Chapter 2
Cardiotoxicity of Anticancer Therapies

Rabih Said, Myles Nickolich, Daniel J. Lenihan, and Apostolia M. Tsimberidou

Introduction

Cardiotoxicity associated with anticancer therapies represents a complex clinical challenge, as well as a major economic and health burden, given the increasing number of cancer survivors [1, 2]. In Western countries, a large number of cancer survivors are at a higher risk of cardiotoxicity-related death than of cancer recurrence [2]. Cardiac impairment due to cancer therapy may require the discontinuation of anticancer agents, including chemotherapeutic, targeted, and biologic

Electronic supplementary material: The online version of this chapter (doi:10.1007/978-3-319-43096-6_2) contains supplementary material, which is available to authorized users.

R. Said
Division of Cancer Medicine, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
Division of Oncology, Department of Internal Medicine, The University of Texas Health Science Center at Houston, Houston, TX 77030, USA
e-mail: Rabih.Said@uth.tmc.edu

M. Nickolich
Department of Internal Medicine, Duke University Medical Center, Durham, NC, USA
e-mail: myles.nickolich@dm.duke.edu

D.J. Lenihan
Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN 37232, USA
e-mail: daniel.lenihan@Vanderbilt.Edu

A.M. Tsimberidou
Division of Cancer Medicine, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
e-mail: atsimber@mdanderson.org

© Springer International Publishing Switzerland 2017
G.G. Kimmick et al. (eds.), Cardio-Oncology, DOI 10.1007/978-3-319-43096-6_2
The risk of cardiotoxicity during cancer therapy varies by therapeutic class and agent as well as by coexisting cardiac disease and concomitant use of other cardiotoxic agents [3]. The use of various cardioprotective agents (e.g., angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-blockers) is critical in preventing and/or reversing cardiac injury related to anticancer therapy [4, 5]. The emergence and rapid adoption of “Cardio-oncology”—a multidisciplinary, integrative clinical approach involving general practitioners, oncologists, and cardiologists to prevent and treat cardiotoxicity in patients being treated for cancer—aims to increase awareness of cardiotoxicity caused by cancer therapy and cardiac risk factors and to optimize the monitoring and treatment of patients with these conditions [3, 6].

This chapter focuses on anticancer agents with potential cardiotoxicity (Table 2.1 and Fig. 2.1). The incidence and type of cardiotoxicity and the most common preventive and therapeutic approaches are summarized in Fig. 2.2.

**Chemotherapy**

**Anthracyclines**

Doxorubicin

Anthracycline-induced cardiotoxicity was initially reported more than four decades ago during the early clinical development of doxorubicin [7, 8]. The incidence of anthracycline-induced heart failure (HF), based on clinical signs and symptoms, was reported to be less than 3% [8]. However, the development of noninvasive monitoring techniques enabled the detection of a higher incidence of cardiac dysfunction [9]. The key mechanisms involved in the pathogenesis of cardiac dysfunction are increased reactive oxygen species and alteration of topoisomerase IIb, which are both associated with damage to cardiomyocytes [10, 11]. Acute cardiac dysfunction is reported in 3.2% of patients receiving anthracyclines [12], and it occurs within several weeks of the initiation of therapy. Acute cardiac dysfunction presents with electrocardiographic abnormalities, including arrhythmias (supraventricular and ventricular), heart block, ventricular dysfunction, increased cardiac filling pressures, HF, and pericarditis-myocarditis syndrome [13–17]. Cardiac dysfunction may present as a reduction in left ventricular ejection fraction (LVEF) in up to 20% of patients and may not become evident until after the completion of chemotherapy [18–20].

These late-occurring complications are serious and consist of HF that develops within a few months to several years (most frequently within 3 months) after anthracycline therapy [8, 21–23]. However, symptomatic HF can occur more than a decade after treatment, which represents a major clinical concern, especially among survivors of childhood malignancies [22]. Chronic cardiomyopathy can present as asymptomatic diastolic or systolic dysfunction, which frequently
Table 2.1  Selected anticancer agents with potential cardiotoxicity

| Agents | Drug class | Cancer clinical use | Type of cardiotoxicity | Frequency |
|--------|------------|---------------------|------------------------|-----------|
| **Chemotherapeutic agents** | | | | |
| Doxorubicin | Anthracyclines | Breast, sarcoma, lung, bladder, gastric, prostate, leukemia, lymphoma, others | LV dysfunction | Common |
| Epirubicin | Anthracyclines | Breast, esophageal, gastric | Arrhythmia | Uncommon |
| Cyclophosphamide | Alkylating agents | Sarcoma, SCT, lymphoma, myeloma, breast | Myopericarditis, arrhythmias | Common |
| Ifosfamide | Alkylating agents | Testicular, sarcoma, lymphoma | Arrhythmias, LV dysfunction | Common |
| Cisplatin | Alkylating agents | Lung, bladder, testicular, sarcoma, breast, esophageal, head and neck | Arrhythmias, ischemia, vascular toxicity | Uncommon |
| 5-Fluorouracil | Antimetabolites | Colon, pancreatic, breast, head and neck | Coronary vasospasm, ischemia, arrhythmias | Common |
| Capecitabine | Antimetabolites | Breast, colon, gastric, pancreatic | Chest pain, ischemia, arrhythmias | Uncommon |
| Fludarabine | Antimetabolites | Lymphoma, leukemia, stem cell transplant | Chest pain | Rare |
| Vinblastine | Antimicrotubule | Lymphoma, testicular, lung, melanoma | Ischemia, hypertension | Common |
| Paclitaxel | Antimicrotubule | Breast, ovarian, lung, sarcoma, bladder, cervical, gastric, esophageal, head and neck | Arrhythmias | Rare |
| Docetaxel | Antimicrotubule | Breast, lung, prostate, gastric, head and neck | Arrhythmias, LV dysfunction | Uncommon |
| **Biologic agents** | | | | |
| Bevacizumab | Antibody (VEGF) | Colon, rectal, cervical, glioblastoma, ovarian, renal, endometrial, sarcoma | Hypertension, LV dysfunction | Common |
| Trastuzumab | Antibody (HER-2) | Breast, gastric, gastro-esophageal | LV dysfunction | Common |

(continued)
| Agents          | Drug class          | Cancer clinical use                                                                 | Type of cardiotoxicity                      | Frequency |
|-----------------|---------------------|-------------------------------------------------------------------------------------|---------------------------------------------|-----------|
| Pertuzumab      | Antibody (HER-2)    | Breast                                                                              | LV dysfunction                             | Uncommon  |
| Alemtuzumab     | Antibody (CD-52)    | Leukemia, stem cell transplant                                                      | Arrhythmias                                | Rare      |
| Cetuximab       | Antibody (EGFR)     | Colon, rectal, head and neck, lung, squamous skin                                   | Ischemia, cardiorespiratory                | Uncommon  |
| Ramucirumab     | Antibody (VEGFR-2)  | Colon, rectal, gast- tric, lung                                                      | Hypertension, thromboembolism              | Common    |
| IL-2            | Immune agent        | Melanoma, renal                                                                     | Capillary leak syndrome, hypotension, myocar- dial toxicity | Common    |
| INF             | Immune agent        | Melanoma, renal, lymphoma                                                            | Arrhythmias, ischemia                      | Common    |

**Tyrosine kinase inhibitors**

| Sunitinib       | VEGFR, PDGFR, c-Kit| Renal, thyroid, sarcoma, GIST, PNET                                                  | Hypertension, LV dysfunction, thrombosis   | Common    |
| Sorafenib       | VEGFR-2, PDGFR, RAF-1, c-Kit | Hepatocellular, renal, thyroid, angiosarcoma, GIST                                   | Hypertension, ischemia, LV dysfunction     | Common    |
| Pazopanib       | VEGFR-1–3, PDGFR, FGFR-1, FGFR-3, c-Kit | Renal, sarcoma, thyroid                                                             | Hypertension, LV dysfunction, arrhythmias, ischemia, thromboembolism | Common    |
| Axitinib        | VEGFR-1–3           | Renal                                                                                | Hypertension, thromboembolism              | Common    |
| Lapatinib       | EGFR1, HER2         | Breast                                                                              | LV dysfunction                             | Uncommon  |
| Imatinib        | BCR/ABL, PDGF, c-Kit| Leukemia, GIST, MDS, melanoma, mastocytosis, sarcoma                                | LV dysfunction, edema                      | Rare      |
| Dasatinib       | BCR/ABL, Src, c-Kit | Leukemia, GIST                                                                      | Pleural effusion, LV dysfunction, arrhythmias | Uncommon  |
| Trametinib      | MEK1/MEK2           | Melanoma                                                                            | Hypertension, LV dysfunction               | Common    |
| Vandetanib      | VEGFR-2, EGFR, RET  | Thyroid                                                                              | Hypertension, prolonged QT                | Common    |
| Ponatinib       | BCR/ABL             | Leukemia                                                                            | LV dysfunction Vascular events             | Rare Common |
|                 |                     |                                                                                     |                                             |           |
progresses to HF. The incidence of cardiac dysfunction is directly related to the cumulative dose of anthracyclines, but it may also occur at low doses [24]. Other risk factors for the development of cardiac dysfunction include being elderly or a child at the time of drug exposure, concomitant administration of other cardiotoxic agents (such as trastuzumab), radiation therapy to the chest, and preexisting cardiovascular disease. Awareness of these risks for cardiac dysfunction may lead to the early identification and treatment of HF [25].
The encapsulation of doxorubicin in a liposomal moiety (pegylated liposomal doxorubicin) allows for the administration of higher cumulative doses with similar efficacy and a lower rate of HF and myocardial damage compared to doxorubicin [26]. Despite the better cardiac safety profile of liposomal doxorubicin compared to doxorubicin [clinical cardiotoxicity (odds ratio [OR] 0.18) and subclinical cardiotoxicity (relative risk [RR] 0.31)] [27], the US Food and Drug Administration (FDA) recommends routine surveillance of LVEF with the use of liposomal doxorubicin.

Dexrazoxane is an ethylenediaminetetraacetic acid (EDTA)-like chelator that binds iron and protects cardiomyocytes from the effects of doxorubicin [28]. The cardioprotective efficacy of dexrazoxane with the use with either doxorubicin or epirubicin has been clinically confirmed [27]; however, some concerns about lower response rate to chemotherapy and secondary leukemia in childhood cancer survivors have arisen [29].

**Epirubicin**

Epirubicin is less cardiotoxic than doxorubicin, and it is sometimes considered the preferred anthracycline [30, 31]. In comparison to doxorubicin, epirubicin significantly decreased the risks of both clinical (OR 0.39, 95% CI [0.2–0.78]) and subclinical (OR 0.30, 95% CI [0.16–0.57]) cardiotoxicity [27]. According to the FDA, the cumulative dose of epirubicin should be limited to 900 mg/m² [2].
**Alkylating Agents**

**Cyclophosphamide**

Cyclophosphamide, which has been associated with reduced cardiac function, pericardial effusion, and decreased electrocardiographic (ECG) voltage (even without pericardial effusion) [32–34], is used in high-dose regimens that accompany stem cell transplantation [35]. The incidence of cyclophosphamide-associated cardiotoxicity is not clearly dose dependent [32, 33]. Cyclophosphamide also causes hemorrhagic myopericarditis with pericardial effusion that is attributed to endothelial capillary damage [32, 36]. These cardiac complications are mostly conservatively managed, but they can in rare instances lead to tamponade and death [32]. Factors that increase the risk of cyclophosphamide-associated cardiotoxicity include prior radiation therapy to the mediastinum or left chest wall, older age, and prior reduced LVEF.

**Ifosfamide**

Cardiotoxicity is infrequently reported with ifosfamide and includes cardiac arrhythmias, ST-T wave changes, and HF (dose related) [37, 38]. Most of these complications are reversible with medical management.

**Cisplatin**

Cisplatin-induced cardiotoxicity includes supraventricular tachycardia, bradycardia, ST-T wave changes, bundle branch block, acute ischemia with or without myocardial infarction, and cardiomyopathy [39, 40]. Cisplatin is also associated with vascular toxicities, including Raynaud’s phenomenon, hypertension, and cerebral ischemic events. Electrolyte abnormalities, commonly seen with cisplatin-induced nephrotoxicity, can also contribute to cardiotoxicity.

**Antimetabolite Agents**

**5-Fluorouracil**

5-Fluorouracil (5-FU)-induced cardiotoxicity can occur in 8–20% of treated patients [41–43]. Chest pain associated with ECG changes is the most common symptom. Other more significant manifestations include myocardial infarction and arrhythmia. Pericarditis and cardiac arrest are less common. The main pathophysiologic mechanism causing these symptoms is likely coronary artery vasospasm. Other mechanisms include endothelial cytotoxicity, myocarditis, and takotsubo
cardiomyopathy [44]. Risk factors include infusion of 5-FU (vs. bolus), preexisting coronary artery disease, and concurrent use of radiation therapy or anthracyclines.

The majority of patients respond to the termination of 5-FU treatment or concurrent antianginal therapy with nitrates; however, death has been reported in a small percentage of patients [45]. Restarting therapy is usually not recommended, unless no other effective therapeutic regimens are available. The available data on calcium channel blockers or nitrates as preventative agents are conflicting [41, 46–49].

Capecitabine

Capecitabine is a prodrug that is metabolized to its active moiety, 5-FU, and has cardiotoxicity similar to that of infusional 5-FU [50]. Patients with a history of 5-FU-induced vasospasm will likely experience recurrent symptoms with capecitabine [51]. The incidence of vasospasm, including chest pain/angina, myocardial infarction, and arrhythmia, in patients receiving capecitabine ranges from 3 to 9 % [50, 52, 53]. The management of capecitabine-induced cardiotoxicity is similar to that of 5-FU-induced cardiotoxicity.

Fludarabine

Chest pain and hypotension have been reported with the use of fludarabine [54]. The combination of fludarabine and melphalan as a conditioning regimen for stem cell transplantation has been associated with cardiac dysfunction [55]. Other antimetabolite agents (cladribine, methotrexate, and cytarabine) have been rarely associated with cardiotoxicity in case reports [56–58].

Antimicrotubule Agents

Vinca Alkaloids

Cardiotoxicity is uncommon with all vinca alkaloids but may be more frequent with vinblastine than with vincristine and vinorelbine [59]; symptoms include hypertension, myocardial ischemia, infarction, and other vaso-occlusive complications [59–61].

Paclitaxel

Paclitaxel is associated with a low incidence of cardiotoxicity that includes asymptomatic bradycardia and heart block [62, 63]. Routine cardiac monitoring is not
required during administration of this agent [62]. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) has the same cardiotoxicity profile as paclitaxel.

**Docetaxel**

Abnormal ECG and angina have been described in patients treated with docetaxel [64, 65]. Docetaxel appears to potentiate the cardiotoxicity of anthracyclines [66].

**Biologic Therapy**

**Bevacizumab**

Bevacizumab, a monoclonal antibody that binds and inactivates vascular endothelial growth factor (VEGF), exerts its anti-tumor effect by preventing microvascular angiogenesis. The most common cardiac adverse event associated with anti-VEGF therapy is hypertension [67]. Preexisting hypertension may predispose patients to worsened hypertension with bevacizumab [68]. While there has been controversy regarding the cardiotoxicity of bevacizumab [69–71], several studies and meta-analyses have identified an increased incidence of HF and decreased LVEF [71]. Early cardiotoxicity manifests as takotsubo cardiomyopathy-like events [72]. However, the pathophysiology of these events is poorly understood [73]. Bevacizumab-induced cardiotoxicity has been noted in patients with renal cell carcinoma (RCC) [70], breast cancer [71, 74], and glioma [75]. In a meta-analysis, the risk of high-grade congestive HF in patients with breast cancer was higher in those receiving bevacizumab than in those receiving placebo (RR 4.74, 95 % CI [1.66–11.18]; \( P = 0.001 \)), without a dose-related effect [74]. The risk of cardiotoxicity is increased when bevacizumab is combined with docetaxel or anthracycline [74, 76].

**Trastuzumab**

Trastuzumab is a monoclonal antibody targeting the human epidermal growth factor receptor-2 (HER2 or ErbB2) and is used for tumors that overexpress HER2 protein, including breast and gastric cancers [77–79]. One meta-analysis demonstrated that trastuzumab significantly increased the incidence of congestive HF (RR 5.11, 90 % CI [3.00–8.72]; \( P < 0.00001 \)) and that the LVEF significantly declined after trastuzumab administration (RR 1.83, 90 % CI [1.36–2.47]; \( P = 0.0008 \)) [80]. Trastuzumab cardiotoxicity is thought to arise from a loss of contractility (rather than from cardiomyocyte death) and thus may be reversible.
Risk factors for trastuzumab-induced cardiotoxicity include prior anthracycline use (worse with doxorubicin >300 mg/m$^2$) [24, 83], preexisting decreased LVEF, hypertension, elevated body mass index, and older age [84].

**Pertuzumab**

Similar to trastuzumab, pertuzumab targets HER2 (ErbB2) receptors through prevention of HER2 homodimerization [85–87]. Recent studies show a clinical benefit with the use of pertuzumab and trastuzumab combination regimens [87, 88]. The addition of pertuzumab to therapy with trastuzumab and docetaxel was not associated with increased cardiotoxicity in the CLEOPATRA trial [89], and a cardiac safety analysis of early-phase trials showed no increase in cardiotoxicity above that of trastuzumab [90]. In one study with trastuzumab and pertuzumab, one of 64 patients developed an LVEF below 40% following the completion of therapy [91], and in another study with the same combination, 3.9% of patients had a decrease of >10% in their pretreatment LVEF assessment following therapy [92]. The FDA recommends assessment of LVEF prior to initiating anti-HER2 therapies such as trastuzumab and pertuzumab followed by reassessment at regular intervals (every 3 months and 6 months after discontinuation of therapy).

The general consensus is to discontinue trastuzumab plus pertuzumab therapy and reassess LVEF while considering cardioprotective treatment with accepted HF-based therapies in the event of a decrease in LVEF to <45% or to 45–49% with a 10% or greater decrease from pretreatment LVEF values.

**Alemtuzumab**

Alemtuzumab is a monoclonal antibody targeting CD52, a cell-surface antigen present on B and T cells that, after binding, leads to antibody-dependent cell lysis. This agent is currently approved for the treatment of B-cell chronic lymphocytic leukemia and relapsing multiple sclerosis [93–95]. One study reported the development of decreased LVEF and/or arrhythmia, including atrial fibrillation and ventricular tachycardia, with the use of alemtuzumab in four of eight patients with mycosis fungoides/Sezary syndrome [96]. Recovery of decreased LVEF was seen after discontinuation of therapy in most patients [96].

**Cetuximab**

Cetuximab is a human/mouse chimeric monoclonal antibody that targets epidermal growth factor receptor (EGFR), resulting in the inhibition of cell growth, apoptosis, cellular VEGF production, and wild-type $KRA$S activation [97]. Cetuximab is
approved for use in KRAS mutation-negative colorectal cancer in combination with FOLFIRI (irinotecan, 5-FU, and leucovorin) or as a single agent in refractory disease. Cetuximab-associated cardiotoxicity events observed in patients with colorectal cancer are limited. One sudden cardiac death was reported in a study of 128 patients undergoing therapy with cetuximab, oxaliplatin, and 5-FU followed by capecitabine [98]. Cetuximab is also approved for the treatment of squamous cell carcinoma of the head and neck, but an FDA black box warning exists for cardiopulmonary arrest, which has been observed in 2% of patients treated with cetuximab and radiation and is thought to be associated with electrolyte abnormalities [99].

Ramucirumab

Ramucirumab is an antiangiogenic monoclonal antibody that targets the VEGF pathway by binding and blocking ligand-mediated activation of VEGF receptor-2 (VEGFR-2) [100–102]. In the REGARD trial, the use of ramucirumab was associated with a higher incidence of hypertension in patients treated with best supportive care plus ramucirumab compared to patients who received best supportive care plus placebo (16% vs. 8%, respectively). The respective rates of arterial thromboembolism were 2% and 1%. One patient treated with ramucirumab developed a myocardial infarction leading to death [100].

Interleukin-2

Interleukin-2 is associated with direct myocardial toxicity [103] and with capillary leak syndrome. These events result in increased cardiac output and decreased systemic vascular resistance with a systemic inflammatory response-like syndrome [104, 105], which can be managed with supportive care [106].

Interferon-Alpha

The use of interferon-alpha is associated with cardiotoxicity, mainly arrhythmias (atrial and ventricular tachycardias and heart block), which are reported in 8–20% of cases [107–109]. One study in melanoma and RCC reported cardiomyopathy in patients treated with interferon-alpha [67, 110]. By contrast, another study demonstrated that only 1% of patients had a decrease in LVEF [111].
Targeted Therapy

**Sunitinib**

Sunitinib is an oral tyrosine kinase inhibitor (TKI) targeting VEGFR, platelet-derived growth factor receptor (PDGFR), c-Kit, and fms-like tyrosine kinase-3. Sunitinib is approved by the FDA for use in RCC, advanced pancreatic neuroendocrine tumors, and imatinib-refractory gastrointestinal stromal tumor (GIST) [112]. A retrospective analysis of patients with GIST treated with sunitinib demonstrated that up to 8% of patients developed clinically significant HF exacerbations, 28% of patients had at least a 10% decrease in LVEF, 9% of patients had a 15% or greater decrease in LVEF, and 47% of patients developed hypertension (>150/100 mmHg) [113–115]. Additionally, hypertension preceded the development of life-threatening HF in selected patients treated with sunitinib, which emphasizes the need for the management of hypertension to prevent HF [116]. As hypertension is a common adverse event of anti-VEGF agents, blood pressure should be closely monitored and aggressively managed during all cycles of anti-VEGF-containing therapy. The decrease in LVEF is likely mediated by direct mitochondrial injury and cardiac myocyte apoptosis through inhibition of rapidly accelerated fibrosarcoma (RAF-1) kinase [113, 117] and inhibition of PDGFR coupled with systemic vasoconstriction, leading to cardiac dysfunction [118]. Sunitinib is also associated with QT prolongation and arrhythmias [119]. Preexisting HF, coronary artery disease, and lower BMI may predispose patients to these adverse cardiovascular effects related to sunitinib [120].

**Sorafenib**

Sorafenib is a small-molecule TKI that inhibits VEGF through inhibition of VEGFR-2, PDGFR, RAF-1, proto-oncogene B-Raf, fms-like tyrosine kinase-3, and c-Kit. Sorafenib is FDA approved for use in RCC, hepatocellular carcinoma, and well-differentiated thyroid cancer [117]. The cardiotoxicity of sorafenib is less well defined than that of sunitinib. In one study, 2.9% of patients with RCC treated with sorafenib developed myocardial ischemia compared with 0.4% of those treated with placebo [121]. In patients with hepatocellular carcinoma, myocardial ischemia was noted in 2.7% of patients treated with sorafenib compared to 1.3% of those treated with placebo [122]. One meta-analysis suggested an RR of 1.78 (95% CI [1.09–2.92]) for the development of hypertension with the use of sorafenib [123].

**Pazopanib**

Pazopanib, a TKI approved for use in soft-tissue sarcoma and RCC, is thought to act through inhibition of surface VEGF receptors 1, 2, and 3, PDGF receptors,
fibroblast growth factor receptor (FGFR)-1 and FGFR-3, c-Kit, transmembrane glycoprotein receptor tyrosine kinase, and interleukin-2 receptor-inducible T-cell kinase [124]. One study showed that 49 % of patients developed hypertension with pazopanib use and 6.6 % of patients showed a decrease in LVEF with therapy compared to 2.4 % of control subjects [125]. Patients receiving pazopanib also showed a concentration-independent QT prolongation [126].

**Axitinib**

Axitinib is a specific TKI for VEGFR-1, VEGFR-2, and VEGFR-3 and is used to treat advanced RCC. Like other VEGF-targeted TKIs, axitinib is associated with an increased risk of hypertension (all grades up to 40 %; grade 3/4, 16 %), thrombotic events, and left ventricular dysfunction [127–130].

**Lapatinib**

Lapatinib is an oral TKI approved for use in HER2-overexpressing breast cancer. Lapatinib inhibits EGFR (ErbB1) and HER2 (ErbB2) [79, 131] and has thus raised concerns that it has a cardiotoxic effect similar to that of trastuzumab [132]. Recent studies, including one phase III trial investigating the use of lapatinib and trastuzumab in HER2-positive breast cancer, have shown that this theoretical risk may not be a reality [133]. An additional study examining pooled data from 44 trials involving lapatinib alone or in combination with trastuzumab or anthracycline-based regimens found that fewer than 5 % of patients experienced clinically significant cardiac events and that 88 % of patients recovered to pretreatment levels (when an LVEF reduction was noted) following discontinuation of drug therapy [132]. Despite these findings, current FDA labeling recommends pretreatment LVEF evaluation, as well as discontinuation of lapatinib in the event of a decrease in LVEF to <50 %.

**Imatinib**

Imatinib is a BCR-ABL TKI and an inhibitor of PDGFR stem cell factor and c-Kit [134]. Shortly after its release, an initial concern about LV contractile dysfunction arose due to a suspected loss in mitochondrial membrane potential thought to be secondary to a cellular stress response induced by imatinib [135]. However, subsequent retrospective studies reviewing toxicities in 1276 patients undergoing therapy for chronic myelogenous leukemia (CML) found that imatinib-associated systolic heart failure was observed in only 0.6 % of patients and that adverse cardiovascular events were seen primarily in elderly patients who had preexisting
cardiovascular disease or coronary artery disease [136, 137]. Similar findings were observed in patients receiving imatinib for GIST [138–140].

**Dasatinib**

Dasatinib is a small-molecule TKI that inhibits imatinib-resistant BRC-ABL kinase [141, 142]. Pleural and pericardial effusions occur with the use of dasatinib, but their mechanisms are unknown. One phase III trial comparing once- with twice-daily dosing of dasatinib in accelerated-phase CML observed 0 and 3% incidences of congestive HF and 12.7 and 24.5% incidences of pleural effusion, respectively [143]. Dasatinib use has also been associated with QT prolongation [144].

**Trametinib**

Trametinib is a selective and potent inhibitor of MEK1/MEK2 that is commonly used for the treatment of advanced melanoma with documented BRAF V600E or V600K mutations. In a phase III clinical trial of patients with melanoma, trametinib was associated with decreased LVEF or ventricular dysfunction in 7% of patients [145]. In 1% of the patients, these events were grade 3 cardiotoxicities, leading to the permanent discontinuation of trametinib [145]. In addition, hypertension was reported in 15% of patients (grade 3, 12%) [145].

**Vandetanib**

Vandetanib, a multi-kinase inhibitor targeting VEGFR-2, EGFR, and RET, is an effective and FDA-approved treatment for medullary thyroid carcinoma [146]. In a phase III clinical trial, vandetanib was associated with a higher risk of hypertension than placebo (32% vs. 5%, respectively). Grade 3/4 hypertension was noted in 9% of patients. In addition, vandetanib was found to be associated with prolonged QTc (all grades, 14%; grade 3/4, 8%) [146].

**Bortezomib**

Bortezomib is a first-generation reversible 26S proteasome inhibitor that leads to cell cycle arrest and apoptosis and is approved for use in mantle cell lymphoma and multiple myeloma [147, 148]. An increased incidence of HF and associated symptoms has been seen with bortezomib use; however, one study suggested similar
rates of HF in patients undergoing therapy for relapsed multiple myeloma with bortezomib or high-dose dexamethasone [149] and found that the effects, if present, did not appear to be dose dependent [148].

**Carfilzomib**

Carfilzomib is a second-generation 26S proteasome inhibitor that causes cell cycle arrest and apoptosis and is approved for use in multiple myeloma [150, 151]. Carfilzomib has been implicated in LVEF reduction, instigation of new-onset HF or exacerbation of preexisting HF, and, in limited cases, myocardial infarction. One study demonstrated that 2 of 257 patients had a myocardial infarction shortly after initiation of carfilzomib therapy and 9 (3.4%) developed grade 3/4 dyspnea; however, the vast majority of patients in this trial had previously been treated with bortezomib [152]. Another study suggested an 11% incidence of HF-associated symptoms following carfilzomib initiation [153]. It is likely that, similar to that with anthracyclines, the cardiac adverse events seen with carfilzomib are not limited to LV systolic dysfunction but include an increase in thrombotic events as well [154].

**Ponatinib**

A BCR-ABL tyrosine kinase inhibitor, ponatinib is approved for use in Philadelphia chromosome-positive acute lymphoblastic leukemia and CML [155]. One phase I study demonstrated that 1% of patients exhibited grade 3/4 HF-like symptoms and 2% of patients exhibited a prolonged QTc during therapy [155]. Another study suggested serious adverse vascular events, with 3% of patients having ponatinib-associated arterial thrombotic events and 9% of patients having arterial thrombotic events observed during therapy (although these were not necessarily considered treatment associated) [156]. Understanding the nature of these events is crucial for the future of this therapy [157].

**Regorafenib**

Regorafenib is a multi-kinase inhibitor approved for use in metastatic colorectal cancer and GIST that targets VEGF receptors 1–3, KIT, PDGFR-alpha, PDGFR-beta, RET, FGFR-1 and FGFR-2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and ABL [158, 159]. Although HF has not been reported with regorafenib, grade 3/4 hypertension is a frequently reported toxicity [158, 160–162].
**Cediranib**

Cediranib is a multi-kinase inhibitor targeting the VEGF pathway and angiogenesis through VEGFR-1, VEGFR-2, and VEGFR-3, PDGFR-alpha/PDGFR-beta, FGFR-1, and c-Kit [163]. As with other inhibitors of the VEGF pathway, hypertension is a primary toxicity of cediranib and has been identified in several studies [163–166], with one phase II study showing that 46% of patients enrolled exhibited hypertension with grade 3 or higher toxicity [167].

**Aflibercept**

Aflibercept is an antiangiogenic agent acting as a decoy receptor for VEGF-A and VEGF-B and placental growth factor composed of components of VEGFR-1 and VEGFR-2 binding domains attached to the Fc portion of a human IgG-1 [168]. One trial showed a significantly increased incidence of hypertension with aflibercept treatment, with grade 3 adverse events occurring in 19% of patients compared to 1.5% of control subjects as well as an increased incidence of arterial-thromboembolic events (1.8% of patients vs. 0.5% of control subjects) and venous-thromboembolic events (7.9% of patients vs. 6.3% of control subjects) [168]. Other studies have also found an increased incidence of hypertension and thromboembolic events in patients receiving aflibercept [169–171].

**Conclusions**

The exponential development of novel therapeutics for the treatment of cancer has prompted extensive research to recognize cardiotoxicity associated with the use of these agents. Early detection and effective therapeutic management of adverse events associated with the use of anticancer drugs have led to the safe and successful development of several breakthrough FDA-approved drugs, which have improved the clinical outcomes of patients with cancer. As cardiotoxicity is a major challenge—associated with severe complications and comorbidities—in the development of novel therapeutic agents [172], rigorous monitoring for adverse events has been successful in eliminating antineoplastic agents with severe cardiotoxicity [173].

In the current review, as expected, results from clinical trials in select patient populations were not always similar to the results derived from observational studies. This difference may be attributed to patient heterogeneity and the innate differences between these types of studies. Interestingly, in many instances case reports and case series raised awareness, thereby emphasizing the need to encourage clinical investigators to publish case reports.
In conclusion, collaborative efforts between cardiologists and oncologists have decreased the incidence of severe cardiotoxicity in patients treated with potentially cardiotoxic or novel anticancer agents and promise to eliminate cardiotoxicity associated with the use of new drugs (Fig. 2.2).

References

1. Thakur A, Witteles RM. Cancer therapy-induced left ventricular dysfunction: interventions and prognosis. J Card Fail. 2014;20:155–8.
2. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, Lamantia G, Colombo N, Cortinovis S, Dessanai MA, Nole F, Veglia F, Cipolla CM. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol. 2010;28:3910–6.
3. Herrmann J, Lerman A, Sandhu NP, Villarraga HR, Mulvagh SL, Kohli M. Evaluation and management of patients with heart disease and cancer: cardio-oncology. Mayo Clin Proc. 2014;89:1287–306.
4. Nakamae H, Tsumura K, Terada Y, Nakane T, Nakamae M, Ohta K, Yamane T, Hino M. 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.
5. Wells QS, Lenihan DJ. Reversibility of left ventricular dysfunction resulting from chemotherapy: can this be expected? Prog Cardiovasc Dis. 2010;53:140–8.
6. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardiac-oncological prevention. J Natl Cancer Inst. 2010;102:14–25.
7. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer. 1973;32:302–14.
8. Von Hoff DD, Layard MW, Basa P, Davis Jr HL, Von Hoff AL, Rozencweig M, Muggia FM. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91:710–7.
9. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003;97:2869–79.
10. Gianni L, Herman EH, Lipshultz SE, Minotti G, Sarvazyan N, Sawyer DB. Anthracycline cardiotoxicity: from bench to bedside. J Clin Oncol. 2008;26:3777–84.
11. Zhang S, Liu X, Bawa-Khalfe T, Lu LS, Lyu YL, Liu LF, Yeh ET. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med. 2012;18:1639–42.
12. Wojnowski L, Kulle B, Schirmer M, Schluter G, Schmidt A, Rosenberger A, Vonhof S, Bieckeboller H, Toliat MR, Suk EK, Tzvetkov M, Kruger A, Seifert S, Kloess M, Hahn H, Loeffler M, Nurnberg P, Pfreundschuh M, Trumper L, Brockmoller J, Hasenfuss G. NAD(P)H oxidase and multidrug resistance protein genetic polymorphisms are associated with doxorubicin-induced cardiotoxicity. Circulation. 2005;112:3754–62.
13. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. N Engl J Med. 1998;339:900–5.
14. Isner JM, Ferrans VJ, Cohen SR, Witkind BG, Virmani R, Gottdiener JS, Beck JR, Roberts WC. Clinical and morphologic cardiac findings after anthracycline chemotherapy. Analysis of 64 patients studied at necropsy. Am J Cardiol. 1983;51:1167–74.
15. Guglin M, Aljayeh M, Saiyad S, Ali R, Curtis AB. Introducing a new entity: chemotherapy-induced arrhythmia. Europace. 2009;11:1579–86.
16. Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. Ann Intern Med. 1996;125:47–58.
17. Steinberg JS, Cohen AJ, Wasserman AG, Cohen P, Ross AM. Acute arrhythmogenicity of doxorubicin administration. Cancer. 1987;60:1213–8.
18. Tirelli U, Errante D, Van Glabbeke M, Teodorovic I, Kluin-Nelemans JC, Thomas J, Bron D, Rosti G, Somers R, Zagonel V, Noordijk EM. CHOP is the standard regimen in patients > or = 70 years of age with intermediate-grade and high-grade non-Hodgkin's lymphoma: results of a randomized study of the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Study Group. J Clin Oncol. 1998;16:27–34.
19. Luminari S, Montanini A, Caballero D, Bologna S, Notter M, Dyer MJ, Chiappella A, Briones J, Petrini M, Barbato A, Kayitlare L, Federico M. Nonpegylated liposomal doxorubicin (MyocetTM) combination (R-COMP) chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL): results from the phase II EUR018 trial. Ann Oncol. 2010;21:1492–9.
20. Cardinale D, Sandri MT, Martinoni A, Tricca A, Civelli M, Lamantia G, Cinieri S, Martinielli G, Cipolla CM, Fiorentini C. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol. 2000;36:517–22.
21. Von Hoff DD, Rozencweig M, Layard M, Slavik M, Muggia FM. Daunomycin-induced cardiotoxicity in children and adults. A review of 110 cases. Am J Med. 1977;62:200–8.
22. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med. 1991;324:808–15.
23. van der Pal HJ, van Dalen EC, Hauptmann M, Kok WE, Caron HN, van den Bos C, Oldenburger F, Koning CC, van Leeuwen FE, Kremer LC. Cardiac function in 5-year survivors of childhood cancer: a long-term follow-up study. Arch Intern Med. 2010;170:1247–55.
24. Bowles EJ, Wellman R, Feigelson HS, Onitilo AA, Freedman AN, Delate T, Allen LA, Nekhlyudov L, Goddard KA, Davis RL, Habel LA, Yood MU, McCarty C, Magid DJ, Wagner EH, Pharmacovigilance ST. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst. 2012;104:1293–305.
25. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, Rubino M, Veglia F, Fiorentini C, Cipolla CM. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010;55:213–20.
26. Safra T, Muggia F, Jeffers S, Tsao-Wei DD, Groshen S, Lyass O, Henderson R, Berry G, Gabizon A. Pegylated liposomal doxorubicin (doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m2. Ann Oncol. 2000;11:1029–33.
27. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, Jones A. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer. 2010;10:337.
28. Seifert CF, Nesser ME, Thompson DF. Dexrazoxane in the prevention of doxorubicin-induced cardiotoxicity. Ann Pharmacother. 1994;28:1063–72.
29. Meadows AT, Friedman DL, Neglia JP, Mertens AC, Donaldson SS, Stovall M, Hammond S, Yasui Y, Inskip PD. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. J Clin Oncol. 2009;27:2356–62.
30. Nair R, Ramakrishnan G, Nair NN, Saikia TK, Parikh PM, Joshi SR, Soman CS, Mukhadan M, Dinshaw KT, Advani SH. A randomized comparison of the efficacy and toxicity of epirubicin and doxorubicin in the treatment of patients with non-Hodgkin's lymphoma. Cancer. 1998;82:2282–8.
31. Ryberg M, Nielsen D, Skovsgaard T, Hansen J, Jensen BV, Dombernowsky P. Epirubicin cardiotoxicity: an analysis of 469 patients with metastatic breast cancer. J Clin Oncol. 1999;16:3502–8.
32. Gottidiener JS, Appelbaum FR, Ferrans VJ, Deisseroth A, Ziegler J. Cardiotoxicity associated with high-dose cyclophosphamide therapy. Arch Intern Med. 1981;141:758–63.
33. 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.

34. Lichtman SM, Ratani MJ, Van Echo DA, Rosner G, Egorin MJ, Budman DR, Vogelzang NJ, Norton L, Schilsy RL. Phase I trial of granulocyte-macrophage colony-stimulating factor plus high-dose cyclophosphamide given every 2 weeks: a Cancer and Leukemia Group B study. J Natl Cancer Inst. 1993;85:1319–26.

35. Zver S, Zadnik V, Bunc M, Rogel P, Cernelc P, Kozelj M. Cardiac toxicity of high-dose cyclophosphamide in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. Int J Hematol. 2007;85:408–14.

36. Appelbaum F, Strauchen JA, Graw Jr RG, Savage DD, Kent KM, Ferrans VJ, Herzig GP. Acute lethal carditis caused by high-dose combination chemotherapy. A unique clinical and pathological entity. Lancet. 1976;1:58–62.

37. Quezado ZM, Wilson WH, Cunnion RE, Parker MM, Reda D, Bryant G, Ognibene FP. High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. Ann Intern Med. 1993;118:31–6.

38. Kandylis K, Vassilomanolakis M, Tsoussis S, Efremidis AP. Ifosfamide cardiotoxicity in humans. Cancer Chemother Pharmacol. 1989;24:395–6.

39. Tomirotti M, Riundi R, Pulici S, Ungaro A, Pedretti D, Villa S, Scanni A. Ischemic cardiopathy from cis-diamminedichloroplatinum (CDDP). Tumori. 1984;70:235–6.

40. Mortimer JE, Crowley J, Eyre H, Weiden P, Eltringham J, Stuckey WJ. A phase II randomized study comparing sequential and combined intraarterial cisplatin and radiation therapy in primary brain tumors. A southwest oncology group study. Cancer. 1992;69:1220–3.

41. Anand AJ. Fluorouracil cardiotoxicity. Ann Pharmacother. 1994;28:374–8.

42. de Forni M, Malet-Martino MC, Jaillais P, Shubinski RE, Bachaud JM, Lemaire L, Canal P, Chevreau C, Carrie D, Soulie P, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. J Clin Oncol. 1992;10:1795–801.

43. Wacker A, Lersch C, Scherpsinski U, Reindl L, Seyfarth M. High incidence of angina pectoris in patients treated with 5-fluorouracil. A planned surveillance study with 102 patients. Oncology. 2003;65:108–12.

44. Grunwald MR, Howie L, Diaz Jr LA. Takotsubo cardiomyopathy and Fluorouracil: case report and review of the literature. J Clin Oncol. 2012;30:e11–4.

45. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. Expert Opin Drug Saf. 2009;8:191–202.

46. Cianci G, Morelli MF, Cannita K, Morese R, Ricevuto E, Di Rocco ZC, Porzio G, Lanfutti Baldi P, Ficorella C. Prophylactic options in patients with 5-fluorouracil-associated cardiotoxicity. Br J Cancer. 2003;88:1507–61.

47. 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;13:197–801.

48. Van Cutsem E, Hoff PM, Blum JL, Abt M, Osterwalder B. Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. Ann Oncol. 2002;13:484–5.
53. Saif MW, Tomita M, Ledbetter L, Diasio RB. Capecitabine-related cardiotoxicity: recognition and management. J Support Oncol. 2008;6:41–8.
54. Gutheil JFD. Antimetabolites. In: Perry MC editor. The chemotherapy sourcebook, 3rd edn. Lippincott, Williams and Wilkins, Philadelphia.
55. Van Besien K, Devine S, Wickrema A, Jessop E, Amin K, Yassine M, Maynard V, Stock W, Peace D, Ravandi F, Chen YH, Hoffman R, Sosman J. Regimen-related toxicity after fludarabine-melphalan conditioning: a prospective study of 31 patients with hematologic malignancies. Bone Marrow Transplant. 2003;32:471–6.
56. Grem JL, King SA, Chun HG, Grever MR. Cardiac complications observed in elderly patients following 2'-deoxycoformycin therapy. Am J Hematol. 1991;38:245–7.
57. Perez-Verdia A, Angulo F, Hardwicke FL, Nugent KM. Acute cardiac toxicity associated with high-dose intravenous methotrexate therapy: case report and review of the literature. Pharmacotherapy. 2005;25:1271–6.
58. Hermans C, Straetmans N, Michaux JL, Ferrant A. Pericarditis induced by high-dose cytosine arabinoside chemotherapy. Ann Hematol. 1997;75:55–7.
59. Kantor AF, Greene MH, Boice JD, Fraumeni Jr JF, Flannery JT. Are vinca alkaloids associated with myocardial infarction? Lancet. 1981;1:1111.
60. Zabernigg A, Gattringer C. Myocardial infarction associated with vinorelbine (Navelbine). Eur J Cancer. 1996;32A:1618–9.
61. Mandel EM, Lewinski U, Djaldetti M. Vincristine-induced myocardial infarction. Cancer. 1975;36:1979–82.
62. Arbuck SG, Strauss H, Rowinsky E, Christian M, Suffness M, Adams J, Oakes M, McGuire W, Reed E, Gibbs H. A reassessment of cardiac toxicity associated with Taxol. J Natl Cancer Inst Monogr. 1993:117–30.
63. 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.
64. Fossella FV, Lee JS, Murphy WK, Lippman SM, Calayag M, Pang A, Chasen M, Shin DM, Glisson B, Benner S, et al. Phase II study of docetaxel for recurrent or metastatic non-small-cell lung cancer. J Clin Oncol. 1994;12:1238–44.
65. Francis P, Schneider J, Hann L, Balmaceda C, Barakat R, Phillips M, Hakes T. Phase II trial of docetaxel in patients with platinum-refractory advanced ovarian cancer. J Clin Oncol. 1994;12:2301–8.
66. Malhotra V, Dorr VJ, Lyss AP, Anderson CM, Westgate S, Reynolds M, Barrett B, Perry MC. Neoadjuvant and adjuvant chemotherapy with doxorubicin and docetaxel in locally advanced breast cancer. Clin Breast Cancer. 2004;5:377–84.
67. des Guetz G, Uzzan B, Chouahnia K, Moreire JF. Cardiovascular toxicity of anti-angiogenic drugs. Target Oncol. 2011;6:197–202.
68. Wicki A, Hermann F, Pretre V, Winterhalder R, Kueng M, von Moos R, Rochlitz C, Hermann R. Pre-existing antihypertensive treatment predicts early increase in blood pressure during bevacizumab therapy: the prospective AVALUE cohort study. Oncol Res Treat. 2014;37:230–6.
69. Hurvitz SA, Bosserman LD, Chan D, Hagenstad CT, Kass FC, Smith FP, Rodriguez GI, Childs BH, Slamon DJ. Cardiac safety results from a phase II, open-label, multicenter, pilot study of two docetaxel-based regimens plus bevacizumab for the adjuvant treatment of subjects with node-positive or high-risk node-negative breast cancer. Springerplus. 2014;3:244.
70. Hall PS, Harshman LC, Srinivas S, Witteles RM. The frequency and severity of cardiovascular toxicity from targeted therapy in advanced renal cell carcinoma patients. JACC Heart Failure. 2013;1:72–8.
71. Qi WX, Fu S, Zhang Q, Guo XM. Bevacizumab increases the risk of severe congestive heart failure in cancer patients: an up-to-date meta-analysis with a focus on different subgroups. Clin Drug Investig. 2014;34:681–90.
72. Franco TH, Khan A, Joshi V, Thomas B. Takotsubo cardiomyopathy in two men receiving bevacizumab for metastatic cancer. Ther Clin Risk Manag. 2008;4:1367–70.
73. Groarke JD, Choueiri TK, Slosky D, Cheng S, Moslehi J. Recognizing and managing left ventricular dysfunction associated with therapeutic inhibition of the vascular endothelial growth factor signaling pathway. Curr Treat Options Cardiovasc Med. 2014;16:335.
74. Choueiri TK, Mayer EL, Je Y, Rosenberg JE, Nguyen PL, Azzi GR, Bellmunt J, Burstein HJ, Schutz FA. Congestive heart failure risk in patients with breast cancer treated with bevacizumab. J Clin Oncol. 2011;29:632–8.
75. Nagane M, Nishikawa R, Narita Y, Kobayashi H, Takano S, Shinoura N, Aoki T, Sugiyama K, Kuratsu J, Muragaki Y, Sawamura Y, Matsutani M. Phase II study of single-agent bevacizumab in Japanese patients with recurrent malignant glioma. Jpn J Clin Oncol. 2012;42:887–95.
76. Yardley DA, Hart L, Waterhouse D, Whorf R, Drosick DR, Murphy P, Badarinath S, Daniel BR, Childs BH, Burris H. Addition of bevacizumab to three docetaxel regimens as adjuvant therapy for early stage breast cancer. Breast Cancer Res Treat. 2013;142:655–65.
77. Andersson M, Lidbrink E, Bjerre K, Wist E, Enevoldsen K, Jensen AB, Karlsson P, Tange UB, Sorensen PG, Moller S, Bergh J, Langker SJ. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. J Clin Oncol. 2011;29:264–71.
78. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehele M, Ruschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687–97.
79. Blackwell KL, Burstein HJ, Storniolo AM, Rugo HS, Sledge G, Aktan G, Ellis C, Florance A, Vukelja S, Bishoff J, Basejla J, O'Shaughnessy J. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012;30:2585–92.
80. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, D’Amico R. Trastuzumab containing regimens for early breast cancer. Cochrane Datab Syst Rev. 2012;4:CD006243.
81. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol. 2005;23:2900–2.
82. Roncalli E, Jeong JH, Rastogi P, Swain SM, Geyer CE Jr., Ewer MS, Rathi V, Fehrenbacher L, Bruksy A, Azar CA, Flynn PJ, Zapas JL, Polikoff J, Gross HM, Biggs DD, Atkins JN, Tan-Chiu E, Zheng P, Youthers G, Mamounas EP, Wolmark N. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol. 2012;30:3792–9.
83. Russell SD, Blackwell KL, Lawrence J, Pippen JE Jr., Roe MT, Wood F, Paton V, Holmgren E, Mahaffey KW. Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. J Clin Oncol. 2010;28:3416–21.
84. Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA, Martino S, Gralow JR, Dakhil SR, Ingle JN, Winer EP, Gelmon KA, Gersh BJ, Jaffe AS, Rodeheffer RJ. 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.
85. Agus DB, Gordon MS, Taylor C, Natale RB, Karlan B, Mendelson DS, Press MF, Allison DE, Sliwkowski MX, Lieberman G, Kelsey SM, Fyfe G. Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer. J Clin Oncol. 2005;23:2534–43.

86. Baselga J, Cortes J, Kim SB, Im SA, Hegg R, Im YH, Roman L, Pedrini JL, Pienkowski T, Knott A, Clark E, Benyunes MC, Ross G, Swain SM. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366:109–19.

87. Baselga J, Gelmon KA, Verma S, Wardley A, Conte P, Miles D, Bianchi G, Cortes J, McNally VA, Ross GA, Fumoleau P, Gianni L. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. J Clin Oncol. 2010;28:1138–44.

88. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, Ciruelos E, Ferrero JM, Schneeweiss A, Heesons C, Clark E, Ross G, Benyunes MC, Cortes J. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372:724–34.

89. Swain SM, Ewer MS, Cortes J, Amadori D, Miles D, Knott A, Clark E, Benyunes MC, Ross G, Baselga J. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. Oncologist. 2013;18:257–64.

90. Miller KD, Dieras V, Harbeck N, Andre F, Mahtani RL, Gianni L, Albain KS, Crivellari D, Fang L, Michelson G, de Haas SL, Burris HA. Phase IIa trial of trastuzumab emtansine with pertuzumab for patients with human epidermal growth factor receptor 2-positive, locally advanced, or metastatic breast cancer. J Clin Oncol. 2014;32:1437–44.

91. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, Tausch C, Seo JH, Tsai YF, Ratmayake J, McNally V, Ross G, Cortes J. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol. 2013;24:2278–84.

92. Dearden CE, Johnson R, Pettengell R, Devereux S, Cwynarski K, Whittaker S, McMillan A. Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma). Br J Haematol. 2011;153:451–85.

93. Ferrajoli A, O’Brien SM, Cortes JE, Giles FJ, Thomas DA, Faderl S, Kurzrock R, Lerner S, Kontoyiannis DP, Keating MJ. Phase II study of alemtuzumab in chronic lymphoproliferative disorders. Cancer. 2003;98:773–8.

94. Jonker DJ, O’Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, Au HJ, Berry SR, Krahn M, Price T, Simes RJ, Tebbutt NC, van Hazel G, Wierzbicki R, Langer C, Moore MJ. Cetuximab for the treatment of colorectal cancer. N Engl J Med. 2007;357:2040–8.

95. Primrose J, Falk S, Finch-Jones M, Valle J, O’Reilly D, Harari PM, Giralt J, Azarnia N, Hornbuckle J, Peterson M, Rees M, Iveson T, Hickish T, Butler R, Stanton L, Dixon E, Little L, Bowers M, Pugh S, Garden OJ, Cunningham D, Maughan T, Bridgewater J. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. Lancet Oncol. 2014;15:601–11.

96. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, Jones CU, Sur R, Rabend J, Jassem J, Ove R, Kies MS, Baselga J, Youssoufian H, Amellal N, Rowsenky EK, Ang KK. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006;354:567–78.
100. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, dos Santos LV, Aprile G, Ferry DR, Melichar B, Tehfe M, Topuzov E, Zalcberg JR, Chau I, Campbell W, Sivan andan C, Pikiel J, Koshiji M, Hsu Y, Liepa AM, Gao L, Schwartz JD, Tabernero J. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma ( REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383:31–9.

101. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD, Ohtsu A. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15:1224–35.

102. Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, Park K, Gorbunova V, Kowalszyn RD, Pikiel J, Czyzewicz G, Orlov SV, Lewanski CR, Thomas M, Bidoli P, Dakhil S, Gans S, Kim JH, Grigoescu A, Karaseva N, Reck M, Cappuzzo F, Alexandris E, Papadopoulos J, Yurasov S, Perol M. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014;384:665–73.

103. Margolin KA, Rayner AA, Hawkins MJ, Atkins MB, Dutcher JP, Fisher RI, Weiss GR, Doroshow JH, Jaffe HS, Roper M, et al. Interleukin-2 and lymphokine-activated killer cell therapy of solid tumors: analysis of toxicity and management guidelines. J Clin Oncol. 1989;7:486–98.

104. Lee RE, Lotze MT, Skibber JM, Tucker E, Bonow RO, Ognibene FP, Carasquillo JA, Shellhamer JH, Parrillo JE, Rosenberg SA. Cardiorespiratory effects of immunotherapy with interleukin-2. J Clin Oncol. 1989;7:7–20.

105. Weiss GR, Margolin KA, Aronson FR, Sznoj M, Atkins MB, Dutcher JP, Gaynor ER, Boldt DH, Doroshow JH, Bar MH, et al. A randomized phase II trial of continuous infusion interleukin-2 or bolus injection interleukin-2 plus lymphokine-activated killer cells for advanced renal cell carcinoma. J Clin Oncol. 1992;10:275–81.

106. White Jr RL, Schwartzentuber DJ, Guleria A, MacFarlane MP, White DE, Tucker E, Rosenberg SA. Cardiopulmonary toxicity of treatment with high dose interleukin-2 in 199 consecutive patients with metastatic melanoma or renal cell carcinoma. Cancer. 1994;74:3212–22.

107. Atkins MB, Hsu J, Lee S, Cohen GI, Flaherty LE, Sosman JA, Sondak VK, Kirkwood JM. Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alpha-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol. 2008;26:5748–54.

108. Kruit WH, Punt KJ, Goey SH, de Mulder PH, van Hooghenhuyze DC, Henzen-Logmans SC, Stoter G. Cardiotoxicity as a dose-limiting factor in a schedule of high dose bolus therapy with interleukin-2 and alpha-interferon. An unexpectedly frequent complication. Cancer. 1994;74:2850–6.

109. Kruit WH, Goey SH, Lamers CH, Gratama JW, Visser B, Schmitz PI, Eggermont AM, Bolhuis RL, Stoter G. High-dose regimen of interleukin-2 and interferon-alpha in combination with lymphokine-activated killer cells in patients with metastatic renal cell cancer. J Immunother. 1997;20:312–20.

110. Khakoo AY, Halushka MK, Rame JE, Rodriguez ER, Kasper EK, Judge DP. Reversible cardiomyopathy caused by administration of interferon alpha. Nat Clin Pract Cardiovasc Med. 2005;2:53–7.

111. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylrik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356:115–24.
112. Force T, Kolaja KL. Cardiotoxicity of kinase inhibitors: the prediction and translation of preclinical models to clinical outcomes. Nat Rev Drug Discov. 2011;10:111–26.

113. Chu TF, Rupnick MA, Kerkela R, Dallabrida SM, Zurakowski D, Nguyen L, Woulfe K, Pravda E, Cassiola F, Desai J, George S, Morgan JA, Harris DM, Ismail NS, Chen JH, Schoen FJ, Van den Abbeele AD, Demetri GD, Force T, Chen MH. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet. 2007;370:2011–9.

114. Zhu X, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. Acta Oncol. (Stockholm, Sweden). 2009;48:9–17.

115. 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.

116. Khakoo AY, Kassiotos CM, Tannir N, Plana JC, Halushka M, Bickford C, Trent 2nd J, Champion JC, Durand JB, Lenihan DJ. Heart failure associated with sunitinib malate: a multitargeted receptor tyrosine kinase inhibitor. Cancer. 2008;112:2500–8.

117. Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Gore M, Desai AA, Patnaik A, Xiong HQ, Rowsinsky E, Abbruzzese JL, Xia C, Simantov R, Schwartz B, O'Dwyer PJ. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2006;24:2505–12.

118. Chintalgattu V, Ai D, Langley RR, Zhang J, Bankson JA, Shih TL, Reddy AK, Coombes KR, Daher IN, Pati S, Patel SS, Pocius JS, Taffet GE, Buja LM, Entman ML, Khakoo AY. Cardiomyocyte PDGFR-beta signaling is an essential component of the mouse cardiac response to load-induced stress. J Clin Invest. 2010;120:472–84.

119. Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarisation (QT interval). Drug Saf. 2013;36:295–316.

120. Telli ML, Witteles RM, Fisher GA, Srinivas S. Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. Ann Oncol. 2008;19:1613–8.

121. Escudier B, Eisen T, Stadler WM, Szczyluk C, Oudard S, Siebels M, Negrerie S, Chevreau C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356:125–34.

122. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zuccon B, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Haussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular cancer. N Engl J Med. 2008;359:378–90.

123. Chen J, Tian CX, Yu M, Lv Q, Cheng NS, Wang Z, Wu X. Efficacy and safety profile of combining sorafenib with chemotherapy in patients with HER2-negative advanced breast cancer: a meta-analysis. J Breast Cancer. 2014;17:61–8.

124. Hurwitz HI, Dowlati A, Saini S, Savage S, Suttle AB, Gibson DM, Hodge JP, Merkle EM, Pandite L. Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res. 2009;15:4220–7.

125. van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, Schoffski P, Aglietta M, Staddon AP, Beppu Y, Le Cesne A, Gelderblom H, Judson IR, Araki N, Ouali M, Marreaud S, Hodge R, Dewji MR, Coens C, Demetri GD, Fletcher CD, Dei Tos AP, Hohenberger P. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379:1879–86.

126. Heath EI, Infante J, Lewis LD, Luu T, Stephenson J, Tan AR, Kasubhai S, LoRusso P, Ma B, Suttle AB, Kleha JF, Ball HA, Dar MM. A randomized, double-blind, placebo-controlled study to evaluate the effect of repeated oral doses of pazopanib on cardiac conduction in patients with solid tumors. Cancer Chemother Pharmacol. 2013;71:565–73.

127. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczyluk C, Hutson TE, Michaelson MD, Gorbunova VA, Gore ME, Rusakov IG, Negrerie S, Ou YC, Castellano D, Lim HY, Uemura H, Tarazi J, Cella D, Chen C, Rosbrook B, Kim S, Motzer RJ. Comparative
effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011;378:1931–9.

128. Rini BI, Schiller JH, Fruehauf JP, Cohen EE, Tarazi JC, Rosbrook B, Bair AH, Ricart AD, Olszanski AJ, Letrent KJ, Kim S, Rixe O. Diastolic blood pressure as a biomarker of axitinib efficacy in solid tumors. Clin Cancer Res. 2011;17:3841–9.

129. Ovadia D, Esquenazi Y, Bucay M, Bacher CR. Association between takotsubo cardiomyopathy and axitinib: case report and review of the literature. J Clin Oncol. 2015;33:e1–3.

130. Abdel-Rahman O, Foud M. Risk of cardiovascular toxicities in patients with solid tumors treated with sunitinib, axitinib, cediranib or regorafenib: an updated systematic review and comparative meta-analysis. Crit Rev Oncol Hematol. 2014;92:194–207.

131. Bachelot T, Romieu G, Campone M, Diers V, Crozet C, Dalenc F, Jimenez M, Le Rhun E, Piersa JY, Goncalves A, Leheurtier M, Domont J, Gutierrez M, Cure H, Ferrero JM, Labbe-Devilliers C. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol. 2013;14:64–71.

132. 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.

133. Baselga J, Bradbury I, Eidtmann H, Di Cosimo S, de Azambuja E, AURA C, Gomez H, Dinh P, Fauria K, Van Dooren V, Aktan G, Goldhirsch A, Chang TW, Horvath Z, Coccia-Portugal M, Domont J, Tseng LM, Kunz G, Sohn JH, Semiglazov V, Serzo G, Palacova M, Probachai V, Pusztai L, Uchta M, Gelber RD, Piccart-Gebhart M. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 2 trial. Lancet. 2012;379:633–40.

134. Brunstein CG, McGlave PB. The biology and treatment of chronic myelogenous leukemia. Oncology (Williston Park). 2001;15:23–31; discussion 31–2, 35.

135. Kerkela R, Grazette L, Yacobi R, Iliescu C, Patten R, Beahm C, Walters B, Shevtsov S, Pesant S, Clubb FJ, Rosenzieag A, Salomon RN, Van Eten RA, Alroy J, Durand JB, Force T. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med. 2006;12:908–16.

136. 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.

137. Maharsy W, Aries A, Mansour O, Komati H, Nemer M. Ageing is a risk factor in imatinib mesylate cardiotoxicity. Eur J Heart Fail. 2014;16:367–76.

138. Verweij J, Casali PG, Kotasek D, Le Cesne A, Reichard P, Judson IR, Issels R, Van Oosterom AT, Van Glabbeke M, Blay JY. Imatinib does not induce cardiac left ventricular failure in gastrointestinal stromal tumours patients: analysis of EORTC-ISG-AGITG study 62005. Eur J Cancer. 2007;43:974–8.

139. Trent JC, Patel SS, Zhang J, Araujo DM, Plana JC, Lenihan DJ, Fan D, Patel SR, Benjamin RS, Kakoo AY. Rare incidence of congestive heart failure in gastrointestinal stromal tumor and other sarcoma patients receiving imatinib mesylate. Cancer. 2010;116:184–92.

140. Saito S, Nakata K, Kajura S, Ando T, Hosokawa A, Sugiyama T. Long-term follow-up outcome of imatinib mesylate treatment for recurrent and unresectable gastrointestinal stromal tumors. Digestion. 2013;87:47–52.

141. Apperley JF, Cortes JE, Kim DW, Roy L, Roboz GI, Rosti G, Bullorsky EO, Abruzzese E, Hochhaus A, Heim D, de Souza CA, Larson RA, Lipton JH, Khoury HJ, Kim HJ, Sillaber C, Hughes TP, Erben P, Van Tornout J, Stone RM. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START a trial. J Clin Oncol. 2009;27:3472–9.

142. Braden HA, Eide CA, O’Hare T, Johnson KJ, Willis SG, Lee FY, Druker BJ, Deininger MW. Comparison of imatinib mesylate, dasatinib (BMS-354825), and nilotinib (AMN107) in an N-ethyl-N-nitrosourea (ENU)-based mutagenesis screen: high efficacy of drug combinations. Blood. 2006;108:2332–8.
143. Kantarjian H, Cortes J, Kim DW, Dohliac-Llacer P, Pasquini R, DiPersio J, Muller MC, Radich JP, Khoury HJ, Khoroshko N, Bradley-Garelik MB, Zhu C, Tallman MS. Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-month median follow-up. Blood. 2009;113:6322–9.

144. Strevel EL, Ing DJ, Siu LL. Molecularly targeted oncology therapeutics and prolongation of the QT interval. J Clin Oncol. 2007;25:3362–71.

145. Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, Demidov LV, Hassel JC, Rutkowski P, Mohr P, Dummer R, Trefzer U, Larkin JM, Utikal J, Dreno B, Nyakas M, Middleton MR, Becker JC, Casey M, Sherman LJ, Wu FS, Ouellet D, Martin AM, Patel K, Schadendorf D, Group MS. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012;367:107–14.

146. Wells Jr SA, Robinson BG, Gallego RF, Dralle H, Fagin JA, Santoro M, Baudin E, Elisei R, Jarzab B, Vasselli JR, Read J, Langmuir P, Ryan AJ, Schumacher MJ. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012;30:134–41.

147. Agathocleous A, Rohatiner A, Rule S, Hunter H, Kerr JP, Neeson SM, Matthews J, Strauss S, Montoto S, Johnson P, Radford J, Lister A. Weekly versus twice weekly bortezomib given in conjunction with rituximab, in patients with recurrent follicular lymphoma, mantle cell lymphoma and Waldenstrom macroglobulinemia. Br J Haematol. 2010;151:346–53.

148. Bringhen S, Larocca A, Rossi D, Cavalli M, Genuardi M, Ria R, Gentili S, Patriarca F, Nozzoli C, Levi A, Guglielmi M, Benevolo G, Callea V, Rizzo V, Cangialosi C, Musto P, De Rosa L, Liberati AM, Grasso M, Falcone AP, Evangelista A, Cavo M, Gaidano G, Boccadoro M, Palumbo A. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood. 2010;116:4745–53.

149. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, Reece D, San-Miguel JF, Blade J, Boccadoro M, Cavenagh J, Dalton WS, Boral AL, Esseltine DL, Porter JB, Schenkein D, Anderson KC. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352:2487–98.

150. Alsina M, Trudel S, Furman RR, Rosen PJ, O’Connor OA, Comenzo RL, Wong A, Kunkel LA, Molineaux CJ, Goy A. A phase I single-agent study of twice-weekly consecutive-day dosing of the proteasome inhibitor carfilzomib in patients with relapsed or refractory multiple myeloma or lymphoma. Clin Cancer Res. 2012;18:4830–40.

151. Kortuem KM, Stewart AK. Carfilzomib. Blood. 2013;121:893–7.

152. Siegel DS, Martin T, Wang M, Vij R, Jakubowiak AJ, Lonial S, Trudel S, Kukreti V, Bahlis N, Alsina M, Chanan-Khan A, Buadi F, Reu FJ, Somlo G, Zonder J, Song K, Stewart AK, Stadtmauer E, Kunkel L, Wear S, Wong AF, Orlofski RZ, Jagannath S. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood. 2012;120:2747–25.

153. Lendvai N, Hilden P, Devlin S, Sandau H, Hassoun H, Lesokhin AM, Tsakos I, Redling K, Koehne G, Chung DJ, Schaffer WL, Giralt SA. A phase 2 single-center study of carfilzomib 56 mg/m2 with or without low-dose dexamethasone in relapsed multiple myeloma. Blood. 2014;124:899–906.

154. Grandin EW, Ky B, Cornell RF, Carver J, Lenihan DJ. Patterns of cardiac toxicity associated with irreversible proteasome inhibition in the treatment of multiple myeloma. J Card Fail. 2015;21:138–44.

155. Cortes JE, Kantarjian H, Shah NP, Bixby D, Mauro MJ, Flinn I, O’Hare T, Hu S, Narasimhan NI, Rivera VM, Clackson T, Turner CD, Haluska FG, Druker BJ, Deininger MW, Talpaz M. Ponatinib in refractory Philadelphia chromosome-positive leukemias. N Engl J Med. 2012;367:2075–88.

156. Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre P, Paquette R, Chuah C, Nicolini FE, Apperley JF, Khoury HJ, Talpaz M, DiPersio J, DeAngelio DJ, Abruzzese E, Rea D, Baccarani M,
Muller MC, Gambacorti-Passerini C, Wong S, Lustgarten S, Rivera VM, Clackton T, Turner CD, Haluska FG, Guilhot F, Deininger MW, Hochhaus A, Hughes T, Goldman JM, Shah NP, Kantarjian H. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013;369:1783–96.

157. Groarke JD, Cheng S, Moslehi J. Cancer-drug discovery and cardiovascular surveillance. N Engl J Med. 2013;369:1779–81.

158. Mross K, Frost A, Steinbild S, Hedbom S, Buchert M, Fasol U, Unger C, Kratzschmar J, Heinig R, Boix O, Christensen O. A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. Clin Cancer Res. 2012;18:2658–67.

159. Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Joensuu H, Badalamenti G, Blackstein M, Le Cesne A, Schoffski P, Maki RG, Bauer S, Nguyen BB, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D, Casali PG and investigators Gs. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID); an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381:295–302.

160. Strumberg D, Scheulen ME, Schultheis B, Richly H, Frost A, Buchert M, Christensen O, Jeffers M, Heinig R, Boix O, Mross K. Regorafenib (BAY 73-4506) in advanced colorectal cancer: a phase I study. Br J Cancer. 2012;106:1722–7.

161. Li J, Qin S, Xu R, Yau TC, Ma B, Pan H, Xu J, Bai Y, Chi Y, Wang L, Yeh KH, Bi F, Cheng Y, Le AT, Lin JK, Liu T, Ma D, Kappeler C, Kalmus J, Kim TW. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2013;381:303–12.

162. Spreafico A, Chi KN, Sridhar SS, Smith DC, Carducci MA, Kavsak P, Wong TS, Wang L,ivy SP, Oza AM. A phase 2 study of cediranib in recurrent or persistent ovarian, peritoneal or fallopian tube cancer: A trial of the Princess Margaret, Chicago and California Phase II Consortia. Gynecol Oncol. 2015;138:55–61.

163. Spreeuw A, Beyaert R, D’Hondt SS, Smith DC, Carducci MA, Kavsak P, Wong TS, Wang L, Ivy SP, Mukherjee SD, Kollmannsberger CK, Sukhai MA, Takebe N, Kamel-Reid S, Siu LL, Hotte SJ. A randomized phase II study of cediranib alone versus cediranib in combination with dasatinib in docetaxel resistant, castration resistant prostate cancer patients. Invest New Drugs. 2014;32:1005–16.

164. Judson I, Scurr M, Gardner K, Barquin E, Marotti M, Collins B, Young H, Jürgensmeier JM, Leahy M. Phase II study of cediranib in patients with advanced gastrointestinal stromal tumors or soft-tissue sarcoma. Clin Cancer Res. 2014;20:3603–12.

165. Matulonis UA, Berlin S, Ivy P, Tymurski K, Krasner C, Zarwan C, Berkenblit A, Campos S, Horowitz N, Cannistra SA, Lee H, Lee J, Roche M, Hill M, Whalen C, Sullivan L, Tran C, Humphreys BD, Pensky RT. Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. J Clin Oncol. 2009;27:5601–6.

166. Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, Ruff P, van Hazel GA, Moiseyenko V, Ferry D, McKendrick J, Polikoff J, Tellier A, Castan R, Allegre C. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012;30:3499–506.
169. Tabernero J, Van Cutsem E, Lakomy R, Prausova J, Ruff P, van Hazel GA, Moiseyenko VM, Ferry DR, McKendrick JJ, Soussan-Lazard K, Chevalier S, Allegra CJ. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. Eur J Cancer (Oxford, England 1990). 2014;50:320–31.

170. Lockhart AC, Rothenberg ML, Dupont J, Cooper W, Chevalier P, Sternas L, Buzenet G, Koehler E, Sosman JA, Schwartz LH, Gultekin DH, Koutcher JA, Donnelly EF, Andal R, Dancy I, Spriggs DR, Tew WP. Phase I study of intravenous vascular endothelial growth factor trap, aflibercept, in patients with advanced solid tumors. J Clin Oncol. 2010;28:207–14.

171. Diaz-Padilla I, Siu LL, San Pedro-Salcedo M, Razak AR, Colevas AD, Shepherd FA, Leigh NB, Neal JW, Thibault A, Liu L, Lisano J, Gao B, Lawson EB, Wakelee HA. A phase I dose-escalation study of aflibercept administered in combination with pemetrexed and cisplatin in patients with advanced solid tumours. Br J Cancer. 2012;107:604–11.

172. Said R, Banchs J, Wheler J, Hess KR, Falchook G, Fu S, Naing A, Hong D, Piha-Paul S, Ye Y, Yeh E, Wolff RA, Tsimberidou AM. The prognostic significance of left ventricular ejection fraction in patients with advanced cancer treated in phase I clinical trials. Ann Oncol. 2014;25:276–82.

173. Subbiah IM, Lenihan DJ, Tsimberidou AM. Cardiovascular toxicity profiles of vascular-disrupting agents. Oncologist. 2011;16:1120–30.
Cardio-Oncology
The Clinical Overlap of Cancer and Heart Disease
Kimmick, G.G.; Lenihan, D.J.; Sawyer, D.B.; Mayer, E.L.;
Hershman, D.L. (Eds.)
2017, XV, 319 p. 55 illus., 49 illus. in color. With online
files/update., Hardcover
ISBN: 978-3-319-43094-2