Cardiotoxicity in cancer therapeutics

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Abstract
It has been increasingly recognized that cardiac disease is a comorbid condition for cancer patients that deserves special attention. Although the primary goal of cancer therapy remains to cure the life-threatening disease, it is also important to maintain the highest possible quality of life, especially since more cancer patients survive either without cancer or with cancer as a manageable, chronic disease. Cardiovascular complications of anticancer therapies have been known for quite some time, particularly with cytotoxic therapies such as anthracyclines used at higher cumulative doses and after mediastinal radiotherapy. Frequently, cancer cells are, or become by mutation, dependent on the activity of specific tyrosine kinases, which promote proliferation and survival. In addition, when tumor size reaches a critical extent, the cancer cells depend on vascularization for further growth and metastasis. The advent of targeted monoclonal antibodies and tyrosine kinase inhibitors has revolutionized the treatment of several types of malignancies. However, many of these targeted growth and survival pathways are also important for the homeostasis of non-cancerous tissue including the myocardium, and modulators may affect protein synthesis and degradation, energy production, calcium handling and tissue integrity.

Keywords: cancer therapy, cardiotoxicity, anthracyclines, cell death, mitochondria

Introduction
Cardiac toxicity associated with cancer therapies can range from asymptomatic subclinical abnormalities, including electrocardiographic changes and temporary left ventricular ejection fraction decline, to life-threatening congestive heart failure or acute coronary syndrome. Delayed toxicities may be less relevant for the acute cancer treatment, but much more so in the neo- and adjuvant setting where the overall duration of treatment can measure several years. Progress has been made in reducing the side effects of oncological treatment, for example by giving an iron chelator for the inhibition of free radicals, by improvements in imaging technologies for radiotherapy, or with different treatment schedules and drug formulations such as liposomes in order to target the therapy more precisely to the tumor [1]. Meanwhile, a large number of molecular targets for new anticancer-therapies have been developed [2].

Cardiotoxicity of cytotoxic chemotherapies
Cytotoxic chemotherapeutic drugs can be divided in anthracyclines, alkylating agents, antimetabolites, microtubule targeting agents, and others. Some of these drugs were discovered as naturally occurring compounds in plants or microorganisms, and they generally lead to growth inhibition and eradication of rapidly dividing cells. Anthracyclines are still widely used for many malignancies, despite their well-described cumulative cardiotoxicity, which is often
irreversible, and can lead to congestive heart failure [1, 3]. While there are a number of discrepancies in studies on anthracycline effects in cardiomyocytes regarding the primary mechanism—which could be explained by differences in drug dosage, animal model, and duration of treatment [4]—the formation of reactive oxygen species (ROS), changes in mitochondrial function [5], and finally mismanagement of cellular calcium handling appears to be a common endpoint [1, 6]. The irreversible loss of cardiomyocytes and hypothetical stem cells might also contribute to the late effects of anthracyclines, which can occur many years after treatment and is especially important for the treatment of pediatric patients [7].

Alkylating agents like cyclophosphamide and cisplatin may cause acute symptoms of chest pain, arrhythmias, and cardiac ischemia with elevated enzymes indicative of myocardial infarction after a single dose [8]. As with the anthracyclines, the formation of ROS is proposed as a cellular mechanism for the cardiotoxicity of alkylating agents. For the class of the antimetabolites, it is mainly 5-fluorouracil (5-FU) that is known for the risk of cancer therapy-associated cardiotoxicity. Coexisting coronary heart disease and hypertension frequently worsens the problem [9]. Microtubule targeting agents, like the taxanes, with paclitaxel as the best-studied example, can lead to bradycardia and other electrical disorders and to thrombosis [8]. The combined use of paclitaxel with anthracyclines enhances their cardiotoxicity [10]. In contrast to other cytotoxic drugs such as the anthracyclines, the effect of paclitaxel on cardiomyocytes does not comprise immediate cell death [11].

Cardiotoxicity of targeted therapies

So-called targeted therapies are usually designed with a molecular target in mind that has already been identified as a modulator of cell division and growth. Ideally, such a target, or family of target proteins, is more commonly found in those cells that have become, for example by genetic mutation, continuously dividing cancer cells. One of the first therapies of this kind, trastuzumab, is based on humanized antibodies against the receptor tyrosine kinase HER2. This receptor is found overexpressed in some tumors, frequently in breast cancer, making the HER2 receptors (corresponding to ErbB2 in rodents) a seemingly ideal target for cancer therapy. However, the use of trastuzumab in combination with anthracyclines was associated with cardiac dysfunction in up to 28% of patients in a pivotal trial [12]. The cardiac dysfunction observed during adjuvant treatment with trastuzumab for up to 2 years seems to be due to an impairment of contractility, rather than loss of cardiomyocytes, and is reversible in the majority of cases [13]. A mechanism without cardiomyocyte loss is also suggested by results from in vitro studies using adult rodent cardiomyocytes [11, 14]. The experience with trastuzumab and the experiments using neuregulin-1 beta in basic cardiovascular research has led to the hypothesis that survival factors such as the endothelium-derived neuregulin-1 beta, which binds to the heterodimer ErbB2/ErbB4 in cardiomyocytes, play an important role for myofibrillar integrity, contractile function and metabolic homeostasis in the myocardium challenged by cytotoxic cancer therapies and in general in stress conditions [14, 15].

The other and larger group of targeted therapies is tyrosine kinase inhibitors (TKIs), which bind to the ATP pocket of tyrosine kinases, either to receptors or intracellular kinases. Many new TKIs are currently in development and in early clinical trials. Among them are inhibitors of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathways that are also important in the cardiovascular system.

**Fig. 1** Primary cardiac microvascular endothelial cells were isolated from adult rats, cultured on glass-bottom dishes, stained alive with JC-1 and examined in the fluorescence microscope after treatment with sunitinib for 18 hours (a: untreated, b: 7.5 nM sunitinib, 15 nM sunitinib, 30 nM sunitinib). High mitochondrial membrane potential promotes the formation of dye aggregates, which fluoresce in red, while low potential results in the appearance of monomeric JC-1 and diffuse green fluorescence.
system. Careful cardiac monitoring seems warranted as these trials proceed [2]. Some TKIs are multi-targeted, i.e., less specific for a single protein kinase. The premise of less selective TKIs is that one or more of these additional targets may also play a role in disease progression and its inhibition will lead to better anticancer efficacy [16].

Antiangiogenic targeted therapies are currently used in clinical practice in the form of antibodies, such as the anti-vascular endothelial growth factor (VEGF)-A therapy bevacizumab, or as TKIs such as sorafenib and sunitinib. Sunitinib inhibits, among others, VEGF receptor 1–3, c-Kit, platelet-derived growth factor receptor (PDGFR)-A/B, rearranged during transfection (RET), FMS related tyrosine kinase 3 (FLT3), and colony stimulating factor 1 receptor (CSF1R) [16]. The mechanism for the observed cardiotoxicity of sunitinib is probably related to the inhibition of 5’ adenosine mono phosphate-activated protein kinase (AMPK) in cardiomyocytes and can lead to cell death at micromolar concentrations in vitro [17, 18]. We and others have observed changes in

![Stressors schematic](image)

**Stressors**
- Anthracyclines
- Taxanes
- Antimetabolites
- Radiation therapy
- Ischemia/reperfusion

**Gene Expression**
- GATA-4
- HIF1

**Cardiomyocytes**
- Cardiac microvascular endothelium
- VEGF-A
- Sunitinib
- Bevacizumab
- Neuregulin
- VEGFR-2
- VEGFR-1
- IMC-A12
- mTOR
- Perifosine
- VEGF-A
- GATA-4
- HIF1

**Cardiomyocytes**
- Gene Expression
- Doxorubicin
- Protein degradation
- Autophagy
- Apoptosis
- Necrosis

**Cardiac microvascular endothelium**
- VEGF-A
- Sunitinib
- Bevacizumab
- Neuregulin
- VEGFR-2
- VEGFR-1

**Proteins**
- Ras/Raf
- MEK
- PI-3-kinase
- Akt/PKB
- ERK1/2
- Bcl-2
- Bcl-XL

**Proteases**
- Oxidative Stress
- Proteasome

**Mitochondria**
- Cytosine C release
- [Ca²⁺]i

**Fig. 2** Some myocardial targets of cancer therapies and potentially cardioprotective signaling pathways in cardiomyocytes and as part of the paracrine signaling of microvascular endothelial cells and cardiomyocytes. Green arrows show therapeutics that potentially interfere with signaling components in the heart, although mentioning a certain therapy does not imply clinically relevant cardiotoxicity. **Top left**: Cytotoxic therapies and other stressors often lead to oxidative stress in cardiomyocytes and can cause protein degradation and cell death. **Top right**: Microvascular endothelial cells, among others, release factors that enhance protein synthesis and survival under stress conditions. Neuregulin and VEGF-A are examples, activating the MAPK and PI3K signaling pathways in cardiomyocytes. **Bottom**: Gene expression depends on transcription factors, which are also targets. GATA-4 drives the expression of antiapoptotic mitochondrial proteins Bcl-2 and Bcl-XL, but is inhibited by doxorubicin, and HIF-1 alpha is important for VEGF-A production in hypoxia, but is inhibited by new targeted and antiangiogenic therapies.
mitochondrial function by sunitinib in different cell types, as visually demonstrated with the cationic dye JC-1, that selectively enters into mitochondria and reversibly changes fluorescence emission color from red to green as the membrane potential decreases (Fig. 1). Antiangiogenic therapies could also have an impact on the heart by the induction of microvascular dysfunction and/or the reduction of microvessel density. However, pathologic changes seen in cultured cells and small rodents do not necessarily translate into clinically significant cardiac toxicity, and the described mitochondrial effect of sunitinib is not a common feature in TKIs with a similar inhibition spectrum [19]. It is important to note, that cardiotoxicity is not a class effect of TKIs, and it is reasonable to assume, that only those therapies targeted at essential kinases in the myocardium and in the vasculature will show cardiotoxicity. Nevertheless, the combined use of therapies, which have not shown significant cardiotoxic potential in single use, could create a potentially harmful and unexpected double-hit on the myocardium.

Conclusions
Cardiovascular side effects of the new signaling inhibitors appear to be particularly relevant in patients with preexisting cardiovascular conditions and risk factors, since they depend on survival pathways that now become targets in modern oncology. Sometimes, it might even appear as oncologists and cardiologists have opposing interests, since most of the cellular factors discussed in recent years for a role in cardioprotection are on the list of new targets under study for their use in anticancer therapy (Fig. 2). On the contrary, given the unique problems presented by the cancer patient with cardiovascular disease, multidisciplinary working among cardiologists, oncologists and cell biologists should be encouraged [20]. Cardiovascular side effects of cancer therapeutics may become a manageable problem in future if we are able to learn more about the role of signaling pathways in the myocardium. Still, this topic will continue to be topical in the years to come.

Acknowledgements
This work was supported by a research grant from the Swiss National Science Foundation (3100A0-120664) to C. Zuppinger.

References