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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 MEDLINE literature search, 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 that 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.

Keywords

cardiovascular complication; cancer therapy; thromboembolism; hypertension; radiation therapy

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).

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In addition, suboptimal blood pressure control may lead to premature discontinuation of chemotherapy, thus affecting cancer therapy directly (2,3).

Incidence

VSP Inhibitors—Bevacizumab, sorafenib, and sunitinib target the VEGF 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). While treatment with anti-hypertensive 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 and ASPIRE studies the incidence of HTN in patients receiving carfilzomib was 17% and 11%, respectively (20,21). Of these events, 3–6% were reported as grade ≥3 and <2% were fatal (22). 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. Re-challenge should be consider only after risk/benefit assessment (22).

Pathophysiology

VEGF enhances the production of nitric oxide and prostacyclin while decreasing endothelin-1 generation (23). VSP inhibitors affect normal vascular homeostasis by interfering with production of nitric oxide (NO) in the arteriolar walls (24). Inhibition of NO leads to vasoconstriction, increased peripheral vascular resistance, and increased blood pressure (24). Bevacizumab reduced endothelial nitric oxide synthase (eNOS) activity leading to HTN (25). Although VEGF is believed to affect the renin-angiotensin system (RAS) (26), anti-VEGF therapy did not alter serum catecholamine, renin, and aldosterone levels (27). Telatinib, a potent inhibitor of VEGFR, induces capillary rarefaction (28). Carfilzomib reduces the vasodilatory response of acetylcholine and induces vasospasm, which can be treated with nitroglycerin (29–31). 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, 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 (32). HTN most commonly occurs within the first month of treatment (33). 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. ACE inhibitors is the preferred first line therapy due to its beneficial effects on PAI-1 expression and proteinuria (25). ACE inhibition also increases the release of endothelial NO

and decreases catabolism of bradykinin (4). ACEI has been shown to significantly improve overall survival in metastatic renal cell carcinoma patients treated with sunitinib (34). 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 which 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 five major etiologic groups (35). Drug amd 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 (36,37). 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 (38).

Dasatinib was first reported to cause PH in 2009 in a CML patient (39). A French registry reported 9 patients treated with dasatinib who subsequently developed moderate to severe PH; the incidence was estimated to be 0.45% (40). 8 patients showed functional improvement 4 months after cessation of dasatinib therapy. In an American study on 41 patients with dasatinib-induced PH, partial or complete reversal of PH was seen following discontinuation of dasatinib (41). The DASISION study comparing dasatinib with imatinib showed 14 (5%) of the 258 dasatinib patients developed PH, compared with 1 (0.4%) in the imatinib patients over a follow-up period of at least 5 years (42). However, only 1 of the 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 over-estimation. Inhibition of SRC kinase by dasatinib was implicated in the development of PH (40). SRC kinase is involved in regulation of smooth muscle proliferation and vasoconstriction so that its inhibition could lead to increased pulmonary vascular resistance (40).

Transthoracic echo is the screening tool of choice for PH. VQ scan and right heart catheterization is necessary to establish the diagnosis of PH. A high index of suspicion and prompt diagnosis are necessary in order to prevent further deterioration. PH can be managed by withholding dasatinib, treating with alternative TKIs, followed by treatment withsildenafil, endothelial antagonist, or calcium channel blocker (40). Patient should be followed monthly with echocardiogram for serial assessment of pulmonary artery pressure. Cancer therapy can be continued with alternative TKIs. Thus, dasatinib-induced PH has a relatively good prognosis if diagnosed and treated early.

PERICARDIAL DISEASES

Pericardial effusion, a manifestation of late-stage malignancies, develops in 5 to 15% of patients with cancer, (43). The most common malignancies associated with pericardial

effusions are lung cancer, breast cancer, leukemia, and lymphoma (43–45). Pericardial effusion caused by breast cancer or lymphoma had better prognosis compared to lung cancer (46). Malignant effusions with negative cytology in early pericardiocentesis usually become positive over time. The pericardial space can be invaded by direct tumor extension or metastatic spread via lymphatics or blood. Pericardial effusion can also develop as a result of chemotherapy, radiation therapy, or from opportunistic infections (47).

Chemotherapies associated with pericardial diseases include anthracyclines, cyclophosphamide, cytarabine, imatinib, dasatinib, interferon-α, arsenic trioxide, and less frequently, docetaxel and 5-fluorouracil (48). All-trans retinoic acid causes a syndrome characterized by fever, hypotension, acute renal failure, and pericardial effusion. High-dose busulfan can cause pericardial and endomyocardial fibrosis 4 to 9 years after treatment (49).

Pericardial disease (effusion and/or constriction) can occur in 6–30% of patients after radiation therapy (50–52). It is the most common manifestation of radiation-induced heart disease, which usually occurs as a result of fibrinous exudates to the pericardial surface, as well as fibrotic changes to the parietal pericardium. Acute pericarditis can occur within days to months following radiation therapy; it is often self-limiting. Chronic pericarditis is often characterized as effusive-constrictive.

Diagnosis and treatment

Electrocardiogram is useful in the diagnosis of acute pericarditis, usually in the setting of recent radiation therapy. However, echocardiography is the imaging modality of choice in the diagnosis of pericardial effusion and cardiac tamponade. Patients are often asymptomatic with small to moderate pericardial effusion, but can present with dyspnea, cough, tachycardia, pulsus paradoxus, and hypotension with impending cardiac tamponade. Echocardiographic features of cardiac tamponade include increase mitral inflow with expiration, diastolic compression of RV, late diastolic collapse of RA, plethora of IVC, and abnormal ventricular septal motion. Emergency pericardiocentesis should be carried out promptly when cardiac tamponade is suspected.

Pericardiocentesis should be carried out for cardiac tamponade, large pericardial effusions (≥ 2cm), or for diagnostic purposes. Factors that carried poorer prognosis for 2-year survival after pericardiocentesis for malignant effusions included age > 65 years, platelet counts < 20,000, lung cancer, presence of malignant cells in the effusion, and drainage duration (46). Pericardial fluid should be sent to for chemistry, microbiology, and cytology. If pericardiocentesis is performed, the drain should be left in place for 3–5 days and surgical pericardial window should be considered if the output drainage is still high 6–7 days after pericardiocentesis. Effusions are more likely to recur with percutaneous pericardiocentesis compared with pericardiotomy, even though there was no difference in length of stay or ICU admission with either approach (47).

Rarely, pericardial effusions are managed with intrapericardial injection of chemotherapeutic agents. In a small series of patients treated with intrapericardial cisplatin for malignant pericardial effusion, 93% and 83% were free of hemodynamically significant recurrent pericardial effusions at 3 and 6 months, respectively (53,54). Intrapericardial bevacizumab

was used to achieve sustained remission in 7 patients (55). However, the preferred management for recurrent pericardial effusion is still surgery (56).

THROMBOEMBOLISM

It is well established that cancer itself predisposes patients to thromboembolic events (57). However, there are considerably more data on venous than arterial thromboses (58,59). Thrombosis in cancer patients is most likely due to release of prothrombotic factors, such as tissue factor, mucin, and cysteine protease, into the circulation to activate the clotting cascade (57). The risk of arterial thromboembolism is higher in the first 6 month after cancer diagnosis and returns to baseline in one year (60). The risk of thromboembolism is higher with certain cancers (lung, pancreatic, colon/rectal, kidney, prostate), with metastatic diseases, and with certain risk factors (use of central venous catheters, immobility, heart failure, atrial fibrillation, hypovolemia, chemotherapy) (58,61) .

Pathophysiology and Incidence

VSP Inhibitors—VSP inhibitors are known to increase the risk of thromboembolism by altering the vascular protective property of the endothelial cells (Table 2) (62). Endothelial injury couples with hypercoagulability and hemodynamic changes followed by thrombosis. Meta-analyses of major VSP inhibitor trials demonstrated an increased risk of thromboembolic events (62–64). The incidence of all grade arterial thrombotic events in patients on VSP inhibitors ranges from 1 to 11% (65). Higher risk of arterial thrombotic events was reported in several meta-analyses of VSP inhibitor trials (62–64). In a meta-analysis of 10,255 patients treated with sorafenib or sunitinib, the incidence of arterial thrombotic events was 1.4% with relative risk of 3.03 when compared to the control group (64). More recently, a meta-analysis of 38,078 patients from all eligible VSP inhibitor trials observed a significantly higher risk of MI (RR 3.54) and arterial thrombotic event (RR 1.80) in the population studied. However, no significant difference between risks of stroke was found between these 2 groups (62).

Several meta-analyses failed to establish increased risk in venous thromboembolism in patients treated with VSP inhibitor compared to control group (66–68). Subsequently, a meta-analysis of all eligible trials of patients treated with VSP inhibitors showed the RRs for DVT and PE were insignificant at 1.14 and 1.18, respectively (62). Although cancer itself is a risk factor for venous thromboembolism, it is not clear whether VSP inhibitors exaggerate this risk (69).

Cisplatin—Jacobson *et al* found a 16.7% incidence of thromboembolic events in 48 patients treated with cisplatin and radiotherapy for cervical cancer (70). In another study of 271 patients with urothelial transitional cell cancer, cisplatin-based chemotherapy was associated with thromboembolic and vascular events in 12.9% of patients; 8.5% of them had DVT or PE. The risk factors include CAD, immobility, prior history of thromboembolic events, and pelvic masses. Cisplatin causes vascular injury (71) and induces platelet activation through a mechanism involving monocyte procoagulant activity (72).

Angiogenesis Inhibitors—Lenalidomide and its parent drug thalidomide increase the risk of thromboembolism when combined with glucocorticoids and/or cytotoxic chemotherapy. This risk is 3–75% for lenalidomide and 1–58% for thalidomide (73). A systematic review demonstrates that patients with multiple myeloma treated with thalidomide- or lenalidomide-based regimens are at higher risk for developing venous thromboembolism (74). Newly diagnosed patients have higher risk than patients who were previously treated. When thalidomide or lenalidomide was combined with dexamethasone and doxorubicin, the risk increased. Aspirin, warfarin with target INR of 2.0 – 3.0, or therapeutic doses of low molecular weight heparin can reduce the risk of venous thromboembolism. However, rates of major bleeding complications are unknown, thus the benefit of prophylaxis is not clear. Thalidomide causes transient elevation in factor VIII and vWF and reduction in soluble thrombomodulin, which may explain the increase in thromboembolism (74,75).

Histone deacetylase inhibitor—Vorinostat, useful in the treatment of cutaneous T-cell lymphoma, is known to increase the risk of thromboembolism in cancer patients (73,76). The rates of PE and DVT with this agent were reported to be 5% and 8%, respectively (77).

Diagnosis, prevention and management

DVT is usually diagnosed by compression ultrasonography and PE by spiral CTA. Ventilation-perfusion scan is employed less frequently for diagnosis of PE due to lower sensitivity and specificity compared with CTA, but is still utilized with compression ultrasonography in patients with renal dysfunction. Magnetic resonance pulmonary angiography is considered in patients with allergy to iodinate contrast media (73,78).

Prevention strategies should be chosen according to specific anticancer drug. The goal is to use the safest form of prophylaxis that reduces the risk of thromboembolism to ≤ 10%. Prevention should be tailored to the presence of risk factors, such as obesity, prior episodes, central venous catheter use, co-morbid conditions, surgery, use of erythropoietin and tamoxifen, concomitant therapy with high dose dexamethasone and/or doxorubicin. For primary prevention, all hospitalized patients should receive either low molecular weight heparin (LMWH) or unfractionated heparin (79). The Khorana VTE risk assessment model for cancer patients may be utilized in the ambulatory setting. This model uses site of cancer, blood cell counts, and BMI to determine a patient's risk. A score of 3 or higher confers a 7.1–41% risk of symptomatic VTE and prophylaxis may be reasonable in these patients (79,80).

VSP Inhibitors—Prior to initiation of VSP inhibitor therapy, cardiovascular risk factors should be aggressively managed (81). A history of prior arterial thromboembolic event (ATE) is not an absolute contraindication to VSP inhibitor therapy; however, VSP inhibitors should be used with caution or avoided in patients with recent cardiovascular events in the preceding 6–12 months. There are no standard guidelines for management of ATEs in patients on VSP inhibitors, so management of such events should be based on standard medical practice (82). VSP inhibitor therapy should be discontinued in grade 3 or higher thromboembolic events (4,83). Increased risk of hemorrhage with VSP inhibitor is not a

contraindication to the use of thrombolytic or anticoagulation therapy when medically appropriate; however, these patients should be closely monitored. Following resolution of acute events, restarting VSP inhibitor should be based on individualized risk versus benefit analysis.

Data from multiple trials have led to widespread use of aspirin for both primary and secondary prevention of arterial ischemia (84,85). Although there are no controlled studies to determine the benefit of aspirin in patients on VSP inhibitors, it is reasonable to start low dose aspirin prophylactically in high-risk patients, e.g. patients with previous ATEs or based on Framingham risk assessment. Furthermore, low dose aspirin may prevent cardiovascular events in patients receiving bevacizumab who are ≥ 65 years with prior history of ATEs (9).

Angiogenesis Inhibitors—Observational studies of thalidomide- and lenalidomide-based regimens in multiple myeloma patients have demonstrated efficacy of prophylaxis with aspirin (81 to 325mg), warfarin, or LMWH (78,86). Single-agent lenalidomide does not constitute high risk of VTE and prophylaxis is not recommended in this setting. Aspirin is an appropriate prophylaxis in patients receiving lenalidomide with low-dose dexamethasone, melphalan or doxorubicin; the incidence of VTE was reduced to less than 10% with aspirin (87–89). Addition of high-dose dexamethasone carries additional risk and likely warrants the use of more aggressive prophylaxis, such as LMWH or full-dose warfarin.

One randomized study compared the use of aspirin and fixed low-dose warfarin *versus* LMWH to prevent thromboembolism in 667 previously untreated multiple myeloma patients receiving thalidomide-containing regimens with or without bortezomib (90). Patients were randomized to aspirin (100 mg/day), warfarin (1.25 mg/day) or LMWH (enoxaparin 40 mg/day). There was no difference in the prevention strategies tested. In the case of single-agent thalidomide, low-dose aspirin should be considered (91). LMWH or full-dose warfarin is recommended in patients receiving angiogenesis inhibitors with dexamethasone, doxorubicin, or multi-agent chemotherapy.

Once the diagnosis of VTE is made, the treatment goal should be to relieve symptoms and to prevent propagation. Patients should be treated in accordance with the American College of Chest Physicians guidelines (82). If a patient develops VTE while on chemotherapy, the therapy should be held and standard anticoagulation, preferably LMWHs, initiated (92). Thrombolytic therapy should be considered if clinically indicated. Cancer therapy can be reinstated once the patient is stable and therapeutic anticoagulation is achieved. Anticoagulation should be continued as long as the patient has active malignancy and therapy is not otherwise contraindicated (79). Anticoagulation should be avoided in the presence of intracranial bleeding, recent surgery, preexisting bleeding diathesis such as thrombocytopenia, platelet count <50,000/μl or coagulopathy (91).

Use of Direct Oral Anticoagulants in Cancer

While direct oral anticoagulants (DOAC), such as dabigatran, rivaroxaban, apixaban, are the preferred oral anticoagulant for the treatment of VTE in patients without cancer, there is limited data for DOAC in cancer patients (93,94). Most trials compared the safety and efficacy of DOAC with warfarin have excluded cancer patients or included a small number

of them. Most of included cancer patients had completed cancer therapy and active cancer patients were excluded.

As already discussed, LMWH is the anticoagulant agent of choice in patients with malignancy. Compared with general population, there are fewer data to support the use of DOACs as first-line agents in patients with malignancy; however, limited data suggest that warfarin and DOACs are of equal efficacy when oral anticoagulants are necessary in cancer patients. Compared with warfarin, therapeutic efficacy with DOACs occurs within one to four hours after ingestion. Sub-group analysis of cancer patients in the ARISTOTLE trial evaluated DOACs for patients with non-valvular atrial fibrillation (95). At baseline, there were 1236 (6.8%) patients with history of cancer and 157 (12.7%) had active cancer or treated within one year. This study did not show difference in stroke or systemic embolization between apixaban and warfarin in cancer patients. Another small prospective study suggests that rivaroxaban is safe and effective for treatment of cancer-associated VTE (96).

QT PROLONGATION

QT interval prolongation is caused by abnormality in depolarization/repolarization that can lead to torsade de pointes (TdP) and sudden death (97). The hERG potassium channel is the molecular target for drugs that prolong QT interval (2,98–101). Cancer patients are more prone to develop QT prolongation following treatment with arsenic trioxide and TKIs (Table 3). Anti-emetics, H2-blockers, proton pump inhibitors, antimicrobial agents, anti-psychotics also contribute to prolong the QT interval (2). In addition, nausea, vomiting, and diarrhea following cancer therapy lead to loss of potassium and magnesium that also prolongs the QT interval.

Incidence

Arsenic Trioxide—Arsenic trioxide is used for the treatment of acute promyelocytic leukemia. The U.S. Multicenter Study of Arsenic Trioxide reported the incidence of QTc interval > 500ms to be 40% (102); other trials reported incidences of QT prolongation with arsenic trioxide ranging from 26 to 93% (73,103). The QT interval became prolonged 1 to 5 weeks after arsenic trioxide treatment and returned to baseline 8 weeks after cessation of therapy (102).

Small Molecule TKI-Inhibitors—4.4% of patients treated with TKIs developed all grade QTc prolongation and 0.8% developed serious arrhythmia (99). However, the incidence of QT prolongation is not affected by the duration of therapy (99). The most common drugs that prolongs QTc when used in conjunction with sunitinib are domperidone or loperamide (104); nonetheless, there were no high-grade arrhythmias or sudden cardiac deaths associated with sunitinib use. Pazopanib and axitinib only confers <1% risk of high-grade QTc prolongation in the absence of TdP. Unfortunately, QT intervals were not available in studies on sorafenib and cediranib (105–107). High-grade QT prolongation is a significant adverse effect of vandetanib therapy. In a trial for metastatic medullary thyroid cancer, the incidence of high-grade QTc prolongation is 8% (108). A meta-analysis reported similar incidence of QTc prolongation for vandetanib (99). This effect is dose-dependent with the

reported incidence of 3.6% in low dose and 12.2% in high-dose. The incidence of QT prolongation is 10% for nilotinib to 10% and16% for lapatinib according to package insert.

Histone deacetylase inhibitor and BRAF inhibitor—The incidence of QTc prolongation with vorinostat ranged from 3.5 – 6% (73). In an open-label study in patients with BRAF(V600) mutation, vemurafenib lengthed QTc to greater than 500 ms in 3% of patients (109).

Diagnosis

QT interval varies with heart rate and has to be adjusted by the RR interval to calculate QTc (110). The Fridericia formula, in which QT is divided by the cubic root of the RR interval, is recommended by the FDA for heart rate correction (111). QTc interval is considered normal at < 430 ms in male and <450 ms in female. CTCAE.4 defines grade 1 QTc prolongation as 450–480 ms, grade 2 as 481–500 ms, and grade 3 as QTc>501 ms. QTc≥501 ms or >60 ms change from baseline and TdP or sudden death is defined as grade 4. QTc >500 ms or >60 ms above baseline have been associated with increased risk for TdP (112).

Management

A baseline ECG should be obtained in all patients and electrolyte abnormalities (particularly hypokalemia and hypomagnesemia) corrected prior to starting treatment (113). It is important to identify drug-drug interactions that prolong the QTc interval. Important medications to consider are domperidone, ondansetron, palosetron, granisetron, prochlorperazine, olanzapine, escitalopram, venlafaxine, sertraline and mirtazapine (99). ECG should be repeated at 7 days after initiation of therapy, according to drug package inserts, and following any dosing changes (56). The 2016 Canadian Cardiovascular Society guideline supports baseline ECG and periodic monitoring of the QTc interval in cancer patients receiving QT-prolonging agents (114). Treatment should be stopped if the QTc is > 500 ms on monitoring (113).

TdP should be managed with 2g of IV magnesium as the initial drug of choice regardless of serum magnesium level. Non-synchronized defibrillation may be indicated. Overdrive pacing (with short-term pacing rates of 90–110ms) may be used to shorten QTc; it is useful when TdP is precipitated by bradycardia. IV isoproterenol titrated to heart rates > 90ms is indicated when temporary pacing is not immediately available. All electrolyte abnormalities should corrected and QT prolonging medications discontinued (115).

ARRHYTHMIAS

Brady- or tachy-arrhythmias (including bradycardia or heart block, as well as atrial fibrillation (AF), supraventricular or ventricular arrhythmias) can be associated with cancer or chemotherapy.

Bradycardia and Heart block

Infiltration of the AV nodes by lymphoma or amyloidosis can cause brady-arrhythmias or heart block (116,117). Vagal paraganglioma, a rare tumor of the neuroendocrine system, can

cause significant heart block (118) and 10% patients with catecholamine-secreting tumors have bradycardia and heart block (119,120). Bradycardia and/or heart block can also be seen in patients with neck mass, with involvement of the vagus nerves (121). Although uncommon, bradycardia and heart block have been linked to cisplatin, irinotecan, paclitaxel, mitoxantrone (and rarely, doxorubicin), octreotide, thalidomide, methotrexate, 5-fluorouracil, and arsenic trioxide (61,73). Ethanol, which is injected percutaneously for treatment of hepatocellular carcinoma, can cause sinus bradycardia and heart block (122).

Management—Majority of patients with bradycardia secondary to chemotherapy are asymptomatic (61). Symptoms associated with bradycardia include fatigue, dizziness, as well as pre-syncope/syncope. Treatment of heart block depends on the type of escape rhythm present. Junctional escape rhythm requires pacemaker only if symptoms are present, whereas ventricular escapes are unstable that requires pacemaker implantation.

When a clear offending drug is identified, alternative therapy should be considered. However, if there is no substitution, patient can be closely monitored while undergoing chemotherapy. When bradycardia is caused by thalidomide without treatment alternative, permanent pacemaker implantation may be necessary to allow for continuation of therapy (123,124). In some cases, heart block will resolve with treatment of the primary malignancy (61,116). Pacemaker placement in patients with persistent symptomatic bradycardia and heart block should follow ACC/AHA guidelines (125). In cancer patients with ongoing infection, a temporary pacemaker may be placed and left in place for a few days until the infection is controlled (61,125). The use of isoproterenol to maintain higher heart rates can also be considered. The final decision should be made after consultation between cardiologist and oncologist.

Tachyarrhythmias

Tachyarrhythmias, such as supraventricular arrhythmias, AF, as well as life-threatening and non-life-threatening ventricular arrhythmias, could occur in cancer patients. A recent study of patients diagnosed with cancer after ICD implantation found that the frequency of ventricular tachycardia and ventricular fibrillation increased significantly after diagnosis, representing a 10-fold increase in arrhythmia burden (126). The incidence of ventricular arrhythmias is significantly higher in patients with stage IV cancer than in those with earlier stages. The most common malignancies associated with ventricular arrhythmias are skin, prostate, and breast cancers. Causations of ventricular arrhythmias in cancer patients include QTc prolonging chemotherapeutic agents, inflammation in advanced cancer (127), direct cardiac involvement by tumor, metabolic derangements relating to nausea/vomiting/diarrhea, decreased oral intake, and electrolyte abnormalities.

A large epidemiologic study of 24,125 patients with newly diagnosed cancer found a 2.4% baseline prevalence of AF, with an additional 1.8% increased incidence after cancer diagnosis (128). Another study examined 28,333 patients with AF compared with 282,260 patients without AF found the prevalence of colorectal cancer to be 0.59% in patients with AF, and only 0.05% in those without AF (129). Another study found postop AF to be more common after breast and colorectal cancer surgery (3.6%) compared with non-cancer

surgery (1.6%) (130). Thus, cancer is associated with higher risk of AF. In patients post thoracic surgery for lung cancer, AF was associated with higher postoperative mortality and was associated with 4-fold higher mortality in 5-year survivors after adjustments for other risk factors.

AF in cancer patients is associated with advanced age, hypoxia, increased sympathetic drive caused by pain as well as physical and emotional stress, and/or paraneoplastic conditions such as autoimmune reactions against atrial structures (131). In addition, cancer drugs known to be associated with AF include cisplatin, 5-fluorouracil, doxorubicin, paclitaxel/docetaxel, ifosfamide, gemcitabine, and mitoxantrone (132). IL-2 with or without interferon, has been associated with AF in patients with metastatic renal cell cancer (133). The mechanisms of AF – induced by IL-2 are unclear, but are likely related to elevations in plasma cytokine concentrations with these agents (134). Inflammation appears to be a common denominator leading to AF in most of these conditions (132).

Ibrutinib, a Bruton kinase inhibitor useful in the treatment of chronic lymphocytic leukemia, is significantly associated with AF (135). In the RESONATE trial, 3% of patients receiving ibrutinib developed AF, whereas the ofatumumab arm had no AF (136). In another study of 56 patients, AF occurred 3–8 months after initiation of ibrutinib and 76% of them developed AF within the first year on this drug (137). Patients were managed with dose-reduction and/or anti-coagulation (138); however, the clinical experience is still limited to make a general recommendation.

Management—Management of tachyarrhythmias in cancer patients is similar to those for non-cancer patients. A useful approach is to distinguish dysrhythmias resulting from chemotherapy and metabolic abnormalities from those associated with structural cardiac abnormalities. Active intervention is required when the arrhythmia results in significant hemodynamic abnormality, or when the rhythm disturbance becomes life threatening. The use of anti-arrhythmic drugs for management of dysrhythmias during cancer therapy poses a particular challenge because of drug-drug interactions. Co-administration of chemotherapy and anti-arrhythmic drugs may lead to increased drug levels due to impaired cytochrome p450 metabolism or P-glycoprotein-mediated transport inhibition (139). Furthermore, both chemotherapy and anti-arrhythmic drugs increase the risk of bradycardias and QT prolongation. In general, class 1A, 1C and III antiarrhythmic drugs are more likely to cause drug interactions and QT prolongation, whereas class 1B drugs are less likely to do so. Among the beta-blocker class of drugs, metoprolol, atenolol and pindolol are less likely to cause drug interactions compared with carvedilol, propranolol, or nadolol. Recommendations for managing drug-drug interactions for some targeted therapies were recently published by Asnani et al (139).

The decision to anti-coagulate in cancer patients with AF should be individualized after consultation with the oncologist. The use of CHADsDS2-VASc and HAS-BLED scores has not been validated in cancer patients (140). Furthermore, cancer generally creates a pro-thrombotic milieu, whereas cancer therapy often increase the bleeding risk due to induction of thrombocytopenia (57). Thus, a careful balance between risk/benefit and involvement of patient and family in decision making is essential.

CARDIOVASCULAR DISEASE WITH RADIATION THERAPY

Radiation therapy affects all cardiac structures including the pericardium, epicardial and microvascular circulation, conduction system, and the myocardium (141). Patients can present with acute pericarditis immediately following radiation therapy or chronic pericarditis decades after radiation therapy (Table 4). Valvular heart disease and coronary artery disease usually presents 5 to 10 years after radiation therapy. We recommend an echocardiogram 5 years after radiation therapy and a stress test or coronary CTA 10 years after radiation therapy (56).

CAD is a major cardiovascular complication of radiation therapy. Women with left chest radiation have increased risk of cardiovascular complications as compared to right-sided radiation (142). Higher doses of radiation were associated with increased risk of major coronary events in women treated for breast cancer (143). This risk began within the first 5 years after radiation therapy and continued until the third decade. This study was based on older radiation techniques involving external beam radiation therapy with higher radiation doses. Newer radiation techniques, including deep inspiration breath hold gating, accelerated partial breast irradiation, and use of modern 3-dimensional planning came with less radiation dosage and may ameliorate dreaded cardiovascular complication. Proton beam therapy is purported to offer great potential to minimizing the risk of cardiovascular events by keeping the mean heart dose at ≤ 1 Gy (144). A SEER database study of 29,102 patients diagnosed with breast cancer from 2000 to 2009 showed a small increase in PCI procedures after radiation therapy: 5.5% vs. 4.5% for left vs. right-sided breast cancer. In those who underwent PCI, left-sided breast cancer carried significantly higher risk of cardiac mortality compared with right-sided breast cancer (145).

Cardiovascular risk factors, such as HTN, diabetes mellitus, dyslipidemia, and obesity, have been shown to significantly increase the risk of CVD and associated complications of radiotherapy (146). The risks are magnified after chemotherapy and/or with 2 or more cardiovascular risk factors. Annual follow up is recommended with ordering of ECG or echocardiogram as clinically indicated. The echocardiography consensus statement recommends evaluation based on signs and symptoms as stated above, and functional non-invasive stress testing within 5 to 10 years of completion of chest radiation therapy (48). Perfusion abnormalities on SPECT perfusion imaging is not always correlated with presence of CAD associated with radiotherapy (147). The role of coronary artery calcium scoring as well as coronary CT angiography in screening for radiation-induced CAD has not been defined. In a study by Hancock et al., a significant proportion of patients who suffered a fatal MI because of radiation-induced CAD had no prior symptoms of angina or heart failure (148). Future research efforts should aim at better identification of this subset of patients.

Autonomic dysfunction is sequelae of radiation therapy (149). Elevated resting heart rate and heart rate recovery (HRR) that worsened with time after radiation were demonstrated in Hodgkin lymphoma survivors referred for stress testing. Abnormal HRR was associated with an increase in all-cause mortality (age-adjusted HR 4.60) (149). These patients could be managed with beta blockers, such as atenolol. The diagnosis, prevention, and management for other radiation-induced cardiovascular complication are summarized in Table 4.

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Abbreviations

AF	Atrial Fibrillation
AI	Aortic Insufficiency
BNP	Brain Natriuretic Peptide
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTA	CT Angiography
CML	Chronic Myeloid Leukemia
CVD	Cardiovascular Disease
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
ECG	Electrocardiography
FDA	Food and Drug Administration
HR	Hazard Ratio
HRR	heart rate recovery
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
IL-2	Interleukin-2
INR	International Normalized Ratio
LBBB	Left Bundle Branch Block
LMWH	Low Molecular Weight Heparin
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction

MI	Myocardial Infarction
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
PE	Pulmonary Embolism
PH	Pulmonary hypertension
PCI	Percutaneous Coronary Intervention
PR	Pulmonary Regurgitation
QTc	Corrected QT
RBBB	Right Bundle Branch Block
RR	Relative Risk
RV	Right ventricle
SEER	Surveillance, Epidemiology, and End Results Program
TAVR	Trans-catheter Aortic Valve Replacement
TdP	Torsades de Pointes
TIA	Transient Ischemic Attack
TKI	Tyrosine Kinase Inhibitor
TR	Tricuspid Regurgitation
VSP	Vascular Endothelial Growth Factor Signaling Pathway
vWF	von Willebrand Factor

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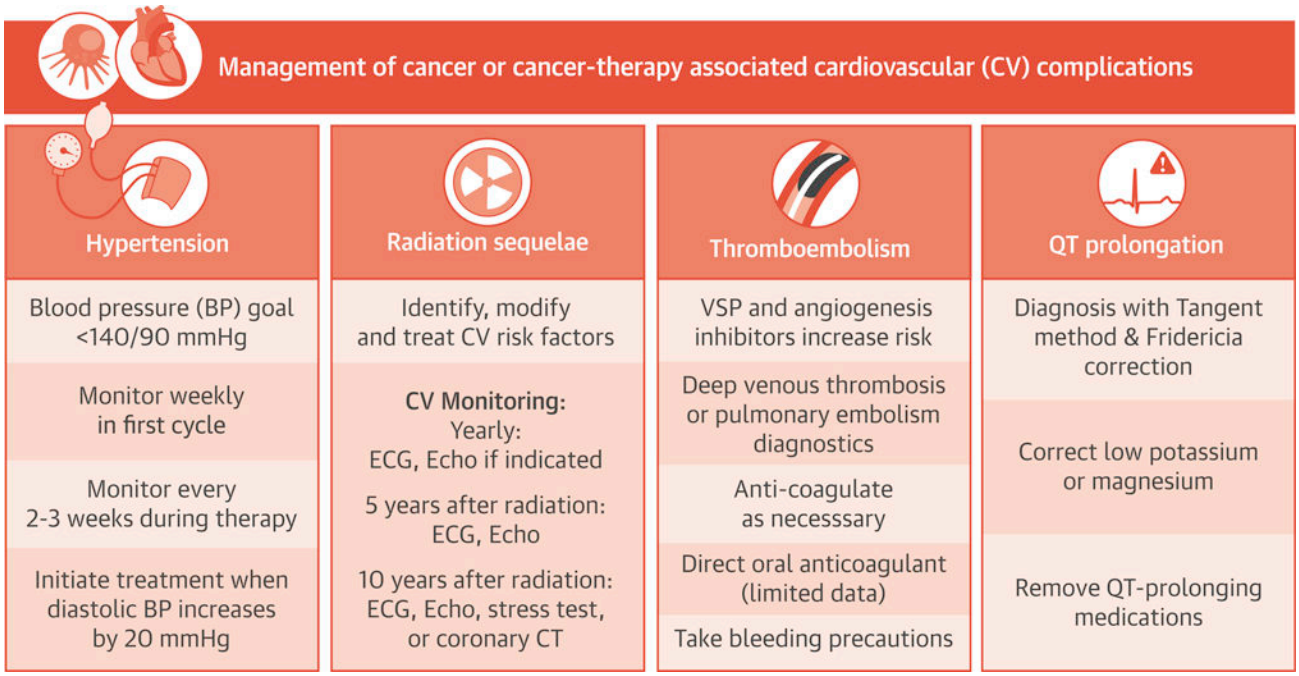
Condensed Abstract

HTN is a common toxicity of VSP inhibitors and requires aggressive management to avoid end organ damage. Pulmonary HTN is a rare complication of dasatinib treatment. Early diagnosis, discontinuation of dasatinib, and substitution of another TKI can reduce the morbidity of this complication. Thromboembolism can be caused by VSP inhibitors and angiogenesis inhibitors that required anti-coagulation therapy. QT prolongation is a frequent consequence of drug therapy; however, torsade-de-pointe is rare unless QTc exceeds 500 ms. Radiation can damage heart valves, the conduction system, pericardium, and myocardium that may take years to develop. Long-term follow up is essential in cancer survivors.



Central Illustration. Management of cancer therapy-induced cardiovascular complications

Best practices in the management of cancer therapy-induced HTN, thromboembolism, QT prolongation, and radiation-induced complications. HTN=hypertension; BP= blood pressure; CT= computed tomography; MR= magnetic resonance imaging; LMWH=low-molecular weight heparin; TdP= torsades de Pointe

Table 1

Anticancer Agents Associated With Hypertension

Chemotherapy Agents	Frequency of Use	Incidence (%)	Comments
Monoclonal antibody-based tyrosine kinase inhibitors			Pre-treatment risk assessment BP goal <140/90 mmHg Weekly BP monitoring in 1st cycle Every 2–3 weeks BP monitoring for duration of therapy Initiate BP treatment when diastolic BP increases by 20 mmHg More than one anti-HTN medication may be needed Avoid diltiazem and verapamil with sorafenib Hold chemotherapy as the last resort Hold bevacizumab if systolic BP> 160 or diastolic BP>100 Early consultation with cardiologist
Bevacizumab (Avastin)	+++	4–35	
Adotratuzumab emitansine (Kadcyla)	+	5.1	
Monoclonal Antibodies			
Alemtuzumab (Campath)	+	14	
Ibritumomab (Zevalin)	NA	7	
Ofatumumab (Arzerra)	+	5–8	
Rituximab (Rituxan)	+++	6–12	
mTor inhibitors			
Everolimus (Afinitor)	++++	4–13	
Temsirolimus (Torisel)	++	7	
Small molecule tyrosine kinase inhibitors			
Pazopanib (Votrient)	++++	42	
Ponatinib (Iclusig)	+	68	
Sorafenib (Nexavar)	++++	7–43	
Sunitinib (Sutent)	++++	5–24	
Axitinib (Inlyta)	++++	40	
Cabozantinib (Cometriq)	NA	33–61	
Ibrutinib (Imbruvica)	++++	17	
Nilotinib (Tasigna)	++++	10–11	
Ramucirumab (Cyramza)	+	16	
Regorafenib (Stivarga)	++++	30–59	
Trametinib (Mekinist)	++++	15	
Vandetanib (Caprelsa)	NA	33	
Ziv-aflibercept (Zaltrap)	+	41	
Proteasome Inhibitors			
Bortezomib (Velcade)	++	6	
Carfilzomib (Kyrpolis)	++	11–17	
Antimetabolites			
Decitabine (Dacogen)	++	6	

Frequency of Use:_This was determined using inpatient and outpatient doses dispensed at MD Anderson Cancer Center during the time period of January 1, 2014 through December 21, 2014.

+ =<1,000 doses dispensed

++ =1,000–5,000 doses dispensed

+++ =5,000–10,000 doses dispensed

++++ =>10,000 doses dispensed

References: (4,56,73)

Table 2

Anticancer Agents Associated With Thromboembolism

Chemotherapy agents	Frequency of Use	Incidence (%)	Comments
Alkylating agents			Risk factors: cancer types, metastatic disease, central venous catheter, heart failure, immobility, AF, previous history of thromboembolism, chemotherapy, hormonal therapy, old age, female Diagnosis: compression ultrasonography, spiral CT, MR Treatment options: aspirin, warfarin, LMWH Limited data with DOAC
Cisplatin (Platinol-AQ)	+++	8.5–16.7	
Angiogenisis inhibitors			
Lenalidomide (revlimid)	+++	3–75	
Thalidomide (thalomid)	++	1–58	
Pomalidomide (pomalyst)	+	3	
Histone deacetylase inhibitor			
Vorinostat (zolinza)	++++	4.7–8	
Monoclonal antibody - against VEGF			
Bevacizumab (avastin)	+++	6–15.1	
mTOR inhibitors			
Everolimus (afinitor)	++++	1–4	
Small molecule tyrosine kinase inhibitors			
Axitinib (Inlyta)	++++	3	
Dabrafenib (tafinlar)	++++	7	
Erlotinib (tarceva)	++++	3.9–11	
Nilotinib (tasigna)	++++	1–10	
Pazopanib (votrient)	++++	1–5	
Ponatinib (iclusig)	+	5	
Sunitinib (sutent)	++++	3	
Trametinib (mekinist)	++++	7	
Ziv-aflibercept (zaltrap)	+	9	

Frequency of Use: See Table 1

References: (56,73)

Table 3

Anticancer Agents Associated With QT Prolongation

Chemotherapy Agents	Frequency of Use	Incidence (%)	Comments
Histone deacetylace inhibitors			Tangent method of QT measurement Fridericia correction formula Correct low K or Mg Remove QTc prolonging medications QTc>500 ms or >60 ms above baseline associated with TdP TdP reported for arsenic trioxide, sunitinib, pazopanib, vandetanib, vemurafenib
Belinostat (beleodaq)	+	4–11	
Vorinostat (zolinza)	++++	3.5–6	
Chemicals			
Arsenic trioxide (trisenox)	++	26–93	
Small molecule tyrosine kinase inhibitors			
Dabrafenib (tafinlar)	++++	2–13	
Dasatinib (sprycel)	++++	<1–3	
Lapatinib (tykerb)	++++	10–16	
Nilotinib (tasigna)	++++	<1–10	
Vandetanib (caprelsa)	++++	8–14	
BRAF inhibitor			
Vemurafenib (Zelboraf)	++++	3	

Frequency of Use: See Table 1

References: (56,73)

Table 4

Radiation-Induced Heart Disease: Diagnosis and Management

Pericardial Disease	
Prevalence	6 – 30%
Description	Pericarditis (acute or chronic), Pericardial Effusion, Pericardial Constriction Most common manifestation of radiation-induced heart disease, and a diagnosis of exclusion. Due to inflammation and impaired drainages to the pericardial surface, fibrotic changes to the parietal pericardium. Acute pericarditis is often self-limiting. Chronic pericarditis is often effusive-constrictive.
Diagnosis	Diagnosis of exclusion after other causes of pericardial disease have been ruled out Echocardiogram, Cardiac MRI, Cardiac CT
Management	Anti-inflammatory drugs for pericarditis Pericardiocentesis for large effusions or tamponade Pericardial window for recurrent pericardial effusions Pericardial stripping for constrictive pericarditis
Coronary Artery Disease	
Prevalence	Up to 85%
Description	Due to epicardial coronary arteries and microcirculatory damage, and sustained inflammation. Usually occurs 10 years after radiation therapy. Involves the LM, ostial LAD and RCA. Lesions are longer, concentric, and tubular.
Diagnosis	Stress echocardiography (could also screen for other causes of RIHD, other than CAD); or stress perfusion imaging ; Cardiac CTA; Possible role for coronary calcium screening
Management	Percutaneous coronary angioplasty or coronary arteries bypass graft (challenging surgery due to fibrosis of pericardium and mediastinum). Aggressive cardiovascular risk factor modification
Valvular Heart Disease	
Prevalence	10 years: 26% AI, 39% MR, 16% TR and 7% PR 20 years: 60% AI, 16% AS, 52% MR, 26% TR, 12% PR
Description	Mean time interval of 12 years after radiation. Diffuse fibrosis of the valvular cusps or leaflets, with or without calcification; no post-inflammatory changes noted. Left-sided valves > right-sided valves. Initial regurgitation related to valve retraction, later stenosis related to thickening/calcification
Diagnosis	Echocardiogram, Cardiac MRI
Management	Serial monitoring with timing of surgery as in ACC/AHA guidelines Valve replacement is preferred over valve repair Consider TAVR, if mediastinum and cardiac anatomy is not amenable to open heart surgery
Conduction System Abnormalities	
Prevalence	Up to 5%
Description	A-V Nodal Block (including high-degree block), bundle branch block (RBBB > than LBBB), fascicular block Tachycardia can be persistent, usually a result of autonomic dysfunction, similar to denervated hearts. Persistent tachycardia could increase risk of tachycardia-induced cardiomyopathy.
Diagnosis	ECG, Telemetry/ambulatory Holter monitor
Management	Permanent pacemaker for high-degree A-V block ICD for life-threatening arrhythmia, sudden death, or secondary prevention Consider sub-pectoral approach for device implantation, if subcutaneous involvement of thoracic radiation
Cardiomyopathy	
Prevalence	Up to 10%
Description	Diastolic dysfunction > Systolic dysfunction; Right ventricle > Left ventricle Due to increased fibrosis in all three layers of the ventricular walls (epicardium, myocardium, and endocardium). May lead to restrictive cardiomyopathy, and rarely to systolic dysfunction.
Diagnosis	Echocardiogram, cardiac MRI
Management	Slow upward titration of ACEI, beta blockade, and aldosterone inhibitors in patients with reduced LV systolic function; Optimize risk factors for diastolic dysfunction, exercise training Inotropic support, VAD, heart transplantation

References: (50,51,140,150–152)