# Cancer drugs: Highlighting the molecular mechanisms of cardiotoxicity

**Keo Tabane and Daniel A. Vorobiof**

Sandton Oncology Centre, Johannesburg, South Africa

Address for correspondence:
Dr D. A. Vorobiof
Sandton Oncology Centre
PO Box 2059
Parklands
2121
South Africa

Email: sandtononcology@iafrica.com

## INTRODUCTION

Cancer therapies have evolved and improved quite significantly over the years. Most available drug therapies effect cancer kill by interfering with the replicative and signalling processes necessary for cell proliferation and survival. These changes are however, unfortunately not limited to cancer cells only, as muscle, including cardiac muscle, bone marrow and the nervous system are potential bystanders which can be negatively affected by cancer therapies.

The commonest drugs known to have cardiotoxic effects include anthracyclines, monoclonal antibodies (such as trastuzumab and bevacizumab), and recently the tyrosine kinase inhibitors which are utilised in the treatment of metastatic renal cell carcinoma, gastrointestinal stromal tumours and pancreatic neuro endocrine tumours.

Other drugs like taxanes and fluoropyrimidines and some alkylating agents also have cardiotoxic effects, via largely unknown mechanisms.

## CHEMOTHERAPY DRUGS

### Anthracyclines

Anthracyclines have long been in use for various cancers including breast cancer, lymphoproliferative disorders, sarcomas and some gastrointestinal cancers among others. Their mechanisms of action

## ABSTRACT

The treatment options for patients with cancer have increased rapidly in the last decade with the introduction of newer chemotherapy drugs, targeted agents and monoclonal antibodies. Most of these drugs are aimed at interrupting proliferative signalling, with consequent apoptosis of cancer cells. Because most of the new drugs are multi-targeted, there is a likelihood of so called "off target" effects, where other kinases which are not the primary targets of the drug, are also inhibited. This has led to unforeseen toxicities and, in this commentary, we will focus on the molecular mechanisms underlying cardiotoxicities as a result of cancer therapies.

However, cardiotoxicity is not a new concern as the older generation chemotherapies, like anthracyclines, are known to commonly cause irreversible cardiomyopathy, mostly as a result of induced DNA damage and oxidative stress. Over the years, clinicians have adopted some methods of diminishing the incidence of this side-effect and therefore improving patient safety.

Trying to decipher the complicated pathways underlying cardiotoxicity helps the scientific community to design new drugs that are tumoricidal, whilst sparing normal tissue and as such limiting unwanted side-effects. This has become ever so important, as oncologists cure more patients of cancer, and some previously incurable cancers are increasingly being converted into chronic illnesses. A relationship between the cardiologist and the oncologist has become mandatory to ensure close monitoring of such patients and offering appropriate management, should cardiotoxicities arise.

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**TABLE I:** Cardiovascular toxicity of anti-cancer drugs

| Toxicity | Drugs |
| --- | --- |
| Congestive heart failure | Anthracyclines<br>Some alkylating agents (e.g. cyclophosphamide)<br>Monoclonal antibodies (e.g. trastuzumab)<br>Tyrosine kinase inhibitors |
| Ischaemic/Thrombo-embolism | 5 Fluoropyrimidines (e.g. 5 fluorouracil)<br>Taxanes (e.g. paclitaxel, docetaxel)<br>Platinum compounds (e.g. cisplatin) |
| Hypertension | Monoclonal antibodies (e.g. bevacizumab)<br>Tyrosine kinase inhibitors (e.g. sunitinib, sorafenib) |
| Brady arrhythmias | Taxanes |
| QT prolongation | Tyrosine kinase inhibitors (e.g. nilotinib) |

include interfering with DNA cross-linking, release of free radicals, and inhibition of both DNA replication and RNA transcription amongst others.[1] Tissues with rapidly dividing cells are most at risk for acute or late toxicities, but most of these resolve over time as new cell regeneration occurs when the offending therapy stops.

The cardiac muscle however, has limited regenerative potential, and this may account for the cardiotoxicity seen, particularly with this class of agents.

The early clinical studies involving anthracyclines did not show significant cardiotoxicity due to limited duration of exposure to the drug, largely on the basis of dose limiting myelosupression. However, with improved supportive care and subsequent prolonged use of these drugs in clinical practice, it has emerged that anthracyclines have a cumulative toxicity on the myocardium, which rises significantly beyond 550mg/m$^2$ for doxorubicin and 900mg/m$^2$ for epirubicin.[2]

Cardiotoxicity of anthracyclines is thought to be mediated by other mechanisms excluding those responsible for tumour cell kill, and this suggests that mechanisms countering this toxicity can be found without interfering with drug efficacy.

Anthracyclines induce myocyte damage and cell death via necrosis and apoptosis. Endomyocardial biopsies performed in patients following anthracycline exposure have shown mitochondrial swelling and chromatin contraction which are cardinal features of apoptotic cell death. Myocyte damage following these drugs is concentration dependant; with apoptosis likely to happen at lower doses of exposure, and necrosis at higher doses.

Another major mechanism of action of anthracyclines is release of oxygen free radicals, and an increase in oxidative stress leading to lipid peroxidation, vacuolation and fibrosis.[3] Anthracyclines are also associated with a decrease in the release of endogenous enzymes, like glutathione peroxidase which role is to scavenge free radicals.[4,5]

Release of reactive oxygen species may trigger apoptosis by cytochrome C and caspase C release, resulting in myocyte death.[6]

The DNA damage induced by anthracyclines may act as another trigger for apoptosis. Among the numerous other mechanisms of action of the anthracyclines, is intercalation of base pairs, which inhibits DNA and RNA synthesis.[7] It is this very mechanism that leads to cumulative cardiotoxicity on the basis of accumulation of DNA mutations.

Sarcomere disruption has also been shown on endomyocardial biopsies of patients following anthracycline exposure. The changes include loss of myofibrils and dilation of the sarcoplasmic reticulum.[8] The breakdown of titin, a giant myofilament protein and a part of the sarcomere in striated muscle, is one of the early events in sarcomeric disruption. In addition to this, anthracyclines also suppress sarcomeric protein synthesis, leading to what Sawyer, et al. have coined "cardiac sarcopenia".[9]

### Fluoropyrimidines

5 Fluorouracil (5FU) is the most common 5 fluoropyrimidine (a pyrimidine antimetabolite), used in the treatment of various cancers including colon, gastric, and head and neck cancers. It has been demonstrated to have a small, but real risk of cardiac toxicity, mainly in the form of arrhythmias and coronary vasospasm. The mechanism of its cardiotoxicity is unclear, but it is thought to be due to vascular spasm secondary to the breakdown products of 5 FU namely fluoro beta-alanine and fluoro acetate. 5 Fluorouracil's most common cardiotoxic effect is angina like chest pain and ischaemic ECG changes. The possible mechanisms of cardiotoxicity are coronary artery thrombosis, interaction with the coagulation system, vasospasm and direct myocardial toxicity. On electron microscopy the changes that occur following 5FU toxicity are seen in the endothelium of the small vessels.[10] Myocarditis has also been demonstrated in some autopsy results.[11]

### Other potential cardiotoxic drugs

Other drugs including alkylating agents, like cyclophosphamide when administered at high doses are also potentially cardiotoxic, though the actual mechanisms of cardiotoxicity are largely unknown.

The platinum compounds cisplatin and carboplatin have also shown to increase the risk of thrombolic events but no specific cardiotoxicity increase has been documented. The cardiotoxicity of cisplatin is thought to be related to the electrolyte imbalances that can occur with cisplatin-induced nephrotoxicity.

Taxanes (originally derived and synthesised from the American and European yew tree) can induce a large spectrum of cardiac disturbances of a varied aetiology. Some of the documented arrhythmias have been attributed to the use of the solvent cremophor.

Taxanes cause mainly bradycardia and a dilated cardiomyopathy, especially when used in combination with anthracyclines. In some series, the incidence of cardiotoxicity has been as high as 20% when the drugs were used in combination.[12] The cardiotoxicity of taxanes is thought to be related to the drug's structural similarity to the yew taxine, a known cardiotoxic alkaloidal.

## MONOCLONAL ANTIBODIES AND TARGETED THERAPIES

### Anti Her 2 receptor drugs: trastuzumab

Trastuzumab is a humanised monoclonal antibody against erb 2 receptor tyrosine kinase, a member of the Endothelial Growth Factor Receptor (EGFR) family. Erb 2 is over-expressed in 20 to 30% of all breast cancers, and patients whose cancers over-express erb 2 have a higher risk of disease recurrence, distant spread and decreased survival. The addition of trastuzumab to chemotherapy, both in the adjuvant and metastatic settings have yielded improvements in disease-free survival and overall survival. [13-15] However, cardiotoxicity has been noted as a side-effect in numerous clinical trials, and is more pronounced in patients who have received an anthracycline. Cardiotoxicity ranges from 3 to 7% when trastuzumab is administered as a single agent, and up to 27% when administered concurrently with an anthracycline.[16]

The mechanisms underlying trastuzumab-related cardiotoxicity are not completely understood. It causes contractile dysfunction that does not, unlike anthracycline-mediated cardiotoxicity, appear to be dose-related. The cardiotoxicity of trastuzumab also is reversible in some cases, even allowing for re-challenging with the drug if the benefit is felt to outweigh the risks in individual patients. Erb 2 plays a major role in embryonic cardiomyocyte development and function. This is evidenced by the fact that germline deletions of erb 2, erb 4 and neuregulin 1 in mice are lethal in mid-gestation due to failure of ventricles to form properly.[17] Neuregulin is a peptide ligand of erb 2 and erb 4 and is produced by cardiac endothelial cells. By binding to erb 4 it causes heterodimerisation of erb 2 and erb 4, leading to autophosphorylation of the hetero-dimer and inducing downstream signalling pathways.[18] These and

other results suggest that erb 2 is essential in cardiac development and function, and that inhibition thereof by trastuzumab is central to the cardiotoxicity of the drug. However, it is unlikely to be this simple, since lapatinib, a dual inhibitor of erb 2 and EGFR has minimal cardiotoxicity, demonstrating that this is unlikely to be the only mechanism.

In addition, it has been postulated that previous use of anthracyclines heightens the risk of trastuzumab-related cardiac dysfunction. Erb 2 signalling also plays a role in regulating sarcomeric structure and inhibition thereof, and accelerates the sarcomeric breakdown that has been previously mentioned in relation to anthracyclines.

### Vascular Endothelial Growth Factor Receptor (VEGFR) inhibitors: bevacizumab

Bevacizumab is an anti-angiogenic drug, a monoclonal antibody against VEGFR. It is effective against a number of cancers including colon, ovarian, lung and renal cell carcinoma. One of the commonest reported side-effects is hypertension, reported to be as high as 23% in some studies.[19] This is in part due to decreased nitric oxide production, which leads to vasoconstriction and an increase in blood pressure. There is also evidence of remodelling of the capillary beds, a process known as capillary rarefaction, in patients exposed to these specific agents. A reduction in the mean dermal capillary density as well as a decreased vasodilatory response was found on skin biopsies performed in patients receiving bevacizumab.[20] As with many other cancer therapies, apoptosis has also been implicated in endothelial cells of patients receiving anti-angiogenic drugs.[21]

### Multi-targeted tyrosine kinase inhibitors: sorafenib, sunitinib and other small molecules

One of the many advances in cancer therapy has been the development of small molecule tyrosine kinase inhibitors for the treatment of various cancers, including renal cell carcinoma, gastro-intestinal stromal tumours (GIST) and chronic myeloid leukaemia (CML). These drugs inhibit multiple tyrosine kinases that drive cellular proliferation. The use of these agents has yielded significant disease-free and overall survival benefits among patients with the different cancers for which they are currently in use.

The potential downside however is the so-called "off-target" effect, resulting in the inhibition of other tyrosine kinases that are not

the primary target of the drug, as these drugs are able to inhibit between 15 to 50 kinases at a time.[22] Sorafenib, for instance, targets VEGFR 2/3, RAF 1,c-kit, PDGFR and FLT 3 amongst others. Such wide effect may lead to the inhibition of other unknown kinases which might be responsible for ventricular function. This may lead to unforeseen cardiac toxicities. For example, in an animal model, RAF 1 deletion led to mitochondrial dysfunction and a myopathic heart.[23] RAF inhibits proapoptotic kinases, ASK 1 and MST 2, and inhibition of RAF thus leads to accelerated apoptosis in selected tissues.

Chintalgattu, et al., have highlighted the importance of PDGFR in the tolerance of the heart to afterload stress. Mice with a deletion of the PDGFR ß gene, with no changes at baseline, developed ventricular dilatation and cardiac failure when exposed to afterload stress.[24]

They further proposed a two-hit hypothesis of cardiotoxicity with sunitinib; a tyrosine kinase inhibitor used for the treatment of renal cell carcinoma and relapsed GIST. The first hit would be an increase in blood pressure, followed by PDGFR inhibition which leads to inability of the cardiac muscle to handle this increase in afterload, with the second hit leading to cardiac failure.

Other investigators have found evidence of mitochondrial damage in relation to treatment with tyrosine kinase inhibitors, and cardiomyocytes treated with these agents demonstrated a loss of mitochondrial action potential and a subsequent decrease in ATP.[25]

Cardiac toxic effects of tyrosine kinase inhibitors range from electrocardiographic changes (QT segment prolongation), a drop in the left ventricle ejection fraction measured by echocardiography or MUGA, to congestive heart failure, and coronary and myo-cardial events.

Sunitinib possibly exerts its cardiotoxicity through the inhibition of PDGF receptors, promoting apoptosis. Sorafenib does it by inhibiting RAF 1. Deletion of its gene in the heart leads to an increased cardiomyocite apoptotic event.[26-27]

Many other potential mechanisms have been postulated, mainly around enhanced apoptosis, and inhibition of anti-apoptotic pro-teins. However, some of those mechanisms by which these drugs cause cardiotoxicity remains unclear.

## CONCLUSION

Cardiotoxicity remains an important concern in cancer care, since it has the potential to reverse the gains made by improved cancer treatment and the discovery of new drugs. The mechanisms of toxicity are not always clear, and there is ongoing work to better elucidate them. Traditional chemotherapy targets rapidly dividing cells (which are not all malignant). New targeted therapies available for the treatment of cancer patients are tailored to the specific genetic changes expressed by each cancer type. Cardiovascular effects of chemotherapy are numerous, different and range from a decrease in myocardial contractility (anthracyclines), increased ischaemic changes (fluoropyrimidines) to those drugs that can affect the conduction system resulting in arrhythmias or blocks (alkylating agents, taxanes). Cardiovascular effects of targeted therapies are also varied and include heart failure, conduction abnormalities, QT prolongation, hypertension and myocardial injury, although systolic dysfunction – which leads to heart failure – is the most common side effect. This is as a result of the fact that those pathways involved in the survival and proliferation of cancer cells can also impact on the survival of non-malignant cells, such as normal cardiomyocytes. Targeting those pathways with the new available molecules, may also produce cardiotoxic effects, mainly cardiomyopathy due to the inhibition of the same kinases in the normal cardiomyocytes. Further understanding of these multiple mechanisms will assist in the development of safer drugs without compromising tumoricidal activity. It will also aid oncologists to improve patient selection, diagnose toxicities early and refer patients timeously to cardiologists. It will enable improved methods of mitigating the risk with stringent monitoring, thereby increasing the levels of patient safety. Albini and others have stressed the need to develop guidelines that include the effects on the cardiovascular system. They have recommended the creation of the new interdisciplinary field of cardio-oncology, where oncologists and cardiologists can work together in an effort to avoid or prevent adverse cardiac effects while patients with cancer are receiving chemotherapy.[28] The relationship between the oncologist and the cardiologist cannot be over-emphasised, as we continue to seek ways to deliver safe and effective cancer care to our patients within a multidisciplinary context.

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