Atherosclerosis, Ischemia, and Anticancer Drugs

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ABSTRACT

The heart is affected by cardiotoxicity of anticancer drugs. Myocardium, pericardium and endocardium can be affected. Besides these coronary arteries can be affected by accelerated atherosclerosis. Various pathogenic mechanisms have been proposed that underlie the ischemic complications of anticancer drugs. In this review we discuss the atherosclerotic and ischemic complications of anticancer drugs.

Key words: Accelerated atherosclerosis, anticancer drugs, cardio-oncology, coronary artery disease, myocardial infarction

Anticancer drugs have been nothing less than a miracle to the patients who have been suffering from cancer. However, the longer life due to these drugs (anticancer drugs) does not come without a price. Various organs such as the skin and the bone marrow take the worst hit. The heart is also affected by the cardiotoxicity of these drugs, and it can be seen any time after the anticancer drugs have been started. This is what the recently emerging field of cardio-oncology aims to study, i.e., the cardiovascular short-term and long-term complications of the cancers and the therapy related to it.[1]

Almost every part of the cardiovascular system can be affected by cancer treatment. All the three layers of the heart – the pericardium, myocardium, and endocardium – can be affected, leading to pericarditis, myocardial fibrosis, and valvular heart disease, respectively. Besides this, the coronary arteries and the conduction system can be adversely affected.[2]

Heart failure, life-threatening arrhythmias, and myocardial ischemia are the most dreaded complication of chemotherapy.[3]

Drugs like 3rd generation Tyrosine kinase inhibitors, VEGF inhibitors and 5-fluorouracil have been found to cause ischemic complications such as myocardial infarction, coronary artery disease, and peripheral arterial disease.

In this review, we discuss the atherosclerotic and ischemic complications of anticancer drugs.

HOW DO ANTICANCER DRUGS CAUSE ISCHEMIA?

Various pathogenic mechanisms underlie the ischemic complications of anticancer agents. It includes vasospasm, endothelial dysfunction, decreased nitric oxide (NO) signaling, increased endothelin signaling, increased oxidative stress, decreased PGI₂ signaling, and platelet activation.[4]

Apart from these mechanisms, patients receiving chemotherapy may have accelerated atherosclerosis due to chemotherapy-induced dyslipidemia and pro-inflammatory state.[5,6]

The role of low-density lipoprotein (LDL) cholesterol in the causation of atherosclerotic diseases is well known.[7] An increase in serum LDL level has been found with bevacizumab.[8]

Gonadotropin-releasing hormone (GnRH) agonist therapy, which is used in the treatment of prostate cancer also increases LDL levels.[9] Patients receiving...
an mTOR-based chemotherapeutic regimen have a higher likelihood of developing dyslipidemia with increased atherogenic small dense Low-density Lipoproteins (sdLDLs).\(^{10}\)

Similarly, sirolimus therapy has been found to be associated with an elevation in PCSK9 levels.\(^{11}\)

Recently, the role of triglyceride in the causation of atherosclerosis has been confirmed by various studies.\(^{12,13}\) Hypertriglyceridemia is seen with drugs like mTOR inhibitors (inhibits the mechanistic target of rapamycin) like everolimus, which is used in advanced progressive pancreatic neuroendocrine tumors, advanced renal cell carcinoma (RCC), advanced hormone receptor-positive breast cancer, and subependymal giant cell astrocytoma associated with tuberous sclerosis.\(^{14}\) Capecitabine, a chemotherapy medication which is used in patients with breast, gastric cancers and colorectal cancers,\(^{15}\) tamoxifen, which is used in the treatment of breast cancer,\(^{16}\) bexarotene, a retinoid used in the treatment of cutaneous T-cell lymphoma,\(^{17}\) have been found to cause hypertriglyceridemia.

Drugs which act against vascular endothelial growth factor including those which inhibit tyrosine kinase increase the blood pressure and the rates of cardiovascular events. Anti-metabolites, the group which includes 5-fluorouracil and capecitabine has been found to be associated with chest pain and increased cardiovascular events. Anthracyclines cause heart failure and may increase CVD risk.\(^{18}\)

**ATHEROSCLEROTIC DISEASES DUE TO TYROSINE KINASE INHIBITORS**

Tyrosine kinase inhibitors (TKIs) are used in the treatment of chronic myelogenous leukemia, Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia, gastrointestinal stromal cell tumor, and various other malignancies. Of these TKIs, imatinib is the oldest and it is found generally well tolerated.\(^{19}\) However, concerns have been raised regarding the cardiac safety of newer TKIs.\(^{20-22}\)

Various cases of arterial occlusive diseases have been reported with TKIs. A study reported that arterial occlusive diseases developed in 25% of the patients who received nilotinib.\(^{23}\)

Fujioka et al. found that out of 369 chronic myeloid leukemia patients who received TKIs, 6.2% developed various arterial occlusive diseases. The incidence of ischemic heart diseases was most common in patients receiving nilotinib.\(^{24}\) Stroke has also been reported with TKI.\(^{25}\)

Among the newer TKIs, dasatinib has been studied and found not to increase the risk for cardiovascular ischemic events compared with external reference populations.\(^{26}\)

The exact mechanism behind the pathogenesis of the arterial occlusive disease remains unknown. Various hypotheses have been proposed to explain the ischemic events seen in the patients receiving TKIs. These include inhibition of “off-target” tyrosine kinases in cardiac muscle cells and vascular endothelium,\(^{27-29}\) induction of an inflammatory/oxidative state,\(^{30}\) endothelial dysfunction,\(^{31}\) decreased proliferation of endothelial cells,\(^{32}\) inhibition of neoangiogenesis by vascular endothelium,\(^{33}\) increased lipid peroxidation due to LOX-1 polymorphism, and a pro-inflammatory state due to low levels of interleukin-10.\(^{34}\)

Coronary artery spasm has also been implicated in the causation of ischemic heart diseases.\(^{35}\)

**PLATINUM-BASED DRUGS – CISPLATIN**

Cisplatin is used in the treatment of various malignancies such as carcinoma bladder, head and neck, lung, ovary, and testes. Apart from these, it is also useful in germ cell tumors, lymphomas, and sarcomas.\(^{36}\) A retrospective study found that of all the chemotherapeutic agents implicated in the causation of stroke, cisplatin was the most common culprit.\(^{37}\)

Cases of myocardial infarction have also been reported with cisplatin.\(^{38}\) Another study reported cases of acute arterial occlusion in patients with and without preexisting moderate peripheral artery disease.\(^{39}\) Various theories have been proposed to explain the atherogenic profile of cisplatin. These include endothelial injury,\(^{40,41}\) endothelial dysfunction and decreased NO production,\(^{42}\) increased levels of fibrinogen, C-reactive protein, von Willebrand factor, plasminogen activator inhibitor-1, and tissue-type plasminogen activator,\(^{43}\) increased oxidative stress due to lipid peroxidation,\(^{44}\) and dyslipidemia with increased levels of LDL-C and thyroglobulin.\(^{45,46}\)

**VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS**

VEGF signal plays an important role in the progression of various malignancies.\(^{47}\) Bevacizumab is used for patients with colon cancer, lung cancer, glioblastoma, and renal cell carcinoma. Sorafenib and axitinib are used in the management of RCC; Ranibizumab is used in patients with diabetic macular edema. Aflibercept is used in colorectal cancers. Other VEGF signaling inhibitors such as sorafenib and axitinib are used in RCC.

Systemic, as well as intravitreal injection of VEGF inhibitors, have been found to be associated with adverse cardiovascular events. Studies have found that patients receiving either of the two, ranibizumab...
and aflibercept, are prone to develop ischemic cardiac disease. It is hypothesized that this effect is due to an increase in atheroma stability, which can lead to leading to plaque rupture.\cite{48,49}

In a study in which bevacizumab was used along with irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer; it was found that bevacizumab group had a numerically higher number of patients affected with thrombotic diseases.\cite{50}

Other studies have shown the complications of systemic administration of VEGF inhibitors for solid tumors and they found that patients receiving VEGF inhibitors were more prone to develop transient ischemic attacks, strokes, and other thrombotic events.\cite{51,52}

The various hypotheses proposed for explaining these thrombotic episodes have been put forward.

Studies have also found evidence of inflammation,\cite{53} endothelial dysfunction leading to decreased NO and PGI2 production and vasoconstriction,\cite{54} an increase in endothelial cell apoptosis, with disruption of the endothelial lining,\cite{55-57} platelet activation,\cite{58} dyslipidemia, with increase in total cholesterol and triglycerides.\cite{59}

All of these can result in thrombotic episodes. Systemic VEGF inhibition increases atherosclerotic lesions by 33% and promotes the generation of superoxide from endothelium leading to increased oxidative stress.\cite{60}

5-FLUOROURACIL AND CAPECITABINE

The antimetabolite fluorouracil is used in the treatment of gastrointestinal, breast, and cervical malignancies. Capecitabine is the produg of 5-FU, and similar to fluorouracil, it is used for the treatment of gastric and breast cancers. Both of these drugs have been known to increase the risk of CVDs.\cite{61} Fluorouracil has been known to cause coronary spasm. Fluorouracil related cardiotoxicity has been reported to present as angina as well as ST segment elevation myocardial infarction.\cite{61,62}

A study reported that 69% of all the cardiac incidents occurred in the first 3 days of the first cycle of 5-FU. Angina was more common than myocardial infarction (45% vs. 22% of patients) whereas myocardial infarction was seen in 22%.\cite{63,64}

A study by Jensen and Sørensen reported that 4.3% of all the patients who received either 5-FU or capecitabine developed angina or acute coronary syndrome. The authors found that the chances of coronary vasospasm increased with decreasing creatinine clearance.\cite{64}

A calcium channel blocker or sublingual nitroglycerine may be of some benefit in the prevention or treatment of 5-FU cardiotoxicity.\cite{61,64}

The authors have different opinions on re-administration of these drugs after a coronary event.\cite{62,64}

Various explanations have been given the vasospasm due to antimetabolites. These include drug-induced endothelial dysfunction and downregulation of endothelial NO synthase (eNOS), increased oxidative stress due to reactive oxygen species (ROS) formation, lipid peroxidation, and rapid glutathione depletion. The increased burden of ROS can cause mitochondrial injury, ultimately culminating in myocardial cell death.\cite{65-70}

PROGRAMMED DEATH-1 INHIBITORS

Cancer immunotherapy is the use of drugs which modulate the immune system to fight cancer. These are the new addition in the armamentarium of anticancer therapy. Immune checkpoint inhibitors (ICIs) are a type of cancer immunotherapy. Currently available ICIs target either of the three molecules, CTLA4, programmed death (PD)-1, and PD-L1.

PD-1 ICIs have been used in patients with various cancers, for example, melanoma, RCC, squamous cell carcinoma, and non-small cell lung cancer (NSCLC), and have been found to increase patient survival when it was compared to conventional chemotherapies.\cite{71}

Animal studies have shown that PD-1 seems to exert significant anti-inflammatory and atheroprotective effects, mostly in early phases of disease progression, and blockade of this molecule for the treatment of cancer may increase cardiovascular risk.\cite{72,73}

Drugs such as pembrolizumab and nivolumab which block PD-1 signaling and are used in patients with advanced melanoma, NSCLC, Hodgkin’s lymphoma, head-and-neck squamous cell carcinoma, and advanced urothelial (bladder) cancer can theoretically lead to progression of atherosclerosis.

ANDROGEN DEPRIVATION THERAPY AND ATHEROSCLEROSIS

Androgen deprivation therapy (ADT) which includes luteinizing hormone-releasing hormone (LHRH) agonists like leuprolide, goserelin and LHRH antagonist like degarelix; anti-androgens like flutamide, bicalutamide are used to delay the growth of the prostate tumor and improve survival in patients affected with prostate cancer are also found to be associated with accelerated atherosclerosis.

Keating et al., for the first time in 2006, found that ADT was associated with increased risk of coronary artery disease and myocardial infarction.\cite{74}

Other studies have also confirmed the association between administration of ADT and increased rate of ischemic heart diseases.\cite{75,76}
CVD risk was highest during the first 6 months of ADT in men who experienced two or more cardiovascular events before therapy.\(^{(77)}\)

ADT leads to the development of metabolic abnormalities, such as hyperglycemia, dyslipidemia, and obesity, which ultimately lead to atherosclerosis.\(^{(78)}\)

Androgens may inhibit this process by stimulating endothelial production of NO, which inhibits platelet aggregation, and inhibiting platelet secretion of thromboxane A2, which has the opposite effect.\(^{(79-81)}\)

Androgens have been found to be associated with decreased expression of pro-inflammatory cytokines.\(^{(82,83)}\)

Testosterone may also stimulate fibrinolysis and resultant clot degradation by increasing expression of tissue plasminogen activator.\(^{(84)}\)

Androgen deprivation is associated with increased total cholesterol and LDL levels.\(^{(9,85,86)}\)

A nested case–control study in the UK found that combined ADT with both LHRH agonists and anti-androgens was associated with a significant increase in the risk of coronary artery disease and acute myocardial infarction.\(^{(87)}\)

**PROTEASOME INHIBITORS**

The proteasome is a protein complex which breaks down proteins which are marked by ubiquitin. Inhibition of the proteasome complex has been found to be an effective strategy for the treatment of cancers. They have been approved for use in multiple myeloma (MM). This group includes drugs such as bortezomib, carfilzomib, marizomib, and ixazomib.\(^{(88)}\)

Bortezomib is a boron-containing peptide. The boron atom in its molecule binds specifically to the catalytic site of 26S proteasome, thereby reversibly inhibiting it.\(^{(89)}\)

The drug has been approved for the management of MM.\(^{(90-92)}\) Bortezomib’s inhibition of proteasome activity may increase endothelial progenitor cell apoptosis and decrease eNOS/NO, thus leading to coronary spasm.\(^{(92)}\)

A large retrospective review of almost 4000 patients in seven Phase II and Phase III clinical trials that led to bortezomib’s approval reported an ischemic heart disease incidence of 1.5%–2.7% in the bortezomib treatment arms.\(^{(93)}\)

More recently, a case report showed that an association between an ischemic heart attack and the bortezomib plus dexamethasone combination might exist. A 79-year-old woman with no past history of CVD developed acute myocardial infarction immediately following bortezomib administration requiring a coronary artery stent.\(^{(92)}\)

Carfilzomib was noted in the ASPIRE trial to have a higher incidence of ischemic heart disease when compared to a control group not receiving carfilzomib, 3.3% compared to 2.1%, respectively.\(^{(94)}\)

Limited evidence from animal studies suggests an endothelium-dependent mechanism by which carfilzomib induces coronary vasospasm or lack of dilation contributing to ischemia.\(^{(95)}\) Nifedipine and nitroglycerin have been found to be effective in treating carfilzomib-induced vasospasm.\(^{(95)}\)

**SUMMARY AND CONCLUSION**

The recognition of cardiac problems related to the treatment of cancer is complex. Identifying patients who are at increased risk for cardiovascular problems associated with the cancer treatment or who develop side effects following treatment is a major component of an evolving area often referred to as cardio-oncology-diagnosing, preventing, and treating patients with cancer and CVDs; the discipline assists in the overall care of cancer patients from cancer diagnosis into survivorship.

Progress in the detection and treatment of cancer has led to an impressive reduction in both mortality and morbidity. Due to their mechanism of action, however, conventional chemotherapeutics and some of the newer anticancer signaling inhibitors carry a substantial risk of cardiovascular side effects that include cardiac dysfunction and heart failure, arterial hypertension, vasospastic and thromboembolic ischemia, dysrhythmia, and QT prolongation. While some of these side effects are irreversible and cause progressive CVD, others induce only temporary dysfunction with no apparent long-term sequelae for the patient.

The challenge for the cardiovascular specialist is to balance the need for lifesaving cancer treatment with the assessment of risk from cancer drug-associated cardiovascular side effects to prevent long-term damage. The management of these complex patients requires careful balance: excessive concern regarding potentially reversible cardiac issues may compromise the administration of highly beneficial anticancer therapies, while underappreciation of cardiac risk may result in lifelong cardiac concerns for a patient who has been cured of their cancer.

Knowledge of the cardiac effects of anticancer agents balanced with knowledge regarding the natural history of the malignancy and the likelihood of tumor response offers such patients the greatest chance for long-term disease-free survival.

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There are no conflicts of interest.

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