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Mechanisms of cardiotoxicity of cancer chemotherapeutic agents: Cardiomyopathy and beyond

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Abstract

Tremendous strides have been made in the treatment of various oncological diseases such that patients are surviving longer and are having better quality of life. However, the success has been tainted by the iatrogenic cardiac toxicities. This is especially concerning in the younger population who are facing cardiac disease such as heart failure in their 30s and 40s as the consequence of the anthracycline's side-effect (used for childhood leukemia and lymphoma). This resulted in the awareness of cardio-toxic effect of anticancer drugs and emergence of a new discipline: Onco-cardiology. Since then numerous anticancer drugs have been correlated to cardiomyopathy. Additionally, other cardiovascular effects have been identified which includes but no limited to the myocardial infarction, thrombosis, hypertension, arrhythmias and pulmonary hypertension. This review examines some of the anticancer agents mitigating cardiotoxicity and presents current knowledge of molecular mechanism(s). The aim of the review is to ignite awareness of emerging cardio-toxic effects as new generation of anticancer agents are being tested in clinical trials and introduced as part of therapeutic armamentarium to our oncological patients.

Introduction

The National Cancer Institute defines cardiotoxicity as “toxicity that affects the heart” (www.cancer.gov/dictionary/). It's quite a simplistic explanation which essentially describes the word “cardiotoxicity” rather than defines it. One of the more accurate clinical descriptions of cardiotoxicity has been formulated by the cardiac review and evaluation committee supervising trastuzumab clinical trials, who defined drug-associated cardiotoxicity as one or more of the following: 1) Cardiomyopathy characterized by a decrease in left ventricular ejection fraction (LVEF) globally or due to regional changes in interventricular septum contraction; 2) symptoms associated with congestive heart failure (CHF); 3) signs associated with HF, such as S3 gallop, tachycardia, or both; 4) decline in initial LVEF of at least 5% to less than 55% with signs and symptoms of heart failure or asymptomatic decrease in LVEF of at least 10% to less than 55%¹. This definition has a

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limited scope as it does not include subclinical cardiovascular damage that may occur early in response to some of the chemotherapeutic agents. Other cardiac factors such as coronary artery disease and rhythm disturbances or other affected cardiovascular organ system such as pulmonary hypertension has been excluded also. Thus, this definition while ideal for cardiomyopathy, does not encompass the broad scope of unwanted cardiovascular effects of the anticancer drugs. Although recent upsurge in the interest of cardio-toxicity mediated by the anticancer drugs has been due to an increased incidence of cardiomyopathy and consequent HF in oncological patients², newer anticancer drugs have different array of cardiovascular effects. Therefore, collaborative efforts between the oncologists and the cardiologists are clearly warranted to screen, identify and manage our cancer patients for cardiac disease so that early intervention can provide boon to this cohort of highly specialized population.

This review paper will discuss chemotherapeutic mediated cardiomyopathy and beyond. It is not an exhaustive review of all the anticancer medication/regimen but it's an attempt to provide examples of cardiovascular toxic effects of some of the prominent anticancer drugs. The paper outlines a clinical perspective and molecular mechanism involved with each anticancer drug. The research effort to attenuate, if not to ameliorate, cardio-toxic effects lies in the deeper understanding of the mechanism(s) behind anticancer mediated cardiotoxicity.

Cardiomyopathy

Anthracyclines

Clinical Perspective—In a retrospective analysis of over 4000 patients treated with doxorubicin (DOX), Von Hoff and colleagues³ found that 2.2% of the patients developed clinical signs and symptoms of CHF. Since the study identified CHF based on clinical assessment, incorporation of subclinical left ventricular dysfunction would result in higher incidence of the cardiovascular disease in DOX patients; as acknowledged by the authors themselves³. This study went on to conclude that the prevalence of heart failure markedly increased with a cumulative dose of 550 mg/m² of DOX³, which is now recognized as one of the greatest determinants in the development of anthracycline mediated heart failure⁴.

Subsequently, the cardiotoxicity in DOX treated patients was prospectively assessed in three clinical trials (two in breast and one in non-small cell lung cancer) conducted between 1988 and 1992. The studies showed that the rate of conventional DOX-related CHF was 5% at a cumulative dose of 400 mg/m², 16% at a dose of 500 mg/m² and 26% at a dose of 550 mg/m²⁴. While there is a clear dose-response associated with cardiotoxicity, histopathologic changes can be seen in endomyocardial biopsy specimens from patients who have received as little as 240 mg/m² of DOX⁵. Moreover, subclinical events occurred in about 30% of the patients, even at doses of 180–240 mg/m²⁶, although they were observed 13 years after the treatment was received. Even doses as low as 100 mg/m² have been associated with reduced cardiac function^{5, 7}. These findings suggest that there is no safe dose of anthracyclines. Conversely, early studies suggested that some patients had no significant cardiac complications despite achievement of the doses as high as 1000mg/m²²³. Therefore, individual susceptibility to cardiomyopathy may vary. However, the current consensus is that DOX causes cardiomyopathy.

Potential Molecular Mechanisms—Anthracycline mediated cardiomyopathy has been studied extensively. Among the pathways implicated in anthracycline mediated toxicity involves production of reactive oxygen species, formation of iron complexes resulting in intracellular damage. However, we identified a direct target of doxorubicin that provides a unifying mechanism encompassing most of the implicated pathways.

It has been well-studied that one of the mechanisms of DOX induced tumor-cytotoxic effect is mediated by topoisomerase II alpha inhibition⁸. Topoisomerase II alpha is an enzyme that regulates the overwinding or underwinding of DNA during its repair process⁹. They play an important role in regulating cellular processes such as replication, transcription, and chromosomal segregation by altering DNA topology⁹. On the other hand, topoisomerase II beta (Top II B) serves the same function in quiescent cells. Since they share catalytic mechanisms and have a high degree of amino acid similarity (~70% identity at the amino acid level)¹⁰; we embarked on a project to study the role of Top II B in murine cardiac cells treated with DOX. We successfully demonstrated that¹¹: (a) in rats, the molecular phenotype of acute and chronic DOX cardiomyopathy is characterized by the formation of a ternary DNA–Top II B–DOX cleavage complex, that triggers double-strand breaks in the DNA; (b) the acute stage is characterized by upregulation of the apoptotic pathway signaling, specifically *Apaf-1*, *Bax*, *Mdm-2* and *Fas*. Under chronic condition, (c) the genes implicated in mitochondrial dysfunction and oxidative phosphorylation were activated by downregulation of peroxisome proliferator activated receptor gamma, coactivator 1 alpha (*Ppargc-1a*) and beta (*Ppargc-1b*)¹¹. This downregulation resulted in (d) decrease in the key components of the electron transport chain such as *Ndufa3*, *Sdha*, and *Atp5a1* thus culminating into (e) ultrastructural mitochondrial damage with vacuolization¹¹. The mitochondria were also (f) dysfunctional as measured by oxygen consumption and changes in mitochondrial membrane potential. The end result was (g) an increase in end systolic and end-diastolic volumes with decrease in ejection fraction¹¹. The formation of the ternary complex is also responsible for the production of most (70%) DOX-induced ROS. Therefore the oxidative stress is preferentially a result of the DOX-induced DNA damage and of the consequent changes in the transcriptome rather than of the redox-cycling of DOX. Transgenic mice with cardiomyocyte-specific deletion of Top II B were indeed protected from the acute and progressive or chronic DOX-induced heart failure, and did not exhibit the severe cardiomyopathic phenotype of the wild type mice. Therefore, Top II B is required to initiate the entire phenotypic cascade of DOX-induced cardiomyopathy¹¹. Other studies also identified the activation of the p53 pathway to DNA-damage and the consequent apoptosis and mitochondrial dysfunction in cultured cardiomyocytes treated with DOX^{12, 13}.

The corroborating evidence of Top II B mechanism is provided by the use of dexrazoxane (DEX). In vivo, DEX has shown significant cardio-protection against DOX in various preclinical models such as mouse, rat, hamster, rabbit, and dog^{14–17}. In addition, the cardioprotective effects were evident in both acute and chronic models of DOX-induced cardiomyopathy^{18, 19}. These findings were extended to human subjects in various clinical trials also^{16, 20–23}. It appears that DEX can block ATP hydrolysis and inhibit the reopening of the ATPase domain, thereby trapping the topoisomerase complex on DNA and blocking enzyme turnover²⁴ which may be its predominant mechanism. Therefore, DEX inhibits

DOX's activity on TOP II B catalytic site, thereby providing cardio-protection. In essence, DOX/DNA/Top II B ternary complex may be the prime mediator of anthracycline mediated cardiomyopathy.

Trastuzumab

Clinical Perspective—The first evidence that trastuzumab might be involved in cardiomyopathy was identified in a pivotal Phase III clinical trial designed to assess its efficacy in the breast cancer patients. The outcome was an improved survival in this cohort²⁵. However, heart failure was detected in 27% of patients treated with the regimen of anthracycline, cyclophosphamide, and trastuzumab²⁵. Subsequently, several large clinical trials confirmed the importance of trastuzumab in increasing disease-free survival from cancer, but also established trastuzumab's association with heart failure^{26, 27}. The incidence of cardiomyopathy dropped to 13% when anthracyclines were not administered concurrently with trastuzumab; although these patients were previously treated with anthracycline. In the adjuvant trials, 1.7–4.1% of trastuzumab-treated patients developed CHF²⁷ when anthracycline was not part of the therapeutic regimen. Thus, trastuzumab came with a black box warning of possible inducing cardiomyopathy.

Potential Molecular Mechanisms—Early studies indicated that Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2), and its activating ligand, neuregulin-1 (Nrg1), play an integral role in the cardiac development. Germline deletion of ERBB2²⁸ or Nrg1²⁹ in the mice results in mid-gestational lethality owing to dysmorphic ventricular development. This suggests that ERBB2 signaling is required for cardiomyocyte proliferation and cardiac development. Mice with the cardiac-specific deletion of ERBB2, after cardiac development, were viable³⁰. However, these mice developed dilated cardiomyopathy as they aged and had decreased survival when subjected to pressure overload induced by aortic banding^{31, 32}. Cardiomyocytes from these mice also exhibited enhanced sensitivity to the anthracyclines, thus alluding to a mechanistic synergy between anthracycline and trastuzumab in clinical population³¹.

ERBB2 activation by its ligand in cardiomyocytes activates the ERK and PI3K/Akt pathways that promotes cardiomyocyte survival during adulthood³³. Expression of the anti-apoptotic protein Bcl-XL in the hearts of ERBB2 cardiac specific deleted newborn mice partially prevented the heart chamber dilation and the impaired contractility seen in adulthood³¹. Thus inhibition of ERBB2 signaling is important in normal cardiomyocyte function. However, unlike trastuzumab, lapatinib, the small molecule dual inhibitor of ERBB2 and EGFR, shows limited depression of cardiac function^{34, 35}, and therefore questioning the underlying mechanism of ERBB2 in mitigating trastuzumab mediated cardiac dysfunction. Similarly, pertuzumab, another inhibitor of ERBB2 signaling also showed marginal development of cardiomyopathy³⁶. Although it is possible that other actions of lapatinib such as activation of AMPK³⁷ and pertuzumab inhibition of ligand-mediated formation of heterodimer³⁸ might confer cardio-protective effect. Therefore, the precise mechanism involved in trastuzumab mediated cardio-toxicity remains elusive.

Myocardial Ischemia

5-Fluorouracil

Clinical Perspective—The incidence of myocardial ischemia ranged from 1.2–1.6% in patients treated with 5-FU, although reports of up to 68% also exists^{39–41}. The proportion increases with escalating doses (~ 10% with 800 mg/m²)³⁹. Other trials have higher incidence of ischemia with mortality rate of 2.2 – 13% attributed to 5-FU^{39, 41, 42}. The mean onset time for the ischemia is generally 72 hours although earlier episodes have also been reported⁴³. The incidence is especially high in patients with previous coronary artery disease (~5–10 fold increase)^{44, 45} and their recurrence rate is high in patients with previous ischemic episodes secondary to 5-FU administration⁴³. Furthermore, mode of administration, specifically continuous infusion of 5-FU have been associated with higher rates of cardiotoxicity (7.6%) as compared with bolus injections (2%)^{39, 40, 46}.

Potential Molecular Mechanisms—Coronary artery thrombosis, arteritis, or vasospasm have been proposed as some of the potential underlying mechanisms⁴⁷. Vasospasm seems to be the working hypothesis, however, the failure of ergonovine and 5-FU to elicit vasospasm during cardiac catheterizations, weakens the potential role of 5-FU–induced vasospasm^{47–50}. In one of the studies, elevated endothelin levels were found with 5-FU administration^{47, 51}. However, the lack of evidence if endothelin was cause or an effect of 5-FU, questions the validity of this pathway. Therefore, alternative mechanisms have been speculated, including direct toxicity of the myocardium, inducing hypercoagulable state, and autoimmune response^{47, 50}. Additionally, metabolic pathways are also implicated. Fluoroacetate is generated from a degradation product of parenteral 5-FU preparations, fluoroacetaldehyde. This accumulation of fluoroacetate interferes with the Krebs cycle^{39, 50}. This may in turn result in citrate accumulation which might be a causative mechanism^{39, 47, 50} as 5-FU has been known to induce dose- and time-dependent depletion of high-energy phosphates in the ventricle^{39, 49}. Other mechanism such as protein kinase C mediated vascular smooth muscle activation and subsequent vasoconstriction by Mosseri *et al*⁵² further add to the complexity of 5-FU mediated cardiotoxicity⁵². Lastly, 5-FU mediated cardio-toxicity may also involve apoptosis of myocardial and endothelial cells resulting in inflammatory lesions mimicking toxic myocarditis^{50, 53}. Therefore, the exact mechanism remains undetermined. A complete analysis of 5-FU putative pathways involved in cardiovascular dysfunction can be found elsewhere⁵⁴.

Hypertension

Bevacizumab

Clinical Perspective—Bevacizumab is a humanized monoclonal antibody against the VEGF-A ligand that binds to its circulating target and downregulates angiogenesis⁵⁵. It has been approved by the European Medicines Agency and by the United States Food and Drug Administration, and it is the first- or second-line chemotherapy for the treatment of many advanced solid tumors, including colorectal cancer (CRC), non-small-cell lung cancer (NSCLC), breast cancer, glioblastoma, renal cell cancer (RCC), ovarian cancer, and cervical cancer^{56–63}. Although the efficacy of bevacizumab has been demonstrated in many clinical

trials, its use has been associated with many cardiovascular events, including high risk hypertension (HTN). Overall incidence of 4%–35% reported in clinical trials^{58, 62, 64}. This variability might be attributed to the different selection criteria used in clinical trials (eg, the age of the patients included), as well as to differences in the definition of HTN.

In Phase I trials, bevacizumab was safely administered at a dose up to 10 mg/kg without dose-limiting toxicities, but mild increases in BP were observed at higher dose levels tested⁶⁵. Interestingly, patients with RCC and breast cancer who received the drug at a dose of 5 mg/kg weekly had a higher risk of developing HTN⁶⁶. The median interval from initiation of bevacizumab to the development of HTN is approximately 4.6–6 months. Bevacizumab-related HTN can develop at any time during treatment, and the data suggest that there is a dose relationship⁶⁷. Specifically, the risk of HTN is increased by three times with low doses and 7.5 times with high doses of bevacizumab⁶⁸. A majority of the patients who developed HTN in clinical trials were treated with antihypertensive medication and continued bevacizumab. This is particularly important, since there is a clear association between the efficacy of and duration of exposure to bevacizumab⁶⁹. However, HTN resistant to medication might lead to discontinuation of bevacizumab in 1.7% of patients⁷⁰. Single cases of hypertensive crisis with encephalopathy and subarachnoid hemorrhage have also been reported⁷⁰.

Potential Molecular Mechanisms—There are supportive evidence for two potential mechanisms by which VEGF signaling pathway (VSP) inhibition may lead to hypertension: 1) acute decreased production of vasodilating factors leading to arteriolar vasoconstriction, and 2) chronic depletion of microvascular endothelial cells leading to a net reduction in normal tissue microvascular density, a process called rarefaction. The evidence for diminished vasodilator production is indirect. The endothelial nitric oxide synthase enzyme is post-translationally activated by the VSP⁷¹. Studies of bevacizumab, incubated with human umbilical vein endothelial cells, demonstrate reduction in nitric oxide production within hours of incubation⁷². The evidence for the second potential mechanism comes from a small clinical trial of 20 patients. In this cohort, bevacizumab induced hypertension was accompanied by endothelial dysfunction and capillary rarefaction; both changes are closely associated with the rise in the blood pressure that was observed in most patients⁷³. Bevacizumab targeted not only the pathological and ‘switched’ vessels feeding the tumor area, but also the ‘normal’ arterioles and capillaries far from the tumor zone in these study patients⁷³. Other systems such as endothelin⁷⁴ and endothelial dysfunction⁷⁵ increase has also been implicated in TKIs mediated hypertension.

Multi-targeted Tyrosine Kinase Inhibitors

Bevacizumab was one of the first approved members of VSP inhibitors as an anticancer agent⁵⁶. The approval of bevacizumab has been followed by FDA approval of five additional VSP inhibitors for various cancer types. Sunitinib (Sutent), sorafenib (Nexavar), pazopanib (Votrient), axitinib (Inlyta), and vandetanib (Caprelsa) are all small molecule multiple tyrosine kinase inhibitors with varying degree of specificities for VEGF receptors. Studies have shown that there seems to be class effect when it comes to hypertension and, like the

therapeutic efficacy, VSP inhibitors also display different degrees of hypertension. This has been extensively discussed elsewhere⁷⁵⁻⁷⁷

Arrhythmias

Bradyarrhythmia

Thalidomide

Clinical Perspective: Thalidomide (a-N-phthalimidoglutarimide) was initially manufactured in West Germany and was marketed as an antiemetic and sedative. It was also used as anxiolytics and for insomnia. Later on when the marketing of over-the-counter thalidomide began for morning sickness, an increase in limb malformation was noted. Therefore, given its serious side-effect of phocomelia (limb malformation), it was discontinued. Over the years it has been found that thalidomide act as a potent immunosuppressive and antiangiogenic agent^{78, 79} by inhibiting the phagocytic ability of inflammatory cells and the production of cytokines, such as tumor necrosis factor- alpha (TNF- α). Therefore, thalidomide emerged as an anticancer agent. Initial trials with thalidomide showed that patients with advanced and refractory multiple myeloma, in whom salvage therapy failed after single and even tandem auto-transplants, one-third of this cohort responded markedly to thalidomide^{80, 81}. Eventually, thalidomide became a member of anti-neoplastic armamentarium in the fight against multiple myeloma.

An observation of bradycardia in thalidomide group prompted Fahdi *et al*⁸² to do a prospective chart review on 200 consecutive patients enrolled in an ongoing phase III clinical trial for patients with multiple myeloma. In this study, patients were randomized to receive either thalidomide or placebo in addition to the standard therapy. It was found that 53% of patients had bradycardia in thalidomide group defined as resting heart rate of < 60 beats per minute. Roughly 15% had heart rate below 30 and five patients (roughly 10% of the bradycardic group) required permanent pacemaker. The bradycardia was neither due to concomitant administration of beta-blocker nor any electrolyte imbalance. The baseline characteristics in both thalidomide and placebo group were well-matched⁸².

Thalidomide induced bradycardia has been also found in non-oncological patients. A pilot study was carried out to determine the efficacy of thalidomide in amyotrophic lateral sclerosis⁸³. Thalidomide was initiated at 100 mg per day for 6 weeks. Thereafter, the dose was increased every week by 50 mg until a target dose of 400 mg per day was achieved with goal of continuing the maximum dose for next 12 weeks. During the last 12 weeks of thalidomide treatment, nine thalidomide patients (50%) developed bradycardia defined as a heart rate below 60 beats per minute (bpm) and ranged from 46 to 59 bpm. Mean heart rate dropped by 17 bpm in the thalidomide treatment. Severe symptomatic bradycardia of 30 bpm occurred in one patient. Furthermore, a patient died from sudden unexpected death. The study was terminated prematurely for safety concerns⁸³. Therefore, thalidomide appears to induce bradycardia in some patients.

Potential Molecular Mechanism: A balance between sympathetic and parasympathetic nervous system balance exists which maintains a narrow physiologic stable heart rate.

Studies have shown that dorsal motor neurons, which are a part of the nucleus of vagus nerve (parasympathetic system), are completely inhibited by TNF- α ⁸⁴. Since, thalidomide inhibits TNF-expression and activity, it could lead to overactivity of the parasympathetic system thus inducing bradycardia⁸². Bradycardic response was decreased by reducing the dose or discontinuing thalidomide, suggesting a reversible effect on sinus node function. Therefore, it is believed that thalidomide-related bradycardia may be due to its action on parasympathetic system and seems to be reversible in nature⁸².

QT Prolongation

Arsenic Trioxide

Clinical Perspective: QT prolongation with arsenic trioxide has been well-reported. The initial studies were looking at use of arsenic trioxide in promyelocytic leukemia. Although significant benefit was achieved in the studied cohort, 63% of the patients displayed QT duration above 500 ms. Compared with baseline, the heart rate-corrected (QTc) interval was prolonged by 30–60 msec in 36.6% of the patients^{85, 86}. Retrospective analysis of Phase I and Phase II trials showed that, in treatment of advanced malignancies, arsenic trioxide resulted in increase in QT interval in 22% of the patients⁸⁷. Furthermore, Schiller *et al*⁸⁸ studied 70 patients who received arsenic for myelodysplastic syndrome and found that 24% patients developed QT prolongation. Although, there were clinically significant arrhythmias secondary to QT prolongation (which included atrioventricular block⁸⁹, torsade de pointes⁹⁰, ventricular tachycardia⁸⁶ and sudden cardiac death⁹¹); other studies with QT prolongation were clinically uneventful⁸⁸.

Potential Molecular Mechanisms: The mechanism proposed ranges from neuropathy to electrolyte changes with arsenic interacting with magnesium⁹⁰. Studies in guinea pigs have shown that prolonged action potential by arsenic trioxide is due to increase in calcium current as well as decreasing membranous expression of hERG channels⁹². However, other studies also suggest a direct inhibition of hERG channels also⁹³. It appears that interplay between elevated calcium and reduced hERG channel expression/activity determines the QT interval in arsenic trioxide treated patient population⁹³.

Multi-targeted Tyrosine Kinase Inhibitors

Clinical Perspective

Multi-targeted tyrosine kinase (TKI) inhibitors disrupt various mitogenic pathways in both cancer cells and the associated vasculature. Among the new medications of this class, sunitinib and its active metabolite SU012662 seemed to prolong QT interval in preclinical trials⁹⁴. This finding was also translated to clinical population as the patients with metastatic renal cell carcinoma, treated with sunitinib resulted in QTc prolongation in 9.5% of the patients⁹⁵. Recently, a retrospective analysis was carried out on the multi-targeted tyrosine kinases. In this multicenter clinical trial four centers in the Netherlands and Italy screened patients who were treated with erlotinib, gefitinib, imatinib, lapatinib, pazopanib, sorafenib, sunitinib, or vemurafenib⁹⁶. A total of 363 patients were eligible for the analyses. At baseline measurement, QTc intervals were significantly longer in females than in males (QTcfemales=404 ms vs QTcmales=399 ms, P=0.027) as expected. A statistically

significant increase was observed in the individual treated with sunitinib, vemurafenib, sorafenib, imatinib, and erlotinib (median 0394;QTc ranging from +7 to +24 ms, $P<0.004$)⁹⁶. Especially, patients treated with vemurafenib were at increased risk of developing a QTc of greater than or equal to 470 ms, a threshold associated with an increased risk for arrhythmias⁹⁶.

Similarly, another meta-analysis was carried out on trials looking at various TKIs (sunitinib, sorafenib, pazopanib, axitinib, vandetanib, cabozantinib, ponatinib and regorafenib)⁹⁷. A total of 6548 patients from 18 trials were selected. QTc prolongation for the TKI vs no TKI arms was 8.66 (95% CI 4.92–15.2, $P<0.001$) versus 2.69 (95% CI 1.33–5.44, $P=0.006$), respectively, with most of the events being asymptomatic QTc prolongation. Furthermore, 4.4% and 0.83% of patients exposed to VEGFR TKI had all-grade and high-grade QTc prolongation, respectively⁹⁷. During subgroup analysis, only sunitinib and vandetanib were associated with a statistically significant increase of QTc prolongation, with higher doses of vandetanib conferring greater risk. The rate of serious arrhythmias including torsades de pointes did not seem to be higher with high-grade QTc prolongation⁹⁷. The risk of QTc prolongation was independent to the duration of the therapy⁹⁷.

Potential Molecular Mechanisms

TKIs mediated QTc interval prolongation is thought to be directly caused by a drug's three-dimensional molecular structure interacting with myocardial hERG K_p channels resulting in delayed impulse conduction⁹⁸. Furthermore, another putative proposed mechanism of QTc prolongation that is not tested in preclinical studies is the inhibition of hERG K_p channel protein trafficking. Interference with the translocation of hERG channel via chaperone proteins from the endoplasmic reticulum to the plasma membrane reduced hERG K_p current⁹⁹, thereby affecting cardiac repolarization. Therefore, hERG channels represents a putative molecular mechanism in TKI induced QTc prolongation.

Thrombosis

Venous Thromboembolism

Thalidomide

Clinical Perspective: Patients who received thalidomide as a monotherapy for the treatment of myeloma had a less than 5% risk of developing VTE⁸¹. However, when thalidomide is a part of a combination chemotherapeutic regimen, the risk is dramatically increased. Thrombosis rates were estimated at 10–20% for myeloma patients receiving thalidomide with dexamethasone¹⁰⁰ and 20–40% for those taking it with doxorubicin^{101, 102}. Rates as high as 43% of VTE were noted in a phase II clinical trial of thalidomide with gemcitabine and continuous infusion of fluorouracil in the treatment of metastatic renal cell carcinoma¹⁰³. Prophylactic LMWH, but not low-dose warfarin, has been shown to significantly reduce the risk of thalidomide-associated VTE¹⁰⁴.

Potential Molecular Mechanisms: The mechanism by which thalidomide stimulates thrombosis is not fully elucidated. In a cross-sectional study of myeloma patients treated with or without thalidomide chemotherapy, levels of protein C, protein S and AT III, as well

as lupus anticoagulant, factor V Leiden, factor II mutation or factor XI did not differ between the two groups¹⁰⁵. One school of thought exists that the synergistic prothrombotic effect may exist between various chemotherapeutic agents and thalidomide resulting in the endothelial cell dysfunction and damage, thereby providing nidus for hypercoagulability¹⁰⁶. Currently it's a good theory but currently lacks empirical data.

Cisplatin

Clinical Perspective: Cisplatin interferes with DNA repair mechanism and therefore being used in numerous malignancies. In a retrospective analysis of the patients suffering from germline cell mutation and consequent cancer, treatment with cisplatin and bleomycin-based chemotherapy increased the risk of thrombosis by 8.4%¹⁰⁷. Specifically, incidence was higher in non-small cell lung cancer patients treated with cisplatin and gemcitabine at 17.6%¹⁰⁸. Patients treated with radiation and low-dose cisplatin had a VTE incidence of 16.7% in invasive cervical cancer cohort. Additionally, patients with ovarian cancer treated with cisplatin, epirubicin and cyclophosphamide had an incidence of 10.6%¹⁰⁹. Furthermore, cisplatin has also been implicated in stroke, recurrent peripheral arterial thrombosis and aortic thrombosis¹¹⁰. Recent meta-analysis of 8,216 patients from 38 randomized trials revealed that cisplatin increased the likelihood of a thromboembolic event by 1.67-fold¹¹¹.

Potential Molecular Mechanisms: The mechanisms by which cisplatin promote thrombosis are not well studied. In vitro evidence suggests that pharmacological doses of cisplatin increase tissue factor (TF) activity without any change in TF expression in human monocytes¹¹². Alternatively, cisplatin has also been shown to induce platelet activation¹¹³, increase von Willebrand factor (vWF) levels^{114, 115}, and induce endothelial cell apoptosis; latter pathway resulting in release of procoagulant endothelial microparticles that are able to generate thrombin through tissue factor independent pathways. Therefore, a succinct mechanism for cisplatin mediated VTE remains undetermined.

Arterial Thromboembolism

Bevacizumab

Clinical Perspective: Bevacizumab has been associated with an increased risk of arterial thromboembolism as defined by myocardial and cerebrovascular events. In a pooled analysis of 1,745 patients from five different randomized controlled trials in metastatic colorectal, non-small cell lung cancer, and metastatic breast cancer patients, the overall incidence of arterial thromboembolisms (ATEs) was 3.8%¹¹⁶. Specifically, the incidence of MI was 1.5% versus 1% in the bevacizumab and the control group, respectively¹¹⁶. In an observational study of 1,953 patients receiving bevacizumab with standard chemotherapy, the incidence of serious ATEs was 1.8% with 0.6% of the total population experiencing MI¹¹⁷. A more recent meta-analysis, which included 12,617 patients from 20 Phase II and III randomized controlled trials, also showed similar incidence of ATEs¹¹⁸. Bevacizumab was associated with a significantly increased risk of cardiac ischemia (RR =2.14; 95% CI: 1.12–4.08), but not stroke (RR =1.37; 95% CI: 0.67–2.79, P=0.39). Patients receiving bevacizumab had an

overall incidence of all-grade ATEs of 3.3%, whereas the incidence of high-grade events was 2% in control patients¹¹⁸.

Potential Molecular Mechanisms: It is well known that the characteristic feature of any ATE includes, disruption of unstable atherosclerotic plaques and the associated activation of platelets¹¹⁹. Bevacizumab might reduce anti-inflammatory effects of chronic VEGF exposure, leading to increased inflammation and atherosclerotic instability, and resulting in plaque rupture and thrombus formation¹²⁰. Additionally, VEGF is important for the proliferation and repair of endothelial cells¹²¹. Therefore, anti-VEGF therapy may compromise these reparative mechanisms, leading to endothelial cell dysfunction and exposing sub-endothelial layer. As a result, the TF is activated, increasing the risk of thrombosis¹²¹. Finally, anti-VEGF therapy causes a reduction in nitric oxide and prostacyclin, as well as an increase in blood viscosity via the overproduction of erythropoietin, all of which comprise predisposing factors for increased risk of thromboembolic events as per Virchow's triad¹²².

Ponatinib—The phase II PACE (ponatinib Ph+ ALL and CML evaluation) study was an open label, single-arm, multi-center trial that included patients with chronic phase CML (CP-CML), accelerated phase CML (AP-CML), blast phase CML (BP-CML), or Ph+ ALL¹²³. This cohort comprised of patients who were either resistant or intolerant to dasatinib/nilotinib or had positive T315I mutation. While the primary and secondary endpoints were in favor of ponatinib, emergence of ATEs was an unexpected findings. Eleven percent of ponatinib developed ATEs, and the event was serious in 8% of the patients. Myocardial infarction or worsening coronary artery disease were the most common ATEs event. Furthermore, patients who experienced a serious ATEs, 62% required a revascularization procedure¹²³. This findings were reinforced in another clinical trial. EPIC was a randomized multicenter phase III, 2-arm open-label trial of ponatinib (45 mg once daily) versus imatinib (400 mg once daily) in the newly diagnosed CP-CML. On 18 October 2013, EPIC was terminated due to the observation of arterial thrombotic events in the ponatinib development program¹²⁴. In total, eleven (7%) ponatinib and three (2%) imatinib patients experienced arterial thrombotic events, designated serious for ten [7%] ponatinib and one [0.7%] imatinib patient(s). Interestingly, ten of the eleven ponatinib patients, and two of three imatinib patients with arterial thrombotic events had 1 or more cardiovascular risk factors¹²⁴. This trial received a lot of notoriety as FDA asked Ariad Pharmaceuticals, makers of ponatinib, to suspend sales due the concerns regarding ponatinib's effect on thromboembolism.

Potential Molecular Mechanisms: Ponatinib, is a strong inhibitor of VEGFR1–3, which explains the high incidence of hypertension¹²⁵. Furthermore, ponatinib inhibits of the angiopoietin receptor TIE-2 (KDR) and all FGFR kinases may enhance vascular toxicity¹²⁶. Thus, it is believed that due to widespread inhibition of various angiogenic receptors, ponatinib, poses a greater risk of vascular toxicity leading to increased ATEs.

Pulmonary Hypertension

Dasatinib

Clinical Perspective—Dasatinib has been implicated in precipitating pulmonary arterial hypertension (PAH). Montani *et al*¹²⁷ reported nine cases of symptomatic PAH in a French pulmonary hypertension registry in patients treated with dasatinib for chronic myelogenous leukemia. The authors estimated that PAH occurred in 0.45% of patients taking this drug. They also reported that PAH can occur as a late complication of dasatinib therapy, occurring 8–48 months after initiation of therapy. During the initial diagnosis, most patients had severe clinical, functional and/or hemodynamic impairment. Unfortunately, some of them required vasoactive drugs and management in the intensive care unit¹²⁷. Clinical and functional improvements were observed after discontinuation of the dasatinib; however, some patients required specific PAH treatment also. Acute vasodilator response was observed in only one out of nine patients, suggesting that increased vasoreactivity may not represent the main mechanism of dasatinib-induced PAH. Indeed, the majority of the patients failed to demonstrate complete hemodynamic recovery and two patients died during follow-up¹²⁷. This observation is surprising because dasatinib has been shown to inhibit growth factors implicated in pulmonary artery smooth muscle cell proliferation. Interestingly, all patients had previously received imatinib before dasatinib and six patients had received nilotinib after dasatinib discontinuation without PAH recurrence. This suggests dasatinib induced PAH is specific to this drug and is not due to a class-effect¹²⁸. In October 2011, the US Food and Drug Administration (FDA) issued a warning regarding cardiopulmonary risks of dasatinib and recommended that patients should be evaluated for signs and symptoms of cardiopulmonary disease before and during dasatinib treatment¹²⁹. Increased PAH incidence was also found at 36 months in the follow-up of the DASISION study (Dasatinib Versus Imatinib Study in Treatment-Naïve CML Patients study). PAH was reported in 3% of the patients in the dasatinib group compared to 0% in imatinib¹³⁰.

Potential Molecular Mechanisms—The working hypothesis is that by inhibiting Src, which plays a critical role in smooth muscle cell proliferation and vasoconstriction, dasatinib alters the proliferation/ antiproliferation equilibrium at the endothelial and pulmonary arterial smooth muscle level¹²⁸ resulting in hypertension. In addition, all other molecular targets specific to dasatinib might be involved, but further research must be done to understand the exact mechanisms involved.

Cyclophosphamide

Clinical Perspective—Ranchoux *et al*¹³¹ reviewed the French pulmonary hypertension network of all documented cases of pulmonary venous occlusive disease (PVOD) to determine the most likely chemotherapeutic agent involved. They reported that of the 179 eligible patients on PVOD, only 27 (15%) could be considered chemotherapy-induced. Of the 37 cases of chemotherapy-associated PVOD, 84% involved alkylating or alkylating-like agents. Nearly half (43%) were represented by cyclophosphamide, followed by near equal frequency of mitomycin C (24.3%) and cisplatin (21.6%) thus implicating cyclophosphamide as the most frequent contributing underlying chemotherapeutic agent for the development of PVOD¹³¹. Chemotherapy-induced PVOD was more frequent in younger

patients (4 to 66 years old; 13 individuals above 50 years; median age 37.8 years) and was independent of the gender (male, 45.9%, versus female, 54.1%)¹³¹. Moreover, approximately 78% of chemotherapy-induced PVOD in the French pulmonary hypertension network presented within 1 year following the initiation of chemotherapy. This is especially ironic as cyclophosphamide is used to treat pulmonary hypertension induced by systemic lupus erythematosus¹³².

Potential Molecular Mechanisms—The precise mechanism is unknown. Rancheros *et al*¹³¹ also conducted animal research and found that mechanism involved in cyclophosphamide mediated pulmonary hypertension might be due to reduced expression of potassium channels, more specifically KCNK3. Although, corroborating evidence or elucidation of other pathways are still pending.

Conclusion

Development of cardiomyopathy, specifically with anthracycline led to the inception of onco-cardiology. Since then chemotherapy has been not only correlated to cardiomyopathies but have been implicated in other cardiovascular side-effects with significant morbidity and mortality. Early recognition, prompt intervention and active prevention will be the cornerstone of ameliorating the cardiovascular adverse events. This requires a collaborative effects of oncologists and cardiologists. This is especially important when numerous newly discovered anticancer drugs are entering the clinical trials. As we strengthen the war against cancer, we should continue to fight the battle for emerging cardiovascular disease in our oncological patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary Title

Cancer survivorship has seen an unprecedented increase due to the new anticancer agents. However, these drugs are marred by cardiovascular side-effect(s). This review highlights the clinical perspective and molecular mechanism(s) behind various cardio-toxic effects of some of the commonly used antineoplastic agents. The goal is to understand, delineate and ameliorate, if not to attenuate, these toxic side-effect profile of the anticancer agents.

Figure 1. Schematic representation of DOX/DNA/Top II Beta ternary Complex

Activation of the ternary complex results in double stranded DNA breaks which upregulates apoptotic signaling pathway. Furthermore, there is production of reactive oxygen species (ROS). Additionally, there is downregulation of peroxisome proliferation activated receptor gamma co-activator 1 alpha and beta (Ppargc-1 α/β) which results in mitochondrial dysfunction and decreased mitochondrial biogenesis. These pathways culminates into cardiotoxicity

Table 1
Cancer Therapies Associated with Cardiac Toxicities

Partial list of commonly used anticancer agents that have shown the corresponding cardiovascular complications.

Commonly used Cancer Drugs with Cardiovascular Complications		
Heart failure/Left Ventricular Dysfunction		
Chemotherapy agents	Incidence (%)	Frequency of Use
Anthracyclines		
Doxorubicin (Adriamycin®)	3–26 ^{*,#}	++++
Epirubicin (Ellence®)	0.9–3.3 [#]	+
Idarubicin (Idamycin PFS®)	5–18 [#]	++
Monoclonal Antibody-based tyrosine kinase inhibitors		
Adotrastuzumab emtansine (Kadcyla®)	1.8 ^b	+
Bevacizumab (Avastin®)	1–10.9	+++
Pertuzumab (Perjeta®)	0.9–16 ^b	+
Trastuzumab (Herceptin®)	2–28 ^b	+++
Myocardial Infarction/Ischemia		
Antimetabolites		
Capecitabine (Xeloda®)	3–9 [#]	++++
Fluorouracil (Adrucil®) ^{39–42, 44, 47, 133–136}	1–68 [§]	++++
Hypertension		
Monoclonal Antibody-based tyrosine kinase inhibitors		
Adotrastuzumab emtansine (Kadcyla®)	5.1	+
Bevacizumab (Avastin®)	23–34 [#]	+++
mTor Inhibitors		
Everolimus (Afinitor®)	4–13	++++
Temsirolimus (Torisel®)	7	++
Small molecule tyrosine kinase inhibitors		
Sorafenib (Nexavar®)	9.4–41 [#]	++++
Sunitinib (Sutent®)	15–34 [#]	++++
Thromboembolism		
Alkylating agent		
Cisplatin (Platinol-AQ®)	8.5	+++
Angiogenesis Inhibitors		
Lenalidomide (Revlimid®) ^{1137–142}	3–75 ^{§b}	+++

Commonly used Cancer Drugs with Cardiovascular Complications		
Thalidomide (Thalomid®) ¹	1–58 ^{<i>s b</i>}	++
Pomalidomide (Pomalyst®) ^{2100, 143–15299, 142–151}	3 ^{<i>s b</i>}	+
Monoclonal Antibody-based tyrosine kinase inhibitor	6–15.1 ^{<i>¶#</i>}	+++
Bevacizumab (Avastin®) ²		
Small molecule tyrosine kinase inhibitors		
Ponatinib (Iclusig®) ²	5 ^{<i>b</i>}	+
Bradycardia		
Angiogenesis Inhibitor		
Thalidomide (Thalomid®) ^{82, 146, 150, 153–15581, 145, 149, 152–1541}	0.12–55 ^{<i>s#</i>}	+
QT Prolongation		
^{156, 157155, 156} Miscellaneous		
Arsenic trioxide (Trisenox®) ^{87, 91, 156, 158–16386, 90, 155, 157–162}	26–93 ^{<i>*#</i>}	++
Small molecule tyrosine kinase inhibitors		
Nilotinib (Tasigna®)	<1–4.1 ^{<i>b</i>}	++++
Vandetanib (Caprelsa®)	8–14 ^{<i>b</i>}	++++

* At cumulative dose of 550 mg/m²

^{*s*} Wide variation exists in the incidence owing to different study design and definition

^{*¶*} When used in combination with other chemotherapies

^{*#*} Listed as a warning/precaution in package insert

^{*b*} Black box warning in package insert

The frequency of use was quantified using inpatient and outpatient doses dispensed at MD Anderson Cancer Center during the time period of January 1, 2014 through December 21, 2014. (+ = <1,000 doses dispensed; ++ = 1,000–5,000 doses dispensed; +++ = 5,000–10,000 doses dispensed; ++++ =>10,000 doses dispensed).