Cardiac dysfunction in patients treated for cancer: a challenge to cardiologists

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INTRODUCTION

The rapid and extensive development of numerous cancer therapies has led to greatly improved patient survival. In parallel with greater survivorship, the incidence of cancer therapy-related cardiac disease (CTRCD) has increased. Therefore, it behoves cardiologists to anticipate the many manifestations of CTRCD, requiring awareness of the nature and extent of the cancer, its genetic type, detailed insight into the treatment to be applied or already given, its possible side effects, and the intrinsic risk to the patient's cardiovascular health at baseline.

A common scenario

The cardiologist's problem is illustrated by the case of an 80-year-old woman. She had been treated successfully for heart failure for 15 years on a beta blocker, an angiotensin receptor blocker, and a loop diuretic. At age 78, she was diagnosed with a moderately differentiated colon carcinoma and commenced continuous chemotherapy following a partial colectomy. In the 3 years before chemotherapy, her left ventricular ejection fraction (LVEF) averaged 0.63. Before treatment, her estimated glomerular filtration rate (eGFR) was 51, and a year later it was 36. Despite continuous treatment with a beta blocker, sodium-glucose transport 2 (SGLT2) inhibitor and furosemide, she developed increasing dyspnoea. Her symptoms raised the possibility of CTRCD; its likelihood depending on the nature of her cancer treatment.

The patient was unable to provide any details beyond taking 6 tablets a day for 2 out of every 3 weeks and a "drip" once every 3 weeks. In the absence of any prior communication from her oncologist to the treating cardiologist, she learned from the clinic that she had been receiving capecitabine and bevacizumab. By referencing the literature, it was established that capecitabine is an antimetabolite, a 5-fluorouracil prodrug, the side effects of which include leukopaenia, bleeding (especially when combined with a vitamin K antagonist), coronary vasospasm, stress cardiomyopathy (takotsubo), proteinuria, hepatic impairment, venous thromboembolism, hypertension, and palmar-plantar erythrodysesthaesia (hand-foot syndrome). Bevacizumab is a monoclonal antibody that blocks vascular endothelial growth factor (VEGF). Its use is associated with hypertension, heart failure, QT prolongation, acute vascular events, such as dissection or stroke, and venous thromboembolism.[1]

Transthoracic echocardiography established her current ejection fraction at 0.51, a fall of 12 percentage points. The QT interval was unchanged. Considering the moderate reduction in her left ventricular function, her treatment was intensified by adding sacubitril/valsartan.[1]

The nature of CTRCD

CTRCD has been sub-classified as causing cardiac dysfunction (an adverse impact on cardiac structure and function in cancer patients, presenting either as asymptomatic cardiac dysfunction or symptomatic heart failure resulting from the therapy received) and that resulting in cardiac toxicity (including myocarditis, vasculitis, arterial and venous thrombosis, hypertension, prolongation of the QT interval, and/or arrhythmia).[2] Indeed, CTRCD may involve cardiac dysfunction, heart failure, coronary artery disease, valvular heart disease, arrhythmia, autonomic dysfunction, arterial hypertension, dyslipidaemia, metabolic syndrome, thromboembolism, peripheral arterial disease, stroke, pulmonary hypertension, and pericardial disease.[1]

In 2022, the European Society of Cardiology (ESC) issued a guideline on cardio-oncology outlining commonly encountered scenarios in cancer treatment. The guideline is extremely complex, describing 17 treatment protocols associated with the risk of CTRCD, and detailing 11 categories of potential cardiac complications, each of which may or may not be associated with a specific protocol.[1] Cancer may affect multiple organs, and their genetic subtype will dictate the particular therapy or combination of therapies to be used. An example is breast cancer with its HER2-positive and BRCA-positive subtypes, for which any suitable agent or a combination of agents could be selected from a list of 21.[3] Each of these agents may affect

cardiovascular function differently. Thus, cancer treatment and its ensuing CTRCD cannot be considered as a "one size fits all" situation.

The proposed pathophysiologic mechanisms underlying CTRCD include oxidative stress, inflammation, calcium overload, VEGF, pyroptosis, and fibrosis.[4] The incidence of developing CTRCD is influenced by the baseline cardiovascular risk profile/pre-existing cardiovascular disease, which increases during the treatment period and diminishes somewhat during long-term follow-up.[2] Fluoropyrimidines (such as 5-fluorouracil) are commonly used in the treatment of gastrointestinal cancers and are the second most common cause of CTRCD.[5] Not only do these agents cause direct cellular damage, but they may also provoke coronary vasospasm, resulting in angina pectoris, acute coronary syndromes, atrial fibrillation, myocarditis, pericarditis, and consequent heart failure.

The most frequent cancers encountered in South Africa are breast (most frequent in females), prostate (most frequent in males), cervix (leading cause of cancer deaths in females), lung (overall leading cause of cancer deaths), and colorectal. Examples of the commonly used therapies among these cancers, their main cardiovascular toxicities, and their appropriate monitoring and treatment are shown in Table I.[4-6]

The role of the cardiologist

The cardiologist's role in CTRCD encompasses the patient's entire journey.[1] At baseline, before treatment starts, the cardiovascular risk factors should be assessed, and any pre-existing cardiovascular disease should be treated effectively. Accurate knowledge of the intended cancer treatment is needed to anticipate and promptly treat potential cardiovascular complications. After treatment cessation, long-term surveillance is necessary to detect cardiovascular complications that may emerge.[1]

Predicting CTRCD

To predict cardiovascular risk during treatment, the patient's individual characteristics (genetics, lifestyle, environment, and their social determinants of health) should be weighed alongside the classical cardiovascular risk factors (smoking, diabetes, hypertension, and dyslipidaemia). Furthermore, the potential cardiotoxicity of the planned treatment, with consideration of its pharmacokinetic and epigenetic factors, should be considered.[7]

Risk prediction combined with standard risk factor algorithms, such as the ESC Cardiovascular Disease Risk Score (SCORE2 or SCORE2-OP, easily accessible on the ESC CVD Risk smartphone application), and the Heart Failure Association of the ESC, and the International Cardio-Oncology Society (HFA-ICOS) score, have proved useful in predicting which patients are more likely to develop CTRCD.[8] Risk assessment enables more frequent monitoring in high-risk patients and reduces the need for more frequent re-evaluation in those at low risk. The application of the HFA-ICOS score is complex, as a non-uniform set of risk factors is applied to individual treatments, and similar risk factors

TABLE I: Commonly encountered cancers in South Africa, illustrating the variety of possible treatments, the main cardiovascular toxicities that may be encountered, and the monitoring and prevention measures that may be applied.[4-6]

Cancer	Agent/s	Main cardiovascular toxicities	Monitor & treat
Breast	Anthracyclines	Cardiomyopathy, heart failure	LVEF, GLS GDMT, including SGLT2 inhibitor
	Human EGFR2 targeting: • Trastuzumab	Reduction in ejection fraction, heart failure	LVEF
	Cyclin independent kinase 4/6 inhibitor	QT prolongation, venous & arterial thrombosis	ECG monitoring
Prostate	Androgen deprivation therapy: • Degarelix • Abiraterone • Enzalutamide	QT prolongation, hypertension, cardiovascular events, arrhythmia	ECG monitoring, BP monitoring
Cervix	Pembrolizumab	Hypertension, arrhythmia	BP monitoring
	5-fluorouracil	Cardiac ischaemia, ACS, MI	hs-troponin T
	Paclitaxel	Cardiomyopathy, tachyarrhythmia, heart block	Transthoracic echo monitoring, ECG monitoring
	Topotecan	Heart failure: low risk	NT-proBNP
Lung	Immune checkpoint inhibitors	Myocarditis, pericarditis, pericardial effusion & tamponade, MI, arrhythmias	Cardiac markers, echo, stop treatment, high-dose steroids, immune modulators
Colorectal	VEGF: • Monoclonal antibodies • Tyrosine kinase inhibitors	Hypertension, myocardial ischaemia, systolic dysfunction, arterial thrombosis, QT prolongation	Frequent BP monitoring, RAASi & DHP CCB

ACS: acute coronary syndrome, BP: blood pressure, DHP CCB: dihydropyridine calcium channel blockers, ECG: electrocardiogram, echo: echocardiogram, eGFR: estimated glomerular filtration rate, GDMT: guideline-directed medical therapy, GLS: global longitudinal shortening, hs-troponin T: high-sensitivity troponin T, LVEF: left ventricular ejection fraction, MI: myocardial infarction, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, RAASi: renin-angiotensin-aldosterone system inhibition, SGLT2: sodium-glucose transport 2, VEGF: vascular endothelial growth factor

are variously treated as indicating very high, high, or moderate risk, based on the specific agent.[9]

Although there is no perfect risk assessment strategy, precise risk calculation should be attempted, as the greatest impact will be among medium- and high-risk individuals, whereas identifying low-risk patients offers potential savings in health costs.[10] For instance, a progressive increase in the occurrence of CTRCD and heart failure was observed in patients rated at baseline as low, medium, or high risk when treated either with trastuzumab or trastuzumab with an anthracycline.[6]

Monitoring for CTRCD

At any stage, monitoring for CTRCD requires meticulous clinical assessment, with evaluation for cardiovascular risk factors and the presence of underlying cardiovascular disease. Electrocardiography is appropriate to exclude cardiac ischaemia and to measure the QT interval. The markers of cardiac injury (high-sensitivity [hs]-troponin T/I and N-terminal prohormone of brain natriuretic peptide [NT-proBNP]) may facilitate CTRCD detection, but do not necessarily constitute standard monitoring.[1] False positive values may be encountered, particularly in the case of hs-troponin I, due to the presence of immunoglobulin-troponin complexes (so-called macrotroponin), which should be suspected when the result is incongruous with the clinical picture and imaging.[1] In this instance, a troponin measurement before treatment initiation may provide important information. Macrotroponin can be identified by specific testing.[11]

The LVEF should be measured before starting treatment by transthoracic echocardiography. Measurement of global longitudinal strain is proposed as a useful parameter, though its superiority to LVEF has been questioned. Serial estimations of LVEF should employ the same methodology on each occasion. A fall in LVEF of 15% or more on treatment is considered significant.[1] Magnetic resonance imaging may be required when the acoustic window does not allow for accurate assessment of the LVEF by transthoracic echo.[5]

Preventing CTRCD

CTRCD prevention includes ensuring patients' adherence to a healthy lifestyle, i.e. smoking cessation, weight control, regular exercise, and a healthy diet. Stringent control of the classical risk factors is important. Attempts to ameliorate CTRCD with beta blockers (carvedilol, metoprolol), renin-angiotensin-aldosterone system inhibitors (enalapril, candesartan), and statins have not yielded convincing results.[12] SGLT2 inhibition has an anticancer effect, as well as being cardioprotective.[13] Recent observational studies of SGLT2 inhibition (dapagliflozin, empagliflozin) demonstrated encouraging improvements in overall survival, cardiac dysfunction, heart failure incidence, and heart failure hospitalisation.[14-16] In a study of 83 women with breast cancer, treatment with spironolactone, a mineralocorticoid receptor antagonist, was associated with lesser rises in troponin I and NT-proBNP, and a smaller impact on LVEF compared with a placebo.[17]

Managing CTRCD

When CTRCD emerges, the risks and benefits of continued treatment should be carefully considered. Whether dose reduction, reduction in the frequency of treatment, temporary interruption, or treatment alteration is indicated depends on balancing the cardiovascular prognosis with that of the cancer.[18] For example, despite the cardiovascular risks of fluoropyrimidine chemotherapy noted above, experience has shown that the overall survival benefit of treatment outweighs the risk.[18]

Atrial fibrillation is among the common arrhythmias encountered in CTRCD. Its occurrence may influence cancer therapy and adversely affect survival. Various cancer drugs have been shown to double or quadruple the risk of atrial fibrillation. The true incidence of atrial fibrillation in cancer therapy is uncertain, as the condition is frequently asymptomatic and is not routinely recorded in trials of anticancer treatment. Most trials only record atrial fibrillation when it arises as a serious complication.[19] Aside from the usual complications of atrial fibrillation, attention should be focused on the anticoagulation strategies in patients who frequently have thrombocytopaenia and are prone to serious bleeding.[19]

Arterial and venous thrombosis and embolism are encountered in up to 55% of cancer patients. The high frequency is accounted for by increases in life expectancy, the use of thrombogenic anticancer treatments, extensive use of central venous catheterisation, and heightened awareness of cancer-associated thrombosis. Deep venous thrombosis and pulmonary embolism are 4–7 times more frequent in cancer patients.[20] The reported mortality rate of venous and arterial thromboembolism is 8.4%, and it is the leading cause of death outside cancer-related deaths.

Cancer patients have a higher risk of bleeding and recurrent venous thromboembolism.[20] Low-molecular-weight heparin treatment has not been successful in countering thrombotic complications. Direct oral anticoagulants are associated with lower recurrence rates and reduced major bleeding. Compared with standard doses, a lower dose of apixaban (2.5 mg bd) was effective in preventing recurrent venous thromboembolism and was coupled with a lower bleeding risk.[21]

Aftercare

Cancer patients' aftercare should ideally be a collaborative effort, providing social support to the patient, family, and caregiver by the primary physician, oncologist, and cardiologist. Allied professionals, such as dieticians, rehabilitation experts, and social workers, should also be involved.[7] Encouraging moderate-to-vigorous exercise in recovered patients should not be overlooked, as it benefits anxiety–depression, physical functioning, cardiac health, and cardiovascular disease, as well as cancer-specific and overall survival.[22]

CONCLUSION

As illustrated by the case presented, communication among the physician or surgeon who made the diagnosis, the treating

oncologist, and the cardiologist responsible for detecting and treating CTRCD is often lacking in the local setting. The increasing number of patients at risk of CTRCD demands closer cooperation and communication between the professionals treating them, acquiring a deeper understanding of their treatment protocols, accurate assessment of their intrinsic risk, appreciation of the potential adverse side effects to which they may be exposed, early detection and management of cardiac complications, and assurance of sustained follow-up once treatment is completed.

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