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FOCUS SEMINAR: CARDIO-ONCOLOGY

STATE-OF-THE-ART REVIEW

Cardiovascular Complications of Cancer Therapy

Best Practices in Diagnosis, Prevention, and Management: Part 2

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ABSTRACT

In this second part of a 2-part review, we will review cancer or cancer therapy–associated systemic and pulmonary hypertension, QT prolongation, arrhythmias, pericardial disease, and radiation-induced cardiotoxicity. This review is based on a MEDLINE search of published data, published clinical guidelines, and best practices in major cancer centers. Newly developed targeted therapy can exert off-target effects causing hypertension, thromboembolism, QT prolongation, and atrial fibrillation. Radiation therapy often accelerates atherosclerosis. Furthermore, radiation can damage the heart valves, the conduction system, and pericardium, which may take years to manifest clinically. Management of pericardial disease in cancer patients also posed clinical challenges. This review highlights the unique opportunity of caring for cancer patients with heart problems caused by cancer or cancer therapy. It is an invitation to action for cardiologists to become familiar with this emerging subspecialty. (J Am Coll Cardiol 2017;70:2552–65)

SYSTEMIC HYPERTENSION

Hypertension (HTN) is the most common cardiovascular comorbidity reported in cancer registries, with a prevalence of 37% (1). Early diagnosis and treatment is essential because HTN is a major risk factor for the development of chemotherapy-induced cardiotoxicity (2). In addition, suboptimal blood pressure control may lead to premature discontinuation of chemotherapy, thus affecting cancer therapy directly (2,3).

INCIDENCE. Vascular endothelial growth factor signaling pathway inhibitors. Bevacizumab, sorafenib, and sunitinib target the vascular endothelial growth factor signaling pathway (VSP) to achieve their therapeutic efficacy at the expense of increased blood pressure (4) (**Table 1**). The incidences of HTN reported in different trials range from 4% to 35% for bevacizumab (5–8), 7% to 43% for sorafenib (9–13), and 5% to 24% for sunitinib (14–18). Although treatment with antihypertensive medications is usually adequate to allow for continuation of cancer therapy, severe HTN requiring hospitalization or discontinuation of therapy occurred in 1.7% of bevacizumab-treated patients (19).

Proteasome inhibitors. HTN, including hypertensive crisis or emergency, was observed during treatment with proteasome inhibitors, primarily carfilzomib. In the ENDEAVOR (Carfilzomib and Dexamethasone versus Bortezomib and Dexamethasone

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for Relapsed Multiple Myeloma Patients) and ASPIRE (Carfizomib, Lenalidomide, and Dexamethasone vs Lenalidomide and Dexamethasone in Subjects with Relapsed Multiple Myeloma) studies, the incidence of HTN in patients receiving carfilzomib was 17% and 11%, respectively (20,21). Of these events, 3% to 6% were reported as grade ≥3 and <2% were fatal (20). Hence, blood pressure monitoring should be regularly performed in all patients receiving carfilzomib. If HTN cannot be adequately controlled, carfilzomib should be withheld and possibly discontinued. Rechallenge should be considered only after risk/benefit assessment (20).

PATHOPHYSIOLOGY. Vascular endothelial growth factor (VEGF) enhances the production of nitric oxide and prostacyclin while decreasing endothelin-1 generation (22). VSP inhibitors affect normal vascular homeostasis by interfering with production of nitric oxide (NO) in the arteriolar walls (23). Inhibition of NO leads to vasoconstriction, increased peripheral vascular resistance, and increased blood pressure (23). Bevacizumab reduced endothelial nitric oxide synthase activity leading to HTN (24). Although VEGF is believed to affect the renin-angiotensin system (25), anti-VEGF therapy did not alter serum catecholamine, renin, and aldosterone levels (26). Telatinib, a potent inhibitor of VEGFR, induces capillary rarefaction (27). Carfilzomib reduces the vasodilatory response of acetylcholine and induces vasospasm, which can be treated with nitroglycerin (28–30). Thus, peripheral vasoconstriction due to impairment of endothelial function is likely to be the mechanism of carfilzomib-induced hypertension.

DIAGNOSIS AND TREATMENT. HTN is defined as blood pressure ≥140/90 mm Hg, based on an average of 2 or more BP readings on 2 or more visits. Clinical evaluation of HTN should include identification of the cause(s) of hypertension and assessment of cardiovascular risk factors (31) **(Central Illustration)**. HTN most commonly occurs within the first month of treatment (32). In cancer patients, the temporal association of blood pressure elevation with new cancer treatment easily established the diagnosis.

Treatment of cancer therapy-induced HTN frequently requires more than a single agent. Angiotensin-converting enzyme inhibitors (ACEIs) are the preferred first-line therapy due to their beneficial effects on plasminogen activator inhibitor-1 expression and proteinuria (24). ACEIs also increase the release of endothelial NO and decrease catabolism of bradykinin (4). ACEIs have been shown to significantly improve overall survival in metastatic renal cell carcinoma patients treated with sunitinib (33). Another consideration in choosing antihypertensive agents is to minimize harmful drug-drug interactions, particularly with sorafenib. Since sorafenib is metabolized via the cytochrome p450 system (mainly CYP3A4), drugs that inhibit the CYP3A4 isoenzyme, such as diltiazem and verapamil, should be avoided. Although HTN is considered as an undesirable side effect of cancer therapy, the increase in blood pressure has been shown to predict efficacy of cancer treatment (4).

PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is a disease of the pulmonary vasculature classified into 5 major etiological groups (34). Drug- and toxin-induced PH is classified as group 1. Cancer can cause PH through obstruction of pulmonary artery from organized fibrotic thrombi due to hypercoagulability, which is classified as group 4 (35,36). Extrinsic compression of the pulmonary vessels from tumors such as pulmonary angiosarcoma or direct intravascular extension from large B cell lymphoma can also lead to group 5 PH (37).

Dasatinib was first reported to cause PH in 2009 in a chronic myeloid leukemia patient (38). A French registry reported that 9 patients treated with dasatinib subsequently developed moderate to severe PH; the incidence was estimated to be 0.45% (39). A total of 8 patients showed functional improvement 4 months after cessation of dasatinib therapy. In an American study of 41 patients with dasatinib-induced PH, partial or complete reversal of PH was seen following discontinuation of dasatinib (40). The DASISION (Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients) comparing dasatinib with imatinib showed that 14 (5%) of the 258 dasatinib patients developed PH, compared with 1 (0.4%) imatinib patient over a follow-up period of at least 5 years (41). However, only 1 dasatinib-treated patient received right heart catheterization that did not support the diagnosis of PH. Thus, the incidence of 5% PH with dasatinib therapy is most likely an overestimation. Inhibition of SRC kinase by dasatinib was implicated in the development of PH (39). SRC kinase is involved in regulation of smooth muscle proliferation and vasoconstriction so that its inhibition could lead to increased pulmonary vascular resistance (39).

Transthoracic echocardiography is the screening tool of choice for PH. A ventilation-perfusion scan and right heart catheterization are necessary to establish the diagnosis of PH. A high index of

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CAD = coronary artery disease
CTA = computed tomography angiography
DOAC = direct oral anticoagulant
DVT = deep vein thrombosis
ECG = electrocardiography
LMWH = low molecular weight heparin
PE = pulmonary embolism
PH = pulmonary hypertension
QTc = corrected QT
RR = relative risk
TdP = torsades de pointes
TKI = tyrosine kinase inhibitor
VSP = vascular endothelial growth factor signaling pathway