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【 EDITORIAL 】

# Dasatinib-induced Pulmonary Hypertension

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In recent years, cardio-oncology has become a field of interest. Cancer drug therapies and radiation therapy are sometimes associated with various cardiovascular complications, such as myocardial damage, myocarditis, pericarditis, coronary artery disease, arrhythmia, hypertension, and pulmonary hypertension (PH). Drug therapies and radiotherapy are reported to induce PH, including pulmonary tumor embolization, thromboembolization, drug-induced PH, and pulmonary veno-occlusive disease. Concerning cancer drug-induced PH in particular, the 6th World Symposium on Pulmonary Hypertension (2018) described a "definite" association between dasatinib and PH (1).

Dasatinib is a second-generation tyrosine kinase inhibitor (TKI) used for chronic myelogenous leukemia (CML) and Philadelphia-positive acute lymphoblastic leukemia (ALL). There have been several reports of cases of PH induced by TKIs other than dasatinib, such as ponatinib and bosutinib (2-4), although nilotinib and imatinib were expected to be useful for treating PH (5, 6). The detailed mechanism underlying how dasatinib induces PH is unclear, but it is interesting that different TKIs can exert opposite effects on PH. A basic study reported that dasatinib causes endothelial cell dysfunction via the increased production of mitochondrial reactive oxidants independent of Src family kinases (7). Furthermore, dasatinib may cause attenuation of the hypoxic pulmonary vasoconstriction and induction of endoplasmic reticulum stress, which may facilitate the development of PH.

Although dasatinib-induced PH may require pulmonary vasodilators for treatment, many cases of improvement with discontinuation of dasatinib alone have been described. Therefore, the early detection of dasatinib-induced PH is very important during cancer treatment. In a previous report from France, dasatinib was discontinued in all 21 patients who developed PH, and pulmonary vasodilators were further administered to 11 patients (8). About one-third of the patients had persistent PH on follow-up. In another report, 41 cases of PH were reported, with complete or partial resolution of PH was noted in 94% and complete resolution in 58% (5). Given these results, PH may be reversible if it is diagnosed early after the onset of endothelial dysfunction.

When considering an early detection program, it is very important to understand the incidence of PH associated with dasatinib administration. According to current reports, the frequency of dasatinib-induced PH is varied. Studies in which PH was diagnosed by right heart catheterization reported an incidence of 0.2-0.45% (5, 9), while studies in which PH was diagnosed mainly by echocardiography reported an incidence of 2.4-5% (10, 11). The incidence reported by Kubota et al. (12) was 5.5%, which was similar as the previous reports. One important point is that PH on echocardiography needs to be interpreted with caution. This is because dasatinib frequently causes pleural effusion, which may also result in PH. Therefore, right heart catheterization is needed to determine if the pulmonary artery itself is involved. Finally, regarding the onset timing, Kubota et al. (12) reported that neither the duration of treatment nor the total dose of dasatinib was associated with the development of PH. A previous study also showed a wide range of time from the start of dasatinib to the onset of PH, with a median of 42 months (8-74 months) reported (8).

Routine echocardiography for screening of PH is not recommended, and it is impossible to follow only high-risk patients by echocardiography, since the risk factors for dasatinib-induced PH are unclear. Therefore, a further prospective echocardiographic follow-up study is needed to determine whether or not screening is worthwhile in terms of clinical economy.

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