STM JOURNALS

Research & Reviews: A Journal of
Pharmacology

https://journals.stmjournals.com/rrjop

ISSN: 2230-9861 (Online)
ISSN: 2349-1299 (Print)
Volume 14, Issue 3, 2024
September–December
DOI (Journal):
10.37591/RRJoP

Review RRJoP

Dasatinib Induced Pulmonary Hypertension

Tanusha Pillai[1,*], Sunitha M.[2], Ganesh N. S.[3]

Abstract

Dasatinib (Das) is a second-generation tyrosine kinase inhibitor that is used in the treatment of chronic myelogenous leukemia (CML) in patients who are resistant or intolerant to imatinib, as well as in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) patients. Dasatinib-induced pulmonary arterial hypertension (PAH) is a known but rare adverse effect of dasatinib and is grouped under Group-1 PAH. The mechanism of PAH development is not fully known, but there are proposed theories and experiments performed, dasatinib is a BCR-ABL1 inhibitor like imatinib and nilotinib, but it also is an Src kinase inhibitor, which could be one of the factors causing PAH. Patients with pre-existing cardiovascular or pulmonary disease may also experience pulmonary hypertension due to factors such as endothelial dysfunction and vasoconstriction. Risk factors include higher doses, prolonged treatment duration, and fluid retention, which can exacerbate pulmonary artery pressure. Regular monitoring for symptoms of PH is essential for early detection and management in patients receiving dasatinib. Usually, the symptoms resolve once the drug is discontinued. The treatment includes prostanoids like Epoprostenol 2ng/kg/min, endothelin receptor antagonists like Bosentan 62.5 mg twice daily, Ambrisentan 10 mg once daily, PDE-5 inhibitors like Sildenafil 5 mg thrice daily or Tadalafil 40 mg once in a day and guanylate cyclase stimulants like Riociguat 1 mg thrice in a day.

Keywords: Dasatinib, pulmonary hypertension, acute lymphoblastic leukemia, Src kinase inhibitors, imatinib-resistant chronic myelogenous leukemia (CML)

INTRODUCTION

Pulmonary hypertension or pulmonary arterial hypertension (PAH) is hemodynamically defined by a mean pulmonary artery pressure (mPAP) >20 mmHg according to the 6th World Symposium on pulmonary hypertension [1]. PAH is usually confirmed by right heart catheterization (RHC) [2].

PAH is usually classified into 5 groups according to their patho-mechanisms and clinical management [3]. Group 1 pulmonary arterial hypertension refers to the condition where the arteries in the lungs become narrowed, its causes could be idiopathic, heritable, drug-induced, or linked with various other conditions [3]. Group 2 corresponds to postcapillary PH which occurs due to left heart disease, valvular heart disease, or due to restrictive cardiomyopathy [4]. Group 3 occurs due to chronic lung diseases or hypoxemia, which occurs in chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, or alveolar hypoventilation disorder [3, 4]. Chronic thromboembolic illness, or chronic thromboembolic pulmonary hypertension (CTEPH), is associated with group 4 PAH [3, 4]. Group 5 includes a miscellaneous complex group of disorders resulting in PAH, consisting of metabolic disorders like glycogen storage disease, thyroid disease, Gaucher disease, systemic

***Author for Correspondence**
Tanusha Pillai
E-mail: tanushapillai2001@gmail.com

[1]Student, Department of Pharmacy, T. John College of Pharmacy, Bangalore, Karnataka, India.
[2]Assistant Professor, Department of Pharmacy Practice, T. John College of Pharmacy, Bangalore, Karnataka, India.
[3]Professor and Head, Department of Pharmaceutics, T. John Collage of Pharmacy, Bangalore, Karnataka, India.

Received Date: November 14, 2024
Accepted Date: December 17, 2024
Published Date: December 31, 2024

Citation: Tanusha Pillai, Sunitha M, Ganesh N. S. Dasatinib Induced Pulmonary Hypertension: A Journal of Pharmacology 2024; 14(3): 92– 95p.

© STM Journals 2024. All Rights Reserved

disorders like sarcoidosis, vasculitis, neurofibromatosis type 1, hematologic diseases like myeloproliferative disorders, and miscellaneous causes such as end-stage renal disease on dialysis, extrinsic compression of pulmonary vessels, embolization of the tumor [4].

Pulmonary hypertension caused by drugs and toxins are grouped under Group 1-PH according to WHO, and the ICD-10 code is I27.21. It is a rare and incurable disease, which affects 11 to 26 cases per million adults [5]. The first drug identified to cause PH was aminorex [2], an anorexic drug that was banned later. Other drugs known to cause PAH include: Fenfluramine, cocaine, sofosbuvir, bleomycin, cyclophosphamide, amiodarone, tyrosine kinase inhibitors: Dasatinib, nilotinib, bosutinib, and ponatinib [6].

PAH is asymptomatic during its initial stages [7]. The common early symptoms include breathlessness, exertional intolerance, fatigue, dyspnea, weakness, syncope, and chest pain [7]. As the condition progresses, patients may experience symptoms such as palpitations, congestive heart failure, ascites, generalized edema, and tachyarrhythmia that are indicative of right-sided heart failure [7].

Chronic myelogenous leukemia (CML) is a myeloproliferative cancer that results from the genetic translocation in the Philadelphia chromosome – t (9;22) (q34;q11.2) which leads to the fusion of BCR and ABL1 genes into the pathogenic BCR-ABL1 oncogene [8], whereas Philadelphia-chromosome positive (Ph+) Acute Lymphoblastic Leukemia (ALL) is also characterized by the presence of reciprocal translocation-t (9;22) (q34;q11), leading to BCR-ABL fusion gene encoding BCR-ABL oncoprotein, that has constitutive tyrosine kinase activity [9]. It is usually treated using BCR-ABL1 targeting tyrosine kinase inhibitors- first generation: imatinib, second generation – dasatinib or nilotinib [8, 9, 10]. Dasatinib was found to be 325 times more potent *in vitro* against unmutated BCR-ABL1 than imatinib [2, 3].

Dasatinib a second-generation tyrosine kinase inhibitor used in the treatment of imatinib-resistant or intolerant CML patients [10, 11], was approved in the United States in November 2007 for treatment of chronic phase CML [12]. Dasatinib acts by binding to the ATP-binding sites in both active and inactive ABL conformations with a higher affinity than imatinib, hence inhibiting BCR-ABL kinase. Moreover, it suppresses tyrosine kinases (c-KIT, PDGFR, EphA2) and Src kinases, interfering with downstream pathways in CML progenitors such as MAPK, Akt, and STAT5. [13]

Dasatinib earlier was given at 70mg twice daily dose, which caused significant pleural effusion in 14-35% of patients which has been attributed to PDGFR- β inhibition or autoimmune-mediated mechanism. [2] The current FDA-approved dosage for dasatinib for patients with chronic phase CML (CML-CP) is 100 mg once a day and 140 mg once daily for the advanced stage [14].

Pathogenesis of Dasatinib Induced Pulmonary Arterial Hypertension

While there is no definitive mechanism established for dasatinib-induced pulmonary arterial hypertension, several proposed mechanisms have been discussed.

Pulmonary arterial hypertension (PAH) results in pathological changes such as vascular remodeling which involves endothelial injury, proliferation, and migration of pulmonary arterial smooth muscle cells (PASMCs) [15], vasoconstriction and thrombosis, all this leading to increased pulmonary vascular resistance [2]. These alterations in physiology lead to pulmonary hypertension.

Platelet-derived growth factor (PDGF) signaling-related cellular proliferation is involved in the development of PH in both animals and humans. Imatinib which can also inhibit the PDGFR, is used as a potential treatment for PAH [2, 16].

Guignabert and colleagues performed an experiment on rats, where dasatinib administration alone

© STM Journals 2024. All Rights Reserved

produced an augmented reaction to monocrotaline and chronic hypoxia, but did not cause PAH [12]. This observation suggests that dasatinib may inhibit certain pathways.

It is considered that dasatinib promotes inflammation of the PASMCs and elevates T-lymphocytes, leukocytes, monocytes, and macrophages leading to PAH. Additionally, it has off-target inhibition of Src, a non-receptor tyrosine kinase family [17].

Src family kinases (SFKs) play an important role in vascular regulation which includes vasodilation and vascular proliferation [12]. Their activity is essential for maintaining normal pulmonary artery function.

TASK-1 (TWIK-related Acid-sensitive K+ channel 1) is a potassium channel that plays a crucial role in regulating cellular excitability and maintaining the membrane potential in various cell types, including pulmonary arterial smooth muscle cells (PA-SMCs). By regulating the flow of potassium ions across the cell membrane, TASK-1 influences the vasodilation and vasoconstriction of the pulmonary arteries. In hypoxia conditions Src phosphorylation is reduced, which decreases TASK-1 activity, which leads to decreased potassium current and increased pulmonary artery vasoconstriction, elevating the blood pressure in these vessels.

In addition to this, the SFK inhibition also reduces the increase in calcium levels which is caused by hypoxia, the calcium signaling also plays a role in increased vasoconstriction, as observed in pulmonary hypertension.

Management of Dasatinib-Induced Pulmonary Arterial Hypertension

Earlier dasatinib was recommended in the dose of 70 mg twice in a day, this caused the most relevant non-hematological adverse effects.

Pleural effusion (PE) was observed in around 14–35% of the patients on dasatinib, this adverse effect is also called as ‘off-target effects’ of dasatinib. This is probably linked to an autoimmune response or inhibition of the PDGFR β, rather than fluid retention. The incidence of severe PE has dropped to under 2% with the approved 100 mg daily dose. Despite adjustments to the dosing regimen, pulmonary arterial hypertension persists as one of the major adverse effects of dasatinib.

Dasatinib-induced PAH can be reversed after discontinuing the drug. Additional management of PAH due to Das can be done by starting pulmonary artery vasodilators, various classes of vasodilators include Phosphodiesterase type-5 inhibitors (PDE-5 inhibitors) such as sildenafil, tadalafil, vardenafil, Endothelin receptor antagonists (ERAs) like ambrisentan, bosentan, macitentan, prostanoids such as epoprostenol, iloprost, treprostinil, beraprost and selexipag, Guanylate cyclase stimulants, or a combinational therapy if required [2].

The prototypes of each class of drug are used in the dose of Epoprostenol 2ng/kg/min, ERAs-Ambrisentan 10 mg once daily, PDE-5 inhibitors like sildenafil 5mg thrice daily or tadalafil 40 mg once in a day and guanylate cyclase stimulants like riociguat 1mg thrice in a day.

CONCLUSIONS

Dasatinib, a second-generation tyrosine kinase inhibitor, has been linked to pulmonary arterial hypertension (PAH) despite not directly causing PAH in animal models. The drug affects key regulatory pathways, including platelet-derived growth factor signaling and Src kinases, leading to increased inflammation and vascular changes that can contribute to PAH. Patients on dasatinib often experience symptoms such as breathlessness, fatigue, and syncope, which can escalate to more severe issues like right-sided heart failure. Understanding these mechanisms is crucial for improving patient management and mitigating the risk of PAH in those undergoing dasatinib treatment.

© STM Journals 2024. All Rights Reserved

Treatment for PAH typically involves using pulmonary vasodilators, which will manage the symptoms and improve the quality of life.

REFERENCES

1. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Euro Respiratory J. 2019;53(1):1801913.
2. Özgür Yurttaş N, Eşkazan AE. Dasatinib-induced pulmonary arterial hypertension. British J Clin Pharmacol. 2018;84(5):835–845.
3. Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bourdin A, et al. Pulmonary arterial hypertension in patients treated by Dasatinib. Circ. 2012;125(17):2128–237.
4. Pahal P, Sharma S. Secondary Pulmonary Hypertension. Treasure Island (FL): StatPearls Publishing; 2024.
5. Hlavaty A, Roustit M, Montani D, Chaumais MC, Guignabert C, Humbert M, Cracowski JL, Khouri C. Identifying new drugs associated with pulmonary arterial hypertension: A WHO pharmacovigilance database disproportionality analysis. British J Clin Pharmacol. 2022;88(12):5227–5237.
6. McGee M, Whitehead N, Martin J, Collins N. Drug-associated pulmonary arterial hypertension. Clin Toxicol. 2018;56(9):801–809.
7. Shah NP, Wallis N, Farber HW, Mauro MJ, Wolf RA, Mattei D, Guha M, Rea D, Peacock A. Clinical features of pulmonary arterial hypertension in patients receiving dasatinib. Am J Hematol. 2015;90(11):1060–1064.
8. Eden RE, Coviello JM. Cancer, Chronic Myelogenous Leukemia (CML, Chronic Granulocytic Leukemia). Treasure Island (FL): StatPearls Publishing; 2020.
9. Saleh K, Fernandez A, Pasquier F. Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia in adults. Cancers. 2022;14(7):1805.
10. Rinaldi I, Winston K. Chronic myeloid leukemia, from pathophysiology to treatment-free remission: a narrative literature review. J Blood Med. 2023:261–277.
11. Ashraf El-Dabh, Acharya D. Pulmonary hypertension with dasatinib and other tyrosine kinase inhibitors. Pulm Circ. 2019;9(3):1–6.
12. Aguilera DG, Tsimberidou AM. Dasatinib in chronic myeloid leukemia: a review. Ther Clin Risk Manag. 2009;281–289.
13. Keskin D, Sadri S, Eskazan AE. Dasatinib for the treatment of chronic myeloid leukemia: patient selection and special considerations. Drug Des Devel Ther. 2016;3:3355–3361.
14. Pullamsetti SS, Berghausen EM, Dabral S, Tretyn A, Butrous E, Savai R, et al. Role of Src tyrosine kinases in experimental pulmonary hypertension. Arterioscler Thromb Vasc Biol. 2012;32(6):1354–1356.
15. Montani D, Seferian A, Savale L, Simonneau G, Humbert M. Drug-induced pulmonary arterial hypertension: a recent outbreak. Euro Respiratory Rev. 2013;22(129):244–250.
16. Jacobs JA, Jahangir E, Ryan JJ. Differentiating pulmonary hypertension associated with protein kinase inhibitors. Pulm Circ. 2022;12(2).
17. Guignabert C, Montani D. Key roles of Src family tyrosine kinases in the integrity of the pulmonary vascular bed. Euro Respiratory J. 2012;41(1):3–4.

© STM Journals 2024. All Rights Reserved