Pulmonary Hypertension Induced by Anticancer Drugs

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Introduction

Among the manifestations of anticancer drug-induced cardiotoxicity involving the pulmonary circulation, the development of pulmonary hypertension (PH) is a rare but well-recognized possible complication of childhood chemotherapy and bone marrow transplantation (BMT) for leukemia [1], while other chemotherapeutic agents such as alkylating drugs (mitomycin C, cyclophosphamide) can determine progressive obstruction of small pulmonary veins rather than the distal pulmonary arterioles, thus leading to pulmonary veno-occlusive disease (PVOD) [2]. The tyrosine-kinase inhibitor (TKI) dasatinib, used as second-line treatment for chronic myelogenous leukemia, represents the most interesting example of a chemotherapeutic drug that can induce PH [3]. When the increase in pulmonary pressure meets the hemodynamics criteria for precapillary PH (defined as mean pulmonary artery pressure of >25 mmHg at rest, with pulmonary artery wedge pressure ≤ 15 mmHg and pulmonary vascular resistance >3 wood units in the absence of other causes of precapillary PH such as lung diseases, chronic thromboembolic PH, or other rare diseases), this condition is diagnosed as drug-induced pulmonary arterial hypertension (PAH), and it is categorized in the group 1 of the clinical classification for PH [4] (Table 14.1).

PAH, regardless of the etiology, is a rare condition that is often difficult to diagnose because of the nonspecific symptoms in the early stage of the disease but has a serious and progressive course, leading to the development of right heart failure and ultimately death [4, 5]. The latest guidelines for diagnosis and treatment of PH classified as *likely* the risk level of dasatinib to induce PAH, while *possible* the risk associated with some chemotherapeutic agents such as alkylating agents (mitomycin C, cyclophosphamide) [4]. Theoretically, PH with unclear or multiple causes may develop in patients with chronic myeloid leukemia per se, independently from chemotherapeutic drugs [6, 7]. However, data from the French PH Registry clearly showed that all incident cases of PH reported in chronic myeloid leukemia occurred only in patients

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A. Russo et al. (eds.), *Cardiovascular Complications in Cancer Therapy*, Current Clinical Pathology,
https://doi.org/10.1007/978-3-319-93402-0_14

Table 14.1 Summary of the main antineoplastic treatments that can induce pulmonary vascular toxicity

Antineoplastic treatment	Clinical feature	Mechanism
Bone marrow transplantation	PAH, PVOD	Endothelial dysfunction
Mitomycin C	PVOD	Endothelial dysfunction/VEGF receptor inhibition
Bleomycin	PH secondary to pulmonary fibrosis	Oxidative damage, relative deficiency of the deactivating enzyme bleomycin hydrolase, genetic susceptibility, and production of inflammatory cytokines
Cyclophosphamide	PVOD, rarely PAH	Endothelial dysfunction
Dasatinib	PAH	Inhibition of tyrosine kinases implicated in cellular proliferation/ pulmonary vascular balance

Abbreviations: *PAH* Pulmonary Arterial Hypertension, *PVOD* Pulmonary Veno-Occlusive Disease, *PH* Pulmonary Hypertension, *VEGF* Vascular Endothelial Growth Factor

treated with dasatinib. Furthermore, a direct link between dasatinib and PH was demonstrated by the clinical and hemodynamic improvement observed after switching dasatinib with another TKI, like nilotinib [3].

As mentioned, cyclophosphamide and other alkylating agents pulmonary vascular toxicity involves predominantly small venules, in the form of PVOD. This condition represents the most severe form of pulmonary hypertension and unfortunately lacks effective pharmacological treatment so far. PVOD is a rare form of PH typically characterized by progressive obstruction of small pulmonary veins, due to a widespread fibrous intimal proliferation of veins and venules, often associated with pulmonary capillary dilatation and proliferation [8]. Its diagnosis is quite a challenge, and it is often misclassified as idiopathic PAH. Chemotherapy-induced PVOD has a fatal course in most of the cases, even if few case reports suggest that specific treatment with the pulmonary vasodilator endothelin receptor antagonist may induce a favorable response [9, 10]. The pathophysiological mechanisms of PVOD are poorly understood. Limited case reports or case series of PVOD induced by polychemotherapeutic treatment have been reported in the literature [10, 11]. Even if a clear relationship between a specific drug and PVOD is difficult to establish because of the use of several combinations of drugs in chemotherapeutic regimens, basing on observations from the literature, it has been demonstrated that a key role in the development of this adverse toxicity is played by alkylating agents and in particular by mitomycin C and cyclophosphamide but also bleomycin and carmustine [2, 12–14]. Moreover, also BMT is considered a risk factor for PAH and PVOD [15, 16].

Mechanisms of Pulmonary Vascular Damage Induced by Bone Marrow Transplantation

Concerning the effects of BMT on pulmonary circulation, it has been known since 1984 a link between BMT and the development of PVOD, thus providing the earliest evidence that bone marrow compartment could adversely affect the pulmonary vasculature [17]. The incidence of PAH in post-childhood cancer therapy and BMT is estimated to be 1.6% based on single-center experience [1]. From a pathophysiological standpoint, it has been shown that bone marrow-derived cells contribute to the pathogenesis of pulmonary arterial hypertension inducing remodeling and inflammation [18]. Endothelial cell injury has been shown after allogenic BMT and has been directly linked to the development of several implications including graft-versus-host disease, PVOD, and endothelial leakage syndrome. Endothelial alterations could occur also in the pulmonary circulation, determining an imbalance in pulmonary vascular mediators, thus causing pulmonary vasoconstriction and remodeling of the vascular structure [1]. Currently, deeper knowledge of the actual mechanisms that underlie the development of BMT-related PH is not available.

Mechanisms of Pulmonary Vascular Damage Induced by Mitomycin C and Bleomycin

Mitomycin C can induce PVOD. This condition is an uncommon form of PH typically characterized by the obstruction of small pulmonary veins and a poor prognosis. Patients with PVOD typically present with precapillary PH, peculiar thoracic high-resolution CT alterations, a low diffusing capacity of the lung for carbon monoxide, and severe hypoxemia. The estimated incidence of PVOD in patients treated with mitomycin is 3.9 per 1000 per year, which is relevantly higher in comparison to its incidence in the general population (0.5/million per year) [11]. Furthermore, females seemed to be more susceptible to mitomycin toxicity.

Several mechanisms have been described to concur in the development of mitomycin-induced PVOD. This drug is an alkylating agent commonly used in several regimens for the treatment of different cancers [19]. The main mechanism of action of this drug implies its covalent binding to DNA determining DNA synthesis inhibition [20]. It results in decrease in cell viability and induces apoptosis in corneal endothelial cells [21]. Recent studies further demonstrated that mitomycin inhibits vascular endothelial growth factor (VEGF) expression [22], causing apoptosis resistance and unlimited endothelial cell proliferation, similar to what happens in the sugen/hypoxic rat model [22]. In rats, intraperitoneal administration of mitomycin caused major remodeling of small pulmonary veins associated with foci of intense microvascular endothelial cell proliferation consistent with PVOD [11]. These alterations were prevented by the administration of amifostine, a cytoprotective adjuvant used in chemotherapeutic and radiotherapeutic regimens involving DNA-binding chemotherapeutic agents [11].

Bleomycin, another chemotherapeutic drug belonging to the class of the antibiotics and commonly used for the treatment of lymphomas, is also associated with the occurrence of PH [23]. The overall risk of pulmonary toxicity is about 10%. Pulmonary hypertension due to bleomycin is secondary to the development of pulmonary fibrosis. The underlying mechanism is mainly related to oxidative damage, relative deficiency of the deactivating enzyme bleomycin hydrolase, genetic susceptibility, and production of inflammatory cytokines [24].

Mechanisms of Pulmonary Vascular Damage Induced by Alkylating Agents

Alkylating agents may be responsible of the development of PVOD rather than PAH, and this form of toxicity has been known for several years [12].

Cyclophosphamide, an alkylating agent, is used as immunosuppressant in several autoimmune diseases and as a common component of multidrug regimens for treatment of hematological and solid cancers. In different animal models, cyclophosphamide demonstrated to be able to induce PH. From a histopathological standpoint, all these models revealed significant alterations of the pulmonary venules and veins, highly suggestive of PVOD [2]. Specifically, cyclophosphamide induced pulmonary vein wall thickening due to adventitial and transmural inflammatory infiltration and fibrosis, muscularization of distal microvessels with foci of pulmonary congestion, consistent with PVOD [2]. It has been demonstrated that endothelial cells are more susceptible to the effector of cyclophosphamide than other cell types [25, 26].

Mechanisms of Pulmonary Vascular Damage Induced by Dasatinib

The actual incidence of PAH during treatment with dasatinib is still a matter of debate, ranging from 0.6% up to 11% [3].

From a clinical standpoint, median delay for dasatinib-induced PAH diagnosis is usually 34 months (ranging from 8 to 40 months after exposure to the drug). Unlike other forms of PAH, dasatinib-induced PAH is often reversible after drug discontinuation or replacement with another TKI, such as nilotinib [3, 27–30]. In some cases, because of the persistence of

symptoms and of the increase in pulmonary arterial pressures, specific treatment with pulmonary vasodilator agents has been prescribed, with beneficial results [3, 27–30].

Dasatinib, as already mentioned above, is an oral second-generation TKI recently approved as a first- or second-line treatment for chronic Philadelphia chromosome-positive (which corresponds to the reciprocal translocation between chromosome 9 and 22, thus causing the Abelson TK gene, ABL, to fuse with the breakpoint cluster region of the BRC gene) myelogenous leukemia [31, 32] and currently approved also for second-line treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia [33]. The BCR/ABL oncogene is responsible for a pathogenic tyrosine kinase signal transduction protein that triggers intracellular signaling, activating multiple transduction cascades. This pathway promotes growth, proliferation, and survival of hematopoietic cells [34] and plays a role in defective DNA repair, alteration of cellular adhesion, and inhibition of apoptosis [35]. Deregulated BCR/ABL tyrosine kinase activity is the molecular marker for chronic myelogenous leukemia. Drugs like imatinib, nilotinib, and dasatinib that target BCR/ABL tyrosine kinase and block its activity lead to the induction of apoptosis and inhibits malignant cells' proliferation [36]. Dasatinib, characterized by a 300-fold higher affinity for BRC/ABL kinase in comparison with imatinib, is more effective in patients who failed treatment with imatinib [37]. However, dasatinib is also able to inhibit several other kinases, including the Src, a family of receptors that play a crucial role in smooth muscle cell proliferation and vasoconstriction. Therefore, is has been hypothesized that this drug could alter the proliferation/antiproliferation balance in endothelial and pulmonary arterial smooth muscle cells, thus determining adverse remodeling of pulmonary arterioles and then PAH [38, 39].

Several receptor tyrosine kinases, such as platelet-derived growth factor (PDGF) receptor beta and VEGF receptor 2, are implicated in the pathophysiology of PAH. In particular, PDGF signaling pathway mediates endothelial cell dysfunction and proliferation and migration of vascular smooth muscular cells [40–42]. It has been demonstrated that, beside perturbation of the balance between vasoconstriction and vasodilation, PDGF ligands and receptors are increased in idiopathic PAH. In addition, PDGF was shown to primarily contribute in vascular smooth muscle cell proliferation and hyperplasia in PAH [43, 44]. Interestingly, another TKI inhibitor, imatinib, has been shown to have anti-vasoproliferative properties and to be effective in improving hemodynamics in both animal models and in a randomized controlled clinical trial [44, 45]. Nevertheless, the use of imatinib for treatment of PAH has been discouraged because of severe adverse events, relevant side effects, and high discontinuation rate during the open-label extension phase study [46].

Mechanistically, imatinib reversed the overexpression and increased phosphorylation of PDGF receptor beta that is present also in pulmonary arteries from animal models of PH, inhibited PDGF receptor-related ERK1/2 activation in lungs of these animals thereby suppressing pulmonary artery smooth muscle cell proliferation and inducing cellular apoptosis [44]. While significantly lower concentrations of dasatinib are needed to obtain BCR/ABL inhibition in comparison to imatinib, the effect of dasatinib on c-kit and PDGF receptor are rather similar. In addition, and differently from imatinib, dasatinib also inhibits the SRC family of kinases [47]. The large spectrum of inhibition of dasatinib led to hypothesize that by inhibiting Src, a family of receptors that play a crucial role in smooth muscle cell proliferation and vasoconstriction, this drug could alter the proliferation/antiproliferation balance in endothelial and pulmonary arterial smooth muscle cells besides its inhibition of PDGF receptor (that instead determines an improvement of pulmonary vascular disease) [38]. Whether this aspect of the compound is causally related to PAH development is still poorly understood.

The extreme differences in terms of effects on pulmonary circulation between imatinib and dasatinib suggest that dasatinib-induced pulmonary vascular toxicity is molecule-related rather than class-related. On the other side, in vivo and

in vitro studies aimed at evaluating the effects of dasatinib and imatinib on pulmonary vasculature demonstrated that both TKI increased levels of nitric oxide, a potent vasodilator, without inducing PAH-related adverse remodeling, thus suggesting that both the drugs could promote beneficial effects for PAH [48]. These results are in contrast with the clinical evidence of dasatinib-induced PAH. In conclusion, there is still poor knowledge about the actual mechanisms underlying the damage of pulmonary vessels induced by dasatinib.

Screening and Clinical Management of Anticancer Drug-Induced Pulmonary Hypertension

Before initiation of antineoplastic drugs that have a known possible risk of causing PAH, baseline evaluation for signs and symptoms of underlying cardiopulmonary disease is mandatory. Echocardiographic assessment, including the search for signs of right ventricular overload, should be considered [49]. Transthoracic echocardiography is used to explore the effects of increase in pulmonary pressure on the heart, especially on the right ventricle, and to estimate pulmonary arterial systolic pressure from continuous wave Doppler measurements of the tricuspid regurgitation [50]. This evaluation before chemotherapy initiation may help in interpretation of follow-up echocardiographic examinations in patients reporting symptoms potentially correlated with the development of PAH, like exercise limitation or exertional dyspnea during treatment. Noninvasive cardiovascular surveillance should be considered in all patients during treatment with cancer drugs known to cause PAH or pulmonary vascular damage, particularly in case of the appearance of new symptoms like exertional dyspnea, fatigue, or angina.

The recently published position paper of the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology suggests to consider echocardiographic evaluation every 3 to 6 months in asymptomatic patients. It is unclear whether patients with baseline signs of right ventricular overload due to comorbidities commonly associated with elevated pulmonary arterial pressure (e.g., chronic obstructive pulmonary disease, left heart dysfunction) are at higher risk of chemotherapy-induced PAH and require more frequent surveillance with echocardiography. When drug-induced PAH is suspected, referral to a specialized pulmonary hypertension team is recommended to assess indications for right heart catheterization [4]. Multidisciplinary team discussions should be held among Cardiologists, Oncologists and Hematologists regarding the risk–benefit ratio of continuing cancer treatment with PAH drug therapy vs. stopping or replacing the culprit drug [4]. Chemotherapy-induced PAH is often reversible with drug cessation (e.g., in the case of dasatinib), although usually without restoration of normal right heart hemodynamics [3]. Targeted therapy for PAH may be useful temporarily or permanently.

Remarks and Conclusion

PH remains a rare complication of antineoplastic drugs, suggesting possible individual susceptibility, and further studies are needed to better understand the underlying mechanisms, to identify patients at risk of developing pulmonary vascular toxicity and how to manage and treat this condition.

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