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Cancer Therapy-Related Pulmonary Hypertension: A Review of Mechanisms and Implications for Clinical Practice

ABSTRACT

Cancer therapy-related pulmonary hypertension is a rare yet potentially fatal cardiotoxicity. However, it is a reversible cause of pulmonary hypertension if detected in its early stages. Cancer therapy-related pulmonary hypertension has been encountered in patients using tyrosine kinase inhibitors, particularly dasatinib. However, it is also well known that many agents used in cancer treatment such as alkylating agents, proteasome inhibitors, thoracic radiation exposure, and immune checkpoint inhibitors are particularly associated with pulmonary hypertension evolution. In case that history, symptoms, and clinical findings suggest a potential cancer therapy-related pulmonary hypertension, echocardiography is considered as the initial tool to detect pulmonary hypertension. If the possibility of pulmonary hypertension is high based on echocardiographic data, cancer treatment, as the initial step, should be discontinued due to its potential risks and other causes for pulmonary hypertension should be investigated thoroughly. Right heart catheterization should be the next step to establish the final diagnosis, and medical management, where appropriate, should be started without delay in these patients according to their pulmonary hypertension subgroup. There exists limited information regarding the diagnostic and management strategies of cancer therapy-related pulmonary hypertension in the current guidelines. In this review article, we aim to present current literature data on the mechanisms and management of cancer therapy-related pulmonary hypertension along with its follow-up algorithm in the setting of cardio-oncology practice.

Keywords: Cardio-oncology, cardiotoxicity, chemotherapy, radiotherapy, pulmonary hypertension

REVIEW

INTRODUCTION

In line with advances in modern cancer treatment, there has been a significant improvement in the survival of cancer patients over the last 3 decades.[1] However, it has been observed that management strategies such as chemotherapy, radiotherapy, and immunotherapy used in cancer treatment harbor a potential risk of complication namely cardiotoxicity.[2] In this regard, cancer therapy-related pulmonary hypertension (CTR-PH) is a rare yet potentially fatal cardiotoxicity.[1,2] Its most notable feature in terms of cardiology practice is that it appears to be a reversible cause of pulmonary hypertension (PH) when diagnosed in its early stages.[3] In terms of cardio-oncology practice, its most important feature is that it might arise as a form of life-threatening cardiotoxicity that leads to an interruption in cancer treatment since existing PH might directly affect the survival of the patient due to a variety of factors including progressive right heart failure.[1,4] Recent evidence demonstrates that the causal relationship between cancer treatment and PH extends far beyond the well-known example of dasatinib and that the awareness of clinicians dealing with cancer treatment should also be raised regarding CTR-PH and its management.[5] Cancer therapy-related pulmonary hypertension, which manifests itself with a variety of non-specific symptoms such as exertional dyspnea, fatigue, and peripheral edema all of which appear to be quite common in cancer patients due to diverse etiologies, may arise as a potentially overlooked cardiotoxicity.[1,5] Proper management of CTR-PH potentially obviates long-term morbidity and mortality of cancer patients, and CTR-PH itself has a key role in

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determining the pattern of cancer management (type of drugs, switch to another medication, etc.).[6]

In this review article, we focus on optimization of management strategies for CTR-PH in cardio-oncology practice along with a particular emphasis on mechanistic and clinical characteristics of this phenomenon.

DEFINITION AND CLASSIFICATION

Pulmonary hypertension is a life-threatening cardiovascular toxicity that is quite challenging to recognize in its initial stages and hence a therapeutic delay in this context may be likely. Mechanistically, it might also be due to the toxic effects of agents used in cancer treatment, cancer itself, or a complex pathophysiological mechanism secondary to hematopoietic stem cell transplantation.[7,8] Pulmonary hypertension is universally considered as a progressive disease primarily manifesting as vascular remodeling, vasoconstriction, and pulmonary vascular obliteration that usually ends up with significant increases in pulmonary artery pressure values, associated right heart failure, and eventual mortality.[8,9] Recent clinical trials have reported that the PH prevalence in the general population is around 1% along with rates of CTR-PH ranging from 0.45% to 15.4% depending on the agents used in the management.[8-10] It has also been demonstrated that the 3-year survival rate of subjects with pulmonary arterial hypertension (PAH) ranges between 58% and 75% with currently available therapeutic agents.[10] Pulmonary hypertension is defined in the 2022 guideline of the European Society of Cardiology as the mean pulmonary artery pressure (mPAP) threshold value >20 mm Hg in right heart catheterization at rest. Figure 1 presents the current hemodynamic classification of PH and associated PH groups.[1]

In the current classification of PH (which guides both the diagnostic and management strategies of PH), all 5 subgroups mentioned may be encountered in cancer patients in association with cancer itself or the treatment of cancer.[1,5] In this review article, we particularly focus on CTR-PH. Drugs used in cancer treatment can cause PH with direct or indirect toxic effects on pulmonary arteries, pulmonary veins, lung parenchyma, and left ventricle.[1,8,9] Figure 2 shows the causal relationship between agents used in cancer treatment and PH.[5-8]

HIGHLIGHTS

- Cancer therapy-related pulmonary hypertension is a rare yet potentially fatal cardiotoxicity.
- Pulmonary artery pressure should be examined with echocardiogram before treatment, every 3 months during treatment, and after treatment in every patient with cancer to whom agents associated with cancer therapy-related pulmonary hypertension are initiated.
- In patients with a high probability of PH based on echocardiographic data, agents potentially associated with cancer therapy-related pulmonary hypertension should be discontinued immediately. Other potential causes of PH should also be investigated thoroughly along with implementation of right heart catheterization as the next step for the final confirmation of pulmonary hypertension. Urgent initiation of medical management (according to the PH subgroup), where appropriate, seems reasonable in these patients.

CANCER THERAPY-RELATED GROUP 1 PULMONARY HYPERTENSION

Group 1 PH, which is termed as PAH, is defined as a mean pulmonary artery pressure value of >20 mm Hg along with a pulmonary artery wedge pressure value of ≤15 mm Hg and a pulmonary vascular resistance value of >2 Wood units according to the most recently published 2022 European Society of Cardiology PH guidelines.[5] Significant increments in pulmonary artery pressure in PAH affect the vascular territories proximal to the pulmonary capillary system and are termed as precapillary PH.[5] Although the exact pathophysiological mechanisms in PAH remain to be established, vascular remodeling and vasoconstriction in the pulmonary arterial bed account for the obliteration of small precapillary arteries and arterioles.[5,10] In the early stages of the disease, enhanced afterload due to vascular remodeling and vasoconstriction is largely offset by an increase in right ventricular contractility and wall thickness.[11] Failure to timely use effective therapies targeting vasoconstriction and vascular remodeling in PAH might lead to progressive right heart failure and ultimately death.[11] Recent data have reported an incidence of approximately 6 cases/million/year and a prevalence of 48-55 cases/million adults.[5] Even though previous data have reported that PAH has been more common in younger ages and females, recent data from the United States and Europe demonstrate a similar gender distribution.[5] Group-1 CTR-PH can be categorized into 2 subgroups: CTR-PH with pure precapillary features (namely classical PAH) and CTR-PH associated with pulmonary veno-occlusive disease (PVOD).[1,5,11]

Group-1 Cancer Therapy-Related Pulmonary Hypertension with Pure Precapillary Features

The primary drugs in this group may be categorized as follows:

Tyrosine Kinase Inhibitors (including dasatinib, bosutinib, ponatinib, imatinib, nilotinib, and lapatinib)

Dasatinib has been introduced as a non-specific tyrosine kinase inhibitor primarily utilized in the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia and chronic myeloid leukemia.[10] Dasatinib also potently inhibits other families of tyrosine kinases, such as c-src, c-kit, c-abl, and eph family, which inhibit bcr-abl (breakpoint cluster region–Abelson oncogene loci) tyrosine kinase.[10-13] The mechanisms suggested explaining the causal association between dasatinib and the PAH evolution may be diverse.[10-14] The first and most widely recognized theory is off-target inhibition of bcr–abl, the most important c-src tyrosine kinase, that appears to be strongly expressed in the pulmonary vascular bed. C-src tyrosine kinase has a key role in maintaining low pulmonary vascular tone. Therefore, off-target inhibition of c-src tyrosine kinase leads to vasoconstriction in the pulmonary vascular system and induces PAH

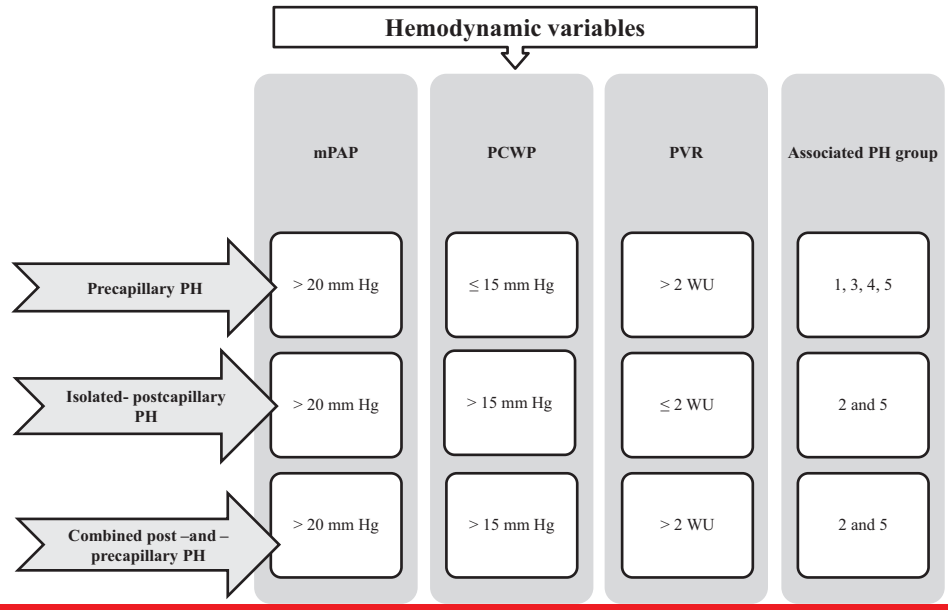

Figure 1. Current hemodynamic classification for PH. PH, pulmonary hypertension.

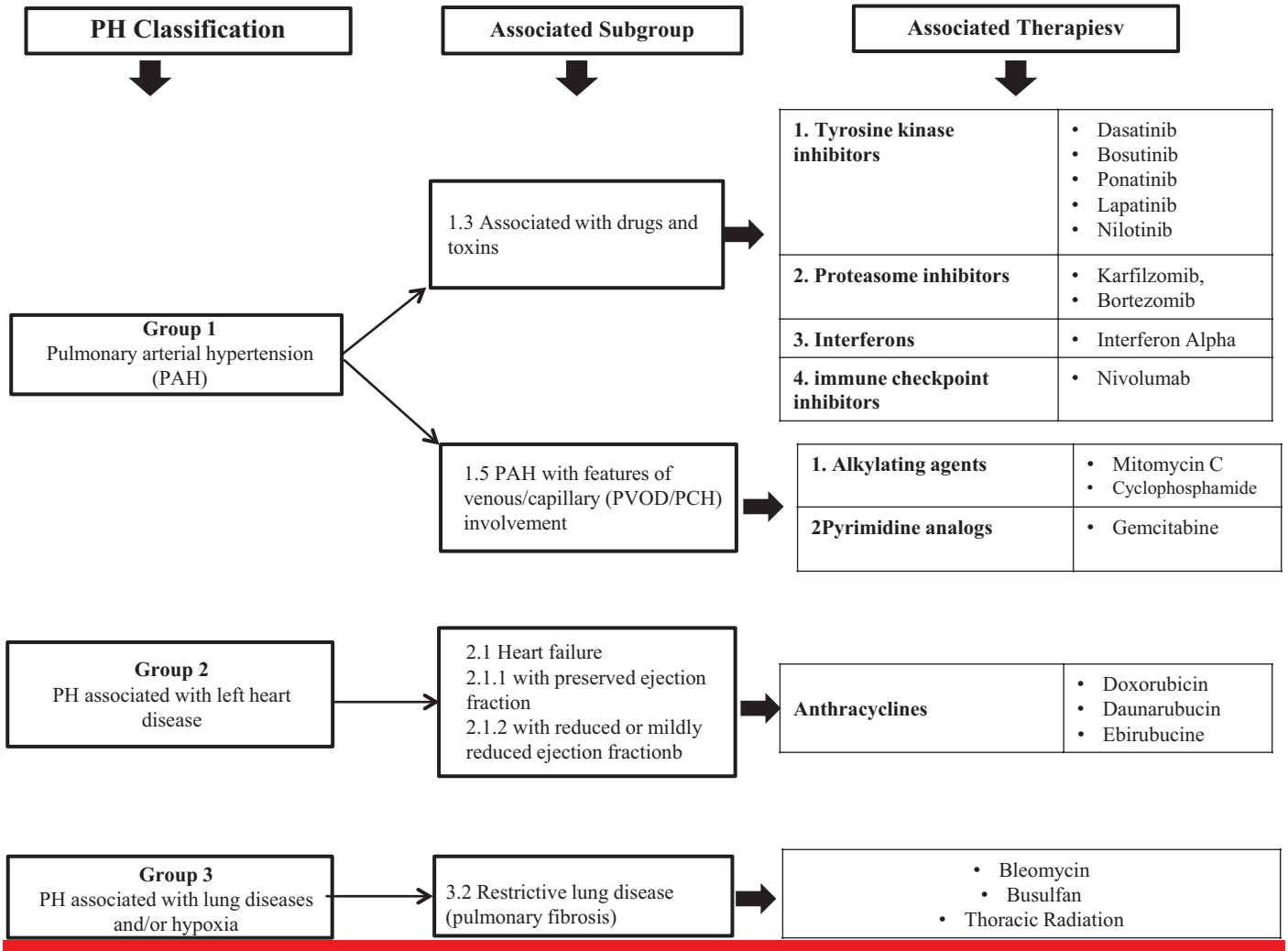

Figure 2. The place of cancer-treatment-related PH in the current PH grouping. PH, pulmonary hypertension.

evolution. Second, dasatinib has also been a potent inhibitor of many growth factor signals, particularly platelet-derived growth factors (PDGFs). The common consequence of PDGF and c-src tyrosine kinase inhibition is the significant proliferation in pulmonary vascular smooth muscle cells that triggers PAH evolution. Third, PAH evolution due to dasatinib might be attributable to the dose-dependent mitochondrial free oxygen radical production in pulmonary vascular smooth muscle cells and associated pulmonary endothelial cell apoptosis. Finally, this agent has been reported to elicit resistant pleural effusion largely through its effects on pulmonary endothelial permeability as a consequence of increased free oxygen radicals.[10-15]

Dasatinib may be regarded as the epitome of drug-induced PAH in cardio-oncology practice.[1] Therefore, it has a "definite" association with PAH.[10] Literature data suggest no predictor for the development of dasatinib-related PAH.[13-15] Pulmonary vascular toxicity in this context is considered to be possibly associated with the molecule itself and hence not a class effect. Around 11% of patients to whom dasatinib is initiated likely develop PAH within 8-40 months of therapy, and approximately two-thirds of PAH cases have been female patients.[15]

Numerous case reports have also reported the potential association of other members of the tyrosine kinase family (bosutinib, ponatinib, imatinib, lapatinib, and nilotinib) with group-1 CTR-PH evolution.[6,16-18] Bosutinib, like dasatinib, also serves as a potent inhibitor of c-src.[19] Cases of moderate-to-severe PAH presenting with progressive exercise intolerance and pericardial effusion have been reported following bosutinib exposure.[19] Ponatinib is a new-generation tyrosine kinase inhibitor used in cases with potential resistance to other tyrosine kinase inhibitors or those exhibiting undesirable side effects associated with these agents. Its indications are similar to those of other tyrosine kinases.[20] In the literature, dasatinib-induced severe PH together with right ventricular failure and severe pleural effusion was reported in a patient who required a switch to ponatinib therapy.[20] Similarly, there are case reports of severe PAH associated with lapatinib and nilotinib use in patients with or without previous administration of another tyrosine kinase inhibitor.[6,17]

Imatinib has been introduced as a broad-spectrum tyrosine kinase inhibitor primarily utilized in the management of chronic myeloid leukemia and myeloproliferative/myelodysplastic disorders.[6,17] Imatinib has been the standard drug for the treatment of chronic myeloid leukemia (CML) and is a first-line specific inhibitor of bcr-abl tyrosine kinase.[21] Interestingly, it has been demonstrated to have inhibitory effects on both c-Kit and PDGF signals (that play a pivotal role in PAH pathogenesis), to increase NO levels in pulmonary endothelial cells, and also to decrease endothelin-1 and mRNA potentially rendering this agent as a potential alternative for PAH management.[21] Interestingly, imatinib, unlike dasatinib, did not reportedly increase free oxygen radicals in endothelial cells and did not induce apoptosis in the pulmonary vascular system.[17,21,22]

Proteasome Inhibitors

Bortezomib works as a reversible proteasome inhibitor mostly utilized in the treatment of multiple myeloma.[13] Patients with bortezomib-induced PH have been reported in the literature.[1,13] However, bortezomib was also shown to successfully reverse pulmonary vascular remodeling in experimental models.[13,23] Even though this may suggest bortezomib as an alternative agent in PAH management, its direct cardiotoxic effects, including myocardial apoptosis, potentially limit its use in this context.[23-25]

Carfilzomib has been introduced as a second-generation proteasome inhibitor indicated in patients with multiple myeloma who fail to respond to bortezomib or who have a multiple myeloma recurrence.[25] Safety analyses on carfilzomib have demonstrated a 2% incidence of CTR-PH associated with this agent.[25] However, carfilzomib has also been reported to effectively reverse pulmonary vascular remodeling and to reduce right ventricular pressure.[25,26] Carfilzomib-induced cardiotoxicity can be prevented with dexrazoxane or pifithrin-α.[25] On the other hand, vasodilators seem to have limited favorable effects on symptoms and survival in this regard. In the future, the combination of carfilzomib, vasodilators, and dexrazoxane may be tested and may potentially be regarded as a groundbreaking strategy for PAH management.[25]

Interferons

Interferon (INF)-α has immunomodulatory and antiproliferative actions and is primarily harnessed in the management of various types of cancer, such as chronic myeloid leukemia, renal cell carcinoma, and melanoma.[10-12] Case reports describing INF-α-associated PAH were reported in the literature. In the context of INF-α-associated PAH, symptoms were previously reported to be severe generally exhibiting no improvement upon discontinuation of treatment.[10,27] Pulmonary arterial hypertension-related symptoms were reported to emerge between the 8th and 36th month of treatment.[12] Regarding the mechanisms of INF-α-related PAH, cytokines and arachidonic acid metabolites might have important implications in the induction of local vasoconstriction, hypertrophy of pulmonary smooth muscles, thromboxane B cascade, and enhanced pulmonary vascular permeability.[6,10,27]

Group-1 Cancer Therapy-Related Pulmonary Hypertension Due to Venous/Capillary Involvement (Pulmonary Veno-Occlusive Disease/Pulmonary Capillary Hemangiomatosis (PCH)):

Pulmonary veno-occlusive disease has been regarded as a form of PAH with an unfavorable prognosis characterized by remodeling and obliteration of small pulmonary veins.[13,28] Pulmonary veno-occlusive disease represents approximately 10% of PAH patients. It may be sporadic or inherited. A significant portion of patients with PVOD is those who undergo bone marrow transplantation and receive combination chemotherapy. Moreover, half of these patients were reported to receive additional radiotherapy in registry studies.[29,30] Case series of PVOD related to different chemotherapeutic regimens, particularly alkylating agents, have

been reported in the literature. Cyclophosphamide and mitomycin have been the leading culprits in this context.[28] In general, these agents are notorious for the evolution of interstitial pneumonia, pulmonary fibrosis, and PAH due to PVOD.[1,13,28]

Cyclophosphamide

Cyclophosphamide has been an indispensable part of the treatment scheme for many cancer types, particularly hematological malignancies and solid organ tumors.[2] Cyclophosphamide has been associated with interstitial pneumonia, alveolar damage, and pulmonary fibrosis. The frequency of these undesirable effects has been around 1.3%.[13,30] The incidence of pneumonia–pulmonary fibrosis was reported to be 35% in subjects managed with high-dose cyclophosphamide and pulmonary radiotherapy.[1,13,28] The combination of cyclophosphamide and radiotherapy generally exerts a synergistic effect in terms of pulmonary toxicities. The fundamental mechanisms regarding cyclo phosphamide-related PVOD comprise pulmonary fibrosis, progressive vascular injury, and remodeling.[28,30] Emerging dyspnea together with an interstitial pattern in a patient on cyclophosphamide therapy strongly suggests a possible toxicity.[28,30]

Mitomycin-C

Mitomycin-C has been introduced as an antineoplastic antibiotic primarily acting through the inhibition of DNA and protein synthesis.[29] Pulmonary vascular injury triggered by mitomycin-C appears to be characterized by endothelial alterations, perivascular edema, emerging thrombus in pulmonary capillaries along with intimal hyperplasia and medial hypertrophy in small arteries. These suggest the direct cytotoxic impact of mitomycin-C.[13,28,29] While the incidence of idiopathic PVOD has been around 0.5/million persons/year in the general population, the incidence of PVOD in patients with anal cancer under mitomycin-C therapy reaches 3.9/1000 patients per year.[29] Given that PVOD exhibits potential manifestations of severe precapillary PH, it might be erroneously classified as PAH in 10% of cases.[29] Hereditary PVOD has been predominantly encountered in males and is related to mutations in the *EIF2AK4* (Eukaryotic Translation Initiation Factor 2 Alpha Kinase 4) gene. Conversely, mitomycin-C-induced PVOD has been generally encountered in females along with a null association with the mutation in the *EIF2AK4* gene.[13,28,29] Fatigue, dyspnea (unproportional to pulmonary function test), hypoxemia, reduced carbon monoxide diffusion capacity, abnormalities on high-resolution lung tomography along with emerging pulmonary edema following initiation of pulmonary vasodilator therapy might suggest PVOD. [28,29] Therefore, a non-invasive diagnostic algorithm has been mostly preferred in an effort to avoid potential complications in this regard. Pulmonary veno-occlusive disease has been a rare form of treatment-resistant PH that is quite challenging to diagnose and has an unfavorable prognosis.[29] Importantly, PVOD should be absolutely differentiated from other causes of PAH before initiation of therapy since standard vasodilator strategies in PAH might possibly be detrimental in patients with PVOD.[13,29]

Cancer Therapy-Related Group-2 Pulmonary Hypertension

The epitome of left heart disease associated with cancer treatment has been subclinical or clinical left ventricular systolic dysfunction that might develop due to a variety of chemotherapeutic agents, especially anthracyclines.[1,31] Anthracyclines have been regarded as the mainstay of therapeutic regimens in the setting of various hematological and organ malignancies, particularly leukemias, breast cancers, lymphomas, and sarcomas.[1,4] Cardiotoxicity of these agents is strongly dose dependent.[1,31] Following a cumulative doxorubicin dose of 250 mg/m^2, cardiotoxicity generally emerges largely depending on patient risk factors and the impact of concomitant therapy.[1,4] Incidence of cardiotoxicity has been 3%-5% when the cumulative doxorubicin dose reaches 400 mg/m^2 and 18%-48% when it reaches 700 mg/m^2.[31] Regarding the mechanisms of ventricular dysfunction in the setting of anthracyclins, there have been a variety of speculated triggers including emerging reactive oxygen radicals, disruption of homeostasis associated with iron and calcium metabolism, mitochondrial dysfunction, and activation of P53 tumor suppressor gene.[1,4,31] Anthracycline-related cardiotoxicity may occur immediately (emerging after a single dose) in the early (occurring within 1 year) or late (emerging years later) stages following therapy.[1,31] In general, most patients are prone to develop left ventricular dysfunction within the first year following discontinuation of therapy.[1,31] Alkylating agents, proteasome inhibitors, human epidermal growth receptor type-2, antibodies, immune checkpoint inhibitors, tyrosine kinase inhibitors, vascular endothelial growth factor inhibitors, and taxanes have also been regarded as cardiotoxic agents that might induce left ventricular dysfunction at variable rates.[1,31] Of note, PH related to left heart disease has been the most frequently encountered form of PH in the clinical setting.[5]

CANCER THERAPY-RELATED GROUP-3 PULMONARY HYPERTENSION

Lung parenchymal disease and associated PH (group-3) have been relevant to drugs that might induce pulmonary fibrosis, especially bleomycin, thoracic radiation, and busulfan.[32-37]

Bleomycin

Bleomycin has been the most renowned agent in terms of pulmonary toxicity.[33,34] Roughly, 10% of patients receiving bleomycin may develop pulmonary toxicity.[34] Pulmonary toxicity associated with bleomycin use may emerge in less than 4 weeks of therapy.[33,34] Pulmonary fibrosis and associated pulmonary hypertension (in later stages) due to bleomycin might be due to its direct toxic effects on endothelial cells, proinflammatory effects through the accumulation of antig en-antibody-immune complexes and through the enhanced release of cytotoxic reactive oxygen radicals.[35,36]

Thoracic Radiation

Radiation therapy, which has been an integral part of the management of many malignancies such as lymphomas, breast cancers, lung cancer, or esophageal cancer, is well known to be associated with complications including pulmonary fibrosis, pneumonitis, and pulmonary vasculopathy.[36,37] Lung damage in this context is usually dose-dependent.

Interestingly, pulmonary toxicity may emerge within 2-3 months following exposure.[36,37] Mechanistically, radiation may also induce intimal damage both in arterioles and venules potentially ending up with vasculopathy.[36] When radiation is used in combination with a chemotherapeutic agent such as bleomycin, a synergistic effect is likely, and may result in a higher rate of pulmonary fibrosis.[36,37]

Busulfan

Busulfan has been known as an alkylating agent primarily utilized for the management of autologous stem cell transplantation, hematological cancers, or solid tumors.[10,32] Several adverse effects of busulfan have been reported, including pulmonary toxicity associated with acute lung injury, chronic interstitial fibrosis, and acute alveolar hemorrhage.[32] Cases with right heart failure requiring hospitalization have been reported 2-4.5 months after autologous stem cell transplantation accompanied by busulfan therapy.[32] In the management of these cases, symptomatic therapy for right heart failure, steroids, or PAH-specific therapy has been used with favorable outcomes.[32] Mechanistically, busulfan was particularly suggested to induce acute endothelial damage leading to precapillary PH.[32]

DIAGNOSIS, TREATMENT, AND FOLLOW-UP STRATEGIES FOR *CANCER THERAPY-RELATED PULMONARY HYPERTENSION*

Recommendations for Diagnosis

The management of CTR-PH should be based on international guidelines for the diagnosis and management of PH.[1,2,4,5] Diagnosis and management should be implemented by a multidisciplinary team.[1,5] A detailed history of the patient and a careful physical examination are essential for an accurate diagnosis. Common yet non-specific symptoms in PH patients are reduced exercise capacity, shortness of breath, fatigue, and fluid retention.[1,5]

Physical examination may show signs of PH and right heart failure, the details of which may be found elsewhere.[1,5] Electrocardiography (ECG) may aid in the detection of right ventricular hypertrophy in patients with suspected CTR-PH. However, normal ECG does not rule out an existing CTR-PH.[1] Echocardiography is the initial imaging modality to evaluate PH in patients with symptoms and/or signs suggestive of CTR-PH.[1,2,4,5] The probability of PH is low when the regurgitation velocity over the tricuspid valve on echocardiography is ≤2.8 m/s, in which case the estimated systolic PAP is ≤35 mm Hg. In case the peak tricuspid regurgitation velocity exceeds 3.4 m/s (PAP is ≥50 mm Hg), the chemotherapeutic agent should be discontinued, and right heart catheterization should be the next approach for definitive diagnosis. Other supportive findings on echocardiogram include right-to-left ventricle (RV/LV) basal diameter ratio >1, acceleration time of the RV outflow tract flow <105 ms, and a large inferior vena cava (>21 mm in diameter) with a blunted inspiratory collapse.[1,5] Vasoreactivity testing (using inhaled iloprost, nitric oxide, or intravenous (IV) epoprostenol) during right heart catheterization is recommended to identify potential candidates for calcium channel blocker therapy.[1,5] Guidelines mostly recommend vasoreactivity testing in the setting of drug-induced PAH (regardless of whether it is CTR-PH or not).[5] A positive vasoreactivity test response is defined as a reduction in mean PAP of ≥10 mm Hg along with an absolute value of ≤40 mm Hg with an amplified or constant cardiac output.[1,5] Moreover, pulmonary artery diameter and PAP should be measured before treatment and in case of emerging symptoms in patients who receive immune checkpoint inhibitors including nivolumab.[38] The diagnosis and follow-up algorithm for CTR-PH is presented in Figure 3.[1,2,4,5]

Recommendations for Management

Importantly, other potential triggers of PH (if any) should be rapidly excluded since the primary goal should be not to interrupt the cancer treatment scheme, if possible, in cancer patients.[39] It is recommended to discontinue dasatinib and perform right heart catheterization in subjects with CML using dasatinib in the presence of symptomatic PH and/or echocardiographic findings strongly suggestive of severe PH.[1,3,39] In case the final diagnosis of dasatinib-induced PAH is confirmed on cardiac catheterization, PAH-specific drugs may be administered to patients according to the status of their functional capacity.[1,39] After a period of interruption, switching to an alternative bcr-abl tyrosine kinase inhibitor seems to be a plausible strategy provided that the value of peak tricuspid velocity falls below 2.8 m/s on follow-up. In case patients receiving dasatinib are asymptomatic and have a tricuspid regurgitation velocity between 2.9 and 3.4 m/s on echocardiogram, dasatinib dose reduction along with serial echocardiographic examination (every 4 weeks) is highly encouraged. In the absence of further increases in tricuspid velocity on follow-up, echocardiographic examinations may be performed every 3 months on dasatinib therapy.[1,5]

The potential reversibility of CTR-PH is invaluable in the general context of PH, a disease with an unfavorable prognosis.[39] Suppression of the inflammatory and proliferative cascade in the early stages with aggressive steroid and PAH-specific therapy generally yields positive results.[39,40] Suggested therapeutic agents comprise sildenafil, bosentan, and prostacyclin in most cases with CTR-PH and calcium channel blockers in a few cases.[3,12-14,40-43] Of note, favorable effects of the currently available drugs largely act through the vasodilation pathway rather than the reversal of vascular remodeling. Accordingly, notwithstanding the interruption of the causative agent along with initiation of the specific PAH therapy, PAH may persist in approximately one-third of dasatinib-related PAH cases and may even recur with the initiation of another tyrosine kinase inhibitor.[3,40,41] Moreover, reduction in dasatinib doses may not serve as a radical solution and may even blunt the therapeutic efficacy of the vasodilator therapy. Therefore, management should be evaluated individually and mostly necessitates referral of these patients to multidisciplinary PH centers.[1]

Pulmonary veno-occlusive disease, the more serious category in group-1 CTR-PH, may be potentially managed with

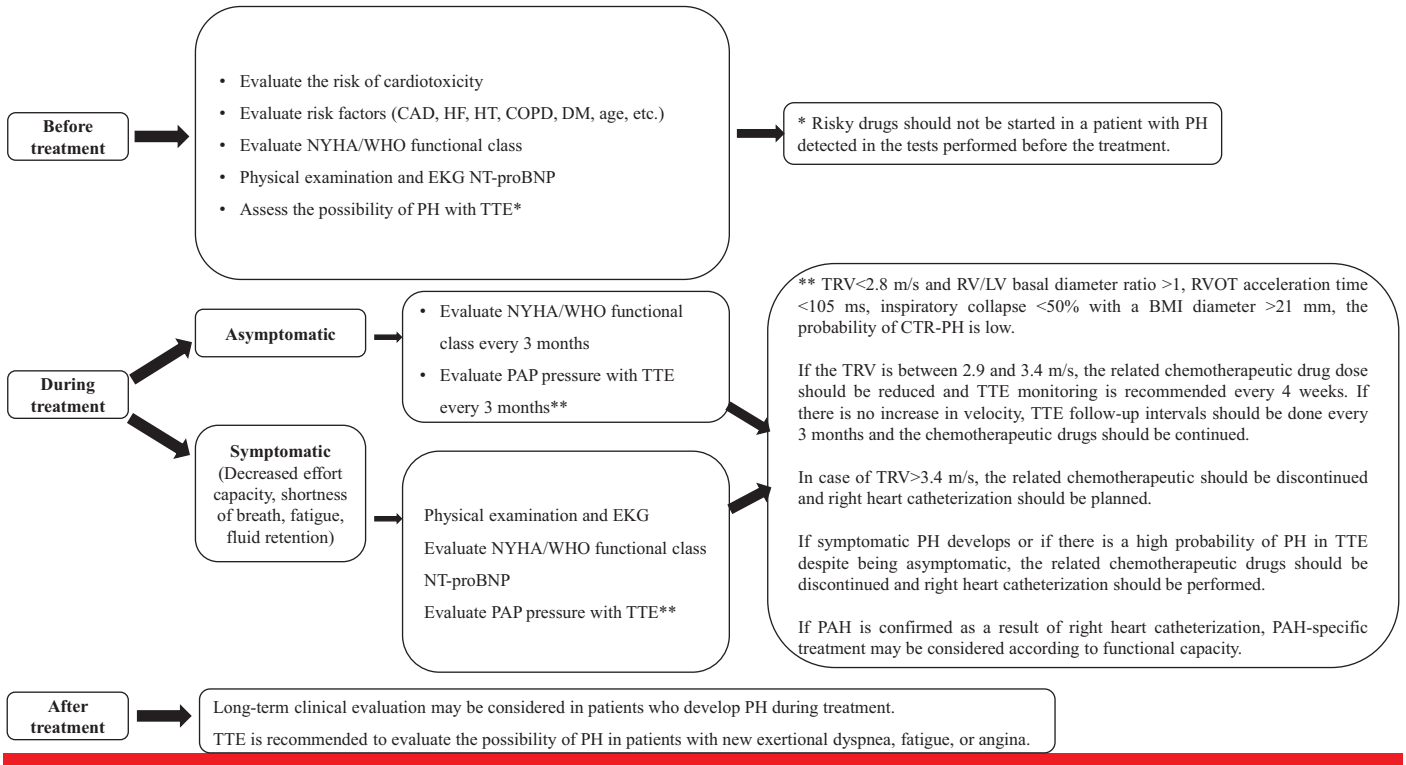

Figure 3. Follow-up algorithm for CTR-PH. CTR-PH, Cancer therapy-related pulmonary hypertension.

immediate cessation of the causative agent together with the initiation of steroid therapy.[11-13] Suggested therapeutic options include vasodilators, immunosuppressive drugs, anticoagulants, and oxygen therapy.[11-13] Unfortunately, PAH-specific therapies may be ineffective or may even worsen the disease course in patients with PVOD (as a consequence of emerging pulmonary edema).[28-30] However, promising results with bosentan as monotherapy or in combination with tadalafil have also been reported previously.[28-30] Therefore, lung transplantation remains as the sole curative treatment for PVOD.[29,30] However, this radical modality has been rarely performed in patients with cancer.

The basic management strategies for CTR-PH in the context of left heart failure and pulmonary parenchymal disease mostly target reduction of drug-related organ toxicity (drug interruption, etc.) and supportive measures for the involved organ system (including aggressive heart failure management, etc.).[5] Importantly, PAH-specific agents are not indicated in these conditions.[1,5]

Follow-up Strategy

Currently, there exists no specific predictor for PH evolution in patients receiving cancer treatment.[1,4,5,13] The issue of whether co-existing conditions such as chronic obstructive pulmonary disease and left ventricular dysfunction might increase the risk of CTR-PH, needs to be established.[31] Cancer patients receiving risky regimens should be under regular follow-up with regard to signs and symptoms of an emerging PH.[1,31] It is generally discouraged to initiate a high-risk regimen (in terms of CTR-PH evolution) in a patient having PH at baseline.[1,31]

CONCLUSION

Cancer therapy-related pulmonary hypertension emerges as a potentially fatal condition particularly when it is overlooked. Therefore, a comprehensive and regular evaluation of risky patients by clinicians with high awareness is of utmost importance for the early diagnosis and management of CTR-PH, which is a reversible cause of PH. Initial echocardiographic evaluation should be performed on cancer patients who are planning to receive a risky regimen in terms of CTR-PH evolution. Moreover, it seems mandatory to discontinue the culprit agent in patients who develop symptomatic PH and/or signs of critical PH on echocardiogram. The causal relation between CTR-PH and dasatinib seems to be definitive in this context. On the other hand, other agents mentioned in the text have also pathogenetic implications, to a variable extent, in CTR-PH evolution. Referral of these patients to multidisciplinary pulmonary hypertension centers for guideline-directed management is generally indicated. Of note, initiation of mono, combined, or sequential PAH-specific therapies is largely determined by the symptomatology and/or clinical signs of patients with PAH according to guidelines and expert opinions. However, further aspects of CTR-PH still need to be elucidated.

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