CHEMOTHERAPY-RELATED CARDIOTOXICITY

Cardiovascular complications of chemotherapy: A synopsis

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ABSTRACT

It is important to identify chemotherapy-related cardiotoxicity as it may impact on the overall survival of cancer patients. The various forms of cardiotoxicity encountered during and after chemotherapy for cancer, include impaired left ventricular function leading to cardiomyopathy (CMO), myocardial ischaemia, hypertension (HTN), thromboembolic states, bradycardia and prolongation of the QT interval predisposing to ventricular arrhythmias. The relationships between specific chemotherapeutic agents and the occurrence of these complications are discussed, highlighting the need for close collaboration between oncologists and cardiologists.
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INTRODUCTION

Cancer treatment frequently entails the combined use of chemotherapy, radiotherapy and surgery to prolong life and provide a cure. Both chemotherapy and radiotherapy have the potential to cause acute or long term cardiovascular complications. The cardiovascular complications of chemotherapy include heart failure, myocardial ischaemia or infarction, thromboembolism, hypertension and arrhythmias. This article reviews the incidence and effects of the various forms of cardiotoxicity caused by both the older and more recent chemotherapeutic agents currently used to treat cancer.

LEFT VENTRICULAR (LV) DYSFUNCTION

Many chemotherapeutic agents have been linked to the development of left ventricular dysfunction (LVD) (Table 1) and/or heart failure (HF). The cumulative dose, administration schedule and concomitant use of other cardiotoxic therapies determine the likelihood of cardiomyopathy (CMO).

Anthracyclines

The anthracycline class of agents is commonly used in the management of a variety of malignancies, most frequently as adjuvant therapy for breast cancer and as systemic treatment of sarcomas, lymphomas and leukaemias. Formal estimates of the worldwide prevalence of anthracycline cardiotoxicity are lacking. Differences among paediatric, adult and elderly populations and the lack of universal criteria for detecting and reporting cardiac events make such estimates even more challenging. Anthracycline cardiotoxicity has been classified into acute; early-onset; chronic; progressive; and late-onset chronic progressive.[1,2] Acute cardiotoxicity is rare. It occurs immediately after infusion of the anthracycline and manifests as a transient acute decline in LV function which is usually reversible.[3]

The early-onset chronic progressive form occurs in patients during therapy or within the first year of therapy.[3]

Late-onset chronic progressive anthracycline-induced cardiotoxicity occurs at least 1 year after completion of therapy. Early and late-onset chronic progressive cardiotoxicity typically presents as a CMO in adults which can progress to heart failure.[2] Cardiotoxicity may only become clinically evident 10 to 20 years after the first dose of chemotherapy.

The risk of cardiotoxicity increases with cumulative doses of anthracyclines. The cumulative dose of doxorubicin above which cardiotoxicity occurs is >400mg/m^2.[3,4,5] For this reason the maximum lifetime cumulative dose of doxorubicin is 400 to 550mg/m^2.[3] Epirubicin or idarubicin appear to have less incidence of HF.[6,7]

Apart from the cumulative dose, the risk factors for anthracycline toxicity include: intravenous bolus administration; higher single doses; history of prior irradiation; the concomitant use of other agents such as cyclophosphamide; trastuzumab and paclitaxel (known to have cardiotoxic effects); female gender; pre-existing cardiovascular disease; age (both young and old); and increased length of time since anthracycline completion.[1,2]

Antibody-based tyrosine kinase inhibitors

Both trastuzumab and bevacizumab are monoclonal antibodies used as targeted oncologic therapies in a variety of malignancies. Approximately 15% of all breast cancers over-express the cell surface receptor Her2. This group is characterised by aggressive tumour behaviour and a worse prognosis. The presence of the Her2 serves as a target for biologic therapies. Use of the humanised monoclonal antibody trastuzumab (Herceptin) directed against the Her2 receptor has revolutionised the treatment of Her2-positive breast cancer. Adjuvant phase 3 trials of trastuzumab have demonstrated a 50% reduction in recurrence of disease and a 33% improvement in survival.

Bevacizumab (Avastin), a humanised monoclonal antibody directed against Vascular Endothelial Growth Factor (VEGF), has significant anti-tumour activity when combined with chemotherapy and has been approved for use in several types of advanced solid tumours including breast, lung, colorectal and renal carcinomas.[8]

TABLE 1: Chemotherapeutic agents associated with the development of Left Ventricular Dysfunction (LVD) and Heart Failure (HF).

Agent	Trade name/s	Reported incidence	Aggravating factors	Malignancy treated
Anthracyclines				
Doxorubicin[1-5] Epirubicin[6-7] Idarubacin[6-7]	Adriamycin Ellence, Pharmorubacin Zavedos, Idamycin	Acute <1% Up to 26% Early chronic progressive 1.6-2.1% Late chronic progressive 1.6-5% Lower incidence with epirubacin and idarubacin	Cumulative dose IV bolus administration High single dose Prior irradiation Use with other agents Female sex Young or elderly Time after treatment	Leukaemia Hodgkin's lymphoma Breast Bladder Ovarian Soft tissue Sarcomas
Alkylating agents				
Cyclophosphamide[14] Ifosfamide[15]	Endoxan Holoxan	7-28% 17%	Dose related Use with other agents Mediastinal radiation	Lymphomas Leukaemia Some brain cancers
Anti-metabolites				
Clofaribine[6-7]	Not registered in RSA	27%		
Proteosome inhibitor				
Bortezomib[16]	Velcade	15% cardiac disorder 5% heart failure		Multiple myeloma
Antibody-based tyrosine kinase inhibitors				
Bevacizumab[8] Trastuzumab[9-11]	Avastin Herceptin	1.7-3% 2-7% but up to 27% incidence in combination therapy	Not dose dependent Age > 50 yrs Low EF before Rx Combination with anthracycline History of CVD Tends to be reversible	Breast, lung, colon, renal carcinomas. Breast carcinoma
Small molecule tyrosine kinase inhibitors				
Dasatinib[17] Lapatinib[18] Imatinib[17] Sunitinib[19]	Sprycel Tykerb Gleevec Sutent	2-4% 1.6% 1.7% 4-11%		Leukaemia Resistant breast cancer Gastrointestinal tumours

When trastuzumab is used as monotherapy the incidence of cardiac dysfunction ranges from 2% to 7% but rises to 27% when used concurrently with anthracyclines.[9-11] Risk factors for CMO with this agent include: age >50yrs; borderline EF before treatment; history of cardiovascular disease; the sequence in which chemotherapy is administered; and prior treatment with anthracyclines.[9-11]

Regimens either avoiding anthracyclines or temporally separating anthracycline and trastuzumab, including BCIRG 006[12] (a Phase 3 randomised study evaluated the use of docetaxel and carboplatin combined with Herceptin following initial adjuvant treatment with doxorubicin and cyclophosphamide chemotherapy for early stage 2 Her2-positive breast cancer) and HERA[13] (a multicentre randomised trial comparing 1 or 2 years of trastuzumab treatment after standard chemotherapy), have reported the lowest rates of significant cardiac dysfunction. In contrast to anthracycline-medicated toxicity, which tends to be dose dependent and irreversible, trastuzumab-related cardiotoxicity generally is not dose dependent nor associated with structural changes on biopsy and tends to be reversible. The majority of patients recover though typically continue using cardiac medications.

Alkylating agents

Cardiotoxicity has been associated with cyclophosphamide therapy.[14] Patients may present with pericardial effusions, HF or myopericarditis. The risk of cardiotoxicity appears to be dose related (>150mg/kg and 1.5g/m²/day) and occurs within 1 to 10 days after the administration of the first dose. Other risk factors include prior anthracycline or mitoxantrone therapy and mediastinal radiation.[6]

Another alkylating agent ifosfamide may also be responsible for cardiotoxicity when used in combination with other agents.[9] Acute onset of HF occurred within 6 to 23 days after the first dose and a dose response trend was observed (doses >12.5g/m²).[15]

Other agents

A host of other chemotherapeutic agents can cause LVD including anti-metabolites such as clofaribine which may cause transient LVD in paediatric patients treated for acute lymphoblastic leukaemia.[6-7] The proteasome inhibitor bortezomib used in the treatment of multiple myeloma can also cause LVD.[16]

The small molecule tyrosine kinase inhibitors such as dasatinib[17] used in the treatment of leukaemia, lapatinib[18] approved for the treatment of trastuzumab-resistant breast cancer and sunitinib[19] used in stromal tumours and renal carcinoma have all been implicated in causing LVD. CMO related to sunitinib may not be reversible.

Diagnosis of Left Ventricular Dysfunction (LVD) and Heart Failure (HF)

The diagnosis of HF is established by combining the clinical history, examination, electrocardiogram, chest radiography, laboratory tests and non-invasive imaging.[20] Biochemical markers such as troponin I[21] and B-type natriuretic peptide[22] may detect myocardial injury before changes in LVEF become apparent. Echocardiography with speckle tracking could be the most sensitive method of detecting early cardiac dysfunction.[23] The regular monitoring of cardiac function during treatment is important and algorithms have been developed for serial monitoring of LV ejection fraction.[24]

Prevention of LVD and HF

The most significant factor for anthracycline-induced CMO is the cumulative dose the patient has received and therefore prevention necessitates minimizing the patient's lifetime cumulative dose. Other preventive measures include altering the method of administration (continuous vs. bolus), use of anthracycline analogues and the addition of cardioprotectants such as dexrazoxane.[3-5]

Treatment of LVD and HF

As there are no specific HF guidelines for cancer patients the usual recommendations should be followed. Risk factor management by controlling hypertension, diabetes and hyperlipidaemia are important. Patients with anthracycline-induced cardiotoxicity may improve on treatment but complete resolution of the underlying process is uncommon and cardiac transplantation may be required.[25] Trastuzumab should be discontinued when HF develops. Cardiac function generally recovers over an average of 6 weeks. Trastuzumab may be resumed once LV function has improved provided that protective medication is given and the patient is closely monitored.[10]

To date 4 case series have evaluated the use of beta blockers in treatment of anthracycline-induced CMO and found to be beneficial.[26] Carvedilol may have an advantage because of its antioxidant properties.[27]

The classification of cardiotoxicity varies and is based on clinical radionuclide angiography and/or echocardiographic criteria. It can be classified as mild (a decrease in EF >10% from baseline with a final value of >50%); moderate (a decrease in EF of >10% from

baseline with a final value of <50% and no symptoms or signs of heart failure); and severe (a decrease in EF of >10% from baseline with a final value of <50% and symptoms or signs of heart failure or a decrease in EF of any % leading to a final value of <40% irrespective of signs or symptoms of heart failure).[28,29]

MYOCARDIAL ISCHAEMIA

Although cardiac ischaemia is uncommonly related to chemotherapy an increased risk of acute coronary syndromes has been associated with cytotoxic agents. Chest pain is common in cancer patients often necessitating a work-up to exclude myocardial ischaemia. Both radiotherapy and chemotherapy are associated with an increased risk of coronary artery disease and/or acute coronary syndromes (ACS).[30]

Fluorouracil (5-FU) an anti-metabolite is one of the best known chemotherapeutic agents causing angina. In rare cases myocardial infarction (MI), arrhythmias, HF, cardiogenic shock and sudden death have been reported.[30-31]

Other chemotherapeutic agents including paclitaxel[32] and docetaxel[33] both anti-microtubular agents have also been associated with causing myocardial ischaemia and even infarction.

Chemotherapy agents implicated in the development of myocardial ischaemia/infarction are shown in Table 2.

Treatment

Patients with ACS should be managed according to the usual guidelines. This may pose a problem in cancer patients because of thrombocytopaenia or recent surgery. In a retrospective study in patients with thrombocytopaenia, aspirin improved the outcome without increasing the risk of bleeding.[34]

HYPERTENSION (HTN)

Hypertension and cancer are often found in the same patient. Epidemiological studies suggest that there is an association between the two and that HTN affects the overall prognosis of cancer patients. More recent chemotherapeutic agents such as the VEGF inhibitors disrupt angiogenesis thus making these patients susceptible to developing HTN.[35]

HTN is common in patients treated with bevacizumab. Most patients continue therapy and are adequately treated with antihypertensives. Complications of bevacizumab-induced HTN have included hypertensive encephalopathy and brain haemorrhage.[8]

Other agents inducing HTN include sorafenib[36] and sunitinib.[37]

Table 3 shows the incidence of HTN associated with some anticancer drugs.

Treatment of HTN

Standard anti-hypertensive therapy is indicated. Discontinuation of anti-angiogenic therapy causing HTN is controversial since the appearance of HTN seems to associate with a greater treatment response.[38] It may be beneficial to use ACE inhibitors as first line therapy due to their ability to prevent plasminogen activator inhibitor-1 expression.[39] Non-dihydropiridine calcium channel blockers such as diltiazem and verapamil should not be used in sorafenib-treated patients since they are both inhibitors of the CYP3A4 iso-enzyme.[40]

TABLE 2: Chemotherapeutic agents implicated in the development of myocardial ischaemia/infarction.

Agent	Trade name	Incidence	Event	Aggravating factors
Fluorouracil[30-31]	Efudex	1-68% (enormous variation in trials)	Mostly angina Rarely Myocardial infarction Cardiogenic shock Sudden death	High doses and continuous infusions Combination chemotherapy
Paclitaxel[32]	Taxol	0.5-5%	Myocardial ischaemia	Prior HTN and CAD
Docetaxel[33]	Taxotere	1.7%	Myocardial ischaemia	
Bevacizumab[8]	Avastin	1.5-1.8%	Arterial thrombotic events	Previous history of arterial thrombotic events Age >65 yrs

TABLE 3: Chemotherapeutic agents associated with the development of hypertension.

Agent	Trade name	Incidence	Malignancy treated
Bevacizumab[8]	Avastin	4-35%	Breast, lung, renal carcinoma
Sorafenib[36]	Nexavar	17-43%	Renal and hepatic carcinoma
Sunitinib[37,38]	Sutent	5-24%	Renal carcinoma

TABLE 4: Chemotherapeutic agents associated with thrombo-embolism.

Agent	Trade name	Incidence	Malignancy treated
Cisplatin[44]	Platin	8.5%	Urothelial transitional cell carcinoma
Vorinostat[45]	Zolinza	4.7-8%	T-cell lymphoma
Thalidomide[41-42]	Thalomid	3-58%	Multiple myeloma

THROMBO-EMBOLISM

Cancer predisposes to a prothrombotic state. The risk is highest in patients with metastatic cancer and in those with risk factors, including the use of central venous lines and associated co-morbidities such as immobility, HF, atrial fibrillation, dehydration and administration of concurrent chemotherapy.[41,42,43] Some drugs that have been associated with a greater risk of thrombo-embolism include cisplatin[44] used in renal tract carcinomas, vorinostat[45] used in T-cell lymphoma and thalidomide[41,42] used for patients with myeloma.

Table 4 shows the incidence of venous thromboembolism with selected agents.

BRADYCARDIA

A variety of circumstances may contribute to the development of bradycardia and heart block in cancer patients. The conduction system can be affected by fibrosis due to ageing, radiation therapy, amyloidosis or a primary cardiac tumour. Several chemotherapeutic agents most commonly paclitaxel and thalidomide may also cause heart block.[46]

Table 5 shows the incidence of heart block with selected agents.

TABLE 5: Chemotherapeutic agents associated with the development of bradycardia/heart block.

Agent	Trade name	Incidence	Malignancy treated
Thalidomide[46]	Thalomid	5-55%	Multiple myeloma
Paclitaxel[32]	Taxol	1-31%	Lung, head and neck, breast carcinomas

QT PROLONGATION

The complications of QT interval prolongation including Torsade de Pointes are rare but can have life threatening consequences. Cancer patients may be particularly prone to QT prolongation since 16% to 36% of cancer patients have baseline ECG abnormalities.[47,48] Cancer patients may have co-morbid diseases including structural heart disease, renal or hepatic dysfunction, as well as using other medications that may themselves prolong the QT interval. Cancer patients may develop electrolyte abnormalities because of nausea, vomiting, diarrhoea and decreased oral intake further predisposing to QT prolongation.[47, 48]

The incidence of QT prolongation with the use of Arsenic Trioxide ranges widely in the published literature from 25%-90%.[49] The QT prolongation potential of both of dasatinib[50] and lapatinib[51] has been reported.

Table 6 shows the incidence of QT prolongation associated with some cancer drugs.

TABLE 6: Chemotherapeutic agents associated with QT prolongation.

Agent	Trade name	Incidence	Malignancy treated
Arsenic trioxide[47-49]	Trisenox	25-90%	Leukaemia
Dasatinib[50]	Sprycel	1-3%	Leukaemia
Lapatinib[51]	Tykerb	16%	Breast cancer

CONCLUSION

Chemotherapy is associated with a wide variety of adverse cardiovascular effects. Patients need to be carefully monitored during and after their cancer treatment. Many cancer patients are not receiving treatment consistent with heart failure guidelines.[52] A great opportunity exists for closer collaboration between cardiologists and oncologists to improve the care of cancer patients receiving cardiotoxic therapy.

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