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Pathophysiology of Pulmonary Hypertension in Patients with Myeloproliferative Neoplasms

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Abstract

Pulmonary hypertension (PH) is a syndrome characterized by marked remodeling of the pulmonary vasculature and a progressive increase in the pulmonary vascular load, resulting in right ventricular hypertrophy and remodeling. PH is a serious complex disorder which is associated with high morbidity and mortality rates. It is considered one of the major complications of myeloproliferative neoplasms (MPNs) mainly in advanced disease. It is classified according to the World Health Organization (WHO) into five groups. MPNs are involved within group 5 PH which is due to an unclear and/or multifactorial etiology. The occurrence of PH in MPNs patients has a bad impact on the prognosis of the disease and on the survival in those patients. The pathogenesis of PH in MPNs patients is multi-factorial. Three characteristic clinical types of PH are recognized as unique pathologic mechanisms in MPNs patients: chronic thromboembolic pulmonary hypertension (CTEPH), precapillary pulmonary hypertension, and drug-induced pulmonary hypertension.

Keywords: Pulmonary hypertension, Myeloproliferative neoplasms**,** Chronic thromboembolic pulmonary hypertension, JAK2 gene mutation.

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Introduction

Pulmonary hypertension (PH) is a syndrome characterized by marked remodeling of the pulmonary vasculature and a progressive increase in the pulmonary vascular load, resulting in right ventricular hypertrophy and remodeling. PH is a serious complex disorder that associated with high morbidity and mortality rates. It is now defined in terms of hemodynamic criteria by amean pulmonary arterial pressure (mPAP) determined by right heart catheterization of more than 20 mm Hg at rest .[(1)] PH is classified according to the World Health Organization (WHO) into five groups.[(2)] PH is considered one of the major complications of myeloproliferative neoplasms (MPNS). MPNs are classified within group 5 PH which occurs due to an unclear and/or multifactorial etiology. MPNs are a wide group of disorders characterized by increased production of myeloid cells due to an abnormal clone of hematopoietic stem cells. Currently, MPNs are classified according to 2016 revised WHO classification into seven subgrups, which include (i) Chronic Myeloid Leukemia (CML); (ii) Chronic Neutrophilic Leukemia, CNL; (iii) Chronic Eosinophilic Leukemia-Non otherwise specified, CEL-NOS; (iv) MPN, unclassifiable (MPN-U); and the three classical Philadelphia-negative MPNs wh-

ich include (v) Polycythemia Vera (PV), (vi) Essential Thrombocythemia (ET), and (vii) Primary Myelofibrosis (PMF). PMF is further sub-classified into "prefibrotic" and "overtly fibrotic" PMF. [3]

Pathophysiology

The pathogenesis of PH in MPNs patients is multi-factorial. MPNs lead to a state of hypercoagulability due to thrombocytosis or erythrocytosis directly induced thrombosis, shear-induced platelet activation and consequent thrombosis in addition to hyperviscosity. Tumor micro-embolism within the pulmonary vasculature, altered membrane structure of red and white blood cells with subsequent clot formation, and splenectomy used in the therapy of MPNs are also contributing factors for the development of MPNs-induced hypercoagulable state. Old age, prior thrombotic events, cardiovascular risk factors, [4] and the presence of inherited thrombophilia such as protein C & S deficiency and factor V Leiden gene mutation, all further increase the possibility of thrombotic events in those patients. Several other factors were found to be responsible for MPNs-associated PH including extra-medullary hematopoiesis within the pulmonary vasculature, obstruction of pulmonary vessels by megakaryocytes, porto-pulmonary hypertension related to organomegaly, pulmonary myeloid infiltration, proliferation of pulmonary myocytes, and development of myelofibrosis [5]

Drug-induced PH in MPNs is also an important possible mechanism. Tyrosine kinase inhibitors mainly dasatinib frequently used in CML therapy are associated with precapillary PH, resembling pulmonary arterial hypertension (PAH).[6] In addition, chemotherapy-induced pulmonary veno-occlusive disease (PVOD) is considered an important form of pulmonary vascular disease.[7] Bone marrow transplantation also potentiates the risk of PVOD in MPNs patients.[8] Three characteristic clinical types of PH are recognized as unique pathologic mechanisms in MPNs patients: CTEPH, precapillary PH, and drug-induced PH.

1- Chronic thromboembolic pulmonary hypertension (CTEPH):-

Aetiology:-

CTEPH is considered one of the major unique possible mechanisms in the development of MPNs-associated PH. MPNs-induced thrombophilia state with subsequent microcirculatory disturbances, and arterial and venous thrombosis.[9] is involved in the occurrednce of CTEPH in patients with MPNs. The pathogenesis of thrombophilia state and subsequent CTEPH in MPNs is multi-factorial. Blood hyperviscosity particularly in PV & ET due to erythrocytosis & thrombocytosis, increased platelets activation and aggregation, and polymorphonuclear leukocyte (PMN) activation are supposed to be contributing factors.[10] Patients harboring JAK2V617F gene mutation have increased activation of polymor-phonuclear leucocytes, increased platelet activation and aggregation, increasing the risk of thrombotic complications in MPNs patients [11]. Splenectomy with subsequent worsening extra-medullary hemato-poiesis within the pulmonary vasculature is also considered a risk factor for the development of CTEPH in patients with MPNs [12]

Treatment:-

Lifelong therapeutic anticoagulation is recommended for all patients with CTEPH. Vitamin K antagonists (VKAs) are recommended for patients with CTEPH while new oral anticoagulants (NOACs) are still lacking evidence. Surgical pulmonary endarterectomy (PEA) is the recommended treatment of choice for CTEPH in operable cases

with accessible pulmonary artery proximal fibrotic lesions. Ballon pulmonary angioplasty (BPA) is recommended for inoperable patients or patients with distal CTEPH eligible for BPA. Medical therapy is recommended for symptomatic inoperable CTEPH patients and patients with residual or recurrent PH after PEA. Riociguat, was reported to increase exercise capacity and decrease pulmonary vascular resistance and thus, improving pulmonary hemodynamics.

So, it is approved for this indication. SC treprostinil and other PAH-specific therapy e.g phosphodiesterase-type 5 inhibitors, endothelin receptor antagonists such as oral bosentan or parenteral prostacyclin analogues may be considered [1]

There are no available specific data concerning the therapy of MPNs-associated CTEPH till now. The management of the underlying MPNs e.g PV and ET is recommended to be in the same manner as in the general population. Aspirin, phlebotomy and cytoreductive therapy with hydroxyurea are recommended. Hydroxyurea was reported to minimize the possibility of thrombotic complications in patients at high risk. This effect can be explained in view of decreasing leukocytes count and minimizing their activation [13]

2-Precapillarpulmonary hypertension:-

Aetiology:-

Several factors are involved in the development of precapillary PH in MPNs including portal hypertension in patients with myelofibrosis, PVOD in response to chemotherapeutic agents and bone marrow transplantation [14], tumor micro-embolism with obstructtion of pulmonary microvasculature by megakaryocytes, extramedullary pulmonary hematopoiesis, and increased angiogenesis in myelofibrosis patients due to secretion of vascular-endothelial growth factor and platelets-derived growth factor from activated platelets leading to increased bone marrow micro-vessel density reflecting the occurrence of a pro-angiogenic phenomenon [15]

Treatment:-

No effective specific therapy for MPNs-associated precapillary PH is approved till now. The therapy should focus on the treatment of the underlying hematologic pathology.

In PV, antiplatelet prophylaxis is standard of care, but its role in PH remains unclear. Cytoreductive therapy such as hydroxyurea may have a role and used in patients at high risk to prevent thrombotic events. [13]

Furthermore, improvement of PAH post-allogenic bone marrow transplant in myelofibrosis has been noted, but robust studies remain lacking. The whole-lung low-dose external beam radiotherapy has been tried as a palliative therapy for MPNs-associated PH with evidence of extramedullary pulmonary hematopoiesis [16]. Ruxolitinib (pan-JAK inhibitor) is recommended for the therapy of patients with myelofibrosis at intermediate or high risk. However, ruxolitinib has been reported to induce worsening of PAH which was reversible after the drug discontinuation [17]. The response of PAH to the conventional therapy in the form of endothelin receptor antagonists, prostacyclin analogues and phosphodiesterase-type 5 inhibitors, should be furth-er evaluated in randomized controlled trials.

3-Drug-inducedpulmonary hypertension:-

Tyrosine kinase inhibitors (TKIs) e.g imatinib, dasatinib, and nilotinib, used in CML therapy, has been involved in the occurrence of PH in CML. PH has been reported more frequently with dasatinib. Clinical, functional, and he-

modynamic improvements are noted 4 months after stoppage of dasatinib therapy [6]. Moreover, nilotinib was found to induce isolated pulmonary vasculitis and stenosis causing PH in a recent case report [18]. Multiple mechanisms may contribute to nilotinib-induced vasculopathy. Nilo-tinib has been reported to cause vascular vasospasm and stenosis and has direct proatherogenic and anti-angiogenic effects on vascular endothelial cells.[19]

Prognosis

The prognosis of MPNs-associated CTEPH and precapillary PH patients is still poor. However, PEA is the recommended gold standard treatment in proximal CTEPH. MPNs-associated PH is still a heterogeneous and challenging clinical entity. Their relative rarity and/or variable clinical presentations has made it challenging to study these entities in randomized clinical trials and make recommendations of an integrated treatment to be widely applied. Much more deep understanding can be obtained from future preclinical studies focusing on identifying the pathogenic mechanisms of pulmonary vasculopathy.

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