Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 53, No. 24, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.02.050

STATE-OF-THE-ART PAPERS

Cardiovascular Complications of Cancer Therapy

Incidence, Pathogenesis, Diagnosis, and Management

Edward T. H. Yeh, MD,*‡ Courtney L. Bickford, PHARMD, BCPS†

Houston, Texas

Cancer treatment today employs a combination of chemotherapy, radiotherapy, and surgery to prolong life and provide cure. However, many of these treatments can cause cardiovascular complications such as heart failure, myocardial ischemia/infarction, hypertension, thromboembolism, and arrhythmias. In this article we review the incidence of cardiotoxicity caused by commonly used chemotherapeutic agents as well as discuss the pathogenesis, diagnosis, management, and prevention of these cardiovascular side effects. Cardiotoxicity related to anticancer treatment is important to recognize as it may have a significant impact on the overall prognosis and survival of cancer patients, and it is likely to remain a significant challenge for both cardiologists and oncologists in the future due to an increasing aging population of patients with cancer and the introduction of many new cancer therapies. (J Am Coll Cardiol 2009;53:2231–47) © 2009 by the American College of Cardiology Foundation

Antineoplastic therapy is frequently complicated by the development of cardiotoxicity. This subject is of rising concern for both cardiologists and oncologists since many of these adverse effects are likely to have significant consequences on patient outcomes. Therefore, identifying and understanding these effects is crucial to the successful management of cancer patients with cardiovascular complications.

The purpose of this review is to attempt to summarize the current state of knowledge of common cardiovascular complications, such as heart failure (HF), myocardial ischemia, hypertension (HTN), thromboembolism, QT prolongation, and bradycardia associated with frequently used anticancer medications at the University of Texas M. D. Anderson Cancer Center (MDACC). A MEDLINE search for each of the aforementioned cardiovascular side effects and associated chemotherapeutic agents was performed. The most recent review articles and key research papers establishing the chemotherapy's incidence, diagnosis, pathophysiology, and management of its cardiovascular complications were included. For anticancer therapies in which the incidence of a particular cardiotoxicity was considered rare, or when there were only case reports available, these agents were excluded from this review. During the literature search conducted for this report, we found that in many cases primary literature was lacking in regard to the rate of these side effects reported in the package insert, particularly for newer targeted therapies. In these instances, the package insert was the only published information available to report the incidence of cardiotoxicity. In addition, scientific abstracts presented at national conferences, the Food and Drug Administration (FDA) website, as well as the extensive clinical experience of the Department of Cardiology at MDACC were utilized to comprise this review. The reported rates of cardiotoxicity were obtained from available published literature and they apply to the follow-up periods for each agent, which were variable. Therefore, in this report, incidence should be understood as the number of new cases of cardiotoxicity described over the variable follow-up period studied.

For every cardiotoxic side effect discussed, a table was created. In each of the tables presented, the incidence of the cardiotoxic side effect being discussed is listed. In addition, the frequency of use for each chemotherapeutic agent in the past year (January 1, 2007 to December 31, 2007) at MDACC is represented. If >5,000 doses per year were dispensed, then the agent was assigned +++; if 1,000 to 5,000 doses per year were dispensed, the agent was assigned ++; lastly, if <1,000 doses were dispensed per year, then + was assigned to correspond to its frequency of use.

HF

Several therapies for cancer have been associated with the development of left ventricular dysfunction (LVD) and/or HF. The cumulative dose, the administration schedule, and the concomitant use of other cardiotoxic therapies determine the likelihood of cardiomyopathy (CMP). Table 1 highlights the incidences of LVD associated with selected chemotherapeutic agents.

From the *Department of Cardiology and the †Division of Pharmacy, University of Texas M. D. Anderson Cancer Center, Houston, Texas; and the ‡Texas Heart Institute/St. Luke's Episcopal Hospital, Houston, Texas. Dr. Yeh is a consultant for Celgene and is the McNair Scholar of the Texas Heart Institute.

Manuscript received August 7, 2008; revised manuscript received January 27, 2009, accepted February 6, 2009.

JACC Vol. 53, No. 24, 2009
June 16, 2009:2231–47

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ACS = acute coronary syndrome
ATE = arterial thrombotic event
ATP = adenosine triphosphate
CMP = cardiomyopathy
CTCL = cutaneous T-cell lymphoma
DVT = deep vein thrombosis
FDA = Food and Drug Administration
HF = heart failure
HTN = hypertension
LMWH = low-molecular-weight heparin
LVD = left ventricular dysfunction
LVEF = left ventricular ejection fraction
MI = myocardial infarction
MUGA = multigated acquisition scan
PE = pulmonary embolism
VEGF = vascular endothelial growth factor
VTE = venous thromboembolism
5-FU = 5-fluorouracil

Incidence. ANTHRACYCLINES. Anthracycline-induced cardiotoxicity has been categorized into acute, early-onset chronic progressive, and late-onset chronic progressive (1,2). Acute cardiotoxicity occurs in <1% of patients immediately after infusion of the anthracycline and manifests as an acute, transient decline in myocardial contractility, which is usually reversible (3). The early-onset chronic progressive form occurs in 1.6% to 2.1% of patients, during therapy or within the first year after treatment (3). Late-onset chronic progressive anthracycline-induced cardiotoxicity occurs at least 1 year after completion of therapy in 1.6% to 5% of patients (3). Early- and late-onset chronic progressive cardiotoxicity typically presents as dilated CMP in adults, which can be progressive (2). Late-occurring cardiotoxicity may not become clinically evident until 10 to 20 years after the first dose of cancer treatment. In addition, the Childhood Cancer Survivor study demonstrated that 30 years after therapy, 73% of pediatric cancer survivors will develop at least 1 chronic physical health condition and 42% a severe, life-threatening or disabling condition, or die of a chronic condition (4). The risk of clinical cardiotoxicity increases with a cumulative dose of anthracycline. Studies that have looked at the cumulative probability of doxorubicin-induced HF have found that it occurs in 3% to 5% with 400 mg/m^2, 7% to 26% at 550 mg/m^2, and 18% to 48% at 700 mg/m^2 (3,5,6). However, in a retrospective review of 3 trials, the incidence of HF was found to be 26% with cumulative doses of 550 mg/m^2 (7). For this reason, the maximum lifetime cumulative dose for doxorubicin is 400 to 550 mg/m^2 (3). However, epirubicin or idarubicin appears to have less incidence of HF (8–10). Risk factors for anthracycline toxicity include cumulative dose; intravenous bolus administration; higher single doses; history of prior irradiation; the use of other concomitant agents known to have cardiotoxic effects such as cyclophosphamide, trastuzumab, and paclitaxel; female gender; underlying cardiovascular disease; age (young and old age); and increased length of time since anthracycline completion (1,2,7).

Table 1 Chemotherapy Associated With Left Ventricular Dysfunction

Chemotherapy Agents	Incidence (%)	Frequency of Use
Anthracyclines		
Doxorubicin (Adriamycin) (6,7)	3–26*	+++
Epirubicin (Ellence) (10)	0.9–3.3	++
Idarubicin (Idamycin PFS) (8)	5–18	+
Alkylating agents		
Cyclophosphamide (Cytoxan) (8,11–13)	7–28	+++
Ifosfamide (Ifex) (8,14)	17	+++
Antimetabolites		
Clofarabine (Clolar) (10)	27	+
Antimicrotubule agents		
Docetaxel (Taxotere) (10,15,16)	2.3–8	++
Monoclonal antibody-based tyrosine kinase inhibitors		
Bevacizumab (Avastin) (10,18,19)	1.7–3	++
Trastuzumab (Herceptin) (20–28)	2–28	++
Proteasome inhibitor		
Bortezomib (Velcade) (10,17)	2–5	++
Small molecule tyrosine kinase inhibitors		
Dasatinib (Sprycel) (10)	2–4	++
Imatinib mesylate (Gleevec) (34,35)	0.5–1.7	+
Lapatinib (Tykerb) (32)	1.5–2.2	+
Sunitinib (Sutent) (36,37)	2.7–11	+++

If 5,000 doses per year were dispensed, then the agent was assigned +++; if 1,000 to 5,000 doses per year were dispensed, the agent was assigned ++; lastly, if 1,000 doses were dispensed per year, then + was assigned to correspond to its frequency of use. *At a cumulative dose of 550 mg/m^2. Medication manufacturers (and locations): Adriamycin, Pharmacia & Upjohn SpA, Milano, Italy; Ellence, Idamycin, and Sutent, Pfizer Inc., New York, New York; Cytoxan, Ifex, and Sprycel, Bristol-Myers Squibb, Princeton, New Jersey; Clolar, Genzyme Oncology, Cambridge, Massachusetts; Taxotere, Sanofi-Aventis U.S. LLC, Bridgewater, New Jersey; Avastin and Herceptin, Genentech Inc., South San Francisco, California; Velcade, Millenium Pharmaceuticals, Cambridge, Massachusetts; Gleevac, Novartis Pharmaceuticals Corp., East Hanover, New Jersey; Tykerb, GlaxoSmithKline, Research Triangle Park, North Carolina.

ALKYLATING AGENTS. *Cyclophosphamide.* HF has been associated with cyclophosphamide therapy in 7% to 28% of patients (8,11–13). Clinical manifestations of cardiotoxicity range from asymptomatic pericardial effusions to HF and myopericarditis (11,13). The risk of cardiotoxicity appears to be dose related (>150 mg/kg and 1.5 g/m^2/day) and occurs within 1 to 10 days after the administration of the first dose of cyclophosphamide (8). Besides total dose, risk factors for cardiotoxicity include prior anthracycline or mitoxantrone therapy and mediastinal radiation (8,12).
Ifosfamide. In a retrospective review of patients treated with ifosfamide combination chemotherapy, cardiotoxicity developed in 17% of patients (8,14). Acute onset of HF occurred within 6 to 23 days after the first dose of ifosfamide, and a dose-response trend was observed (doses ≥12.5 g/m^2) (8).

ANTIMETABOLITES. *Clofarabine.* According to the package insert, LVD was noted in 27% of pediatric acute lymphoblastic leukemia patients. In most cases, LVD appeared to be transient (10).

ANTIMICROTUBULE AGENTS. *Docetaxel.* The incidence of HF associated with docetaxel ranges from 2.3% to 8% (10,15,16). In a trial comparing docetaxel plus doxoru-

bicin and cyclophosphamide (TAC) with fluorouracil plus doxorubicin and cyclophosphamide (FAC) in 1,491 breast cancer patients, the overall incidence of HF at 55 months was 1.6% in the TAC group versus 0.7% in the FAC group (15). At 70 months' follow-up, HF was reported in 2.3% of the docetaxel arm compared with 0.9% of the control arm (10). However, the incidence of docetaxel-induced HF was higher (8%) in another breast cancer trial (16).

PROTEASOME INHIBITOR. *Bortezomib.* In a pivotal clinical trial, 669 multiple myeloma patients were treated with bortezomib or high-dose dexamethasone (17). The incidence of cardiac disorders during treatment with bortezomib was 15% versus 13% in those patients treated with dexamethasone. HF events occurred in 5% of bortezomib-treated patients and in 4% of dexamethasone-treated patients. Two percent of patients in each of the treatment groups developed HF (10,17).

ANTIBODY-BASED TYROSINE KINASE INHIBITORS. *Bevacizumab.* The incidence of HF ranges from 1.7% to 3%. Per the prescribing information, HF developed in 24 of 1,459 patients (1.7%) treated with bevacizumab during clinical trials (10). In 2 phase III clinical studies in metastatic breast cancer patients, the rate of grade 3 to 4 HF or CMP in the bevacizumab-treated arms was 2.2% to 3% (18,19).

Trastuzumab. The overall incidence of trastuzumab varies in the literature from 2% to 28%. The incidence of cardiac dysfunction ranges from 2% to 7% when trastuzumab is used as monotherapy, 2% to 13% when trastuzumab is used in combination with paclitaxel, and up to 27% when trastuzumab is used concurrently with anthracyclines plus cyclophosphamide (20–27). In a recent study looking at the long-term cardiac tolerability of trastuzumab at MDACC, the overall incidence of cardiotoxicity was 28% (28). Cited risk factors for trastuzumab-induced CMP include age >50 years, borderline left ventricular ejection fraction (LVEF) before treatment, history of cardiovascular disease, the sequence in which chemotherapy is administered, and prior treatment with anthracyclines (cumulative doses >300 mg/m^2) (20,26,28–31).

SMALL MOLECULE TYROSINE KINASE INHIBITORS. *Dasatinib.* The incidence of HF reported with dasatinib therapy ranges from 2% to 4%. In patients with leukemia across all dasatinib studies (n = 2,182), HF or cardiac dysfunction (all grades) occurred in 2%, with grade 3 or 4 occurring in 1% of these patients (10). During the phase III dose-optimization study, HF or LVD was reported in up to 4% of chronic phase chronic myeloid leukemia patients receiving dasatinib. Grade 3 or 4 HF/LVD occurred in up to 2% of patients (10).

Lapatinib. The cardiac safety of lapatinib was recently evaluated in a pooled analysis of 3,689 patients enrolled in phase I to III lapatinib clinical trials (32). Cardiac events were defined as symptomatic (grade 3 or 4 LVD) or asymptomatic (LVEF decreases ≥20% relative to baseline and below the institution's lower limit of normal; no symptoms). Of the 3,689 patients, 60 (1.6%) experienced a cardiac event. Asymptomatic cardiac events were reported in 53 patients (1.4%), and symptomatic events occurred in 7 (0.2%). In patients treated with prior anthracyclines, trastuzumab, or neither, the incidence of cardiac events was 2.2%, 1.7%, and 1.5%, respectively. The mean time to onset of cardiac events was 13 weeks (32).

Imatinib mesylate. The exact incidence of cardiotoxicity associated with imatinib is unknown. The idea that imatinib causes cardiotoxicity was first introduced by Kerkela et al. (33) when they reported 10 patients who developed severe HF while on imatinib therapy. In addition, they showed that imatinib-treated mice develop left ventricular contractile dysfunction and cellular abnormalities suggestive of toxic myopathy (33). In correspondence to this report, Novartis conducted a retrospective review of their clinical database containing 6 registration trials of 2,327 patients treated with imatinib monotherapy. The incidence of HF was 0.5% (34). Similarly, among 1,276 patients treated with imatinib during clinical trials at MDACC, 22 patients (1.7%) developed HF (35).

Sunitinib. Early clinical trials involving patients with gastrointestinal stromal tumor and metastatic renal cell cancer reported LVD in 4% to 11% of patients (36). Recently, 2 retrospective reviews have been published examining the cardiotoxicity of sunitinib (36,37). Chu et al. (37) retrospectively reviewed all cardiovascular events in 75 imatinib-resistant metastatic gastrointestinal stromal tumor patients. Eleven percent of patients had a cardiac event, with New York Heart Association functional class III to IV HF recorded in 8% of patients. In another retrospective review, 6 of 224 (2.7%) sunitinib-treated patients developed HF (36). The only significant risk factor associated with the development of HF was coronary artery disease (37). The mean time to development of HF was variable, 22 days to 27 weeks (36,37). Sunitinib-induced HF appears to respond well to medical therapy; however, CMP may not be completely reversible (36).

Pathophysiology. *Anthracyclines.* There are several hypotheses to explain the mechanism of anthracycline-induced cardiotoxicity, but free radical formation is generally accepted as the main mechanism. Other mechanisms have also been postulated including apoptosis; transcriptional changes in intracellular adenosine triphosphate (ATP) production in cardiac myocytes; down-regulation of messenger ribonucleic acid expression for sarcoplasmic reticulum calcium-ATPase, which decreases cardiac contractility; prolonged drug-related depression in cardiac glutathione peroxidase activity; and respiratory defects associated with mitochondrial deoxyribonucleic acid damage (3). However, it has recently been proposed that doxorubicin may cause cardiotoxicity through its interference with topoisomerase II beta (38).

Cyclophosphamide. The precise mechanism of cyclophosphamide cardiotoxicity is unknown. It is hypothesized that

cyclophosphamide causes direct endothelial injury, followed by extravasation of toxic metabolites resulting in damage to cardiomyocytes, interstitial hemorrhage, and edema (8,12,13,39). Intracapillary microemboli may develop as well, resulting in ischemic myocardial damage (13,39). Myocardial ischemia caused from coronary vasospasm is another proposed mechanism of cardiotoxicity (8).

Ifosfamide. Given that ifosfamide and cyclophosphamide are structurally similar, it is possible that ifosfamide may induce HF through a similar mechanism. However, no histopathological evidence of hemorrhagic myocarditis, which is the hallmark of cyclophosphamide toxicity, was found in ifosfamide-treated patients (14). It has also been proposed that since ifosfamide causes nephrotoxicity, the decrease in glomerular filtration rate may delay elimination of cardiotoxic metabolites. In addition, fluid disturbances, acid-base, and electrolyte disturbances related to tubular defects may be factors contributing to cardiac disturbances (14).

Bevacizumab. The mechanism of HF associated with bevacizumab may be related to uncontrolled HTN and inhibition of vascular endothelial growth factor (VEGF)/VEGF receptor signaling (40). Animal studies have demonstrated that angiogenesis plays a key role in the normal adaptive response to a pressure load. Studies that have utilized strategies mimicking the mechanism of bevacizumab have shown that pressure overload resulted in reduction of myocardial capillary density, global contractile dysfunction, cardiac fibrosis, and eventually decompensated HF (40).

Trastuzumab and lapatinib. Cardiotoxicity caused by trastuzumab is most likely secondary to inhibition of cardiomyocyte human epidermal growth factor receptor 2, also known as ErbB2 signaling, thereby interfering with normal growth, repair, and survival of cardiomyocytes (22,41,42). By binding to ErbB2, it may regulate mitochondrial integrity through the BCL-X proteins, leading to ATP depletion and contractile dysfunction (43). In a study by Sawyer et al. (44), the addition of an antibody to ErbB2 in mice exposed to anthracyclines caused increasing myofibrillar disarray, which may explain the contractile dysfunction seen in patients treated with concurrent trastuzumab and anthracyclines. Other mechanisms include drug–drug interactions and immune-mediated destruction of cardiomyocytes (45). There may also be a mechanism of cardiotoxicity independent of ErbB2 signaling, since both lapatinib and trastuzumab inhibit ErbB2, but trastuzumab is associated with a higher incidence of HF (30).

Bortezomib. The mechanism of HF associated with bortezomib is unknown, but it has been proposed that it may cause cardiotoxicity through proteasome inhibition (46). In chronic CMP, it is thought that the ubiquitin–proteasome system may be activated, and that this may be an adaptive mechanism for maintaining a normal stroke volume. In addition, susceptibility to cardiovascular disease has been attributed to an age-related decrease in proteasome activity. Therefore, in patients who possess a baseline presence of subclinical CMP, the ubiquitin–proteasome system is activated, and this may predispose them to bortezomib cardiotoxicity (46).

Dasatinib. The mechanism of dasatinib-induced cardiotoxicity may be similar to imatinib since they are both inhibitors of Abl. Besides Abl, dasatinib also inhibits Src and a number of other kinases, which may be involved in the development of cardiotoxicity as well (40).

Imatinib. Imatinib may induce cardiotoxicity through inhibition of c-Abl (33,43). Cultured cardiomyocytes with an imatinib-resistant mutant of c-Abl are largely protected from imatinib cardiotoxicity, suggesting that c-Abl has a previously unrecognized survival function in cardiomyocytes (33). A recent study by Fernandez et al. (47) demonstrated that a redesign of imatinib appears to reduce its cardiotoxic effects.

Sunitinib. Animal studies have shown that sunitinib induces mitochondrial damage in cardiomyocytes, but no apoptosis (37). Khakoo et al. (36) hypothesize that HTN may also play an important role, since sunitinib may inhibit a receptor tyrosine kinase that helps to regulate the response of cardiomyocytes in the setting of hypertensive stress. Lastly, Force et al. (43) suggest that sunitinib may cause cardiotoxicity through inhibition of ribosomal S6 kinase, leading to the activation of the intrinsic apoptotic pathway and ATP depletion.

Diagnosis. HF is a clinical diagnosis, which combines a thorough clinical history of the patient and physical examination combined with diagnostic tests such as electrocardiogram, chest radiography, and laboratory tests. According to the American College of Cardiology/American Heart Association guidelines, a panel of routine blood tests should be obtained, and noninvasive imaging (e.g., contrast echocardiography, multigated acquisition scan [MUGA]) should be used in conjunction to evaluate cardiac function.

Monitoring. To detect cardiac dysfunction in patients who are treated with chemotherapy, regular monitoring of the heart function during treatment is important. A baseline evaluation of LVEF needs to be obtained for comparison, and it is recommended that the same methodology be used for comparing serial studies. Serial assessment of LVEF was first shown to be useful in clinical practice by Alexander et al. (49). Based on their experiences, algorithms have been developed for serial monitoring of LVEF during anthracycline-based therapy (50,51). Measuring systolic function through evaluation of the LVEF with either MUGA or echocardiography is one of the most commonly used measurements in monitoring and diagnosing chemotherapy-induced CMP; however, it is not sensitive for early detection of pre-clinical cardiac disease (subclinical), and it is influenced by contractility and pre-load/afterload effects leading to transient changes. Therefore, other measurements of systolic function (e.g., fraction shortening) and diastolic function (e.g., E/A ratio) have been used to detect early cardiotoxicity in addition to LVEF (52).

Endomyocardial biopsy remains the gold standard for diagnosis since it is the most sensitive and specific; however,

the invasiveness of the procedure limits its use. MUGA scans are noninvasive, which make them an attractive option for routine clinical monitoring; however, MUGA scans primarily detect drops in LVEF, but no other information can be obtained. In addition, it is insensitive for detecting early toxicity. In contrast, echocardiography, which is also noninvasive, can identify both systolic and diastolic dysfunction, as well as valvular and pericardial disease (52).

Biochemical markers may also indicate myocardial injury before the changes in LVEF are apparent. Troponin, as a biomarker of cardiotoxicity associated with chemotherapy, has been investigated, but the utility of troponin testing depends on a prospective definition of a cutoff with good specificity for clinically significant HF. In 1 study, the elevation of troponin I soon after high-dose chemotherapy predicted the future development of LVEF depression (53), and in another study, troponin I elevations identified patients at different risks of future cardiac events (54). B-type natriuretic peptide has also been shown to be positively correlated with cardiac events and subclinical cardiotoxicity, particularly with evidence to suggest it correlates more to diastolic as opposed to systolic dysfunction (55–57).

Prevention. Since one of the most significant risk factors for anthracycline-induced CMP is the cumulative dose the patient has received, one of the most significant preventative measures is to minimize the patient's lifetime cumulative dose (3). Other preventative measures that have been shown to decrease cardiotoxicity associated with anthracyclines include altering the anthracycline administration (e.g., continuous infusion vs. bolus administration), use of anthracycline analogues (e.g., idarubicin, epirubicin, mitoxantrone) or liposomal anthracyclines, and the addition of cardioprotectants (e.g., dexrazoxane) to anthracycline treatment (3).

Treatment. Currently, there are no HF guidelines developed specifically for cancer patients. Until then, the guidelines published by the American College of Cardiology/American Heart Association and Heart Failure Society of America should be followed. Medical management of patients with stage A disease should focus on risk-factor reduction by controlling HTN, diabetes, and hyperlipidemia, with the goal of preventing remodeling. Treatment of stage B, C, and D aims at improving survival, slowing disease progression, and alleviating symptoms. All patients should be on a combination of an angiotensin-converting enzyme (ACE) inhibitors or an angiotensin II receptor blocker and a beta-blocker unless contraindicated. These medications have been shown to reverse remodeling thereby improving survival. Patients with advanced HF usually require additional measures such as diuretics, digoxin, or aldosterone antagonists. Patients with end-stage HF with refractory symptoms at rest despite maximal medical therapy and without evidence of cancer recurrence could be considered for synchronized pacing, ventricular assist device, or cardiac transplantation (48). Patients with anthracycline-induced cardiotoxicity may show clinical improvement in response to treatment, but because myocyte death is characteristic of this entity, resolution of the underlying process does not usually occur (22).

There is some evidence supporting the use of ACE inhibitors in patients with anthracycline-induced CMP (58–60). In cancer patients undergoing high-dose chemotherapy, enalapril was shown to prevent a decline in LVEF as well as cardiac events when compared with the control group (58). Although ACE inhibitors may be beneficial compared with placebo, they do not prevent progressive cardiac dysfunction in all patients. In an observational study of 18 children treated with enalapril for LVD or HF, the beneficial effects of enalapril diminished after 6 to 10 years due to progressive left ventricular wall thinning (59). In another study of pediatric cancer survivors with subclinical cardiac dysfunction, enalapril reduced left ventricular end-systolic wall stress, but this was not associated with an improvement in exercise capacity, contractile state, or ejection fraction compared with that seen with placebo (60).

The relationship between acute toxicity and the subsequent development of early and late cardiotoxicity is unclear. In a small randomized trial, the angiotensin II receptor blocker, valsartan, blocked all of the acute effects of anthracycline treatment (61). Additional clinical trials are required to determine if blocking acute toxicity decreases the risk of subsequently developing early or late cardiotoxicity.

To date, there have been 4 case series that have evaluated the benefit of beta-blockers in the treatment of anthracycline-induced CMP (62–65). Of the beta-blockers, carvedilol may have therapeutic advantages over the others in anthracycline-induced CMP since it has been shown to possess antioxidant properties (66). Moreover, in a recent clinical trial, the use of carvedilol prophylactically protected systolic and diastolic function compared with placebo in patients treated with anthracycline chemotherapy (67).

Discontinuation of trastuzumab is generally recommended when clinically significant HF occurs. However, patients who experience cardiotoxicity while receiving trastuzumab generally recover their cardiac function when trastuzumab is discontinued over a mean time period of 1.5 months (68). Patients who have experienced benefit with trastuzumab therapy and who have improved cardiac function while on a standard heart regimen may restart trastuzumab therapy while on protective HF medications and close cardiac monitoring (68). In addition, Memorial-Sloan-Kettering Cancer Center has proposed guidelines for the management of patients treated with trastuzumab based on physical status and LVEF (69).

Ischemia

Chest pain is a common cardiac event experienced by cancer patients, often necessitating a work-up for myocardial ischemia. Several forms of cancer treatment (e.g., radiation, chemotherapy) are associated with an increased risk of coronary artery disease and/or acute coronary syndrome

Table 2 Chemotherapy Associated With Ischemia

Chemotherapy Agents	Incidence (%)	Frequency of Use
Antimetabolites		
Capecitabine (Xeloda) (71,74,83–85)	3–9	+++
Fluorouracil (Adrucil) (8,70,71,73–79)	1–68*	+++
Antimicrotubule agents		
Paclitaxel (Taxol) (90,91)	<1–5	+++
Docetaxel (Taxotere) (10,92)	1.7	++
Monoclonal antibody-based tyrosine kinase inhibitor		
Bevacizumab (Avastin) (10,93,94)	0.6–1.5	++
Small molecule tyrosine kinase inhibitors		
Erlotinib (Tarceva) (10)	2.3	+++
Sorafenib (Nexavar) (10,96)	2.7–3	+++

For an explanation of the + symbols, please see Table 1. *The incidence of ischemia varies widely in the literature for 5-fluorouracil due to the differences in study design, definition of ischemia, and numbers of patients. Medication manufacturers and locations: Xeloda, Roche Laboratories Inc., Nutley, New Jersey; Adrucil, Sicor Pharmaceuticals, Irvine, California; Taxol, Bristol-Myers Squibb, Princeton, New Jersey; Tarceva, OSI Pharmaceuticals Inc., Melville, New York; Nexavar, Bayer HealthCare Pharmaceuticals, Inc., Wayne, New Jersey; see Table 1 for others.

(ACS). Chemotherapeutic agents implicated in the development of myocardial ischemia/infarction are highlighted in Table 2.

Incidence. ANTIMETABOLITES. *Fluorouracil.* The most common symptom associated with 5-fluorouracil (5-FU) cardiotoxicity is angina-like chest pain. In rare cases, myocardial infarction (MI), arrhythmias, HF, cardiogenic shock, and sudden death have been reported (70,71). The incidence of cardiotoxicity associated with 5-FU varies in the literature ranging anywhere from 1% to 68% (8,70–79). Cardiac events tend to occur within 2 to 5 days of starting therapy, lasting up to 48 h (70). Ischemic electrocardiogram (ECG) changes have been reported in 68% of patients, but only 43% have elevations in serum cardiac markers (80). The overall mortality has been estimated to be 2.2% to 13% (73,76,78). Risk factors have not firmly been established, but high doses (>800 mg/m^2) and continuous infusions of 5-FU have been associated with higher rates of cardiotoxicity (7.6%) as compared with bolus injections (2%) (70,73,80). Other commonly cited risk factors include history of cardiovascular disease, prior mediastinal radiation, and the concurrent use of chemotherapy (71–75,77,78,81,82).

Capecitabine. The incidence and risk factors of cardiotoxicity associated with capecitabine remain poorly defined. Currently, the majority of the literature citing the incidence of capecitabine-induced myocardial ischemia/infarction exists only as case reports or retrospective reviews. One prospective review in 644 patients found the incidence of capecitabine-associated cardiotoxicity to be 5.5% (74). From the 4 retrospective reviews published, the incidence of cardiotoxicity ranges from 3% to 9% (71,83–85). In the case reports reviewed, the dosages of capecitabine ranged from 1,500 to 2,500 mg/m^2/day, and typical angina symptoms appeared 3 h to 4 days after therapy (72,79,80,82,86–89). ECG changes such as ST-segment elevation were noted in many cases (72,79,80,82,86,89) and when serum cardiac markers were checked, they were normal (72,80,86,89) except in 1 case (79). Echocardiography (72,80,82,87–89) and coronary angiogram were normal (72,80,82,86,87). Previous cardiac disease was not a consistent risk factor since it was not present in some cases (72,80,88), but present in others (79,82,83,89). Lastly, a history of 5-FU cardiotoxicity may be considered a risk factor for such effects related to capecitabine therapy (84,86).

ANTIMICROTUBULE AGENTS. *Paclitaxel.* Cases of myocardial ischemia and infarction associated with paclitaxel administration have been described. Rowinsky et al. (90) reviewed the cardiac events in 4 clinical trials, and reported that manifestations of cardiac ischemia were observed in 5% of patients. In 198 patients treated with paclitaxel for ovarian cancer, 0.5% experienced a MI (91). Lastly, in a review of the Cancer Therapy Evaluation Program's Adverse Drug Reaction database, which followed treatment of more than 3,400 patients, the overall incidence of grade 4 and 5 cardiac events was 0.29% (91). These events occurred during and up to 14 days after paclitaxel administration (91). Most of the cases reported that patients had known cardiac risk factors including HTN and coronary artery disease.

Docetaxel. In the package insert, the incidence of myocardial ischemia associated with docetaxel is 1.7% (10). This incidence comes from a clinical trial conducted by Vermorken et al. (92), which randomized 355 patients with inoperable, locally advanced squamous cell carcinoma of the head and neck to receive a standard regimen of cisplatin and 5-FU or the same regimen plus docetaxel. Myocardial ischemia was reported in 1.7% of the docetaxel arm compared with 0.6% of the control arm (10,92). The authors did not publish this side effect in the clinical trial; therefore, the only information available for myocardial ischemia was found in the package insert.

MONOCLONAL ANTIBODY-BASED TYROSINE KINASE INHIBITORS. *Bevacizumab.* Arterial thrombotic events (ATEs) tend to occur more frequently in patients treated with bevacizumab with chemotherapy as compared with patients treated with chemotherapy alone (10). In a pooled analysis of 1,745 patients from 5 randomized controlled trials in metastatic colorectal, nonsmall cell lung cancer, and metastatic breast cancer patients, the overall incidence of ATEs was 3.8% (93). When looking at MI/angina specifically, the incidence was 1.5% versus 1% in the bevacizumab group as compared with the control group, respectively (93). In an ongoing observational study of 1,953 patients receiving bevacizumab plus chemotherapy, the incidence of serious ATEs was 1.8%. Of the patients identified with an ATE, 11 patients had a MI (0.6%) (94). Bevacizumab-associated ATEs were reported to occur at any time during therapy, although in both studies mentioned, the median time to event was approximately 3 months. Events did not seem to be associated with dose or cumulative exposure. Age >65

years (93) and a history of prior ATEs were identified as risk factors (93,94).

SMALL MOLECULE TYROSINE KINASE INHIBITORS. *Erlotinib.* MI/ischemia was reported in 2.3% of patients who received erlotinib 100 mg/day with gemcitabine, compared with that seen in 1.2% of patients who received gemcitabine alone, for the treatment of pancreatic cancer (10). The manufacturer obtained these results in a trial conducted by Moore et al. (95); however, the incidence of thromboembolism was not published.

Sorafenib. Approximately 3% of patients in clinical trials have experienced myocardial ischemia with sorafenib. In an unpublished clinical trial, MI/ischemia occurred among 2.7% of hepatocellular cancer patients treated with sorafenib compared with 1.3% of patients in the placebo group (10). Similarly, sorafenib was associated with a higher incidence of MI/ischemia compared with placebo among patients treated for renal cell carcinoma (3% vs. <1%) (96).

Pathophysiology. FLUOROURACIL AND CAPECITABINE. The pathogenesis of cardiotoxicity associated with 5-FU and capecitabine is unknown. Coronary artery thrombosis, arteritis, or vasospasm has been proposed as the most likely underlying mechanisms (74). However, the failure of ergonovine and 5-FU to elicit vasospasm during cardiac catheterizations, in addition to the variable efficacy of coronary vasodilating medications weakens the idea of 5-FU–induced vasospasm (74,81,86,97). In 1 study, increased endothelin-1 levels were found in some patients, supporting the theory of coronary vasospasm, but the authors of this study questioned if the release of endothelin-1 from normal coronary artery endothelial cells was the primary cause or a consequence of 5-FU–related endothelial activation leading to cardiotoxicity (74,98).

Therefore, alternative mechanisms have been developed, including direct toxicity on myocardium, interaction with coagulation system, and autoimmune responses (74,86). Accumulation of 5-FU and its metabolites due to dihydropyrimidine deficiency may increase 5-FU–related cardiotoxicity, although the relationship between these 2 is unknown (84). Animal models have suggested an accumulation of citrate in myocardial cells may be the causative mechanism (73,74,86). This accumulation is attributed to fluoroacetate formation, which interferes with the Krebs cycle. Fluoroacetate is generated from a degradation product of parenteral 5-FU preparations, fluoroacetaldehyde (73,86). Animal studies have also shown the potential for 5-FU to induce dose- and time-dependent depletion of high-energy phosphates in the ventricle (86,97). Lastly, apoptosis of myocardial cells and endothelial cells may result in inflammatory lesions mimicking toxic myocarditis (84,86).

PACLITAXEL. Myocardial ischemia associated with paclitaxel is thought to be multifactorial in etiology, with other drugs and underlying heart disease as possible contributing factors (90). In addition, the Cremophor EL vehicle in which paclitaxel is formulated may be responsible for its cardiac toxicity, and the mechanism is likely due to its induction of histamine release (90).

BEVACIZUMAB. The mechanism associated with bevacizumab-induced arterial thrombosis is unclear. It is thought, however, that VEGF may be involved. VEGF stimulates endothelial cell proliferation, promotes endothelial cell survival, and helps maintain vascular integrity (99). Therefore, 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. As a result of subendothelial collagen exposure, tissue factor is activated increasing the risk for thrombotic events to occur (99,100). In addition, inhibiting VEGF causes reduction in nitric oxide and prostacyclin, as well as increases hematocrit and blood viscosity via overproduction of erythropoietin, all of which may predispose patients to an increased risk of thromboembolic events (99).

Diagnosis. The diagnosis of an ACS is based upon the patient's clinical presentation, ECG changes, and elevations in cardiac enzymes. In 2007, the Joint Task Force of the European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association, and the World Health Federation redefined acute MI as a term that should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia (101).

Treatment. Patients with suspected ACS should be managed according to the guidelines established by American College of Cardiology and American Heart Association (102,103). Cornerstones in ACS therapy include percutaneous coronary intervention, antiplatelet and anticoagulant therapy, all of which may pose a problem in certain cancer patients due to either thrombocytopenia or recent surgery. Currently, there are no guidelines or prospective studies that include such patients. However, in a retrospective study, aspirin use significantly improved 7-day survival in cancer patients with thrombocytopenia and ACS without increasing the bleeding risk (104). In addition, treatment with beta-blockers also led to significantly improved 7-day survival in cancer patients with ACS (104).

5-FU AND CAPECITABINE. 5-FU or capecitabine therapy should be discontinued in patients who develop chest pain. In addition, antianginal therapy and a work-up for ischemia should be initiated. Based on the idea that coronary artery spasm is involved in the mechanism of cardiac injury, prophylactic treatment with coronary vasodilators (e.g., nitrates and calcium-channel blockers) has been investigated. However, the results of these studies have not shown a consistent benefit. Rechallenging patients with 5-FU or capecitabine who previously had cardiotoxicity related to these agents remains controversial. A rechallenge with these agents should be reserved only for patients having no alternative therapeutic interventions and should be administered in a supervised environment. It may also be prudent

to carefully monitor patients with risk factors for 5-FU or capecitabine-induced cardiotoxicity (70,78,81,84).

SORAFENIB. According to the package insert, temporary or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischemia.

BEVACIZUMAB. Because studies excluded patients who had any history of stroke or MI within 12 months of enrollment, the risks and benefits of bevacizumab treatment among these patients have not been established. Bevacizumab therapy should be discontinued in patients who develop severe ATEs during treatment. The safety of restarting of bevacizumab therapy after resolution of an ATE has not been studied (10).

HTN

HTN and cancer often coexist in the same patient. In fact, high blood pressure is the most frequent comorbid condition reported in cancer registries (105). Additionally, epidemiological studies suggest the possibility that there is an association between the 2 and that HTN affects the overall prognosis of cancer patients (106). New approaches to cancer treatment disrupt angiogenesis; thereby patients receiving these agents often will develop HTN (105). Table 3 highlights the incidences of clinically significant HTN associated with selected anticancer agents.

Incidence. BEVACIZUMAB. HTN (any grade) is a common adverse effect occurring in patients treated with bevacizumab, with an overall incidence of 4% to 35% reported in clinical trials (18,19,107–112). Grade 3 HTN occurred in 11% to 18% of patients (18,19,107,108). HTN developed at any time during therapy, and some data suggest there is a dose relationship (108). Most patients who developed HTN in clinical trials were adequately treated with antihypertensives and continued bevacizumab therapy. However, worsening HTN requiring hospitalization or discontinuation of bevacizumab therapy occurred in up to 1.7% of patients (10). Complications of bevacizumab-induced HTN have included hypertensive encephalopathy and central nervous system hemorrhage (10).

SORAFENIB. HTN is a major adverse effect of sorafenib therapy occurring in 17% to 43% of patients in clinical trials (96,113–116). Grade 3 or 4 HTN occurred in 1.4% to 38% (96,113–116). In a recent meta-analysis involving 4,599 patients treated with sorafenib therapy, the overall incidence of HTN was 23.4%. Grade 3 or 4 HTN ranged from 2.1% to 30.7% (117).

SUNITINIB. In clinical trials, sunitinib was associated with HTN, with the incidence varying from 5% to 24% (118–122). Grade 3 HTN occurred in 2% to 8% (118–122). In a retrospective review, sunitinib was found to have increased blood pressure (>150/100 mm Hg) in 47% of patients, with grade 3 HTN seen in 17%. HTN occurred within the first 4 weeks of therapy (37).

Pathophysiology. The mechanism of antiangiogenic therapy-related HTN is not fully understood. However, it is thought to be related to VEGF inhibition, which decreases nitric oxide production in the wall of the arterioles and other resistance vessels (99). Nitric oxide is a natural vasodilator, thereby blocking its production promotes vasoconstriction, increased peripheral vascular resistance and blood pressure (99). Because bevacizumab decreases endothelial nitric oxide synthase activity, this may stimulate plasminogen activator inhibitor-1 expression, leading to an increased risk of HTN (123). It has also been hypothesized that VEGF may have effects on the renin-angiotensin system (124). However, Veronese et al. (125) demonstrated that serum catecholamine, renin, and aldosterone levels did not change during anti-VEGF therapy, lessening the likelihood that the onset of HTN has an adrenergic or a renovascular etiology. Finally it has been speculated that VEGF inhibition may be responsible for cholesterol emboli syndrome, which may account for bevacizumab-induced acute complications including HTN (126).

Diagnosis. HTN is defined by JNC 7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) as blood pressure ≥140/90 mm Hg. The JNC 7 classification of blood pressure for adults is based on the average of 2 or more properly measured blood pressure readings on 2 or more visits. JNC 7 classifies individuals with HTN into various stages based on measured blood pressure values. When evaluating patients with HTN there are 3 objectives: 1) identify the causes of HTN; 2) assess lifestyle and recognize cardiovascular risk factors or comorbid conditions that may affect prognosis or guide the choice of treatment; and 3) evaluate the presence or absence of target organ damage associated with HTN (127).

Treatment. The primary goal in the treatment of HTN is to reduce morbidity and mortality and lower the risk of associated target organ damage (e.g., cardiovascular and cerebrovascular events, renal failure). In treating HTN induced by antiangiogenic therapies, standard antihypertensive medications should be initiated in concordance with JNC guidelines (127). HTN induced by bevacizumab, sorafenib, and sunitinib will most likely require more than 1 antihypertensive medication, and close blood pressure monitoring is recommended. Discontinuation of antiangiogenic therapy due to HTN is controversial since the appearance of

Table 3 Chemotherapy Associated With Hypertension

Chemotherapy Agents	Incidence	Frequency of Use
Monoclonal antibody-based tyrosine kinase inhibitor		
Bevacizumab (Avastin) (18,19,107–112)	4–35	++
Small molecule tyrosine kinase inhibitors		
Sorafenib (Nexavar) (96,113–116)	17–43	+++
Sunitinib (Sutent) (37,118–122)	5–47	+++

For an explanation of the + symbols, please see Table 1. Medication manufacturers and locations as in Tables 1 and 2.

HTN, particularly grade 3, seems to be associated with higher treatment response (128).

When choosing an antihypertensive agent, there is evidence that some antihypertensives may be more effective than others, since the biological effect of these medications on angiogenesis differs (117). In addition, it may be beneficial to use ACE inhibitors as first-line therapy due to their ability to prevent proteinuria and plasminogen activator inhibitor-1 expression (123). In vivo studies have also shown that ACE inhibitors have the potential to reduce microcirculatory changes, decrease the catabolism of bradykinin, and increase release of endothelial nitric oxide (109).

Drug–drug interactions should also be considered 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 in combination with sorafenib since they are both inhibitors of the CYP3A4 isoenzyme, thereby substantially increasing sorafenib levels. If a calcium-channel blocker is added, amlodipine and nifedipine are preferred. The use of phosphodiesterase inhibitors or nitrates to increase nitric oxide levels has been suggested when treating HTN associated with sorafenib therapy, although further clinical studies are necessary (117). Finally, since HTN is a risk factor for the development of HF, medications that have been shown to be beneficial in preventing morbidity and mortality in HF patients (e.g., carvedilol, metoprolol succinate, ACE inhibitors, and angiotensin receptor blockers) may be considered as first-line agents for treating HTN associated with antiangiogenic therapy as well.

Thromboembolism

Cancer is known to produce a prothrombotic state. The risk of thrombosis appears to be highest in cancer patients with metastatic disease and in those with established risk factors. Risk factors include the use of central venous catheters and associated comorbidities such as immobility, HF, atrial fibrillation, dehydration, and administration of concurrent chemotherapy (129). Table 4 highlights the incidences of clinically significant venous thromboembolism (VTE) associated with selected chemotherapeutic agents.

Table 4 Chemotherapy Associated With Venous Thromboembolism

Chemotherapy Agents	Incidence (%)	Frequency of Use
Alkylating agents		
Cisplatin (Platinol-AQ) (130)	8.5	+++
Angiogenesis inhibitors		
Lenalidomide (Revlimid) (144–149)	3–75*	+
Thalidomide (Thalomid) (133–143)	1–58*	+
Histone deacetylase inhibitor		
Vorinostat (Zolinza) (10,131,132)	4.7–8	+
Small molecule tyrosine kinase inhibitors		
Erlotinib (Tarceva) (10)	3.9–11	+++

For an explanation of the + symbols, please see Table 1. *The incidence of venous thromboembolism varies widely in the literature for angiogenesis inhibitors depending on the patient's disease status, concomitant use of high- or low-dose dexamethasone, erythropoietin, or other chemotherapeutic agents, and whether or not thromboprophylaxis was employed during the study period. Medication manufacturers and locations: Platinol-AQ, Bristol-Myers Squibb, Princeton, New Jersey; Revlimid and Thalomid, Celgene Corp., Summit, New Jersey; Zolinza, Merck & Co. Inc., Whitehouse Station, New Jersey; Tarceva, OSI Pharmaceuticals Inc., Melville, New York.

Incidence. CISPLATIN. Platinum-based therapy has been shown to increase the risk of thrombotic events in cancer patients. In a retrospective review of 271 consecutive patients with urothelial transitional cell carcinoma receiving cisplatin-based chemotherapy, vascular events occurred in 35 patients (12.9%). When separating out the thromboembolic events in the 35 patients, 23 patients (8.5%) experienced a deep vein thrombosis (DVT) or pulmonary embolism (PE). Of these patients, 74% had events within the first 2 cycles of chemotherapy, and most patients had predisposing risk factors such as large pelvic masses, coronary artery disease, immobility, or a prior history of a thromboembolic event (130).

VORINOSTAT. The incidence of thromboembolism associated with vorinostat is 4.7% (10). This number is based on the unpublished combined results of 2 clinical studies evaluating vorinostat in the treatment of 86 patients with cutaneous T-cell lymphoma (CTCL) (10). However, 2 trials have been published reporting the frequency of thromboembolism associated with vorinostat. A phase IIb trial conducted in 74 CTCL patients found the incidence of thromboembolic events was 5.4% (131). In addition, Duvic et al. (132) established that PE and DVT occurred in 5% and 8% of patients, respectively.

THALIDOMIDE. Of the chemotherapeutic agents, thalidomide is most commonly associated with the development of thromboembolic complications. Thalidomide monotherapy is associated with low rates of thrombosis (<5%) (133,134). However, this risk increases dramatically (3% to 58%) when thalidomide is used in newly diagnosed patients, as well as when used in combination with dexamethasone or chemotherapy, particularly doxorubicin, in the absence of thromboprophylaxis (133–143). Overall, the median time to onset of a thrombotic event associated with thalidomide was around 3 months (141).

LENALIDOMIDE. Lenalidomide is a thalidomide analog with a favorable toxicity profile that differs from the parent molecule. However, it appears that the thrombotic risk is still significant with lenalidomide. In clinical studies, the incidence of thromboembolism has varied widely among reports, ranging anywhere from 3% to 75% (144–149). As a single agent, lenalidomide does not significantly increase the risk of VTE (141). However, the rate of thrombosis fluctuates considerably depending on the patients' disease status, concomitant use of high- or low-dose dexamethasone, erythropoietin, or other chemotherapeutic agents, and whether or not thromboprophylaxis was employed during the study period (150). Risk factors associated with increased rates of VTE include high doses of dexamethasone,

erythropoietin administration, and in 1 study, the rate was highest (75%) in newly diagnosed patients (141,150).

ERLOTINIB. DVT has been reported in 3.9% of patients receiving erlotinib in combination with gemcitabine, compared with 1.2% of patients who received gemcitabine alone, for the treatment of pancreatic cancer. The overall incidence of grade 3 or 4 thrombotic events, including DVT, was 11% in the erlotinib group plus gemcitabine arm and 9% in the gemcitabine only arm (10). The manufacturer obtained these results from a trial conducted by Moore et al. (95); however, the incidence of thromboembolism was not published.

Pathophysiology. Malignancy is associated with a baseline hypercoagulable state due to many factors including release of 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, and alteration of endothelial surface (142). Due to the complexity of this situation where multiple hemostatic abnormalities exist, the mechanisms by which anticancer treatments contribute to thrombosis remains to be clarified. Potential factors that may contribute to chemotherapy-induced thrombogenesis include the release of procoagulants and cytokines by chemotherapy-induced tumor cell damage, direct endothelial damage, as well as hepatotoxicity from chemotherapeutic agents leading to decreased production of normally produced anticoagulants (130).

CISPLATIN. With cisplatin, there is some laboratory evidence suggesting that it induces platelet activation and aggregation, possibly through a mechanism involving monocyte procoagulant activity. Cisplatin-based therapies may also alter endothelial cell integrity (130). Finally, cisplatin may elevate von Willebrand factor levels, cause hypomagnesemia-induced vasospasm, and have antiangiogenic activity (151,152).

THALIDOMIDE AND LENALIDOMIDE. It has been suggested that thalidomide-induced thromboembolism may involve its direct action on endothelial cells previously damaged by doxorubicin (134). It also may involve an interaction between platelets and the endothelium (136,142). Increased platelet aggregation and von Willebrand factor have been found in patients treated with thalidomide (136). Since lenalidomide is an analog of thalidomide, these same mechanisms may be responsible for its thrombosis.

Diagnosis. The diagnostic test of choice for DVT is compression ultrasonography, due to its high sensitivity and specificity. When PE is suspected, spiral computed tomography angiography is the diagnostic test of choice. Nuclear medicine techniques (e.g., ventilation/perfusion scan) are utilized less frequently. Magnetic resonance pulmonary angiography may be considered an alternative to computed tomography pulmonary angiography in patients who have contraindications to iodinated contrast media (141).

Prevention of thromboembolism. THALIDOMIDE AND LENALIDOMIDE. Due to the risk of thrombotic events, several preventative strategies have been investigated. There have been no randomized, prospective trials directly comparing different anticoagulants; therefore, there are no firm guidelines on the management of these patients. However, the International Myeloma Working Group recently published recommendations regarding the prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma patients (141). In this review, the authors advise tailoring the choice of thromboprophylaxis based on individual risk factors (e.g., age, obesity, previous VTE, central venous catheter, immobility, comorbidities, concomitant medications, surgery, inherited thrombophilia), as well as myeloma-related risk factors (diagnosis and hyperviscosity) and myeloma therapy-related risk factors (concomitant steroids, doxorubicin). The panel recommended no prophylaxis in those patients receiving thalidomide or lenalidomide as a single agent. Aspirin (81 to 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 2 or more individual/myeloma-related risk factors or those receiving concomitant high-dose dexamethasone or doxorubicin (141). Ongoing randomized trials comparing aspirin, warfarin, and LMWH will help to define an optimal prophylaxis strategy (141).

Treatment of thromboembolism. Once a VTE is diagnosed, the goal of treatment is to relieve symptoms and prevent embolization and recurrence. Patients who develop VTE should be treated in accordance to established guidelines put forth by the American College of Chest Physicians. In general, for patients with VTE and cancer, the guidelines recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy, followed by anticoagulant therapy with warfarin or LMWH indefinitely or until the cancer is resolved (153).

THALIDOMIDE AND LENALIDOMIDE. LMWH (enoxaparin, dalteparin, or nadroparin) should be used as initial treatment, with a transition to warfarin therapy targeting an international normalized ratio of 2 to 3, if the risk on concurrent thrombocytopenia is low. The optimal duration of therapy remains controversial; however, extended therapy is recommended due to the high risk of recurrence (>10%)

Table 5 Chemotherapy Associated With Bradycardia*

Chemotherapy Agents	Incidence (%)	Frequency of Use
Angiogenesis inhibitor		
Thalidomide (Thalomid) (138,140,156–159)	0.12–55*	+
Antimicrotubule agent		
Paclitaxel (Taxol) (10,90,91,154,155)	<0.1–31*	+++

For an explanation of the + symbols, please see Table 1. *The incidence of bradycardia varies widely in the literature for these agents due to the differences in study design, definition of bradycardia, and numbers of patients. Medication manufacturers and locations as in Tables 2 and 4.

in the year after discontinuation of anticoagulant therapy in cancer patients who have had a VTE (141). It is also recommended that it is reasonable to briefly discontinue thalidomide or lenalidomide and resume therapy once full anticoagulation has been established (141).

Bradycardia

Bradycardia and heart block may be caused by multiple conditions in cancer patients. Fibrosis due to old age or radiation therapy, in addition to conditions like amyloidosis and primary cardiac tumors, can affect the cardiac conduction system (129). Also, in patients with cancer, bradycardia and heart block have been associated with several chemotherapeutic agents, with the 2 most clinically significant agents being paclitaxel and thalidomide. Table 5 highlights the incidences of bradycardia associated with selected chemotherapeutic agents.

Incidence. PACLITAXEL. Cardiac toxicity was first recognized during continuous monitoring of patients receiving paclitaxel treatment, which was performed due to the high incidence of serious hypersensitivity reactions noted during early phase I clinical trials. After cardiac events were noted, patients with known cardiac disease or on any medication that may interfere with cardiac conduction were excluded from clinical trials (91). Paclitaxel has been shown to cause cardiac arrhythmias, including an asymptomatic bradycardia that is reversible (90,154,155). The incidence of bradycardia caused by paclitaxel varies in the literature from <0.1% to 31% (10,90,91,154,155).

THALIDOMIDE. The incidence of bradycardia associated with thalidomide is not reported in the package insert. Post-marketing surveillance studies have reported an adverse event reporting rate of 0.12% (156). Correspondingly, in a phase III trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma patients, sinus bradycardia in the thalidomide group was seen in only 2% of patients (137). Although these reports suggest that the incidence of bradycardia appears to be low, other studies have found the rate of sinus bradycardia associated with thalidomide therapy to be anywhere from 5% to 55% (138,140,157–159).

Pathophysiology. PACLITAXEL. It has been suggested that paclitaxel may cause arrhythmias via its effects on the Purkinje system or extracardiac autonomic control (154). In addition, Cremophor EL, which is the vehicle that paclitaxel is formulated in, may be responsible for its cardiac disturbances. In cases of hypersensitivity reactions, Cremophor EL is known to induce histamine release (90). Stimulation of the histamine receptors in the cardiac tissue can increase myocardial oxygen demand as well as coronary vasoconstriction and chronotropic effects (91). In animal studies, stimulation of the H1 receptors has resulted in prolongation of atrioventricular conduction, depression of conduction in the Purkinje tissue, myocardial cell injury, and ventricular arrhythmias (91). Therefore, activation of histamine receptors in cardiac tissue may be a plausible explanation for the cardiotoxicity reported with paclitaxel (91). Of note, paclitaxel is formulated with the highest concentration of Cremophor EL per dose of all agents in clinical use, and if Cremophor EL is the agent responsible for the cardiac toxicity, the mechanism is likely due to its induction of histamine release (90).

THALIDOMIDE. The underlying mechanism of thalidomide-induced bradycardia remains unclear. It has been postulated, however, that the bradycardia may be due to central sedative effects or an activation of the vasovagal pathway. Thalidomide has been shown to reduce tumor necrosis factor-alpha levels, and as a consequence, this causes 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 and exacerbate underlying conduction disturbances. In addition, it has also been proposed that thalidomide may induce hypothyroidism in some patients leading to bradycardia (158,160).

Diagnosis. Bradycardia is typically defined as a heart rate <60 beats/min. Many patients are asymptomatic with a heart rate lower than 50 beats/min; however, some patients may have associated symptoms such as fatigue, limitations in physically activity, syncope, or dizziness. Diagnostic tests to determine the type of bradycardia include an electrocardiogram, Holter monitor, and screening for underlying disorders such as thyroid disease or electrolyte abnormalities.

Treatment. PACLITAXEL. In general, bradycardia associated with paclitaxel use is without clinical significance; however, some patients have required pacemaker implantation. According to the package insert, frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities (10). In addition, all patients should be given a pre-medication regimen before paclitaxel infusion to prevent severe hypersensitivity reactions. Since histamine release has been implicated as a possible mechanism for paclitaxel-induced bradycardia, this may also aid in the prevention of bradycardia as well. In any case, bradycardia alone does not appear to be an indication to discontinue paclitaxel treatment, since many of these cases are asymptomatic. However, if the patient develops bradycardia with progressive atrioventricular conduction disturbances and/or clinically significant hemodynamic effects, paclitaxel discontinuation is warranted.

THALIDOMIDE. Treatment of bradycardia depends on whether the patient is symptomatic. If the patient is asymptomatic, no treatment is usually necessary, but careful observation is warranted. In some cases, a reduction in the daily dosing of thalidomide may be required. For the treatment of symptomatic bradycardia, thalidomide therapy should be discontinued. Furthermore, in patients with

symptomatic third-degree atrioventricular block, a permanent pacemaker is indicated. In multiple myeloma patients with disease responsive to thalidomide therapy where no other therapeutic alternatives are available, these patients have had pacemakers implanted to be able to continue thalidomide (160,161). In all cases, concomitant medication inducing bradycardia such as beta-blockers, calcium-channel blockers, and digoxin should be avoided. In addition, a thyroid-stimulating hormone level should be obtained in these patients to rule out hypothyroidism as a cause of bradycardia.

QT Prolongation

QT interval prolongation is an abnormality of the electrical activity of the heart that places individuals at risk for ventricular arrhythmias. Cancer patients may be particularly prone to QT prolongation, since 16% to 36% of cancer patients have been shown to have baseline ECG abnormalities (129,162). In addition, cancer patients have a high prevalence of comorbid diseases, including structural heart disease, renal and hepatic dysfunction, as well as use concomitant medications that are known to prolong the QT interval (e.g., antiemetics, antifungals, quinolone antibiotics). Furthermore, cancer patients often experience nausea, vomiting, diarrhea, and decreased oral intake, which may lead to electrolyte disturbances, placing the patient at risk for QT prolongation (129,162). Table 6 highlights the incidences of QT prolongation associated with selected chemotherapeutic agents.

Incidence. ARSENIC TRIOXIDE. The incidence of QT prolongation ranges widely in the published literature largely due to the small number of patients in each of the clinical trials. In the package insert, the U.S. Multicenter Study of Arsenic Trioxide is the only published data utilized to report the incidence of QT prolongation (163). In this trial, over 460 ECG tracings from 40 patients with refractory or relapsed acute promyelocytic leukemia treated with arsenic were evaluated for QT prolongation. Sixteen of 40 patients (40%) had at least 1 ECG tracing with a QTc interval >500 ms. The QT interval was prolonged anywhere from 1 to 5 weeks after arsenic infusion, and then returned to baseline by the end of 8 weeks after arsenic therapy (10,163). However, in other trials the incidence of QT prolongation ranges from 26% to 93% (164–170).

Table 6 Chemotherapy Associated With QT Prolongation*

Chemotherapy Agents	Incidence (%)	Frequency of Use
Histone deacetylase inhibitor		
Vorinostat (Zolinza) (10,131)	3.5–6	+
Miscellaneous		
Arsenic trioxide (Trisenox) (10,163–170)	26–93*	+
Small molecule tyrosine kinase inhibitors		
Dasatinib (Sprycel) (10)	<1–3	++
Lapatinib (Tykerb) (10)	16	+
Nilotinib (Tasigna) (171–173)	1–10	+

For an explanation of the + symbols, please see Table 1. *The incidence of QT prolongation varies widely in the literature for arsenic due to the differences in study design, definition of QT prolongation, and numbers of patients. Medication manufacturers and locations: Trisenox, Cephalon Oncology, Frazer, Pennsylvania; Tasigna, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey; others as in Tables 1 and 4.

DASATINIB. In an FDA review of chronic myeloid leukemia patients treated with dasatinib, 9 patients (1.8%) of the safety population had at least 1 episode of QT prolongation reported as an adverse event, and 7 additional patients (1.4%) were found to have QTc prolongation of ≥500 ms on ECG. Furthermore, in a briefing document for Oncology Drug Advisory Committee, QT prolongation was reported to occur in 2% to 3% of patients treated with dasatinib (FDA websites). Finally, the package insert states that 9 patients have had QTc prolongation reported as an adverse event and that 3 patients (<1%) experienced a QTC interval >500 ms (10).

LAPATINIB. The QT prolongation potential of lapatinib was assessed in an uncontrolled, open-label dose escalation study in advanced cancer patients. Eighty-one patients received daily doses of lapatinib ranging from 175 to 1,800 mg/day. Serial ECGs were collected to evaluate the effect of lapatinib on QT intervals. Thirteen (16%) of the 81 subjects were found to have either QTc >480 ms or an increase in QTc >60 ms from baseline on ECG (10). To date, there is no published information on this particular study.

NILOTINIB. According to the package insert, the incidence of QT prolongation is 1% to 10%, and as part of the approval for nilotinib, the FDA has stipulated that nilotinib carry a black box warning for QT prolongation. In a phase I study of 119 patients treated with nilotinib, the QT interval appeared to increase by 5 to 15 ms; however, an exact incidence of QT prolongation was not reported in this trial (171). Additionally, in a phase II open-label study, 3 (1%) of 280 patients had QTc intervals >500 ms (172). Finally, in a phase II trial, increases of >60 ms were observed in 5 patients (4%) (173).

VORINOSTAT. The incidence of prolonged QT interval with vorinostat has been reported in 3.5% to 6% of patients (10). A definitive study of the effect of vorinostat on QTc has not been conducted. However, in a total of 86 CTCL patients, 3 patients (3.5%) had QTc prolongation (10). In addition, a retrospective analysis of 3 phase 1 and 2 phase 2 studies was conducted by the manufacturer, and 5 (4.3%) of the 116 patients studied had QT prolongation (10). In 49 non-CTCL patients from 3 clinical trials who had complete evaluations of the QT interval, 3 (6%) patients experienced QT prolongation (10). Of the trials used to calculate the incidence of QT prolongation found in the package insert, only 1 of these trials is published. In a phase IIb trial conducted in 74 patients with CTCL, QTc prolongation was noted in 3 (4%) patients (131).

Pathophysiology. The mechanism underlying QT prolongation associated with the medications mentioned in the

preceding text remains unknown. When discussing drug-induced QT prolongation, it is now understood that the blockade of delayed rectifier potassium current by medications is at least in part responsible for their pro-arrhythmic effect. In addition, 1 or more risk factors in the presence of underlying long QT syndrome may lead to significant QT interval prolongation (174).

Diagnosis. QT prolongation is an electrocardiographic diagnosis. The definition of QT prolongation varies in the medical literature, and definitive values that place patients at risk for ventricular complications have not been established. Guidelines for assessment of prolonged QTc values provide clinical direction in the assessment of patients at risk for cardiac events. A QTc interval is considered normal if it is ≤440 ms and prolonged in men and women if it is longer than >450 and >470 ms, respectively. Increases of ≥60 ms from baseline or >500 ms after administration of a medication raise concern about the potential risk of an arrhythmia. Both congenital and acquired factors may be responsible for QT interval prolongation. Some of the most commonly cited risk factors include female gender, elderly age, myocardial ischemia/infarction, HF, electrolyte imbalances, bradycardia, and medications with QT-prolonging effects (174).

Treatment. With each of the anticancer medications reviewed, the manufacturer has made recommendations for baseline and periodic ECG monitoring, as well as dosage adjustments or discontinuation of therapy that may be necessary in the face of QT prolongation. In addition, all of these agents should be used cautiously in patients with risk factors for developing QT prolongation (e.g., electrolyte abnormalities, congenital long QT syndrome, concomitant antiarrhythmic medicines or other drugs known to cause QT prolongation, cumulative high-dose anthracycline therapy). In addition, hypokalemia and hypomagnesemia should be corrected before initiating these medications (10). Finally, before treatment patients should be informed of the risk of arrhythmias and to report any cardiac symptoms such as palpitations.

The complications of QT interval prolongation, including arrhythmias and torsade de pointes, are rare but can have life-threatening consequences. If a patient does develop torsade de pointes, intravenous magnesium sulfate 2 g is the initial therapy of choice regardless of serum magnesium level. Nonsynchronized defibrillation may be indicated if sustained, hemodynamically unstable polymorphic ventricular tachycardia or fibrillation develops. Overdrive transvenous pacing may be used to shorten the QTc. Pacing is highly effective in preventing recurrence and may be useful in cases refractory to magnesium or when torsade de pointes is precipitated by bradycardia. If overdrive pacing is initiated, short-term pacing rates of 90 to 110 beats/min should be used. Isoproterenol titrated to a heart rate ≥90 beats/min is another option in patients, and it is useful when temporary pacing is unavailable or while preparing for transvenous catheter insertion. In addition, it is always imperative to maintain serum potassium levels in the high-normal range, and discontinue any QT prolonging medications and drugs interfering with patients' metabolism (175).

Reprint requests and correspondence: Dr. Edward T. H. Yeh, The University of Texas M. D. Anderson Cancer Center, Department of Cardiology, 1400 Pressler Street, Room 11.5028, Houston, Texas 77030. E-mail: etyeh@mdanderson.org.

REFERENCES

1. Grenier MA, Lipshultz SE. Epidemiology of anthracycline cardiotoxicity in children and adults. Semin Oncol 1998;25:72–85.
2. Lipshultz SE, Alvarez JA, Scully RE. Anthracycline associated cardiotoxicity in survivors of childhood cancer. Heart 2008;94:525–33.
3. 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.
4. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355:1572–82.
5. Swain SM, Whaley FS, Gerber MC, et al. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol 1997;15:1318–32.
6. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979;91:710–7.
7. 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.
8. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. Drug Saf 2000;22:263–302.
9. Gharib MI, Burnett AK. Chemotherapy-induced cardiotoxicity: current practice and prospects of prophylaxis. Eur J Heart Fail 2002;4:235–42.
10. Vorinostat (Zolinza). Package Insert. Whitehouse Station, NJ: Merck & Co. Inc.
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, Rappeport 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. Quezado ZM, Wilson WH, Cunnion RE, et al. High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. Ann Intern Med 1993;118:31–6.
15. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352:2302–13.
16. Marty M, Cognetti F, Maraninchi D, 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, 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, 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, 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. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20:1215–21.

21. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–92.
22. Ewer MS, O'Shaughnessy JA. Cardiac toxicity of trastuzumab-related regimens in HER2-overexpressing breast cancer. Clin Breast Cancer 2007;7:600–7.
23. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673–84.
24. Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. J Clin Oncol 2007;25:3859–65.
25. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719–26.
26. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008;26:1231–8.
27. Tripathy D, Slamon DJ, Cobleigh M, et al. Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. J Clin Oncol 2004;22:1063–70.
28. Guarneri V, Lenihan DJ, Valero V, et al. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. J Clin Oncol 2006;24:4107–15.
29. Gianni L, Salvatorelli E, Minotti G. Anthracycline cardiotoxicity in breast cancer patients: synergism with trastuzumab and taxanes. Cardiovasc Toxicol 2007;7:67–71.
30. Guglin M, Cutro R, Mishkin JD. Trastuzumab-induced cardiomyopathy. J Card Fail 2008;14:437–44.
31. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 2005;23:7811–9.
32. Perez EA, Koehler M, Byrne J, Preston AJ, Rappold E, Ewer MS. Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. Mayo Clin Proc 2008;83:679–86.
33. Kerkela R, Grazette L, Yacobi R, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med 2006;12:908–16.
34. 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.
35. 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.
36. Khakoo AY, Kassiotis CM, Tannir N, et al. Heart failure associated with sunitinib malate: a multitargeted receptor tyrosine kinase inhibitor. Cancer 2008;112:2500–8.
37. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet 2007;370:2011–9.
38. Lyu YL, Kerrigan JE, Lin CP, et al. Topoisomerase IIbeta mediated DNA double-strand breaks: implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. Cancer Res 2007;67:8839–46.
39. Morandi P, Ruffini PA, Benvenuto GM, Raimondi R, Fosser V. Cardiac toxicity of high-dose chemotherapy. Bone Marrow Transplant 2005;35:323–34.
40. Chen MH, Kerkela R, Force T. Mechanisms of cardiac dysfunction associated with tyrosine kinase inhibitor cancer therapeutics. Circulation 2008;118:84–95.
41. Crone SA, Zhao YY, Fan L, et al. ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med 2002;8:459–65.
42. Ozcelik C, Erdmann B, Pilz B, 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.
43. Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. Nat Rev Cancer 2007;7:332–44.
44. Sawyer DB, Zuppinger C, Miller TA, Eppenberger HM, Suter TM. Modulation of anthracycline-induced myofibrillar disarray in rat ventricular myocytes by neuregulin-1beta and anti-erbB2: potential mechanism for trastuzumab-induced cardiotoxicity. Circulation 2002;105:1551–4.
45. Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. J Clin Oncol 2004;22:322–9.
46. 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.
47. Fernandez A, Sanguino A, Peng Z, et al. An anticancer C-Kit kinase inhibitor is reengineered to make it more active and less cardiotoxic. J Clin Invest 2007;117:4044–54.
48. Hunt SA; American College of Cardiology, American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2005;46:e1–82.
49. Alexander J, Dainiak N, Berger HJ, et al. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. N Engl J Med 1979;300:278–83.
50. Schwartz RG, McKenzie WB, Alexander J, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. Am J Med 1987;82:1109–18.
51. Steinherz LJ, Graham T, Hurwitz R, et al. Guidelines for cardiac monitoring of children during and after anthracycline therapy: report of the Cardiology Committee of the Children's Cancer Study Group. Pediatrics 1992;89:942–9.
52. 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.
53. Cardinale D, Sandri MT, Martinoni A, et al. Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. Ann Oncol 2002;13:710–5.
54. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation 2004;109:2749–54.
55. Lenihan DJ, Massey MR, Baysinger KB, et al. Superior detection of cardiotoxicity during chemotherapy using biomarkers (abstr). J Cardiac Failure 2007;13 Suppl 2:S151.
56. Meinardi MT, van Veldhuisen DJ, Gietema JA, 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.
57. Nousiainen T, Vanninen E, Jantunen E, et al. Natriuretic peptides during the development of doxorubicin-induced left ventricular diastolic dysfunction. J Intern Med 2002;251:228–34.
58. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation 2006;114:2474–81.
59. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Long-term enalapril therapy for left ventricular dysfunction in doxorubicin-treated survivors of childhood cancer. J Clin Oncol 2002;20:4517–22.
60. Silber JH, Cnaan A, Clark BJ, et al. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. J Clin Oncol 2004;22:820–8.
61. Nakamae H, Tsumura K, Terada Y, et al. Notable effects of angiotensin II receptor blocker, valsartan, on acute cardiotoxic changes after standard chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone. Cancer 2005;104:2492–8.
62. Fazio S, Palmieri EA, Ferravante B, Bone F, Biondi B, Sacca L. Doxorubicin-induced cardiomyopathy treated with carvedilol. Clin Cardiol 1998;21:777–9.
63. Mukai Y, Yoshida T, Nakaike R, et al. Five cases of anthracycline-induced cardiomyopathy effectively treated with carvedilol. Intern Med 2004;43:1087–8.
64. Noori A, Lindenfeld J, Wolfel E, Ferguson D, Bristow MR, Lowes BD. Beta-blockade in adriamycin-induced cardiomyopathy. J Card Fail 2000;6:115–9.
65. Shaddy RE, Olsen SL, Bristow MR, et al. Efficacy and safety of metoprolol in the treatment of doxorubicin-induced cardiomyopathy in pediatric patients. Am Heart J 1995;129:197–9.

66. Oliveira PJ, Bjork JA, Santos MS, et al. Carvedilol-mediated antioxidant protection against doxorubicin-induced cardiac mitochondrial toxicity. Toxicol Appl Pharmacol 2004;200:159–68.
67. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol 2006;48:2258–62.
68. Ewer MS, Vooletich MT, Durand JB, 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.
69. Keefe DL. Trastuzumab-associated cardiotoxicity. Cancer 2002;95:1592–600.
70. Meyer CC, Calis KA, Burke LB, Walawander CA, Grasela TH. Symptomatic cardiotoxicity associated with 5-fluorouracil. Pharmacotherapy 1997;17:729–36.
71. 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.
72. Cardinale D, Colombo A, Colombo N. Acute coronary syndrome induced by oral capecitabine. Can J Cardiol 2006;22:251–3.
73. de Forni M, Malet-Martino MC, Jaillais P, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. J Clin Oncol 1992;10:1795–801.
74. Kosmas C, Kallistratos MS, Kopterides P, et al. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. J Cancer Res Clin Oncol 2008;134:75–82.
75. Rezkalla S, Kloner RA, Ensley J, et al. Continuous ambulatory ECG monitoring during fluorouracil therapy: a prospective study. J Clin Oncol 1989;7:509–14.
76. Robben NC, Pippas AW, Moore JO. The syndrome of 5-fluorouracil cardiotoxicity. An elusive cardiopathy. Cancer 1993;71:493–509.
77. Labianca R, Beretta G, Clerici M, Fraschini P, Luporini G. Cardiac toxicity of 5-fluorouracil: a study on 1083 patients [in Italian]. Tumori 1982;68:505–10.
78. Jensen SA, Sorensen JB. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. Cancer Chemother Pharmacol 2006;58:487–93.
79. Singer M. Cardiotoxicity and capecitabine: a case report. Clin J Oncol Nurs 2003;7:72–5.
80. Bertolini A, Flumano M, Fusco O, et al. Acute cardiotoxicity during capecitabine treatment: a case report [in Italian]. Tumori 2001;87:200–6.
81. Anand AJ. Fluorouracil cardiotoxicity. Ann Pharmacother 1994;28:374–8.
82. Schnetzler B, Popova N, Collao Lamb C, Sappino AP. Coronary spasm induced by capecitabine. Ann Oncol 2001;12:723–4.
83. Ng M, Cunningham D, Norman AR. The frequency and pattern of cardiotoxicity observed with capecitabine used in conjunction with oxaliplatin in patients treated for advanced colorectal cancer (CRC). Eur J Cancer 2005;41:1542–6.
84. Saif MW, Tomita M, Ledbetter L, Diasio RB. Capecitabine-related cardiotoxicity: recognition and management. J Support Oncol 2008;6:41–8.
85. Walko CM, Lindley C. Capecitabine: a review. Clin Ther 2005;27:23–44.
86. 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.
87. Arbea L, Coma-Canella I, Martinez-Monge R, Garcia-Foncillas J. A case of capecitabine-induced coronary microspasm in a patient with rectal cancer. World J Gastroenterol 2007;13:2135–7.
88. Sestito A, Sgueglia GA, Pozzo C, et al. Coronary artery spasm induced by capecitabine. J Cardiovasc Med (Hagerstown) 2006;7:136–8.
89. Papadopoulos CA, Wilson H. Capecitabine-associated coronary vasospasm: a case report. Emerg Med J 2008;25:307–9.
90. 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.
91. Arbuck SG, Strauss H, Rowinsky E, et al. A reassessment of cardiac toxicity associated with taxol. J Natl Cancer Inst Monogr 1993:117–30.
92. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695–704.
93. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst 2007;99:1232–9.
94. Sugrue MM, Yi J, Purdie D, Dong W, Grothey A, Kozloff M, and the BRiTE Study Investigators. Serious arterial thromboembolic events (sATE) in patients (pts) with metastatic colorectal cancer (mCRC) treated with bevacizumab (BV): results from the BRiTE registry. J Clin Oncol 2007;25 Suppl 18:4136.
95. Moore MJ, Goldstein D, Hamm J, 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.
96. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125–34.
97. Freeman NJ, Costanza ME. 5-Fluorouracil-associated cardiotoxicity. Cancer 1988;61:36–45.
98. Porta C, Moroni M, Ferrari S, Nastasi G. Endothelin-1 and 5-fluorouracil-induced cardiotoxicity. Neoplasma 1998;45:81–2.
99. Kamba T, McDonald DM. Mechanisms of adverse effects of anti-VEGF therapy for cancer. Br J Cancer 2007;96:1788–95.
100. Kilickap S, Abali H, Celik I. Bevacizumab, bleeding, thrombosis, and warfarin. J Clin Oncol 2003;21:3542, author reply 3543.
101. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50:2173–95.
102. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction). J Am Coll Cardiol 2007;50:e1–157.
103. Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2008;51:210–47.
104. Sarkiss MG, Yusuf SW, Warneke CL, et al. Impact of aspirin therapy in cancer patients with thrombocytopenia and acute coronary syndromes. Cancer 2007;109:621–7.
105. Jain M, Townsend RR. Chemotherapy agents and hypertension: a focus on angiogenesis blockade. Curr Hypertens Rep 2007;9:320–8.
106. Ray A, Ray S, Koner BC. Hypertension, cancer and angiogenesis: relevant epidemiological and pharmacological aspects. Indian J Pharmacol 2004;36:341–7.
107. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–42.
108. Kabbinavar FF, Schulz J, McCleod M, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. J Clin Oncol 2005;23:3697–705.
109. Pande A, Lombardo J, Spangenthal E, Javle M. Hypertension secondary to anti-angiogenic therapy: experience with bevacizumab. Anticancer Res 2007;27:3465–70.
110. Cobleigh MA, Langmuir VK, Sledge GW, et al. A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Semin Oncol 2003;30:117–24.
111. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184–91.
112. Yang JC, Haworth L, Sherry RM, 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.
113. Procopio G, Verzoni E, Gevorgyan A, et al. Safety and activity of sorafenib in different histotypes of advanced renal cell carcinoma. Oncology 2007;73:204–9.
114. Furuse J, Ishii H, Nakachi K, Suzuki E, Shimizu S, Nakajima K. Phase I study of sorafenib in Japanese patients with hepatocellular carcinoma. Cancer Sci 2008;99:159–65.

115. Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2006;24:2505–12.
116. Riechelmann RP, Chin S, Wang L, et al. Sorafenib for metastatic renal cancer: the Princess Margaret experience. Am J Clin Oncol 2008;31:182–7.
117. Wu S, Chen JJ, Kudelka A, Lu J, Zhu X. Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. Lancet Oncol 2008;9:117–23.
118. Burstein HJ, Elias AD, Rugo HS, 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.
119. Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol 2006;24:16–24.
120. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329–38.
121. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.
122. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006;295:2516–24.
123. Dincer M, Altundag K. Angiotensin-converting enzyme inhibitors for bevacizumab-induced hypertension. Ann Pharmacother 2006;40:2278–9.
124. Sane DC, Anton L, Brosnihan KB. Angiogenic growth factors and hypertension. Angiogenesis 2004;7:193–201.
125. Veronese ML, Mosenkis A, Flaherty KT, et al. Mechanisms of hypertension associated with BAY 43-9006. J Clin Oncol 2006;24:1363–9.
126. Mir O, Mouthon L, Alexandre J, et al. Bevacizumab-induced cardiovascular events: a consequence of cholesterol emboli syndrome? J Natl Cancer Inst 2007;99:85–6.
127. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–52.
128. Rixe O, Billemont B, Izzedine H. Hypertension as a predictive factor of sunitinib activity. Ann Oncol 2007;18:1117.
129. Yusuf SW, Razeghi P, Yeh ET. The diagnosis and management of cardiovascular disease in cancer patients. Curr Probl Cardiol 2008;33:163–96.
130. 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.
131. Olsen EA, Kim YH, Kuzel TM, 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.
132. Duvic M, Talpur R, Ni X, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007;109:31–9.
133. Rajkumar SV. Thalidomide therapy and deep venous thrombosis in multiple myeloma. Mayo Clin Proc 2005;80:1549–51.
134. Rodeghiero F, Elice F. Thalidomide and thrombosis. Pathophysiol Haemost Thromb 2003;33 Suppl 1:15–8.
135. Rajkumar SV, Hayman S, Gertz MA, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. J Clin Oncol 2002;20:4319–23.
136. Baz R, Li L, Kottke-Marchant K, 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.
137. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2006;24:431–6.
138. Rajkumar SV, Rosinol L, Hussein M, 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.
139. Cavo M, Zamagni E, Cellini C, et al. Deep-vein thrombosis in patients with multiple myeloma receiving first-line thalidomide-dexamethasone therapy. Blood 2002;100:2272–3.
140. Palladini G, Perfetti V, Perlini S, et al. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). Blood 2005;105:2949–51.
141. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22:414–23.
142. Zangari M, Elice F, Fink L, Tricot G. Thrombosis in multiple myeloma. Expert Rev Anticancer Ther 2007;7:307–15.
143. Anagnostopoulos A, Weber D, Rankin K, Delasalle K, Alexanian R. Thalidomide and dexamethasone for resistant multiple myeloma. Br J Haematol 2003;121:768–71.
144. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357:2123–32.
145. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood 2005;106:4050–3.
146. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133–42.
147. Zonder JA, Barlogie B, Durie BG, McCoy J, Crowley J, Hussein MA. Thrombotic complications in patients with newly diagnosed multiple myeloma treated with lenalidomide and dexamethasone: benefit of aspirin prophylaxis. Blood 2006;108:403, author reply 404.
148. Hirsh J. Risk of thrombosis with lenalidomide and its prevention with aspirin. Chest 2007;131:275–7.
149. Richardson PG, Blood E, Mitsiades CS, et al. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. Blood 2006;108:3458–64.
150. Menon SP, Rajkumar SV, Lacy M, Falco P, Palumbo A. Thromboembolic events with lenalidomide-based therapy for multiple myeloma. Cancer 2008;112:1522–8.
151. Icli F, Karaoguz H, Dincol D, et al. Severe vascular toxicity associated with cisplatin-based chemotherapy. Cancer 1993;72:587–93.
152. Miller KD, Sweeney CJ, Sledge GW Jr. Redefining the target: chemotherapeutics as antiangiogenics. J Clin Oncol 2001;19:1195–206.
153. 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–545S.
154. McGuire WP, Rowinsky EK, Rosenshein NB, et al. Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. Ann Intern Med 1989;111:273–9.
155. Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC. Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol 1993;20:1–15.
156. Clark TE, Edom N, Larson J, Lindsey LJ. Thalomid (Thalidomide) capsules: a review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing. Drug Saf 2001;24:87–117.
157. Singhal S, Mehta J. Thalidomide in cancer: potential uses and limitations. BioDrugs 2001;15:163–72.
158. Fahdi IE, Gaddam V, Saucedo JF, et al. Bradycardia during therapy for multiple myeloma with thalidomide. Am J Cardiol 2004;93:1052–5.
159. Schutt P, Ebeling P, Buttkereit U, et al. Thalidomide in combination with dexamethasone for pretreated patients with multiple myeloma: serum level of soluble interleukin-2 receptor as a predictive factor for response rate and for survival. Ann Hematol 2005;84:594–600.
160. Kaur A, Yu SS, Lee AJ, Chiao TB. Thalidomide-induced sinus bradycardia. Ann Pharmacother 2003;37:1040–3.
161. Ghobrial IM, Rajkumar SV. Management of thalidomide toxicity. J Support Oncol 2003;1:194–205.
162. Strevel EL, Ing DJ, Siu LL. Molecularly targeted oncology therapeutics and prolongation of the QT interval. J Clin Oncol 2007;25:3362–71.
163. Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. J Clin Oncol 2001;19:3852–60.

164. Huang SY, Chang CS, Tang JL, et al. Acute and chronic arsenic poisoning associated with treatment of acute promyelocytic leukaemia. Br J Haematol 1998;103:1092–5.
165. Ohnishi K, Yoshida H, Shigeno K, et al. Arsenic trioxide therapy for relapsed or refractory Japanese patients with acute promyelocytic leukemia: need for careful electrocardiogram monitoring. Leukemia 2002;16:617–22.
166. Westervelt P, Brown RA, Adkins DR, et al. Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. Blood 2001;98:266–71.
167. Shigeno K, Naito K, Sahara N, 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.
168. Singer JW. Cardiac toxicity of arsenic trioxide. Blood 2001;98:1633, author reply 1633–4.
169. Unnikrishnan D, Dutcher JP, Garl S, Varshneya N, Lucariello R, Wiernik PH. Cardiac monitoring of patients receiving arsenic trioxide therapy. Br J Haematol 2004;124:610–7.
170. Barbey JT, Pezzullo JC, Soignet SL. Effect of arsenic trioxide on QT interval in patients with advanced malignancies. J Clin Oncol 2003;21:3609–15.
171. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. N Engl J Med 2006;354:2542–51.
172. Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly 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.
173. le Coutre P, Ottmann OG, Giles F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or -intolerant accelerated-phase chronic myelogenous leukemia. Blood 2008;111:1834–9.
174. Vorchheimer DA. What is QT interval prolongation? J Fam Pract 2005;Suppl:S4–7.
175. 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.

Key Words: cancer ■ cardiotoxicity ■ therapy ■ heart failure.