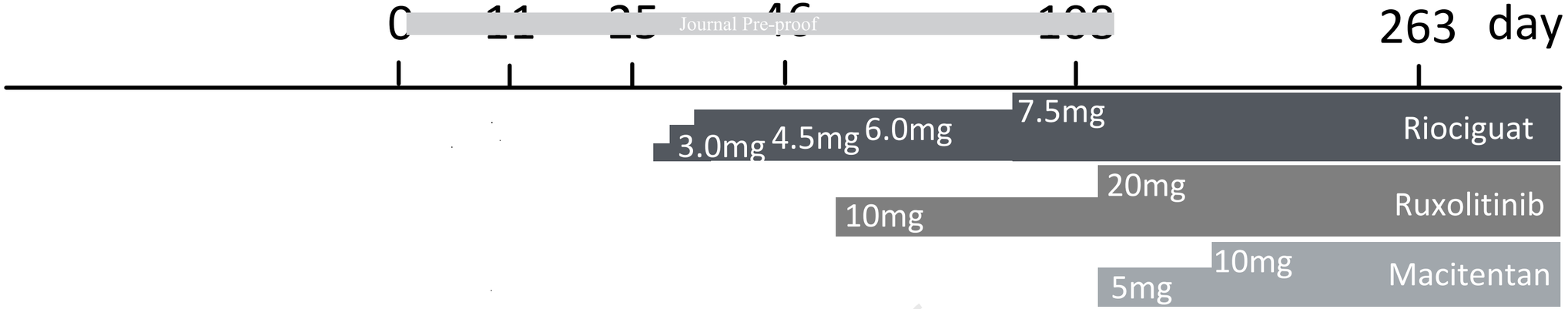
Table 1: Left heart disease risk factors and clinical time-course changes in cardiac medications except PH-targeted medications

Left Heart Disease Risk Factors	
Atrial Fibrillation	(+)
Body mass index	16.9 (the 25th day):
Hypertension	(−)
Diabetes mellitus	(−)
Coronary artery disease	(−)

Clinical time-course changes in cardiac medications except PH-targeted medications						
	Before admission	Day 11	Day 25	Day 46	Day 108	Day 263
Furosemide (mg)	40	60	20	20	20	20
Spironolactone (mg)	50	50	0	0	0	0
Tolvaptan (mg)	0	0	3.75	3.75	7.5	7.5
Bisoprolol (mg)	5	5	2.5	1.25	1.25	0
Digoxin (mg)	0	0	0	0	0	0.125
Dobutamine (mcg/kg/min.)	0	3	0	0	0	0

Administration of furosemide was switched from oral to intravenous on admission. Furosemide infusion was started at 40 mg daily and increased to a maximum of 60mg. Furosemide was switched from intravenous to oral 20mg daily on the 17th day. Spironolactone was discontinued due to hyperkalemia on the 21st day. Tolvaptan was started at 3.75 mg daily on the 12th day and increased to 7.5 mg daily on the 109th day. Bisoprolol had switched to digoxin 0.125 mg daily on the 109th day.

Figure 1



mPAP (mmHg)	36	35	35	31	27
sPAP (mmHg)	56	68	54	46	46
dPAP (mmHg)	24	23	21	22	15
PVR(Wood units)	7.9	14.7	6.7	7.7	3.8
PAWP (mmHg)	16	6	12	11	13
RAP (mmHg)	19	5	7	12	7
DPG (mmHg)	8	17	9	11	2
CI (L/min/m^2)	1.8	1.6	2.7	2.0	2.8
RVSWI (g/m/beat/m^2)	4.5	9.1	13.0	6.7	12.7
PAPi	1.7	9.0	4.7	2.0	4.4
6MWD (m)			234	300	340
BNP (pg/mL)	234.9	158.4	111.0	63.3	47.8
WHO-FC	IV	III	III	III	II
Systolic BP; HR	92; 89	96; 71	92; 78	93; 76	112; 61
Pericardial effusion	+	+	-	-	-
REVEAL 2.0 score	17	15	13	13	6

Journal Pre-proof