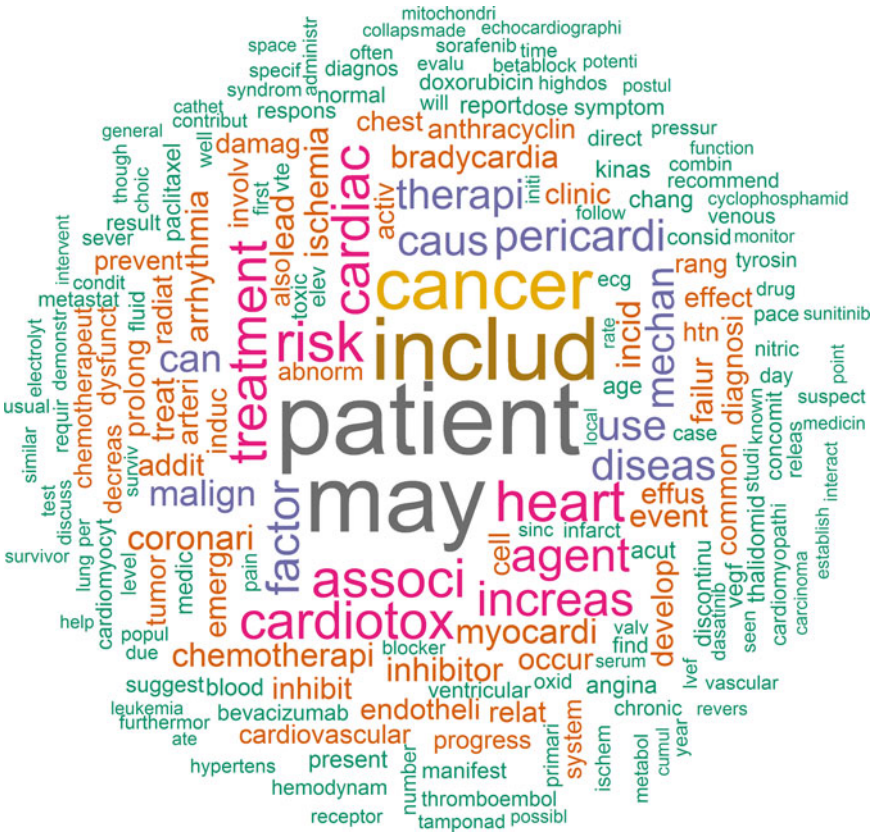
Cardiovascular Emergencies

Adam H. Miller



A.H. Miller, MD, MSMM, MSCS (✉)
Department of Surgical Oncology, UT MD Anderson Cancer Center, Houston, TX, USA
e-mail: ahmiller@mdanderson.org

K.H. Todd, C.R. Thomas, Jr. (eds.), *Oncologic Emergency Medicine*, DOI 10.1007/978-3-319-26387-8_15

Introduction

In this chapter we will explore, in some detail, cardiovascular conditions encountered in oncologic emergency medicine and discuss chemotherapy and radiotherapy contributions to their etiology. The chapter will discuss potential and known mechanisms of action for commonly used cancer therapies. Furthermore, comprehensive diagnosis and treatment discussions will provide emergency physicians with the tools to manage oncology-related cardiovascular emergencies encountered in clinical practice.

The most common oncocardiologic emergencies involve (1) arrhythmias, (2) ischemic heart disease, (3) heart failure, (4) thromboembolic disease, (5) hypertension, and (6) malignant pericardial effusion.

Arrhythmias

Arrhythmias often require patients to seek emergency department (ED) attention. Arrhythmias may be related to a patient's malignancy and cancer treatment or may be the result of an unrelated medical problem. Milder symptoms include "palpitations" or "fluttering in the chest," while more serious sequelae include near syncope or syncope. Patients may present after experiencing transient or permanent neurologic deficits, peripheral embolization, or acute claudication as the result of clot migration.

(a) Primary arrhythmias are disturbances that arise from cardiac and pericardial structures. These can be caused by focal (involving one or more localized areas of the myocardium) or diffuse abnormalities. These can occur in cancer and non-cancer patients and may be related to ischemia; increased intracardiac pressure and wall stress; congestive, hypertrophic, and infiltrative cardiomyopathy (CMP); and fibrosis related to age. Several other abnormalities may be more common in the cancer patient including intracardiac thrombi, primary (benign myxomas, malignant sarcomas) and metastatic malignant intracardiac tumors (carcinoma of the lung, breast, malignant melanoma, lymphoma, and leukemia), amyloid infiltration, myopericarditis, pericardial constriction, and cardiomyopathy related to antitumor agents.

(b) Secondary arrhythmias arise from unidentifiable structural or localized metabolic abnormalities including general toxic reactions to drugs or chemicals; increased sympathetic states related to anxiety; mediator release, i.e., pheochromocytoma, carcinoid tumors, or hyperthyroidism; and derangements of metabolism, i.e., fluid and electrolyte abnormalities. Additionally in cancer, tumor lysis may create an environment that is arrhythmogenic [109].

Table 1 Incidence of QT prolongation in patients associated with specific chemotherapeutic agents including arsenic trioxide, dasatinib, lapatinib, nilotinib, and vorinostat

Chemotherapeutic agent	Incidence of QT prolongation
Arsenic trioxide	26–93 % (may persist from 1 to 5 weeks after infusion) [14, 87, 88]
Dasatinib	<1–3 % (FDA website) [14]
Lapatinib	Up to 16 % [14]
Nilotinib	1–10 % [14, 89, 90]
Vorinostat	3.5–6 % [14]

1. *QT prolongation* may lead to ventricular arrhythmias (Table 1). Cancer patients are at increased risk of QT prolongation since 16–36 % have baseline ECG abnormalities [79, 86]. The cancer patient is commonly treated with QT-prolonging medications other than the chemotherapy, including antiemetics, antifungals, and quinolone antibiotics. Other comorbidities that may be arrhythmogenic include structural heart disease, renal or hepatic dysfunction, and electrolyte abnormalities resulting from vomiting, diarrhea, and decreased oral intake.

   Mechanism: the mechanism by which these chemotherapeutic agents cause QT prolongation is in part blockage of delayed rectifier potassium current [91].

   Diagnosis of QT prolongation is made by ECG interpretation. The ECG-QTc interval is considered normal when ≤440 ms and prolonged in men and women if longer than >450 and >470 ms, respectively. Increases of ≥60 ms from baseline or >500 ms after administration of a medication raise the risk of an arrhythmia. Predisposing factors include female gender, heart failure (HF), elderly age, myocardial infarct (MI)/ischemia, electrolyte imbalances, bradycardia, and chemotherapeutic medications mentioned above [91].

   Treatment includes periodic ECG monitoring and assessment for other agents and conditions that increase the risk of QT prolongation, i.e., electrolyte abnormalities (secondary arrhythmia), congenital long QT syndrome, concomitant antiarrhythmic medicines or other drugs known to cause QT prolongation, and cumulative high-dose anthracycline therapy. Dosage adjustment and/or discontinuation of predisposing agents may be required [14]. Emergency complications of QT prolongation include ventricular arrhythmias, particularly torsade de pointes.

   Treatment of torsades de pointes (polymorphic ventricular tachycardia) includes intravenous magnesium sulfate 2 g initially regardless of the serum magnesium level. Nonsynchronized defibrillation may be appropriate if sustained, hemodynamically unstable polymorphic ventricular tachycardia or fibrillation develops. Overdrive transcutaneous pacing may be indicated to shorten the QTc. Pacing is effective in preventing recurrence and may be useful in cases refractory to magnesium or when

torsades de pointes is precipitated by bradycardia. If overdrive pacing is initiated, short-term pacing rates of 90–110 beats per minute should be used. Isoproterenol titrated to a heart rate of ≥90 beats per minute is another option and is useful when temporary pacing is unavailable or while preparing for intravenous catheter insertion. Remember to always maintain serum potassium levels in the high-normal range and discontinue any QT-prolonging medications and drugs interfering with patients' metabolism [93]. The goal in the emergency setting must be directed toward hemodynamic stabilization, discovery of correctable pathologies, and control of symptoms.

2. *Bradycardia and heart block* in cancer patients may be caused by fibrosis due to old age or radiation therapy, amyloidosis, and primary cardiac tumors (primary arrhythmia) as these are conditions that potentially affect the cardiac conduction system [79]. Additionally, bradycardia and heart block have been associated with the chemotherapeutic agents paclitaxel and thalidomide.
   (a) Paclitaxel cardiotoxicity manifests with an asymptomatic bradycardia that is reversible [67, 80, 81], and the incidence of this manifestation ranges from between <0.1 and 31 % [14, 66, 67, 80, 81].

   Mechanism postulated for paclitaxel to cause arrhythmias is via its effects on the Purkinje system or extracardiac autonomic control [80]. Additionally, the vehicle Cremophor EL that paclitaxel is formulated in may cause cardiac disturbances. In the case of hypersensitivity reactions, Cremophor EL is known to induce histamine release [66]. Histamine release in the cardiac tissue can increase myocardial oxygen demand as well as coronary vasoconstriction and chronotropic effects [67].

   (b) Thalidomide-induce bradycardia is reported to occur in 0.12–55 % of patients treated [82–84].

   Mechanism of this induced bradycardia has been postulated to be due to central sedative effects or an activation of the vasovagal pathway. Thalidomide reduces tumor necrosis factor-alpha levels causing rapid and complete inhibition of the dorsal motor neurons (part of the nucleus of the vagus nerve). This could lead to over-reactivity of the parasympathetic nervous system resulting in bradycardia. Additionally, thalidomide-induced hypothyroidism may cause bradycardia [83, 85].

   Diagnosis of bradycardia is typically defined as a heart rate <60 beats per minute. Thyroid disease or electrolyte abnormalities should be considered for these cases.

   Treatment for bradycardia associated with paclitaxel can range from monitoring only to pacemaker implantation. Cardiac monitoring for the first hour of paclitaxel infusion is recommended [14]. Bradycardia associated with thalidomide use depends on the severity of clinical symptoms. Certainly if symptoms are clinically significant, the agent should be discontinued. If third-degree heart block is present, a permanent pacemaker is indicated. All concomitant medication inducing bradycardia including beta-blockers, calcium-channel blockers, and digoxin should be discontinued.

Ischemic Heart Disease

When a cancer patient presents to the ED experiencing chest pain [50], they often require a workup and treatment for myocardial ischemia. Chest pain can be a manifestation of unstable angina and acute coronary syndrome both of which refer to more serious cardiac etiologies of ischemic heart disease. Unstable angina includes new-onset angina, angina at rest, acceleration of angina, and post-infarct angina. Acute coronary syndrome encompasses unstable angina but additionally includes non-ST elevation and ST-elevation myocardial infarction [110]. Therapies to combat cancer that may be associated with increased risk of coronary artery disease and/or acute coronary syndrome (ACS) include radiation and chemotherapy. Some of the chemotherapeutic agents implicated include:

1. Alkylating agents including cyclophosphamide: These have been postulated to cause intracapillary microemboli and resultant ischemic myocardial damage [13, 27]. Furthermore, coronary vasospasm has been proposed as a mechanism by which cyclophosphamide cause ischemia [10].
2. Antimetabolites include capecitabine (Xeloda) and 5-Fluorouracil (Adrucil). The most common symptom of 5-Fluorouracil (5-FU) cardiotoxicity is angina-like chest pain. It is less commonly associated with myocardial infarction (MI), arrhythmias, heart failure (HF), cardiogenic shock, and sudden death [51, 52]. The incidence of cardiotoxicity associated with 5-FU ranges in the literature between 1 and 68 % [10, 51–58]. Cardiac events occur within 2–5 days after initiation of therapy and may last up to 48 h [51]. Ischemic electrocardiogram (ECG) changes have been reported in 68 % of patients; however, only 43 % have elevations of serum cardiac markers [59]. Mortality is estimated to be 2.2–13 % [54, 57]. High doses (>800 mg/m^2) and continuous infusions are associated with increased risk for cardiotoxicity (7.6 %) as compared to bolus injections (2 %) [51, 54, 59]. Other risk factors for cardiotoxicity include history of cardiovascular disease, prior mediastinal radiation, and concurrent use of chemotherapy [52–55, 57, 58]. Capecitabine-induced cardiotoxicity (including myocardial ischemia/infarct) incidence is between 3 and 9 % [52, 55, 60, 61]. Typical anginal

symptoms appear 3–4 h after therapy with dosages ranging from 1500 to 2500 mg/m^2/day [51–60]. ECG changes including ST-segment elevations are noted in many cases while serum cardiac markers are normal [51–60]. Furthermore, echocardiography and coronary angiograms are often normal, and previous cardiac disease is not a consistent risk factor [51–65]. Coronary artery thrombosis, arteritis, or vasospasm has been suggested though unproven as the pathogenesis of cardiotoxicity associated with 5-FU and capecitabine [55]. Other mechanisms may include direct myocardial toxicity, interaction with the coagulation system, and autoimmune responses [55, 62].

3. Antimicrotubule agents, including paclitaxel (Taxol), have been described in cases of myocardial ischemia/infarct. Several clinical trials report cardiac ischemia in 5 % of patients [66], though others have reported a lower incidence [67]. In the case of docetaxel (Taxotere) administration, the incidence of MI is 1.7 % [14, 68]. Myocardial ischemia associated with paclitaxel is thought to be augmented by underlying heart disease though the Cremophor EL vehicle in which it is formulated is perhaps responsible for toxicity related to its induction of histamine release [66].
4. Monoclonal antibody-based tyrosine kinase inhibitors, including bevacizumab (Avastin), cause arterial thrombotic events (ATEs) more frequently in cancer patients treated with combination chemotherapy rather than as a single agent [14]. In a pooled analysis of five trials treating metastatic colorectal cancer, non-small cell lung cancer, and metastatic breast cancer, the overall ATE incidence was 3.8 % [69]. MI/angina is reported to occur in 0.6 % of bevacizumab-treated patients [69]. ATEs may occur at any time during therapy, with the median time to event being approximately 3 months. These events are not associated with dose or cumulative exposure. Age >65 and a previous ATE are risk factors [69, 70]. The *mechanism* associated with bevacizumab-induced arterial thrombosis is thought to involve VEGF. VEGF stimulates endothelial cell proliferation, promotes endothelial cell survival, and helps maintain vascular integrity [71]. Thus, anti-VEGF therapy may decrease the regenerative capability of endothelial cells in response to trauma, leading to endothelial cell dysfunction and defects in the interior vascular lining, exposing subendothelial collagen. This exposure to collagen-activated tissue factor increases the risk for thromboembolic events [71, 72]. Additionally, inhibiting VEGF causes a reduction in nitric oxide and prostacyclin and increases hematocrit and blood viscosity via overproduction of erythropoietin, predisposing the patient to thromboembolism [72].
5. Small-molecule tyrosine kinase inhibitors, including erlotinib (Tarceva) and sorafenib (Nexavar), are associated with MI/ischemia in 2.3 % of patients receiving 100 mg/day erlotinib with gemcitabine compared with 1.2 % when receiving gemcitabine alone for the treatment of pancreatic cancer [14, 73]. With regard to sorafenib, approximately 3 % of patients in clinical trials experience myocardial ischemia. Sorafenib is associated with a higher incidence of MI/ischemia compared to placebo among patients treated for renal cell carcinoma (3 % vs. <1 %) [74].

Diagnosis of ACS is made based on the patient's clinical presentation, ECG changes, and the elevation of cardiac enzymes [75, 76].

Treatment of patients with cancer and suspected ACS should follow established ACC and AHA guidelines [77]. Caveats to consider in the cancer patient with chest pain and suspected ACS are that coronary artery occlusion due to arterial embolism [111, 112] and coronary artery vasospasm that may or may not be related to anticancer therapy are considerably more common in the cancer patient than the general population. Treatment guidelines [77] include percutaneous coronary intervention, antiplatelet, and anticoagulant therapy, all of which can be complicated when treating an emergency cancer patient due to concomitant thrombocytopenia or recent surgery. The only data-driven intervention, albeit derived from a retrospective study, is that aspirin use improves 7-day survival in cancer patients with thrombocytopenia and ACS without increasing bleeding risk [78]. Also, beta-blockers use leads to improved 7-day survival in cancer patients with ACS [78]. When patients develop chest pain concurrent with 5-FU and capecitabine therapy, immediate cessation of the agent and antianginal therapy should be employed and an ischemia workup initiated. The use of vasodilators including nitrates and calcium-channel blockers is also advised. Decisions to restart the offending agent should be made by the treating oncology team. Sorafenib should be discontinued when patients develop cardiac ischemia, and bevacizumab should be discontinued if severe ATEs occur. In the emergent evaluation of cancer patients with suspected ACS, potentially correctable exacerbating factors (anemia, hyperthyroidism, or shunting of blood through a vascular tumor) and the increased risk of thrombolysis or revascularization (owing to increased bleeding or intracranial metastasis) should be considered prior to the initiation of a treatment plan. Thrombolytic agents are absolutely contraindicated in the presence of primary or metastatic brain lesions.

Heart Failure (HF)

Heart failure (HF) is newly diagnosed in 700,000 people each year in the United States. HF in cancer patients may be related to the malignancy or its treatment (Table 2). Several different coexisting factors may contribute to cardiac dysfunction. This cardiac dysfunction may remain subclinical until the systolic

Table 2 Clinically relevant findings to diagnose heart failure per the Framingham criteria [103] and the American College of Cardiology/American Heart Association classification [104]

Criteria source	Criteria/classification	Clinical findings/symptoms manifested in heart failure
Framingham criteria	Major criteria	Jugular vein distension
		Rales
		Paroxysmal nocturnal dyspnea or orthopnea
		Cardiomegaly
		Acute pulmonary edema
		S3 gallop
		Hepatojugular reflex
		Increased venous pressure >16 cm of water
	Minor criteria	Ankle edema
		Dyspnea on exertion
		Pleural effusion
		Tachycardia (>120 bpm)
		Hepatomegaly
		Night cough
		Vital capacity reduction of 1/3 from maximum
	Major or minor criteria	Weight loss of 4.5 kg or more in 5 days in response to treatment
American College of Cardiology/American Heart Association	Class I	Asymptomatic
	Class II	Mild symptoms with moderate exertion
	Class III	Symptoms with minimal activity
	Class IV	Symptoms at rest

function deteriorates below some trigger value. The clinically relevant findings to diagnosis HF are established as per the Framingham Criteria when either two major or one major and two minor criterion are present [103].

Patient with Class I and II heart failure can often be managed in the outpatient setting, while patients with Class III and IV heart failure often need admission to the hospital for symptomatic treatment.

The following discussion involves chemotherapy-associated left ventricular dysfunction (LVD) and/or heart failure (HF) [2, 3, 4] (Table 2).

1. Anthracycline agents, including doxorubicin (Adriamycin), epirubicin (Ellence), and idarubicin (Idamycin), can lead to acute, early-onset chronic progressive, and late-onset chronic progressive cardiotoxicity [6, 7]. Acute cardiotoxicity occurs in <1 % of patients immediately after anthracycline infusion and manifests with acute, transient decline in myocardial contractility. This is usually reversible [8]. The early-onset chronic progressive occurs in 1.6–2.1 % of patients during the first year [8] and the late-onset chronic progressive in 1.6–5 %. The late-onset chronic progressive form typically presents as a dilated cardiomyopathy in adults [7]. Late-occurring cardiotoxicity may not manifest clinically until 10–20 years after treatment. The risk of clinical toxicity increases with the cumulative dose of anthracycline, bolus administration, history of prior radiation, the use of other concomitant agents known to have cardiotoxicity, female gender, underlying cardiovascular disease, age (young and old), and an increased length of time since anthracycline completion [6, 7, 9]. These agents are more toxic in cancer patients with existing cardiac disease, particularly coronary artery disease. Pathophysiologic mechanisms of anthracycline cardiotoxicity, including doxorubicin, are dose dependent and involve redox cycling and the generation of reactive oxygen species (ROS). Zhang et al. demonstrated that cardiomyocyte-specific deletion of Top2b (encoding topoisomerase-IIb) protects cardiomyocytes from doxorubicin-induced DNA double-strand breaks and transcriptome changes responsible for defective mitochondrial biogenesis and ROS formation. In mice, cardiomyocyte-specific deletion of Top2b protects them from the development of doxorubicin-induced progressive heart failure, thus suggesting that doxorubicin-induced cardiotoxicity is mediated by topoisomerase-II beta [5]. Recent single-center studies suggest that ACE inhibitors and beta-blockers are efficacious in the treatment of chemotherapy-induced cardiomyopathy.
2. Alkylating agents including cyclophosphamide (Cytoxan) and ifosfamide (Ifex) have been associated with heart failure in 7–28 % of patients [10–13]. This cardiotoxicity may range from asymptomatic pericardial effusions to HF and myopericarditis [11, 13]. The risk of cardiotoxicity appears to be dose related and occurs within 1–10 days after administration of the first dose [10]. Additional risk factors include prior anthracycline or mitoxantrone therapy and mediastinal radiation [10, 12]. The pathophysiologic mechanism of cyclophosphamide cardiotoxicity is hypothesized to involve direct endothelial injury, followed by extravasation of toxic metabolites resulting in damage to cardiomyocytes, interstitial hemorrhage, and edema [10–13, 27]. Ifosfamide similarly may induce HF.
3. Antimetabolites including clofarabine may cause transient left ventricular dysfunction in up to 27 % of pediatric patients with acute lymphoblastic leukemia [14].
4. Antimicrotubule agents including docetaxel (Taxotere) are associated with HF incidence between 2.3 and 8 % [15, 16].
5. Proteasome inhibitors including bortezomib in the treatment of multiple myeloma are associated with the development of HF [17].
6. Monoclonal antibody-based tyrosine kinase inhibitors including bevacizumab and trastuzumab have been associated with the development of HF. In the former, the incidence is between 1.7 and 3 % [18, 19] and the later between 2 and 28 % [20, 21]. The mechanism of bevacizumab-induced HF may be related to uncontrolled

hypertension and inhibition of vascular endothelial growth factor (VEGF)/VEGF receptor signaling [28]. Trastuzumab and lapatinib may cause cardiotoxicity secondary to inhibition of cardiomyocyte human epidermal growth factor receptor 2 (ErbB2 signaling) by interfering with normal growth, repair, and survival of the cardiomyocytes [29–31]. Binding to ErbB2 may regulate mitochondrial integrity through the BCL-X proteins, leading to ATP depletion and contractility dysfunction [32, 33].

7. Small-molecule tyrosine kinase inhibitors including dasatinib, lapatinib, imatinib mesylate, and sunitinib have been associated with various cardiotoxicities. Dasatinib is associated with HF in 2 and 4 % of patients treated for leukemia [14]. Lapatinib is associated with LVD in 1.6 % [22]. Imatinib mesylate cardiotoxicity has been reported to be between 0.5 and 1.7 % [23, 24]. Sunitinib treatment of gastrointestinal stromal tumor and metastatic renal cell cancer is associated with LVD in 4–11 % of patients [25]. Dasatinib toxicity mechanisms may be similar to imatinib since they are both inhibitors of Abl. Dasatinib also inhibits Src and a number of other kinases that may be involved in the development of cardiotoxicity [28]. The mechanism of imatinib cardiotoxicity may be through inhibition of c-Abl [32, 34]. The possible mechanism of sunitinib cardiotoxicity, postulated from animal studies, points to its induction of mitochondrial damage in cardiomyocytes, but no apoptosis [26]. A hypothesized mechanism is that HTN may play an important role, since it may inhibit a receptor tyrosine kinase that helps regulate the response of cardiomyocytes in HTN. Additionally, it may inhibit ribosomal S6 kinase, leading to the activation of the intrinsic apoptotic pathway and ATP depletion [25]. Furthermore, coronary artery disease may be a risk factor associated with the development of HF [26].

Diagnosing to detect cardiac dysfunction during chemotherapy, regular monitoring of heart function is important. A baseline evaluation of LVEF should be obtained. Alexander et al. [35] first demonstrated serial assessment of LVEF to be useful in clinical practice. Furthermore, HF and cardiomyopathy should be defined utilizing a thorough clinical history and physical exam of the patient, combined with diagnostic testing including electrocardiograms, chest radiography, routine blood testing, and in the patient with suspected or known HF, to obtain noninvasive imaging, e.g., contrast echocardiography, and multi-gated acquisition scan [MUGA] to evaluate cardiac function [36]. Still, endocardial biopsy remains the gold standard for diagnosis of CMP. It is the most sensitive and specific; however, the invasiveness of the procedure limits its use.

Biochemical markers may be used to detect changes in LVEF. One study of troponin I demonstrated elevation soon after high-dose chemotherapy predicted the future development of LVEF depression [37], and another study demonstrated that troponin I elevation identifies patients at higher risks of future cardiac events [38]. Additionally, B-type natriuretic peptide is positively correlated with cardiac events and subclinical cardiotoxicity, more specifically to diastolic than systolic dysfunction [39, 40]. Preventive measures to minimize the risk of anthracycline-induced CMP relate to the cumulative lifetime dose of the drug [8]. Other measures recommended to decrease anthracycline-induced cardiotoxicity include continuous rather than bolus administration; use of anthracycline analogs including idarubicin, epirubicin, and mitoxantrone, or liposomal anthracyclines; and the addition of cardioprotectants including dexrazoxane. Dexrazoxane may cause cardiomyocyte-specific deletion of Top2b (encoding topoisomerase-IIb) that protects cardiomyocytes from doxorubicin-induced DNA double-stranded breaks and transcriptome changes that are responsible for defective mitochondrial biogenesis and reactive oxygen species (ROS) formation [5].

Treatment of anthracycline-induced HF includes beta-blockers and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker [41]. These interventions have been shown to reverse cardiac remodeling and improve survival. Advanced HF usually requires additional measures including diuretics, digoxin, or aldosterone antagonists. End-stage HF patients without cancer recurrence could be considered for synchronized pacing, ventricular assist devices, or cardiac transplant [41]. Enalapril has been shown to prevent a decline in LVEF as well as cardiac events in cancer patients treated with high-dose chemotherapy [42]. Other studies of angiotensin-converting enzyme inhibitors demonstrated that they do not prevent progressive cardiac dysfunction in all patients [43, 44]. Beta-blockers have also emerged as standard-recommended treatment [41] in anthracycline-induced CMP [45, 46]. Carvedilol may have some therapeutic advantages as it may possess some antioxidant properties [47, 48]. Trastuzumab-induced cardiotoxicity generally reverses over a mean time period of 1.5 months after discontinuation of the agent [49].

Venous Thromboembolism (VTE)

Cancer is a prothrombotic state. The risk of VTE appears to be highest in metastatic disease and in those with established risk factors. Risk factors include the use of central venous catheters and associated comorbidities including immobility, HF, atrial fibrillation, dehydration, and concurrent chemotherapy [79]. The following discussion will elaborate on several chemotherapeutic agents shown to induce VTE disease:

1. Cisplatin is a platinum-based therapy that increases the risk of thrombotic events. The incidence is between 8.5 and 12.9 % in those treated for urothelial transitional cell carcinoma [94]. Seventy-four percent of these events,

including DVT and PE, occurred within the first two cycles of treatment [94].
2. Vorinostat-associated TE incidence ranges from 4.7 to 8 % [14, 95, 96].
3. Thalidomide-associated TE incidence ranges from <5–58 %, depending on whether it is used in newly diagnosed patients or whether it is used in combination with dexamethasone or other chemotherapy, specifically doxorubicin [97–102]. The median time to an event is 3 months [99].
4. Lenalidomide-associated TE incidence ranges from 3 to 75 % 144–149. Similar to thalidomide, lenalidomide TE incidence rates vary based on whether it is used in combination with dexamethasone or other chemotherapy, including doxorubicin [102] and erythropoietin (75 %), in newly diagnosed patients [99, 102].
5. Erlotinib-associated TE events have been reported in 1.2 and 11 % of patients [14, 73].

The pathophysiology of VTE involved the baseline hypercoagulable state seen in cancer. The contributory factors include high levels of inflammatory cytokines with activation of the clotting system and inhibition of natural anticoagulant mechanisms, particularly the activated protein C system, impaired fibrin polymerization and reduced fibrinolysis, as well as alteration of endothelial surfaces.

Anticancer treatments contribute to thrombogenesis by the release of procoagulants and cytokines through chemotherapy-induced tumor cell damage, direct endothelial damage, as well as hepatotoxicity, leading to decreased production of normally produced anticoagulants [94]. With respect to the mechanism of cisplatin-associated TE, some evidence suggests that it induces platelet activation and aggregation, possibly involving monocyte procoagulant activity. Cisplatin-based therapies may also alter endothelial cell integrity [94]. Additionally, cisplatin may elevate von Willebrand factor levels, cause hypomagnesemia-induced vasospasm, and have antiangiogenic activity [131, 132]. With regard to thalidomide- and lenalidomide-associated TE, the mechanism may involve direct action on endothelial cells previously damaged by doxorubicin [98]. It may also involve interactions between platelets and the endothelium [100, 133]. Increased platelet aggregation and von Willebrand factor have been found in patients treated with thalidomide.

Diagnosis: The test of choice for DVT is compression ultrasonography, as it is both sensitive and specific. When PE is suspected, spiral computed tomography angiography is the diagnostic test of choice. Nuclear medicine techniques, e.g., ventilation/perfusion scan, can also be utilized. Magnetic resonance pulmonary angiography may be considered in patients who have contraindications to iodinated contrast media [99].

Prevention of TE associated with thalidomide and lenalidomide has been investigated by the International Myeloma Working Group who recommend tailoring the choice of thromboprophylaxis based on individual risk factors including age, obesity, previous VTE, central venous catheter, immobility, comorbidities, concomitant medications, surgery, inherited thrombophilia, myeloma-related risk factors (diagnosis and hyperviscosity), and myeloma therapy-related risk factors (concomitant steroids, doxorubicin). When using thalidomide and lenalidomide alone, no therapy is recommended. Otherwise, aspirin (81–325 mg) may be used in patients with no risk factors or ≤1 risk factor for VTE. Low-molecular-weight heparin (LMWH) equivalent to 40 mg enoxaparin or full-dose warfarin is recommended for those with two or more individual/melanoma-related risk factors or those receiving concomitant high-dose dexamethasone or doxorubicin [99].

Treatment of TE is to relieve symptoms and prevent embolization and recurrence. Treatment should adhere to guidelines put forth by the American College of Chest Physicians. Treatment of patients with TE and cancer should consist of low-molecular-weight heparin (LMWH) for the first 3–6 months, followed by either warfarin or LMWH indefinitely or until the cancer is resolved [134].

Hypertension (HTN)

Hypertension (HTN) and cancer are common (37 %) [92, 113]. The prevalence before chemotherapy is similar to that in the general population (29 %) [114]. The chemotherapeutic agents given these patients to treat their cancer disrupt angiogenesis, thereby inducing the development of HTN [92] (Table 3). The mechanism of antiangiogenic therapy-related HTN is thought to be related to VEGF inhibition. VEGF inhibition decreases nitric oxide production in the wall of the arterioles and other resistant vessels [71]. As nitric oxide is a vasodilator, its inhibition promotes vasoconstriction, increased peripheral vascular resistance, and blood pressure [71].

Bevacizumab decreases endothelial nitric oxide synthetase activity which may stimulate plasminogen activator inhibitor-1 expression, leading to an increased risk of HTN [120]. Other hypotheses include that VEGF inhibition may affect the renin–angiotensin system [121] and may also be

Table 3 Common chemotherapeutic agents and their associated incidence of hypertension

Chemotherapeutic agent	Associated incidence of hypertension
Bevacizumab	The incidence is 4–35 % [18, 19, 115–117]. Treat with antihypertensive agents while bevacizumab is continued [14]
Sorafenib	17–43 % of those treated [74] [118, 119],
Sunitinib	Ranges from 2 to 8 % [124, 125]. HTN is seen within the first 4 weeks of therapy [26]

responsible for cholesterol emboli syndrome leading to bevacizumab-induced complications [122, 123].

Diagnosis of HTN is defined by the Seventh Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure as blood pressure ≥140/90 mmHg.

Treatment of antiangiogenic therapy-induced HTN requires standard antihypertensives. Bevacizumab-, sorafenib-, and sunitinib-induced HTN may require combination antihypertensives, and the question of chemotherapy discontinuation is controversial. ACE inhibitors may be preferred as first-line therapy due to their ability to prevent proteinuria and plasminogen activator inhibitor-1 expression [120] and their potential to reduce microcirculatory changes, decrease the catabolism of bradykinin, and increase release of endothelial nitric oxide [116]. Consideration of drug–drug interactions is advised in sorafenib-treated patients. Sorafenib is metabolized via the cytochrome p450 system, mainly by CYP3A4. Dihydropyridine calcium-channel blockers, e.g., diltiazem and verapamil, should not be used as they are similarly metabolized. Amlodipine or nifedipine is preferred. Phosphodiesterase inhibitors or nitrates to increase nitric oxide levels have been suggested, though not proven, to be effective [126]. As HTN is a risk factor for HF, it may be beneficial to deploy medications that prevent morbidity and mortality of HF including carvedilol, metoprolol succinate, ACE inhibitors, and angiotensin receptor blockers.

Malignant Pericardial Effusion

Malignant pericardial effusion occurs when there is excess fluid collection in the pericardial space (sac) caused by malignancy. This condition usually occurs because of obstruction of lymphatic drainage or an excess of fluid secretion from tumor nodules on the pericardial surface. Normally, the pericardial sac contains a small amount of pericardial fluid (25–35 ml), and it has a very limited ability to distend. When larger amounts of pericardial fluid develop rapidly, a pericardial effusion may progress to tamponade. Patients may present with fatigue, dyspnea, orthopnea, pleuritic chest pain, syncope, or arrhythmia. Physical exam findings range from normal sinus to sinus tachycardia, jugular venous distention, organomegaly, pulsus paradoxus (>10 mmHg drop in systolic blood pressure during inspiration), lower extremities edema, hypotension, and, eventually, circulatory collapse. Pulsus paradoxus can be seen in the absence of tamponade in patients with lung cancer or other conditions accompanied by significant lung disease or cor pulmonale. In patients with chest malignancies, a finding of pulsus paradoxus suggests effusion, but not necessarily, tamponade.

Diagnosis includes EKG findings of low QRS voltage, electrical alternans, and nonspecific ST-T wave changes. Chest radiographs may reveal cardiomegaly ("water-bottle" silhouette). Computed tomography and magnetic resonance imaging frequently detect pericardial effusion as an incidental finding. These modalities have limited ability to quantify the effusion. Two-dimensional echocardiography is the diagnostic test of choice since it can help with establishing diagnosis and also guide management. Size of the pericardial effusion is typically graded as minimal, small, moderate (<2 cm), or large (>2 cm). Fibrous strands are frequently seen in the pericardial space by echocardiography but are difficult to differentiate from the occasional tumor mass invading the pericardial space. Echocardiographic signs of cardiac tamponade include right atrial compression and diastolic collapse of the right ventricle as well as cardiac "rocking" (a side-to-side or front-to-back movement of the heart) [106]. Alterations in the respiratory variation of Doppler flow patterns across the mitral valve can be helpful in evaluating the hemodynamic effects of pericardial effusion. Inferior vena cava dilatation that does not collapse with inspiration ("sniffing") and (occasionally) left atrial collapse in late diastole and early systole may be seen. Doppler criteria for cardiac tamponade include a 25 % decrease in E-flow velocity amplitude during inspiration seen on the flow pattern of the mitral valve and/or a 25 % decrease in flow velocity across the tricuspid valve with expiration.

Common neoplasms associated with malignant pericardial disease are carcinomas of the lung and breast. Malignant melanoma is the tumor most likely to metastasize to the heart. Lymphomas (both Hodgkin's and non-Hodgkin's), leukemias, and gastrointestinal neoplasms are also associated with pericardial effusions [105]. Although malignant pericardial effusion can occur as an early manifestation, they are usually a late finding in patients with metastases. The majority of patients are asymptomatic, and the effusion is discovered incidentally on cardiac ultrasound ordered for other reasons during their treatment.

Treatment depends on the patient's hemodynamic stability. Echocardiography-guided pericardiocentesis with the placement of a drainage catheter into the pericardial space is the treatment of choice in patients with hemodynamic compromise [108]. Complications are infrequent though pericardial bleeding can result when a coronary artery is damaged, and pneumothorax is especially common in patients with coexisting emphysema.

A surgical pleuropericardial window can be made to obviate the need for repetitive pericardiocentesis. This is usually achieved in the operating room setting; however, it is possible to perform under local anesthesia in the ED or intensive care unit.

For patients with hemodynamic compromise and a rapid accumulation of fluid, the pleuropericardial window offers the most definitive therapy. The use of local chemotherapeutic agents or agents given to sclerose the pericardium will prevent fluid reaccumulation in many patients [107].

Cardiovascular Effects of Radiotherapy

Radiation therapy to the chest area can cause heart damage by four mechanisms. Radiation heart damage can (1) produce direct muscle fiber damage leading to progressive loss of heart function, (2) injure vessels supplying the heart muscle with blood leading to ischemia and possible myocardial infarction, (3) cause pericardial inflammation leading to compression and constriction of the heart muscle, and (4) cause valve damage leading to valve narrowing or leakage [129]. Evidence suggests that mean radiation doses of ≤20 Gy to the heart increase the risk of cardiotoxicity [127, 128] and that interactions of radiation and other drug treatments, i.e., anthracyclines and tyrosine kinase inhibitors, and conventional cardiovascular risk factors, i.e., smoking and hypertension, can compound cardiotoxicity risk.

Because cancer is one of the two most common causes of mortality and morbidity worldwide [1, 130], we have provided you with the most relevant data concerning the cardiovascular side effects of chemo- and radiation therapy. As medicine becomes more able to treat malignancy and the number of survivors in the adult population increases, so does the likelihood of encountering a patient complaining of manifestations of these antineoplastic interventions [1].

References

1. Yeh ETH. Onco-cardiology: the time has come. Tex Heart Inst J. 2011;38(3):246–7.
2. Yeh ETH, Bickford CL. Cardiovascular complications of cancer therapy. J Am Coll Cardiol. 2009;53:2231–47.
3. Dahar IN, Yeh ETH. Vascular complications of selected cancer therapies. Nat Clin Pract Cardiovasc Med. 2008;5(12):797–805. www.nature.com/clinicalpractice/cardio.
4. Ewer MS, Durand JB, Swafford J, Yusuf SW. Emergency cardiac problems. Chapter 14. Hollan-Frei Oncology Emergencies.
5. Zhang S, Liu X, Bawa-Khalfe T, Lu LS, Lyu YL, Liu LF, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med. 2012;18(11):1639–42. doi:10.1038/nm.2919.
6. Grenier MA, Lipshultz SE. Epidemiology of anthracycline cardiotoxicity in children and adults. Semin Oncol. 1998;25:72–85.
7. Lipshultz SE, Alvarez JA, Scully RE. Anthracycline associated cardiotoxicity in survivors of childhood cancer. Heart. 2008;94:525–33.
8. Wouters KA, Kremer LC, Miller TL, Herman EH, Lipshultz SE. Protecting against anthracycline-induced myocardial damage: a review of the most promising strategies. Br J Haematol. 2005;131:561–78.
9. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003;97:2869–79.
10. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. Drug Saf. 2000;22:263–302.
11. Braverman AC, Antin JH, Plappert MT, Cook EF, Lee RT. Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. J Clin Oncol. 1991;9:1215–23.
12. Goldberg MA, Antin JH, Guinan EC, Rappaport JM. Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. Blood. 1986;68:1114–8.
13. Gottdiener JS, Appelbaum FR, Ferrans VJ, Deisseroth A, Ziegler J. Cardiotoxicity associated with high-dose cyclophosphamide therapy. Arch Intern Med. 1981;141:758–63.
14. Vorinostat (Zolinza). Package insert. Whitehouse Station, NJ: Merck & Co, Inc; 2013.
15. Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, Weaver C, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 2005;352:2302–13.
16. Marty M, Cognetti F, Maraninchi D, Snyder R, Maurice L, Tubiana-Hulin M, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 2005;23:4265–74.
17. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352:2487–98.
18. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007;357:2666–76.
19. Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol. 2005;23:792–9.
20. Tripathy D, Slamon DJ, Cobleigh M, Arnold A, Saleh M, Mortimer JE, et al. Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. J Clin Oncol. 2004;22:1063–70.
21. Guarneri V, Lenihan DJ, Valero V, Durand JB, Broglio K, Hess KR, et al. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the MD Anderson Cancer Center experience. J Clin Oncol. 2006;24:4107–15.
22. Perez EA, Koehler M, Byrne J, Preston AL, Rappold E, Ewer MS. Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. Mayo Clin Proc. 2008;83:679–86.
23. Hatfield A, Owen S, Pilot PR. In reply to 'cardiotoxicity of the cancer therapeutic agent imatinib mesylate'. Nat Med. 2007;13:13. author reply 15-6.
24. Atallah E, Durand JB, Kantarjian H, Cortes J. Congestive heart failure is a rare event in patients receiving imatinib therapy. Blood. 2007;110:1233–7.
25. Khokoo AY, Kassiotis CM, Tannir N, Plana JC, Halushka M, Bickford C, et al. Heart failure associated with sunitinib malate: a multitargeted receptor tyrosine kinase inhibitor. Cancer. 2008;112:2500–8.
26. Chu TF, Rupnick MA, Kerkela R, Dallabrida SM, Zurakowski D, Nguyen L, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet. 2007;370:2011–9.
27. Morandi P, Ruffini PA, Benvenuto GM, Raimondi R, Fosser V. Cardiac toxicity of high-dose chemotherapy. Bone Marrow Transplant. 2005;35:323–34.
28. Chen MH, Kerkela R, Force T. Mechanisms of cardiac dysfunction associated with tyrosine kinase inhibitor cancer therapeutics. Circulation. 2008;118:84–95.
29. Ewer MS, O'Shaughnessy JA. Cardiac toxicity of trastuzumab-related regimens in HER2 overexpressing breast cancer. Clin Breast Cancer. 2007;7:600–7.
30. Crone SA, Zhao YY, Fan L, Gu Y, Minamisawa S, Liu Y, et al. ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med. 2002;8:459–65.
31. Ozcelik C, Erdmann B, Pilz B, Wettschureck N, Britsch S, Hubner N, et al. Conditional mutation of the ErbB2(HER2) receptor

in cardiomyocytes leads to dilated cardiomyopathy. Proc Natl Acad Sci U S A. 2002;99:8880–5.
32. Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. Nat Rev Cancer. 2007;7:332–44.
33. Voortman J, Giaccone G. Severe reversible cardiac failure after bortezomib treatment combined with chemotherapy in a non-small cell lung cancer patient: a case report. BMC Cancer. 2006;6:129.
34. Kerkela R, Grazette L, Yacobi R, Iliescu C, Patten R, Beahm C, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med. 2006;12:908–16.
35. Alexander J, Dainiak N, Berger HF, Goldman L, Johnstone D, Reduto L, et al. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. N Engl J Med. 1979;300:278–83.
36. Ganz WI, Sridhar KS, Ganz SS, Gonzalez R, Chakko S, Serafini A. Review of tests for monitoring doxorubicin-induced cardiomyopathy. Oncology. 1996;53:461–70.
37. Cardinale D, Sandri MT, Martinoni A, Borghini E, Civelli M, Lamantia G, et al. Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. Ann Oncol. 2002;13:710–5.
38. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic value of troponin in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004;109:2749–54.
39. Lenihan DJ, Massey MR, Baysinger KB. Superior detection of cardiotoxicity during chemotherapy using biomarders (abstr). J Card Fail. 2007;13 Suppl 2:S151.
40. Meinardi MT, van Veldhuisen DJ, Gietema JA, Dolsma WV, Boomsma F, van den Berg MP, et al. Prospective evaluation of early cardiac damage induced by epirubicin-containing adjuvant chemotherapy and locoregional radiotherapy in breast cancer patients. J Clin Oncol. 2001;19:2746–53.
41. Hunt SA. American College of Cardiology, American Heart Association Task Force on Practice Guidelines. ACC/AHA 2001 and 2005 guideline updates for the diagnosis and management of chronic heart failure in the adult. J Am Coll Cardiol. 2005;46:e1–82.
42. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation. 2006;114:2474–81.
43. Lipshultz SE, Lipsitz SR, Sallan SE, Simbre VC 2nd, Shaikh SL, Mone SM, et al. Long-term enalapril therapy for left ventricular dysfunction in doxorubicin-treated survivors of childhood cancer. J Clin Oncol. 2002;20:4517–22.
44. Silber JH, Cnaan A, Clark BJ, Paridon SM, Chin AJ, Rychik J, et al. Enalapril to prevent cardiac function decline in log-term survivors of pediatric cancer exposed to anthracyclines. J Clin Oncol. 2004;22:820–8.
45. Fazio S, Palmieri EA, Ferravante B, Bone F, Biondi B, Sacca L. Doxorubicin-induced cardiomyopathy treated with carvedilol. Clin Cardiol. 1998;21:777–9.
46. Mukai Y, Yoshida T, Nakaike R, Mukai N, Iwato K, Kyo T, et al. Five cases of anthracycline-induced cardiomyopathy effectively treated with carvedilol. Intern Med. 2004;43:1087–8.
47. Oliveira PJ, Bjork JA, Santos MS, Leino RL, Froberg MK, Moreno AJ, et al. Carvedilol-mediated antioxidant protection against doxorubicin-induced cardiac mitochondrial toxicity. Toxicol Appl Pharmacol. 2004;200:159–68.
48. Kalay N, Basar E, Ozdogru I, Er O, Cetinkaya Y, Dogan A, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol. 2006;48:2258–62.
49. Ewer MS, Vooletich MT, Durand JB, Woods ML, Davis JR, Valero V, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol. 2005;23:7820–6.
50. Miller AH, Cruz-Carreras MT, Miller SA, Miller HE, Page VD. Is there coronary artery disease in the cancer patient who manifests with chest pain, shortness of breath and/or tachycardia? A retrospective observational cohort. Support Care Cancer. 2015;23(2):419–26.
51. Meyer CC, Calis KA, Burde LB, Walawander CA, Grasela TH. Symptomatic cardiotoxicity associated with 5-fluorouracil. Pharmacotherapy. 1997;17:729–36.
52. Van Cutsem E, Hoff PM, Blum JL, Abt M, Osterwalder B. Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. Ann Oncol. 2002;13:484–5.
53. Cardinale D, Colombo A, Colombo N. Acute coronary syndrome induced by oral capecitabine. Can J Cardiol. 2006;22:251–3.
54. De Forni M, Malet-Martino MC, Jaillais P, Shubinski RE, Bachaud JM, Lemaire L, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. J Clin Oncol. 1992;10:1795–801.
55. Kosmas C, Kallistratos MS, Kopterides P, Syrios J, Skopelitis H, Mylonakis N, et al. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. J Cacer Res Clin Oncol. 2008;134:75–82.
56. Labianca R, Berreta G, Clerici M, Fraschini P, Luporini G. Cardiac toxicity of 5-fluorouracil: a study on 1083 patients [in Italian]. Tumori. 1982;68:505–10.
57. Jensen SA, Sorensen JB. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. Cancer Chemother Pharmacol. 2006;58:487–93.
58. Anand AJ. Fluorouracil cardiotoxicity. Ann Pharmacother. 1994;28:374–8.
59. Bertolini A, Flumano M, Fusco O, Muffatti A, Scarinci A, Pontiggia G, et al. Acute cardiotoxicity during capecitabine treatment: a case report [in Italian]. Tumori. 2001;87:200–6.
60. Saif MW, Tomita M, Ledbetter L, Diasio RB. Capecitabine-related cardiotoxicity: recognition and management. J Support Oncol. 2008;6:41–8.
61. Walko CM, Lindley C. Capecitabine: a review. Clin Ther. 2005;27:23–44.
62. Frickhofen N, Beck FJ, Jung B, Fuhr HG, Andrasch H, Sigmund M. Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. Ann Oncol. 2002;13:797–801.
63. Arbea L, Coma-Canella I, Martinez-monge R, Garcia-Foncillas J. A case of capecitabine-induced coronary artery microspasm in a patient with rectal cancer. World J Gastroenterol. 2007;13:2135–7.
64. Sestito A, Sgueglia GA, Pozzo C, Cassano A, Barone C, Crea F, et al. Coronary artery spasm induced by capecitabine. J Cardiovasc Med (Hagerstown). 2006;7:136–8.
65. Papadopoulos CA, Wilson H. Capecitabine-associated coronary vasospasm: a case report. Emerg Med J. 2008;25:307–9.
66. Rowinsky EK, McGuire WP, Guarnieri T, Fisherman JS, Christian MC, Donehower RC. Cardiac disturbances during the administration of taxol. J Clin Oncol. 1991;9:1704–12.
67. Arbuck SG, Strauss H, Rowinsky E, Christian M, Suffness M, Adams J, et al. A reassessment of cardiac toxicity associated with taxol. J Natl Cancer Inst Monogr. 1993;15:117–30.
68. Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med. 2007;357:1695–704.
69. Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst. 2007;99:1232–9.

70. Sugrue MM, Yi J, Purdie D, Dong W, Grothey A, Kozloff M, et al. Serious arterial thromboembolic events (sATE) in patients with metastatic colorectal cancer (mCRC) treated with bevacizumab (BV): results from the BRiTE registry. J Clin Oncol. 2007;25 Suppl 18:4136.
71. Kamba T, McDonald DM. Mechanisms of adverse effects of anti-VEGF therapy for cancer. Br J Cancer. 2007;96:1788–95.
72. Kilickap S, Abali H, Celik I. Bevacizumab, bleeding, thrombosis, and warfarin. J Clin Oncol. 2003;21:3542. author reply 3543.
73. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007;25:1960–6.
74. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356:125–34.
75. Miller AH, Pepe PE, Peshock R, Bhore R, Yancy CC, Xuan L, et al. Is coronary computed tomography angiography a resource sparing strategy in the risk stratification and evaluation of acute chest pain? Results of a randomized controlled trial. Acad Emerg Med. 2011;18(5):458–67.
76. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol. 2007;50:2173–95.
77. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al. American College of Cardiology, American Heart Association Task Force on Practice Guidelines. ACC/AHA 2007 guideline updates for the management of patients with unstable angina/non-ST-elevation myocardial infarction. J Am Coll Cardiol. 2007;50:e1–157.
78. Sarkiss MG, Yusuf SW, Warneke CL, Botz G, Lakkis N, Hirch-Ginsburg C, et al. Impact of aspirin therapy in cancer patients with thrombocytopenia and acute coronary syndromes. Cancer. 2007;109:621–7.
79. Yusuf SW, Razeghi P, Yeh ET. The diagnosis and management of cardiovascular disease in cancer patients. Curr Probl Cardiol. 2008;33:163–96.
80. McGuire WP, Rowinsky EK, Rosenshein NB, Grumbine FC, Ettinger DS, Armstrong DK, et al. Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. Ann Intern Med. 1989;111:273–9.
81. Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC. Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol. 1993;20:1–15.
82. Clark TE, Edom N, Larson J, Lindsey LJ. Thalomid (Thalidomide) capsules: a review of the first 18 months of spontaneous post-marketing adverse event surveillance, including off-label prescribing. Drug Saf. 2001;24:87–117.
83. Fahdi IE, Gaddam V, Saucedo J, Kishan CV, Vyas K, Deneke MG, et al. Bradycardia during therapy for multiple myeloma with thalidomide. Am J Cardiol. 2004;93:1052–5.
84. Rajkumar SV, Rosinol L, Hussein M, Catalano J, Jedrzejczak W, Lucy L, et al. Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. J Clin Oncol. 2008;26:2171–7.
85. Kaur A, Yu SS, Lee AJ, Chiao TB. Thalidomide-induced sinus bradycardia. Ann Pharmacother. 2003;37:1040–3.
86. Strevel EL, Ing DJ, Siu LL. Molecularly targeted oncology therapeutics and prolongation of the QT interval. J Clin Oncol. 2007;25:3362–71.
87. Shigeno K, Naito K, Sahara N, Kobayashi M, Nakamura S, Fujisawa S, et al. Arsenic trioxide therapy in relapsed or refractory Japanese patients with acute promyelocytic leukemia: updated outcomes of the phase II study and postremission therapies. Int J Hematol. 2005;82:224–9.
88. Singer JW. Cardiac toxicity of arsenic trioxide. Blood. 2001; 98:1633. author reply 1633-4.
89. Kantarjian H, Giles F, Wunderle L, Bhalla K, O'Brien S, Wassmann B, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. N Engl J Med. 2006;354:2542–51.
90. Kantarjian HM, Giles F, Gattermann N, Bhalla K, Alimena G, Palandri F, et al. Nilotinib (formally AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. Blood. 2007;110:3540–6.
91. Vorchheimer DA. What is QT interval prolongation? J Fam Pract. 2005;2005(Suppl):S4–7.
92. Jain M, Townsend RR. Chemotherapy agents and hypertension: a focus on angiogenesis blockage. Curr Hypertens Rep. 2007;9: 320–8.
93. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. Am Heart J. 2007;153:891–9.
94. Czaykowski PM, Moore MJ, Tannock IF. High risk of vascular events in patients with urothelial transitional cell carcinoma treated with cisplatin based chemotherapy. J Urol. 1998;160:2021–4.
95. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol. 2007;25:3109–15.
96. Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood. 2007;109:31–9.
97. Rajkumar SV. Thalidomide therapy and deep venous thrombosis in multiple myeloma. Mayo Clin Proc. 2005;80:1549–51.
98. Rodeghiero F, Elice F. Thalidomide and thrombosis. Pathophysiol Haemost Thromb. 2003;33 Suppl 1:15–8.
99. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008;22:414–23.
100. Zangari M, Elice F, Fink L, Tricot G. Thrombosis in multiple myeloma. Expert Rev Anticancer Ther. 2007;7:307–15.
101. Anagnostopoulos A, Weber D, Rankin K, Delasalle K, Alexanian R. Thalidomide and dexamethasone for resistant multiple myeloma. Br J Haematol. 2003;121:768–71.
102. Menon SP, Rajkumar SV, Lacy M, Falco P, Palumbo A. Thromboembolic events with lenalidomide-based therapy for multiple myeloma. Cancer. 2008;112:1522–8.
103. Goldstein DJ, Oz MC, Rose EA. Implantable left ventricular assist devices. N Engl J Med. 1998;339(21):1522–33.
104. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119(14):e391–479.
105. McKenna Jr RJ, Ali MK, Ewer MS, Frazier OH. Pleural and pericardial effusions in cancer patients. Curr Probl Cancer. 1985;9:1–44.
106. Kralstein J, Frishman W. Malignant pericardial diseases: diagnosis and treatment. Am Heart J. 1987;113:785–90.
107. Imazio M, Brucato A, Mayosi BM, Derosa FG, Lestuzzi C, Macor A, et al. Medical therapy of pericardial diseases: part II: noninfectious pericarditis, pericardial effusion and constrictive pericarditis. J Cardiovasc Med (Hagerstown). 2010;11(11):785–94.

108. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Outcomes of clinically significant idiopathic pericardial effusion requiring intervention. Am J Cardiol. 2003;91(6):704–7.
109. Canadian Adverse Drug reaction newsletter. Drugs causing prolongation of QT interval and torsades de pointes. Can. Med. Assoc. J. 1998;103–4.
110. Theroux P, Fuster V. Acute coronary syndromes: unstable angina and non-Q-wave myocardial infarction. Circulation. 1998;97: 1195–206.
111. Ali MK, Ewer MS, Cangir A, Fisher DJ. Coronary artery embolism following cancer chemotherapy. J Pediatr Hematol Oncol. 1987;9:200–3.
112. Prizel KR, Hutchins GM, Bulkley BH. Coronary artery embolism and myocardial infarction: a clinicopathologic study of 55 patients. Ann Intern Med. 1978;88:155–61.
113. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel Jr E. Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA. 2004;291(20):2441–7.
114. Maitland ML, Bakris GL, Black HR, Chen HX, Durand JB, Elliott WJ, et al. Cardiovascular Toxicities panel, convened by the angiogenesis task force of the National Cancer Institute Investigational Drug Steering committee. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. J Natl Cancer Inst. 2010;102(9):596–604.
115. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350:2335–42.
116. Pande A, Lombardo J, Spangenthal E, Javle M. Hypertension secondary to anti-angiogenic therapy: experience with bevacizumab. Anticancer Res. 2007;30:117–24.
117. Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med. 2003;349:427–34.
118. Procopio G, Verzoni E, Gevorgyan A, Mancin M, Pusceddu S, Catena L, et al. Safety and activity of sorafenib in different histotypes of advanced renal cell carcinoma. Oncology. 2007;73:204–9.
119. Riechelmann RP, Chin S, Wang L, Tannock IF, Berthold DR, Moore MJ, et al. Sorafenib for metastatic renal cancer: the Princess Margaret experience. Am J Clin Oncol. 2008;31:182–7.
120. Dincer M, Altundag K. Angiotensin-converting enzyme inhibitors for bevacizumab-induced hypertension. Ann Pharmacother. 2006;40:2278–9.
121. Sane DC, Anton L, Brosnihan KB. Angiogenic growth factors and hypertension. Angiogenesis. 2004;7:193–201.
122. Veronese ML, Mosenkis A, Flaherty KT, Gallagher M, Stevenson JP, Townsend RR, et al. Mechanisms of hypertension associated with BAY 43-9006. J Clin Oncol. 2006;24:1363–9.
123. Mir O, Mouthon L, Alexandre J, Mallion JM, Deray G, Guillevin L, et al. Bevacizumab-induced cardiovascular events: a consequence of cholesterol emboli syndrome. J Natl Cancer Inst. 2007;99:85–6.
124. Burstein HJ, Elias AD, Rugo HS, Cobleigh MA, Wolff AC, Eisenberg PD, et al. Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2008;26:1810–6.
125. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal cell carcinoma. N Engl J Med. 2007;356:115–24.
126. Wu S, Chen JJ, Kudelka A, Lu J, Zhu X. Incidence and risk of hypertension with sorafenib in patients with cancer: a systemic review and meta-analysis. Lancet Oncol. 2008;9(2):117–23.
127. Tukenova M, Guibout C, Oberlin O, Doyon F, Mousannif A, Haddy N, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. J Clin Oncol. 2010;28(8):1308–15 [published erratum appears in J Clin Oncol 2010;28(19):3205].
128. Taylor CW, Nisbet A, McGale P, Darby SC. Cardiac exposures in breast cancer radiotherapy: 19502–1990s. Int J Radiat Oncol Biol Phys. 2007;69(5):1484–95.
129. Darby SC, Cutter DJ, Boerma M, Constine LS, Fajardo LF, Kodama K, et al. Radiation-related heart disease: current knowledge and future prospects. Int J Radiat Oncol Biol Phys. 2010;76(3):656–65.
130. Fuster V, Voute J. MDGs: chronic diseases are not on the agenda. Lancet. 2005;366(9496):1512–4.
131. Icli F, Karaoguz H, Dincol D, Demirkazik A, Gunel N, Karaoquz R, et al. Severe vascular toxicity associated with cisplatin-based chemotherapy. Cancer. 1993;72:587–93.
132. Miller KD, Sweeny CJ, Sledge Jr GW. Redefining the target: chemotherapeutics as antiangiogenics. J Clin Oncol. 2001;19: 1195–206.
133. Baz R, Li L, Kottke-Merchant K, Srkalovic G, McGowan B, Yiannaki E, et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. Mayo Clin Proc. 2005; 80:1568–74.
134. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest. 2008;133:454S–545.