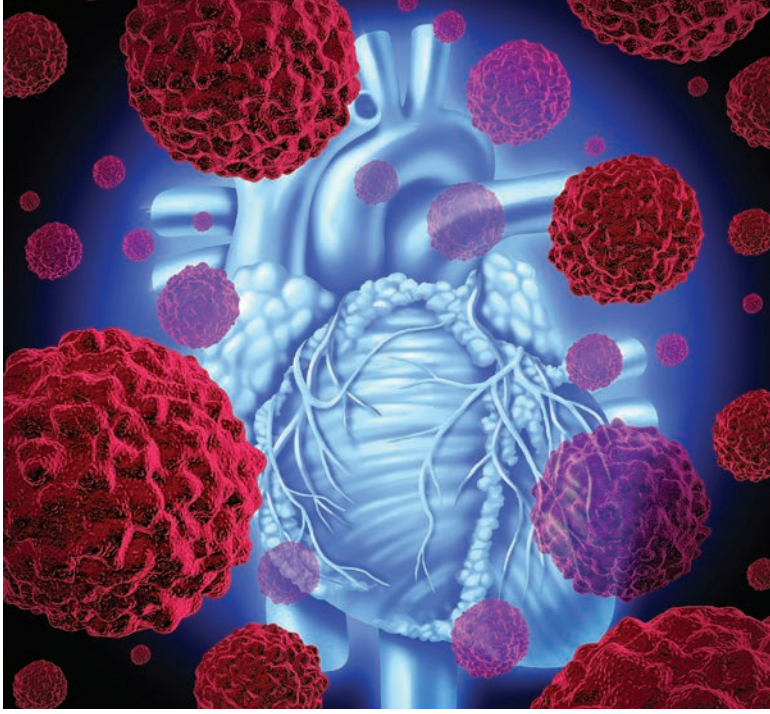
Cardio-oncology

The intersection between heart and cancer care



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Cardio-oncology is a rapidly emerging subspecialty that has gained momentum due to increasing insights into how cancer and its various treatment options can adversely affect the cardiovascular (CV) system. It focuses on the different aspects of CV care for patients with cancer who are undergoing or who have completed cancer treatment and involves optimisation and management of CV health, early detection of cardiac complications of cancer treatment and long-term follow up and surveillance.

KEY POINTS

- Cardiovascular disease (CVD) and cancer are intrinsically linked in a bidirectional fashion: the presence of CVD increases the risk of cancer, and prior cancer, cancer treatment, or both, significantly increases the risk of CVD.
- Many modern cancer therapies, including chemotherapy, targeted therapies, immunotherapy and radiotherapy, carry significant risk of cardiotoxicity, which can manifest acutely or many years after treatment.
- With early detection and modern treatment resulting in improving rates of cancer survivorship, CVD represents a leading (yet preventable) cause of mortality and morbidity among cancer survivors.
- Cardio-oncology is an emerging multidisciplinary field that focuses on preventing, detecting and managing cardiovascular complications in patients with cancer and survivors related to cancer therapies and common risk factors.
- Pretreatment cardiac risk stratification, careful monitoring during treatment and long-term surveillance post treatment form key components of cardio-oncology. The GP has a key role within this longitudinal and multidisciplinary model of care.

Cardiovascular disease (CVD) and cancer are two leading causes of death in Australia. Although historically they have been viewed as distinct entities, emerging contemporary evidence suggests a closely linked and bidirectional relationship, with a substantially increased risk of CVD in patients with cancer but also a higher risk of developing certain cancers in patients with established CVD.[1] Despite this clear association, current or past cancer or exposure to cancer treatments have yet to be routinely incorporated in risk-stratification calculators such as the Australian CVD risk calculator or primary prevention guidelines.[2] Additionally, with improving and emerging cancer treatments, there has been a steady increase in cancer survivorship since the 1990s. In this context, cardiac side effects of cancer treatments and CVD associated with cancer or cancer-related therapies are emerging as major causes of morbidity and mortality in patients with, or who have survived, cancer.

The emerging field of cardio-oncology thus seeks to undertake a multidisciplinary approach in identifying, preventing and treating patients who are at risk of, or experience, cardiovascular (CV) side effects or sequelae of their cancer or cancer treatments.

A bidirectional relationship

In recent years, evidence has emerged highlighting a strong link between cancer and CVD. Many common traditional CV risk factors have now been linked to the development of certain cancers and worse outcomes after the development of cancer. Hypertension is associated with an increased risk of developing renal and colorectal cancer, alongside an increased risk of cancer mortality as compared with normotensive individuals.[3,4]

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Dyslipidaemia has been linked with development of colorectal and breast cancer, whereas diabetes mellitus is associated with a higher risk of breast, colorectal, biliary tract and endometrial cancers.[5-7] Although the strong link between smoking and atherosclerotic CVD and cancer (e.g. lung cancer) is well-established, other modifiable lifestyle factors such as obesity and sedentary lifestyle are now emerging as strong risk factors for the development of a broad range of solid-organ and haematological cancers.[8,9]

Disregarding cardiac toxicities associated with cancer therapies, patients with cancer have a higher burden of CVD than the population without. Studies have shown higher rates of myocardial infarction, heart failure, stroke and CV death after a new diagnosis of cancer, with the risk particularly high in the first three months after diagnosis.[10,11] The inverse is also true, with studies showing the presence of atherosclerotic CVD and non-atherosclerotic CVD (e.g. heart failure) conferring a higher risk of developing cancer, even when accounting for shared risk factors.[12-14] Thus, a new diagnosis of cancer represents an opportunity to screen and assess for CVD and associated risk factors. Similarly, the presence of established CVD or cardiac risk factors may alert a clinician to a heightened cancer risk and presents an opportunity to engage the patient in age-appropriate cancer screening.

Cancer therapy-related cardiac dysfunction

Patients receiving, or who have received, cancer therapies, including chemotherapy, molecular targeted therapies, immunotherapy and radiotherapy, are at risk of developing cancer therapy-related cardiac dysfunction (CTRCD). The risk of CTRCD is dependent on treatment factors (degree of expected cardiotoxicity) and patient factors, including the presence of CV risk factors or a known history of heart disease. Common cancer pharmacotherapies and their potential CV toxicity profile are summarised in the Table.[15]

Anthracyclines

Anthracyclines (e.g. doxorubicin and idarubicin) are important components of many chemotherapy regimens. However, anthracycline toxicity is often encountered and may result in temporary or permanent reduction in left ventricular function with risk of heart failure and subsequent CV mortality, particularly if not detected early.[16] Anthracycline-induced cardiotoxicity is dose-dependent and cumulative; therefore, pretreatment evaluation (discussed below) and close monitoring during treatment are necessary to mitigate this risk.[15]

Fluoropyrimidines

Fluoropyrimidines (e.g. capecitabine and fluorouracil) are often-used chemotherapy agents and are the second most common cancer treatment associated with cardiotoxicity (after anthracyclines).[17] Cardiotoxicity related to fluoropyrimidines may manifest with chest pain/angina (possibly secondary to coronary artery vasospasm or direct myocardial toxicity), arrhythmia or heart failure and may range from minor or self-limiting to serious and even fatal.[17] Unlike the dose-dependent toxicity profile of anthracyclines, cardiotoxicity from fluoropyrimidines tends to occur most often around the time of the first dose.

HER2-targeted agents

HER2-targeted agents including trastuzumab and newer agents such as pertuzumab and lapatinib are critical components in the treatment of HER2-positive breast cancer (comprising 15-20% of breast cancer cases). Trastuzumab, a monoclonal antibody targeting HER2, is associated with a small-to-modest risk of cardiotoxicity, most often manifesting as an asymptomatic decrease in left ventricular ejection fraction (LVEF) and less often by clinical heart failure.[18] Risk factors associated with higher risk include previous or current anthracycline use, age over 50 years and obesity.[19] Trastuzumab-related cardiotoxicity is often reversible with treatment discontinuation and rechallenge is often considered after recovery of LVEF.

Radiation therapy

Radiation therapy (RT) has contributed to significant improvements in prognosis and survival for many patients with Hodgkin lymphoma, breast cancer and other malignancies involving the thorax. However, incidental radiation to the heart places patients at risk of early and late-onset cardiac complications, particularly as these patients often receive concurrent cardiotoxic chemotherapy agents.

Pericarditis is an uncommon acute manifestation of radiation injury, whereas intermediate to late complications can include chronic pericardial disease, coronary artery disease, valvular heart disease, cardiomyopathy (e.g. heart failure with preserved ejection fraction) and arrhythmia manifesting years or decades after initial treatment. Factors influencing the risk of cardiac complications include total dose and volume of RT and the extent by which the heart is included in the field of treatment.

Studies following up patients treated for Hodgkin lymphoma show disproportionately higher long-term rates of valvular heart disease, ischaemic heart disease and heart failure after mediastinal radiation, particularly in patients receiving treatment from a young age.[20,21] Although historical modes of RT delivery for breast cancer and other malignancies involving the thorax increased the risk of CVD,[22] modern techniques that reduce the total dose of radiation and amount of heart in the treatment field appear to have reduced the risk of late cardiac complications.

Immune checkpoint inhibitors

Immune checkpoint inhibitors (e.g. atezolizumab, nivolumab and pembrolizumab) have significantly improved cancer survival outcomes; however, these agents come with the risk of a broad range of immune-related adverse effects, which can rarely include cardiac toxicities that can range from asymptomatic reduction in LVEF to acute fulminant myocarditis, cardiogenic shock, life-threatening arrhythmia and death.[23]

TABLE. EXAMPLES OF CANCER PHARMACOTHERAPIES AND POTENTIAL CARDIOVASCULAR EFFECTS[15]

Treatment	Examples	Cancers treated	Potential cardiotoxicities
Anthracyclines	Daunorubicin Doxorubicin Epirubicin Idarubicin	Leukaemia Lymphoma Breast cancer	Heart failure or LV dysfunction Arrhythmia QT prolongation
Fluoropyrimidines	Capecitabine Fluorouracil	Head or neck cancer GI cancer Breast cancer	Angina or myocardial ischaemia Coronary artery vasospasm Heart failure Arrhythmia
HER2-targeted agents	Lapatinib Pertuzumab Trastuzumab	HER2-positive breast cancer	LV dysfunction (usually reversible)
VEGF inhibitors	Bevacizumab Lenvatinib Sorafenib Sunitinib	Various solid organ malignancies	Hypertension (common) LV dysfunction Myocardial ischaemia Arterial or venous thrombotic events QT prolongation
Tyrosine kinase inhibitors	Dasatinib Imatinib Nilotinib Ponatinib	Chronic myeloid leukaemia	Pulmonary hypertension (dasatinib) Pleural and pericardial effusions Myocardial ischaemia Arrhythmia QT prolongation
Bruton kinase inhibitors	Acalabrutinib Ibrutinib	Lymphoid malignancies	Hypertension Atrial fibrillation Heart failure
Alkylating agents	Cyclophosphamide Melphalan	Various haematological and solid organ cancers	Atrial fibrillation Heart failure
Immunomodulatory drugs	Lenalidomide Pomalidomide Thalidomide	Multiple myeloma Other haematological malignancies	Hypertension Venous thromboembolism Heart failure Myocardial ischaemia
Proteasome inhibitors	Carfilzomib Bortezomib	Multiple myeloma Other haematological malignancies	Hypertension Venous thromboembolism Heart failure Arrhythmia
RAF inhibitors	Dabrafenib Encorafenib Vemurafenib	Melanoma (often as combination treatment)	Hypertension (common) Venous thromboembolism Heart failure QT prolongation Arrhythmia
MEK inhibitors	Selumetinib Trametinib		
Immune checkpoint inhibitors	Atezolizumab Nivolumab Pembrolizumab	Various solid organ malignancies	LV dysfunction Heart failure Myocarditis Arrhythmia
Androgen deprivation therapies	Abiraterone Bicalutamide Degarelix Enzalutamide Goserelin	Prostate cancer	Hypertension Impaired glucose tolerance or diabetes mellitus Heart failure Ischaemic heart disease

Abbreviations: GI = gastrointestinal; HER2 = human epidermal growth factor receptor 2; LV = left ventricular; MEK = mitogen-activated protein kinase; RAF = rapidly accelerated fibrosarcoma; VEGF = vascular endothelial growth factor.

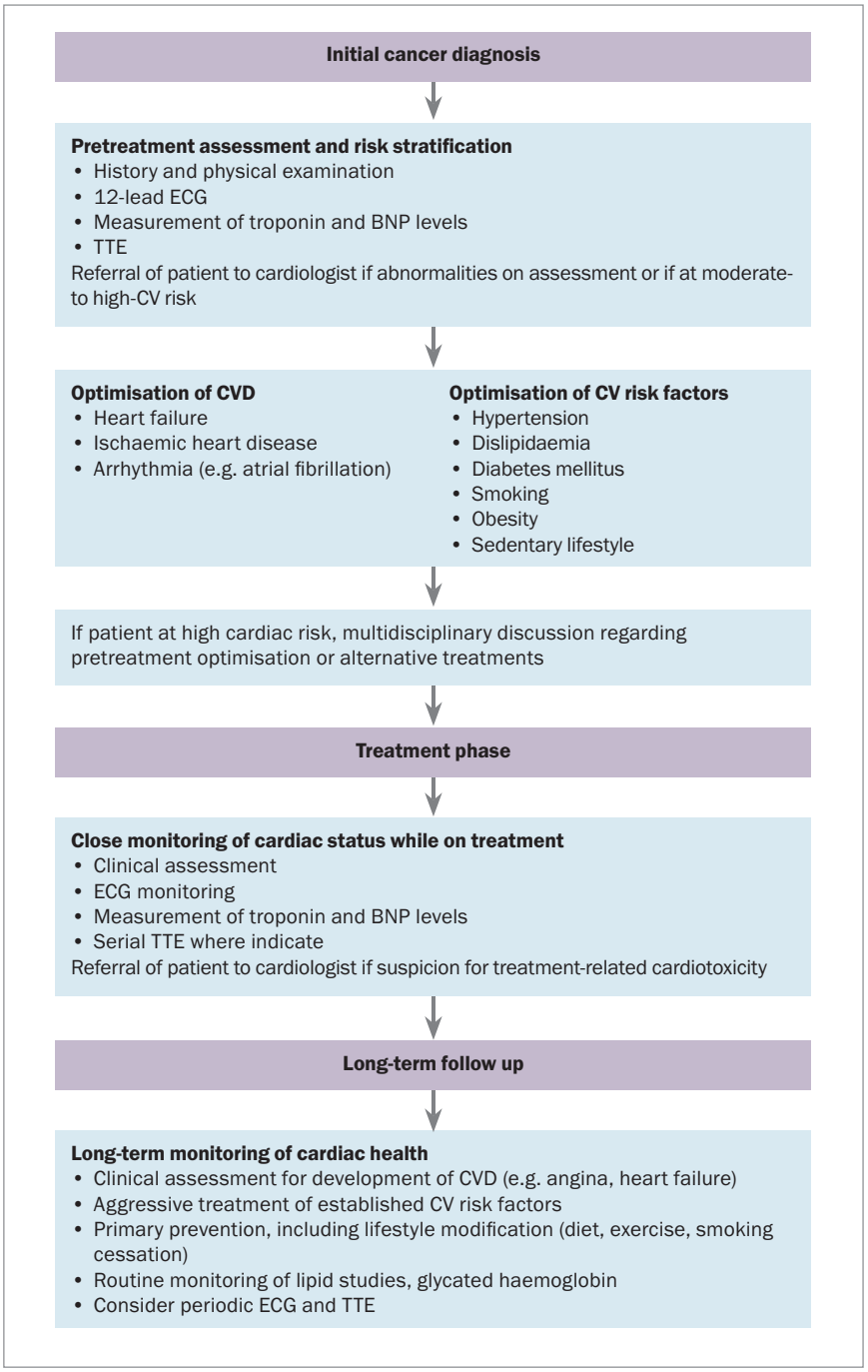

Figure 1. Cardio-oncology: steps in a patient's cancer-treatment journey, highlighting the need for early risk stratification, ongoing surveillance and proactive management of CV risk factors. GPs have an integral role in the longitudinal CV and oncological care of patients with cancer, including with initial diagnosis and risk stratification, monitoring patients while on treatment and long-term follow up. Throughout a patient's cancer journey, GPs or other members of the cancer multidisciplinary team (oncologists, haematologists) may consider referring patients to a cardiologist if necessary.

Abbreviations: BNP = brain natriuretic peptide; CV = cardiovascular; CVD = cardiovascular disease; ECG = electrocardiogram; TTE = transthoracic echocardiogram.

Pretreatment cardiac assessment

Personalised cardiac preventive strategies should optimally be considered at the time of cancer diagnosis and before cancer treatment (Figure 1). This provides an opportunity for open discussion with the patient regarding their risk of cardiotoxicity based on their cardiac risk factors and planned treatment and allows for a shared decision-making model of care.[15] Patients who are planned to receive treatment with potential cardiotoxic effects should undergo pretreatment assessment and education (Table, Figure 2).

Clinical assessment includes a comprehensive history that considers:

- the presence of established CV conditions (e.g. heart failure, ischaemic heart disease, arrhythmia and stroke)
- vascular risk factors and degree of control (e.g. hypertension, diabetes mellitus, hyperlipidaemia and family history)
- medications and lifestyle factors (e.g. alcohol excess, smoking and level of activity).

History should also screen for symptoms that may suggest an undiagnosed cardiac condition, including chest pain or angina, shortness of breath, orthopnoea, paroxysmal nocturnal dyspnoea, ankle swelling or palpitations, the presence of which may suggest the need for further investigation.

A physical examination with assessment of vital signs and a focus on cardiac and respiratory examination assessing for features of fluid overload should be performed. A 12-lead electrocardiogram is also routinely recommended in the pretreatment evaluation and is useful in assessing for arrhythmia, QT-prolongation or features of structural abnormalities (e.g. left ventricular hypertrophy), the presence of which may signify the need for further evaluation.[15]

Pretreatment assessment of high-sensitivity troponin and natriuretic peptides (brain natriuretic peptide [BNP] or N-terminal pro b-type natriuretic peptide [NT-pro-BNP]) levels may be considered,

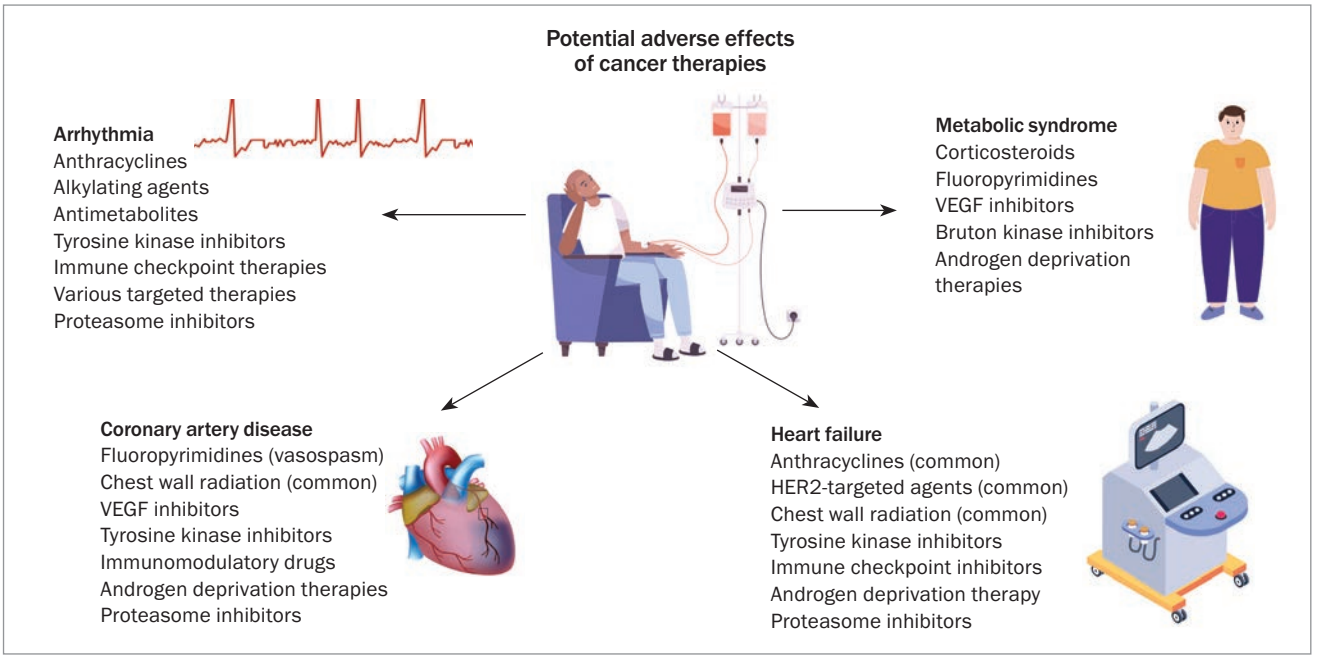

Figure 2. Common cardiovascular effects of cancer therapies.
Abbreviations: HER2 = human epidermal growth factor receptor 2; VEGF = vascular endothelial growth factor.

particularly if the planned treatment is considered high risk (e.g. anthracyclines or HER2-targeted therapies). These baseline levels can be used as comparators if measurement of routine cardiac serum biomarker levels is needed during treatment to detect subclinical cardiac injury. The presence of elevated levels at baseline may suggest a higher future risk of treatment-related cardiotoxicity and hence the need for further investigations or specialist assessment.[15]

A baseline transthoracic echocardiogram (TTE) is recommended in many patients planned to undergo potentially cardiotoxic cancer treatments. This is a useful investigation to provide a baseline assessment of cardiac function and identify any structural or functional abnormalities of the heart before treatment as part of risk stratification. In the presence of known CVD, a TTE is useful in determining the severity of the condition. The presence of reduced LVEF (<55%), abnormalities in global longitudinal strain or other structural abnormalities are risk factors for cancer treatment-related cardiac toxicity, although a normal TTE does not preclude their development.

Cardiac MRI is an additional modality that is useful in the prediction, assessment and management of CTRCD (e.g. detecting subtle declines in LVEF with treatment and diagnosing complications of treatment such as immune checkpoint inhibitor myocarditis).

The identification of new or inadequately treated medical or lifestyle CV risk factors allows for an opportunity for aggressive management and optimisation before, or concurrently with, planned cancer treatment in line with primary prevention guidelines.[2] Newly diagnosed, suspected or known CVD identified in patients as part of the pretreatment evaluation represents a substantial risk of cardiotoxicity and such patients should be referred for specialist cardiology assessment.[15]

Although standardised risk stratification algorithms are yet to be incorporated into Australian guidelines, the HFA-ICOS risk calculator, developed by the Heart Failure Association of the European Society of Cardiology Cardio-Oncology Study Group in collaboration with the International Cardio-Oncology Society, is a useful and online-accessible tool (available at https://www.cancercalc.com/hfa-icos_cardio_oncology_risk_assessment.php). This calculator considers the proposed treatment, patient characteristics and risk factors in stratifying an individual's risk of developing treatment-related cardiotoxicity.[24] Patients classified into low or moderate risk are appropriate for close oncology and primary care follow up, with referral of patients to a cardiologist if there is concern for cardiotoxicity. Patients in the high- and very-high-risk categories should be referred for cardio-oncology assessment with risk and benefits of proceeding to treatment (as well as alternatives) discussed within a multidisciplinary setting.[15]

Cardiac assessment after cancer treatment

With modern cancer treatments, cancer is often curable or managed to the point where it is considered a chronic non-life-limiting disease. In this setting, CVD becomes a major life-limiting comorbidity

in patients who have been previously treated for cancer who survive beyond five years.[25]

Survival of patients with childhood and adolescent cancer has increased significantly in recent decades; however, such patients represent a high-risk demographic for future CV sequalae. Treatments for haematological malignancies often involve cardiotoxic chemotherapy agents in combination with chest RT and significantly increases the risk of acute cardiotoxicity but also may result in cardiac dysfunction many years later (e.g. in survivors of childhood cancers). Manifestations can include valvular heart disease, cardiac failure, ischaemic heart disease and pericardial disease and represent a significant cause of morbidity and mortality in childhood cancer survivors.

Similarly, beyond the risks of acute treatment-related cardiotoxicity, survivors of adult-onset cancers are at a more than twofold risk of fatal heart disease compared with the general population.[26] This risk of long-term CVD increases significantly when patients have undergone potentially cardiotoxic cancer treatments or RT where the heart is within the treatment field. RT-related CV toxicity can develop five to 10 years after treatment and may cause coronary artery disease and heart failure at an incidence up to sixfold higher than that in the general population.[15] Recipients of haematopoietic stem cell transplants are also at risk of late CV complications, which remain a leading cause of mortality and morbidity in survivors.[27]

Similar to a pretreatment assessment, optimisation and maintenance of CV health during and after cancer treatment involves an initial clinical assessment (Figure 1). The history should focus on the timeline and details of prior cancer diagnosis; treatments (and associated complications), particularly dose and duration of potentially cardiotoxic treatments, radiotherapy and maintenance therapies (e.g. HER2-targeted treatment or androgen deprivation therapy); and current status of the cancer (cured, under surveillance, etc). Specific questioning as to symptomatology that may indicate an underlying CV disorder should be undertaken alongside a thorough review of CV risk factors (and level of control), current medications and lifestyle factors. A focused physical examination should also be performed, similar to that previously outlined. Investigations should include a 12-lead electrocardiogram, routine laboratory tests including a complete blood examination, biochemistry (with renal and liver function) and screening for CV risk factors such as hyperlipidaemia, diabetes mellitus, etc.

In all cancer survivors, annual CV risk assessment should be undertaken as well as patient education, optimisation of CV risk factors and promotion of a healthy lifestyle,[2] with referral for cardiology assessment should they develop new cardiac signs or symptoms. Referral to a cardiologist with periodic TTE surveillance should also be considered for patients who are at moderate or high risk – i.e. those at moderate or high baseline CV toxicity risk, those who received moderate- or high-intensity anthracycline therapy or chest RT, high-risk haematopoietic stem-cell transplant recipients or those with established CVD or poorly controlled CV risk factors.[15]

Future direction

As cancer survivorship becomes more common, it is important for practitioners in both primary care and specialist fields to become familiar with the bidirectional link between cancer and CVD and proficient in assessing and optimising CV health before, during and after cancer treatment. Within this emerging field, the GP has a vital role in the multidisciplinary team, which includes:

- assessing and identifying patients experiencing, or who are at risk of, cardiac consequences of cancer treatments
- optimising CV risk factors before, during and after treatment
- providing patient advocacy and education and promoting healthy lifestyle choices
- co-ordinating care among subspecialty services as appropriate.

Future directions for cardio-oncology in Australia should focus on increasing both patient and clinician awareness of the potential for CTRCD and expanding access through integrated, multidisciplinary models of care that link primary care, allied health and specialist services. Improving access to dedicated cardio-oncology services, in particular to patients from rural and remote locations, as well as Indigenous patients through the development of regional hubs (e.g. via outreach clinics, telehealth), will be necessary to bridge the gap to this often-underserved population. Ongoing research into precision prevention and risk stratification will further enhance outcomes, ensuring that patients with or who have survived cancer in Australia receive effective and co-ordinated CV care.

Conclusion

Cardio-oncology sits at the critical intersection of heart and cancer care, addressing the growing need to prevent, detect and manage CV complications in patients with cancer and cancer survivors. As cancer treatments continue to improve survival, the burden of CVD as a leading cause of morbidity and mortality among this population cannot be overlooked. As such, a multidisciplinary, patient-centred approach with a focus on early risk stratification, ongoing surveillance and proactive management of CV risk factors should be considered standard of care. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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