PERSPECTIVE

Effect of chemotherapy on the heart

DUNCAN GUY BMedSci, MB BS, FRACP, PhD

Many chemotherapy agents can have cardiac side effects, most commonly cardiomyopathy, but also hypertension, angina, arrhythmias and pericarditis. Early recognition and treatment can often normalise cardiac function and allow patients to continue necessary chemotherapy.

Key points

- **Many old and new chemotherapeutic agents can have cardiac effects, including cardiomyopathy, hypertension, angina, arrhythmias and rarely pericarditis.**
- **Anthracyclines and trastuzumab are the most likely agents to cause cardiomyopathy; consequent heart failure usually responds quickly to standard treatment.**
- **Chemotherapy-induced hypertension needs to be controlled quickly so that patients can continue cancer treatment.**
- **Early detection and treatment of cardiac side effects can enable many patients to continue cancer treatment.**

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Dr Guy is a Cardiologist with a special interest in chemotherapy and cancer-related heart disease, based in north-west Sydney, NSW.

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Patients with cancer who are undergoing chemotherapy have an increased incidence of cardiovascular complications. This is especially the case in patients with underlying heart disease. Chemotherapeutic agents can cause cardiomyopathy, hypertension, anginal chest pain, arrhythmias and rarely pericarditis. The incidence of cardiac side effects in those receiving potentially cardiotoxic chemotherapy is less than 5% in most studies, unless the patient has been treated with multiple potentially cardiotoxic agents, where some studies have found the incidence to be as high as 27%.[1,2]

There are many new chemotherapy agents available to oncologists that have increased cure rates and improved long-term survival, including targeted antibody and small molecule treatments. However, in some patients, especially where the newer agents are combined with older agents such as the anthracyclines, there can be significant cardiac morbidity.[2] Early detection and appropriate treatment of cardiac side effects can allow many of these patients to continue their cancer treatment. Some chemotherapy agents commonly implicated in causing cardiac side effects are listed in Boxes 1 and 2.

Cardiomyopathy

Cardiomyopathy is the most common cardiac complication of chemotherapy. It can occur early in treatment or in some cases may be a delayed effect. The agents that cause cardiomyopathy most frequently are the anthracyclines and the monoclonal antibody trastuzumab (antibody to human epidermal growth factor receptor 2 [HER2]).[1,2] Both these agents are commonly used in the treatment of breast cancer. It is common practice for patients to have their cardiac function assessed before commencing these agents, and it is a requirement for patients receiving trastuzumab to have regular assessment of cardiac function during treatment. Other chemotherapy agents that more commonly cause cardiomyopathy are listed in Box 1.

Presentation

Given that oncologists routinely monitor their patients' cardiac function, it is unusual for patients receiving chemotherapy to develop symptoms of overt heart failure. However, patients with chemotherapy-related cardiomyopathy can present with the usual symptoms of heart failure,

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1. Chemotherapy agents more commonly implicated in causing cardiomyopathy
• **Anthracyclines:** doxorubicin, daunorubicin, idarubicin, epirubicin and mitoxantrone • **Epidermal growth factor receptor inhibitors:** trastuzumab (antihuman epidermal growth factor receptor 2 [HER2] monoclonal antibody), lapatinib (epidermal growth factor receptor and HER2 receptor inhibitor) and trastuzumab emtansine (anti-HER2 antibody + cytotoxic) • **Alkylating agent:** cyclophosphamide • **Small molecule kinase inhibitors:** sorafenib, sunitinib, trametinib

2. Other cardiac side effects and the chemotherapy agents more commonly implicated
• **Hypertension:** bevacizumab, sorafenib, sunitinib • **Angina:** fluorouracil, capecitabine, etoposide • **Arrhythmias:** paclitaxel • **Pericarditis and effusion:** cytarabine, bleomycin

including shortness of breath, orthopnoea and ankle swelling. This form of cardiomyopathy may occur in younger patients, particularly women receiving long-term trastuzumab treatment for breast cancer. As these patients are not typical of those who usually present with heart failure, it is important to keep the possibility in mind.

Investigation

If there is a clinical suspicion of cardiomyopathy then imaging of the heart is important. Transthoracic echocardiography is the best method for assessing heart function in these patients. If transthoracic echocardiography is not available then a gated heart pool scan can give an accurate measurement of left ventricular ejection fraction (LVEF).

It is important to remember that although chemotherapy is a likely cause of cardiomyopathy in these patients, the usual underlying conditions such as cardiac ischaemia and valvular disease can still occur in patients receiving chemotherapy and need to be excluded as causative or contributing factors.

Treatment

Treatment of cardiomyopathy aims to normalise the LVEF so that patients can continue chemotherapy. Patients should ideally be managed in conjunction with a cardiologist who has experience in this condition. Fortunately, chemotherapy-related cardiomyopathy usually responds quickly to standard heart failure treatment. The key medications are β-blockers and ACE inhibitors. Often the patients are younger and identified before the LVEF decreases too far, and hence can usually tolerate rapid dosage escalation.

Trastuzumab-induced cardiomyopathy is detected routinely with the imaging required to access this medication. Treatment should be instituted if the LVEF decreases more than 10% from baseline or is less than 45%. Most patients respond well to traditional heart failure treatments.[2]

Duration of treatment

The exact mechanism that causes chemotherapy-related cardiomyopathy has not been elucidated. Clinical trials in this area are lacking and hence do not provide definitive guidance. It appears that anthracycline-related cardiomyopathy involves chronic damage and hence therapy will most likely be required long term.

In contrast, trastuzumab appears to have a 'stunning' effect that is reversible once chemotherapy is ceased, and long-term treatment is less likely to be needed. It is my current practice to withdraw cardiac medication three months after cessation of trastuzumab and then to check the LVEF three months later to ensure it has remained normal. A confounding factor is that many patients with breast cancer are treated with both anthracycline-based chemotherapy and trastuzumab. Hence, it is important to ensure that cardiac function remains normal if heart failure therapy is ceased.

Hypertension

Vascular endothelial growth factor (VEGF) is an increasingly common target for chemotherapy agents but also has an important role in blood pressure homeostasis. In clinical trials of the anti-VEGF monoclonal antibody, bevacizumab, and the kinase inhibitors, sorafenib and sunitinib, the incidence of severe hypertension (requiring more than one agent for control or causing symptoms of malignant hypertension) was between 6 and 7%, and 22% of patients developed mild hypertension.[3-5]

Hypertension needs to be controlled quickly so that patients can continue chemotherapy. Blood pressure management depends on the severity of the hypertension and comorbidities. The general approach is similar to that used for essential hypertension except that dose escalation is usually faster to bring the blood pressure under control. Sorafenib and sunitinib are metabolised by cytochrome P450, and hence diltiazem and verapamil should be avoided.

Chest pain

The uracil analogue fluorouracil is well described as causing angina and in some cases myocardial infarction. Capecitabine is metabolised to fluorouracil and similarly can induce chest pain and ischaemia. The mechanism is not known, although a vasospastic phenomenon is thought to be involved. Etoposide, a podophyllotoxin derivative, has also been associated with acute coronary syndromes in case reports.

Patients receiving chemotherapy who develop angina need to be assessed thoroughly for underlying coronary disease. If the chemotherapy can be stopped then angina usually does not recur. Many patients, however, would benefit from continuing the chemotherapy, and in these cases treatment with angina medication is indicated. There are no large trials to guide choice of therapy, but given that a vasospastic aetiology may be involved, the initial agents should target vasospasm.

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Hence I tend to prescribe nitrate patches, ivabradine or nifedipine. It should be noted that the β-blocker carvedilol interacts strongly with capecitabine and should be avoided in patients using capecitabine.

Conduction abnormalities

Both bradyarrhythmias and tachyarrhythmias have been observed in patients receiving chemotherapy. These arrhythmias are usually transient and resolve once the course of chemotherapy is completed. For most chemotherapeutic agents, arrhythmias are uncommon. However, paclitaxel commonly causes bradycardia; in one study, 29% of patients receiving paclitaxel had asymptomatic bradycardia.[6]

Pericarditis and effusions

Pericarditis and pericardial effusions are uncommon side effects of chemotherapy but in some patients can lead to a significant effusion and cardiac tamponade. Determining whether a pericardial effusion is caused by pericarditis or malignancy is important as this will influence treatment decisions. Pericardial drainage is necessary at times for relief of cardiac tamponade and as a diagnostic procedure. Most cardiac effusions are self-limiting and patients require only observation.

Conclusion

Cancer treatments have entered an exciting new era with the development of targeted antibody and small-molecule therapies to complement or take the place of traditional chemotherapy treatments. It is important for GPs to be vigilant and consider the possibility of cardiac complications in patients receiving cancer treatment. Early detection and treatment in most patients can normalise cardiac function and allow the patients to continue their cancer treatment. It should be remembered that the more common causes of cardiac disease also occur in patients being treated for cancer, and nonchemotherapy causes for cardiac problems should be kept in mind. **CT**

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