I - Cardiovascular complications

1 Cardiac Complications of Cancer and Anticancer Treatment

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Introduction

Neoplastic diseases can be associated with severe, sometimes fatal, cardiac complications such as pericardial effusion and cardiac tamponade. In addition, several anticancer agents can induce potentially irreversible cardiac dysfunction, and the development of targeted therapies has recently widened the cardiotoxic spectrum of antineoplastic drugs.

Increasing the chance of survival as a consequence of improvements in cancer diagnosis and treatment highlights the relevance of this topic, since cardiac complications can adversely affect survival and quality of life independently of cancer prognosis. In this chapter, we briefly review the cardiac complications of both neoplastic diseases and cancer treatments, describing their incidence and aetiology, and focusing on strategies to evaluate, treat and prevent this wide spectrum of disorders.

Malignant Pericardial Effusion and Cardiac Tamponade

Aetiology

Malignant cardiac involvement is not an infrequent event, its incidence at autopsy being around 10% in patients with known malignancies.

Neoplastic diseases that most frequently present involvement of the pericardium are advanced lung cancer (approximately 30% of patients with lung cancer present pericardial involvement), breast cancer (approximately 25% of patients), malignant melanoma (40%–70% of patients) and leukaemia and lymphomas (around 15% of patients). In addition, chemotherapy-related effusions are occasionally observed (up to 1%–2% incidence) following exposure to busulfan, cytarabine, cyclophosphamide or tretinoin, especially when these drugs are used at high doses or in combination for the treatment of haematological malignancies.

Evaluation

As fluid accumulates in the pericardium, the increase in intrapericardial pressure affects diastolic filling of the heart, leading to decreased cardiac output. Symptoms may arise gradually or rapidly, depending on fluid accumulation rate, and may range from dyspnoea, chest pain, cough, palpitations and orthopnoea, to fatigue, anxiety and confusion. At physical examination, tachycardia, decreased heart sounds, neck vein distension, peripheral oedema and pericardial friction rubs may be present. Pulsus paradoxus, defined as an inspiratory decrease of more than 10 mmHg in systolic pressure, is a rare but suggestive sign of pericardial effusion. As cardiac tamponade develops, patients may show signs of low-output shock.

At initial evaluation, a chest radiograph may provide evidence of an enlarged cardiac silhouette, while at electrocardiography (ECG) low-voltage complexes and electrical alternans are suggestive of pericardial effusion. However, two-dimensional echocardiography is considered the standard method for diagnosing pericardial effusion.

Pericardiocentesis is usually needed to establish aetiology, the malignant nature of pericardial effusion being confirmed by identification of malignant cells at cytological examination.

Treatment

Treatment depends on the underlying aetiology and symptom progression. In patients with minimal symptoms without haemodynamic implications, systemic management is warranted, especially in chemosensitive cancers, and radiotherapy may also be indicated.

In patients with mild hypotension, rapid volume expansion by infusion of normal saline or Ringer's lactate may increase the right ventricular filling pressure above the pericardial pressure, improving cardiac output. However, immediate pericardiocentesis is mandatory and life-saving for patients with tamponade. If no systemic therapy can control the pericardial effusion, local measures, such as subxiphoid pericardiostomy, with or without intrapericardial instillation of sclerosing or cytotoxic agents, percutaneous balloon pericardiotomy and pericardial window, may be considered.

Chemotherapy-related Heart Failure

Aetiology

One of the most common manifestations of cardiotoxicity associated with anticancer therapies is the development of left ventricular dysfunction (LVD) and overt heart failure (HF). According to the definition proposed by the Cardiac Review and Evaluation Committee, LVD is characterised by:

- A decrease in cardiac LV ejection fraction (LVEF), that is either global or more severe in the septum;
- Symptoms of congestive heart failure (CHF);
- Associated signs of CHF, including but not limited to S3 gallop, tachycardia or both;
- Decline in LVEF of at least 5% to below 55% with accompanying signs or symptoms of CHF, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms.

Two distinct forms are identifiable. Type I cardiac dysfunction, typically induced by cytotoxic agents, is due, at least in part, to oxidative stress on the cardiac muscle, resulting in free radical formation and cell death. It is irreversible and typically associated with significant ultrastructural changes at biopsy.

Type II, typically induced by biological agents, is associated with reversible myocardial dysfunction rather than structural damage. It is highly reversible (up to 79%) and generally not dose-related.

Anthracyclines and cytotoxics with cumulative dose-related cardiotoxicity: type I agents

Even if several cytotoxic agents have been associated with cardiac toxicity (Table 1), anthracycline-induced cardiotoxicity is the most studied, given their frequency of use and resulting morbidity.

It may present as acute, subacute or late. Acute toxicity occurs during or immediately after infusion, and includes arrhythmias sometimes accompanied by an acute, transient decline in myocardial contractility, which is usually reversible and not dose-dependent. Subacute toxicity occurs within a few weeks of treatment, and clinically resembles myocarditis with oedema and thickening of the LV walls, accompanied by diastolic dysfunction. These two forms are, however, rare (1%–4%).

The most significant cardiac effect of anthracyclines is chronic cardiac toxicity leading to LVD and congestive HF. Symptoms usually appear during the first post-treatment year, but may occur even after 10–20 years. Prognosis is poor, with a 50% 2-year mortality in untreated established LVD.

Table 1 Antineoplastic Drugs Associated with Left Ventricular Dysfunction (LVD)

Compound	Incidence
Type I agents	
Doxorubicin 400 mg/m^2	7%–26%
Doxorubicin 550 mg/m^2	18%–48%
Epirubicin	0.9%–3.3%
Liposomal anthracyclines	2%
Mitoxantrone >150 mg/m^2	2.6%
Cyclophosphamide (high dose)	7%–28%
Ifosfamide	17%
Type II agents	
Trastuzumab	2%–27%
Lapatinib	1.5%–2.2%
Sunitinib	2%–11%
Bevacizumab	1.7%–3%
Imatinib	0.5%–1.7%
Trametinib	5%–7%

The most important risk factor for late cardiac toxicity is cumulative anthracycline dose. The associated incidence of HF is about 3%–5% with a doxorubicin cumulative dose of 400 mg/m^2, and 18%–48% with a

cumulative dose of 700 mg/m^2. For this reason, a cumulative doxorubicin dose of 450–550 mg/m^2 is empirically considered as the highest allowed in clinical practice. Other anthracyclines, such as epirubicin, idarubicin and daunorubicin, induce cardiotoxicity less frequently (0.9%–3.3%), allowing administration of different cumulative doses (900–1000 mg/m^2 for epirubicin, 100 mg/m^2 for idarubicin, 600 mg/m^2 for daunorubicin).

However, there is a considerable variability in the individual dose–response relationship for cardiac toxicity, and symptoms of CHF may also occur at lower doses. Additional risk factors for anthracycline cardiotoxicity include extremes of age, female gender, underlying cardiovascular (CV) diseases, and predisposing factors such as hypertension and smoking. Moreover, intravenous bolus administration and higher single doses of anthracyclines, concomitant use of cyclophosphamide, taxanes or trastuzumab, and previous mediastinal irradiation can increase the risk of developing cardiac toxicity. Liposomal anthracyclines are generally associated with a lower rate of cardiotoxicity compared to standard anthracyclines; for pegylated liposomal doxorubicin, which has been the most extensively studied, clear evidence shows a better cardiac safety profile. However, high cumulative doses of liposomal anthracyclines may still be associated with cardiac damage (Safra 2003).

The use of cardioprotectants such as dexrazoxane, which acts by chelating iron and decreasing iron-mediated free radical formation, has confirmed efficacy against anthracycline-related cardiac damage. Use of dexrazoxane, however, is recommended, both in the USA and in Europe, only for adult patients with advanced or metastatic breast cancer who have already received >300 mg/m^2 doxorubicin, and who may benefit from continued doxorubicin-containing therapy.

Monoclonal antibodies and targeted agents not associated with cumulative dose-related cardiotoxicity: type II agents

Several targeted agents have been identified as causing type II cardiac dysfunction (Table 1), trastuzumab being one of the first shown to adversely affect cardiac function. In patients with advanced disease, the incidence of LVD ranges from 2%–7% when trastuzumab is used as monotherapy, to 2%–13% up to 27% when in combination with paclitaxel

and anthracyclines plus cyclophosphamide, respectively. Trastuzumab-related cardiotoxicity includes various degrees of asymptomatic decreased LVEF or, less frequently, symptomatic CHF. Typically, it does not appear to be dose-dependent. Patients who develop cardiotoxicity generally improve once trastuzumab is discontinued, and retreatment is usually possible with a low incidence of LVD recurrence.

Risk factors include partially altered baseline LVEF values, elderly age, prior cardiac diseases, previous cardiotoxic treatments (including mediastinal irradiation and anthracyclines) and CV risk factors.

The temporary cardiomyocyte dysfunction caused by trastuzumab is probably secondary to inhibition of cardiomyocyte human ErbB2 signalling, thereby interfering with normal growth, repair and survival. Apart from HER2-targeting agents, other target agents, such as the antiangiogenic drugs sunitinib and bevacizumab and some tyrosine kinase inhibitors (TKIs) such as imatinib, are also known for their association with LVD.

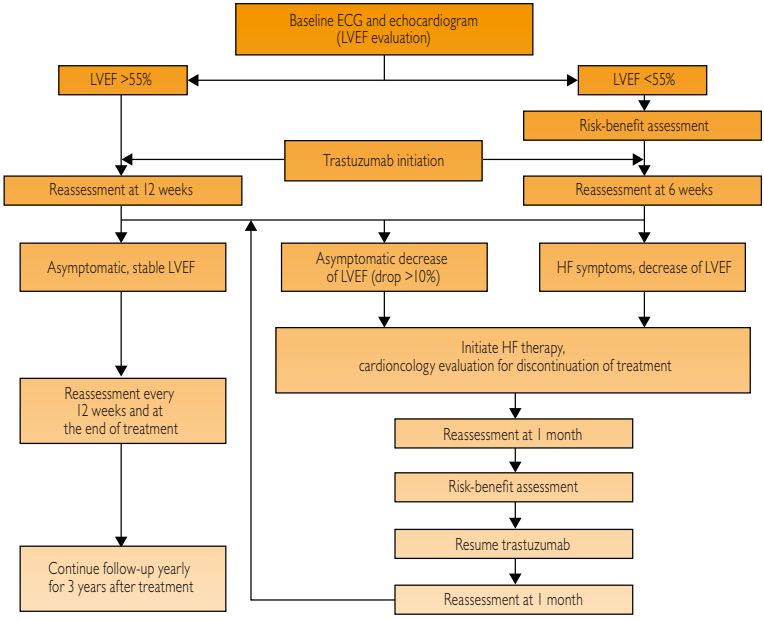
Evaluation and Treatment

Prevention is the best approach to minimise chemotherapy-induced cardiotoxicity. Careful drug selection should be based on a detailed patient history focused on CV risk factors, pre-existing CV disorders and previous exposure to chemotherapeutic agents or mediastinal irradiation. The introduction of a drug-free interval between anthracyclines and trastuzumab, or the administration of anthracycline-free regimens, can lower the potential risk of cardiac damage. Additionally, patients should be encouraged to actively reduce CV risk through blood pressure (BP) control, lipid level reduction, smoking cessation and lifestyle modifications. Even so, careful serial monitoring of the LV, using Doppler echocardiography or gated radionuclide scan with multiple acquisitions (MUGA scan), is advisable. Serial evaluation should always be conducted using the same procedure.

The monitoring schedule can be adapted according to the drug, cumulative dose, length of treatment and CV risk profile of the patient. Generally, in the adjuvant setting, serial monitoring of cardiac function every 3 months has been proposed, while patients treated for metastatic disease can be monitored less frequently in the absence of symptoms.

An assessment of cardiac function is recommended 4 and 10 years after anthracycline therapy in patients who were treated at <15 years of age, or even older if the cumulative dose of doxorubicin is >240 mg/m^2 or epirubicin >360 mg/m^2.

Cardiospecific biomarkers, such as troponin I and brain natriuretic peptide (BNP) concentrations, have also been shown to be valid diagnostic tools for the early identification and monitoring of cardiotoxicity. They are minimally invasive and less expensive than echocardiography. Nevertheless, the standardisation of their use in clinical practice is still under debate.



ECG, Electrocardiogram; HF, heart failure; LVEF, left ventricular ejection fraction.

Figure 1 An example of trastuzumab-related cardiotoxicity management.
Modified from: Todaro MC, Oreto L, Qamar R, et al. Cardioncology: state of the heart. Int J Cardiol 2013; 168:680–687, with permission from Elsevier.

If a decline in LVEF does occur, even in the absence of symptoms, early treatment with angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers and beta-blocker administration, unless contraindicated, should be considered.

When using anthracycline-containing regimens, a reduction in LVEF of ≥20% from baseline or a confirmed LVEF decrease <50% requires discontinuation of therapy, evaluation of medical LVD treatment and further clinical and echocardiographic re-evaluations. If LVEF declines to <40%, chemotherapy should be stopped and alternatives discussed.

When managing trastuzumab-related cardiotoxicity, "stopping/restarting" rules are usually effective, and their use is recommended (Figure 1).

Arterial Hypertension

Hypertension is a relatively common and dose-related side effect of several antiangiogenic drugs (Table 2). It can occur at any time after therapy initiation; however, pre-existing hypertension is an important risk factor for complications.

Clinical trials of bevacizumab reported grade 3–4 hypertension in approximately 10% of patients, with rare cases of hypertensive crisis, encephalopathy or intracranial haemorrhage. In trials with antiangiogenic multitarget kinase inhibitors, such as sunitinib or sorafenib, the incidence of grade 3–4 hypertension was even higher, and in some rare cases hypertension was associated with reversible posterior leukoencephalopathy syndrome, a clinical event characterised by headache, seizures, impaired vision and acute hypertension (Todaro et al, 2013).

Several mechanisms have been proposed to explain antiangiogenic-induced hypertension, including decreased nitric oxide signalling in the wall of arterioles, increased endothelin-1 production and capillary rarefaction. Arterial hypertension developing through these mechanisms is an on-target side effect, and may play a role as a pharmacodynamic biomarker for vascular endothelial growth factor (VEGF) inhibition.

However, hypertension may also be secondary to renal thrombotic microangiopathy or to glomerular damage, hence the importance of

Table 2 Antineoplastic Agents Associated with Arterial Hypertension

Agent	Mechanism of action	Incidence of G3–G4 hypertension
Bevacizumab	*Anti-VEGF-A Ab*	0.4%–18%
Sorafenib	*Multitarget TKI*	0.35%–30.7%
Sunitinib	*Multitarget TKI*	2.4%–14.8%
Pazopanib	*Multitarget TKI*	7.0%–11.0%
Axitinib	*Multitarget TKI*	23%
Ramucirumab	*Anti-VEGFR2 Ab*	7.6%–14.7%
Aflibercept	*Anti-VEGF trap*	19.3%–23%

Ab, Antibody; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.

investigating renal abnormalities through evaluation of creatinine clearance, proteinuria and microscopic haematuria while on active therapy. Proteinuria is usually monitored during treatment by dipstick urine analysis. Patients who develop proteinuria (confirmed using 24-hour urine collection) or reduced renal function (glomerular filtration rate [GFR] <60 ml/min per 1.73 m^2) should be referred to a nephrologist. It should also be considered whether to put on hold, or definitively discontinue, treatment according to the severity of proteinuria, based on the manufacturer's recommendations.

As hypertension and cancer can frequently coexist in the same patient, patients who are candidates for treatment with antiangiogenic agents should be screened at baseline for hypertension and for existing kidney disease. Anti-hypertensive therapy should be implemented or optimised before starting treatment, to prevent antiangiogenic-induced uncontrolled hypertension and avoid the development of serious complications. Repeated BP measurements are recommended during treatment with antiangiogenic drugs, with the aim of implementing early active anti-hypertensive therapy to maintain BP <140/90 mmHg, rather than withdrawing treatment. Since these patients are at increased risk of LVD, preferred antihypertensive agents should include ACE inhibitors and dihydropyridine calcium channel blockers (CCBs), although there are minimal data to suggest the superiority of a class of agents. Non-dihydropyridine CCBs should be avoided in sorafenib-induced hypertension, due to drug interactions that

may result in higher levels of sorafenib. Discontinuation of treatment may be applicable if systolic BP is >200 mmHg, diastolic BP >100 mmHg, or in case of hypertensive crisis.

Myocardial Ischaemia

Aetiology

Several antineoplastic agents are associated with an increased risk of coronary artery disease and/or acute coronary syndrome (Table 3).

Table 3 Antineoplastic Agents Associated with Myocardial Ischaemia

Agent	Incidence
5-Fluorouracil	7%–10%
Capecitabine	3%–9%
Paclitaxel	0.29%–5%
Docetaxel	1.7%
Bevacizumab	0.6%–1.5%
Sorafenib	2.7%–3%

The most common is 5-fluorouracil (5-FU), especially when used as a continuous infusion (7%–10% incidence), in combination with cisplatin or in patients with a history of coronary artery disease. Although it appears less toxic than 5-FU, capecitabine may also elicit myocardial ischaemia. These acute coronary syndromes seem to be related to endothelial dysfunction and vasospasm of coronary arteries.

By contrast, for antiangiogenic agents, inhibition of VEGF itself seems to be responsible for the increased risk of cardiac ischaemia and infarction through reduction of the regenerative capacity of endothelial cells, thus causing defects that expose procoagulant phospholipids on the luminal plasma membrane, leading to thrombosis.

Evaluation and Treatment

Baseline ECG evaluation is recommended when treating patients with drugs known to be associated with myocardial ischaemia. Thoracic pain is usually the presenting symptom, but some cases may present with

ventricular arrhythmias and cardiac arrest. If chest pain occurs during 5-FU infusion, the infusion must be stopped immediately, and antianginal therapy and a work-up for ischaemia should be initiated. ECG may show evidence of an ST-segment elevation, while coronary angiography is usually consistent with coronary artery spasm.

While nitrates and calcium channel blockers are used to treat 5-FU-related coronary syndromes, their usefulness as a prophylactic measure to prevent ischaemia during therapy is still controversial.

Re-challenging patients after treatment-related myocardial ischaemia remains a questionable practice. It should be reserved for patients having no alternative therapeutic interventions, and administered in a supervised environment.

Arrhythmias

Aetiology

Multiple conditions may cause arrhythmias in cancer patients. Fibrosis due to old age or radiation therapy, or coronary or myocardial disease secondary to cancer therapy, can all affect the cardiac conduction system. Several chemotherapeutic agents have been associated with bradycardia and heart block, the most clinically significant being paclitaxel (incidence of asymptomatic bradycardia up to 30% in phase II studies) and thalidomide (incidence ranging from 0.12% up to 55%). In addition, some new target agents such as crizotinib have also been associated with profound asymptomatic sinus bradycardia (in 5% of patients).

Evaluation and Treatment

Generally, bradycardia presents with an asymptomatic heart rate <50 beats/min; nevertheless, some patients may have associated symptoms such as fatigue, syncope or dizziness. Diagnostic tests include an ECG, Holter monitoring and screening for underlying disorders, such as thyroid disease or electrolyte abnormalities.

Bradycardia associated with paclitaxel is generally without clinical significance, as many cases are asymptomatic. However, if patients develop

bradycardia with progressive atrioventricular conduction disturbances and/or clinically significant haemodynamic effects, paclitaxel discontinuation is warranted, and some patients might require pacemaker implantation. Whenever haemodynamic instability is imminent or life-threatening, active intervention according to advanced cardiac life-support protocols is mandatory.

With crizotinib, bradycardia presents as a pharmacodynamic effect, with hearth rate progressively decreasing when serum concentrations of this agent increase. Thus, special attention should be given to drug–drug interactions, which might result in an increased concentration of crizotinib. In addition, concurrent heart rate-lowering agents such as beta-blockers or CCBs should be used with caution in these patients.

QT Prolongation

Aetiology

QT interval prolongation is an abnormality of the electrical activity of the heart, which places individuals at risk for life-threatening ventricular arrhythmias, including torsade de pointes (TdP) and sudden cardiac death.

Cancer patients are particularly prone to QT prolongation (16%–36% incidence at baseline), probably due to the high prevalence of concomitant diseases, as well as concomitant medications that are known to prolong the QT interval (e.g. antiemetics, antifungals, quinolone antibiotics). Furthermore, electrolyte disturbances caused by nausea, vomiting and diarrhoea increase the risk for QT prolongation.

Several novel anticancer therapies including histone deacetylase inhibitors, multitargeted TKIs, and Src/Abl kinase inhibitors are associated with QT prolongation. Arsenic trioxide, a uniquely effective drug in relapsed acute promyelocytic leukaemia, is also known to provoke QT prolongation (incidence ranging from 26%–93%) and TdP.

Evaluation and Treatment

Drugs known to provoke QT prolongation should be used cautiously in patients with risk factors. ECGs should be performed at baseline, and

regularly while on therapy, using Bazett or Fridericia formulae to correct QT for heart rate (QTc). A baseline QTc >450 ms in men and >470 ms in women should be considered abnormal, and conditions associated with QT prolongation, such as hypomagnesaemia and hypokalaemia, should be investigated and treated before starting therapy.

Non-cancer medications that may prolong the QTc interval should be administered cautiously and, due to drug interactions, treatment with CYP3A4 inhibitors should also be carefully evaluated. Patients should be informed to report any cardiac symptoms such as palpitations.

Manufacturers' recommendations on QTc-prolonging agents usually include details on baseline and periodic ECG monitoring requirements, as well as dosage adjustments necessary in case of QT prolongation. Increases of >60 ms from baseline or QTc >500 ms usually raise concern about the potential risk of arrhythmia, and treatment withdrawal should be evaluated.

In case of TdP, the involved drug should be stopped and patients should be monitored closely in an intensive care unit. Magnesium infusion and shortening of the QT interval by increasing heart rate should be undertaken. Non-synchronised defibrillation may be indicated if sustained, haemodynamically unstable polymorphic ventricular tachycardia or fibrillation develop.

Radiation Therapy-induced Cardiotoxicity

Chest radiation, used to treat lymphoma, breast and lung cancers, is associated with an increased risk of late cardiovascular effects through two mechanisms: microvascular disruption leading to cellular death and fibrosis, and accelerated macrovascular atherosclerosis. These affect not only the myocardium but also the pericardium, coronary arteries, and the heart valvular and conduction systems.

The risk of cardiac disease depends mostly on the radiation dose (dose >30 Gy), volume of the heart exposed (improvements in radiation techniques seem to reduce it) and radiation delivery techniques (dose per fraction >2 Gy). However, other risk factors include age (younger patients are at higher risk), longer time since exposure (incidence of

heart disease continues to increase even 30 years after radiation), gender, exposure to other cardiotoxic treatments, or other CV risk factors.

High-risk patients, such as those who received a mediastinal/heart dose of >30 Gy as children or young adults, should be followed up closely.

Declaration of Interest:

Dr Griguolo has reported no conflicts of interest.
Dr Guarneri has reported no conflicts of interest.

Further Reading

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