REVIEW ARTICLE

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Cardiotoxicity of Chemotherapeutic Agents

Incidence, Treatment and Prevention

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Contents

Abstract

Cytostatic antibiotics of the anthracycline class are the best known of the chemotherapeutic agents that cause cardiotoxicity. Alkylating agents such as cyclophosphamide, ifosfamide, cisplatin, carmustine, busulfan, chlormethine and mitomycin have also been associated with cardiotoxicity. Other agents that may induce a cardiac event include paclitaxel, etoposide, teniposide, the vinca alkaloids, fluorouracil, cytarabine, amsacrine, cladribine, asparaginase, tretinoin and pentostatin. Cardiotoxicity is rare with some agents, but may occur in >20% of patients treated with doxorubicin, daunorubicin or fluorouracil.

Cardiac events may include mild blood pressure changes, thrombosis, electrocardiographic changes, arrhythmias, myocarditis, pericarditis, myocardial infarction, cardiomyopathy, cardiac failure (left ventricular failure) and congestive heart failure. These may occur during or shortly after treatment, within days or weeks after treatment, or may not be apparent until months, and sometimes years, after completion of chemotherapy.

A number of risk factors may predispose a patient to cardiotoxicity. These are: cumulative dose (anthracyclines, mitomycin); total dose administered during a day or a course (cyclophosphamide, ifosfamide, carmustine, fluorouracil, cytarabine); rate of administration (anthracyclines, fluorouracil); schedule of administration (anthracyclines); mediastinal radiation; age; female gender; concurrent administration of cardiotoxic agents; prior anthracycline chemotherapy; history of or pre-existing cardiovascular disorders; and electrolyte imbalances such as hypokalaemia and hypomagnesaemia. The potential for cardiotoxicity should be recognised before therapy is initiated. Patients should be screened for risk factors, and an attempt to modify them should be made.

Monitoring for cardiac events and their treatment will usually depend on the signs and symptoms anticipated and exhibited. Patients may be asymptomatic, with the only manifestation being electrocardiographic changes. Continuous cardiac monitoring, baseline and regular electrocardiographic and echocardiographic studies, radionuclide angiography and measurement of serum electrolytes and cardiac enzymes may be considered in patients with risk factors or those with a history of cardiotoxicity.

Treatment of most cardiac events induced by chemotherapy is symptomatic. Agents that can be used prophylactically are few, although dexrazoxane, a cardioprotective agent specific for anthracycline chemotherapy, has been approved by the US Food and Drug Administration. Cardiotoxicity can be prevented by screening and modifying risk factors, aggressively monitoring for signs and symptoms as chemotherapy is administered, and continuing follow-up after completion of a course or the entire treatment. Prompt measures such as discontinuation or modification of chemotherapy or use of appropriate drug therapy should be initiated on the basis of changes in monitoring parameters before the patient exhibits signs and symptoms of cardiotoxicity.

As early as 1967, there were reports of heart failure in children treated with doxorubicin for leukaemia.[1] Since then, there has been an increased awareness of cardiotoxicity as a potential chemotherapy-related adverse event. Cardiotoxicity can be dose limiting, and thus have immense impact on treatment. Aggressive and combination chemotherapy has achieved remission in most types of cancers. However, concerns for, or manifestations of, cardiac adverse events may result in discontinuation of or

reluctance to use a particular agent at an effective dose. Cytostatic antibiotics of the anthracycline class have been clearly associated with cardiotoxicity. However, there are a number of other chemotherapy agents that cause cardiotoxicity and yet are not well recognised (table I).

Cardiac events associated with chemotherapy vary in incidence and may occur acutely (during or shortly after treatment), subacutely (within days or weeks after completion of chemotherapy) or chronically (weeks to months after drug administration). They may also occur as late sequelae, many years after the end of treatment. Cardiac events associated with chemotherapy may consist of mild blood pressure changes, thrombosis, electrocardiographic (ECG) changes, arrhythmias, myocarditis, pericarditis, myocardial infarction, cardiomyopathy, cardiac failure (left ventricular failure), and congestive heart failure (CHF). Cardiotoxicity may depend on the dose administered during each course or on the total cumulative dose, or may be completely independent of the dose.

The purpose of this article is to provide a comprehensive review of the adverse cardiac events associated with the use of various chemotherapeutic agents, including their incidence, manifestations, treatment and prevention. All chemotherapy agents approved by the US Food and Drug Administration (FDA) were reviewed except for immunomodulators such as interferons and interleukins and the hormonal agents. Cardiac adverse events such as 'arrhythmia', 'tachycardia', 'bradycardia', 'atrial flutter', 'atrial fibrillation', 'ventricular fibrillation', 'hypertension', 'myocardial infarction' and 'congestive heart failure' were considered and a Medline search was conducted for each of the chemotherapy agents, combining them with keyword and text word searches for terms such as 'cardiotoxicity' and the cardiac events stated above. The search was then limited to humans (clinical trials, patient series and case reports) and English language journals covering the period from January 1966 to July 1998.

1. Cytostatic Antibiotics

1.1 Anthracyclines

The anthracyclines doxorubicin and daunorubicin are cytostatic antibiotics isolated from fungi belonging to the species Streptomyces. Doxorubicin has broad spectrum activity against both haematological cancers and solid tumours.[2] It is used in the treatment of acute leukaemias, both lymphocytic and myelogenous,[3] non–Hodgkin's lymphoma,[4] and Hodgkin's disease.[5] Doxorubicin is also effective against nonhaematological tumours, e.g. osteogenic sarcoma,[6,7] Ewing's sarcoma and Wilm's tumour,[8] and breast carcinoma.[9,10] Daunorubicin has demonstrated activity against acute lymphocytic leukaemia and acute nonlymphocytic leukaemia.[11-15]

Anthracyclines have exhibited a clear dose-response relationship in several curative chemotherapeutic regimens.[16,17] However, the cardiotoxicity of these agents requires dose reduction that may reduce survival and remission rates.

1.1.1 Types of Cardiotoxicity

Anthracycline-induced cardiotoxicity has been recognised for more than 20 years. It has been described as 3 distinct types of cardiotoxicity.

Acute or Subacute Cardiotoxicity

Acute or subacute injury is a rare form of cardiotoxicity that may occur immediately after a single dose or a course of anthracycline therapy, with clinical manifestations occurring within a week of treatment. These may be in the form of transient electrophysiological abnormalities, a pericarditis-myocarditis syndrome or acute left ventricular failure.[18-21] The electrophysiological abnormalities may present as nonspecific ST and T wave changes, T wave flattening, decreased QRS voltage and prolongation of QT interval. Sinus tachycardia is the most common rhythm disturbance. ECG changes may be seen in 20 to 30% of the patients.[22] Arrhythmias, including ventricular, supraventricular and junctional tachycardia, are seen in 0.5 to 3% of patients with an overall incidence of 0.7%.[22] More serious arrhythmias, such as atrial flutter or

Table I. Cardiotoxicity of chemotherapeutic agents

Drug	Incidence	Dose	Onset	Duration	Risk factors	Signs and symptoms	Treatment	Monitoring parameters and prevention
Cytostatic antibiotics								
Doxorubicin, daunorubicin	**Acute or subacute** ECG changes 20-30%, arrhythmias 0.5–3% (dose unknown) **Early onset chronic** At <400 mg/m^2, 0.14%; at 550 mg/m^2, 7% **Late onset chronic** 18-65%		**Acute or subacute** Within a week after a single dose or a course **Early onset chronic** 0-231 days (within a year) **Late onset chronic** 4-15 years after completion	NA	Cumulative dose, rate and schedule of anthracycline administration, age, mediastinal radiation therapy, female gender, history of cardiac disorders	**Acute or subacute** ECG changes, sinus tachycardia, arrhythmias, pericarditis/ myocarditis **Early onset chronic** CHF **Late onset chronic** CHF	**Arrhythmias, ECG changes** Observe and treat based on seriousness of clinical signs and symptoms per institutional and/or ECC/AHA guidelines **CHF** Diuretics, ACE inhibitors, digoxin per institutional and/or ACTION HF guidelines **Pericarditis** Evaluate for pericardiocentesis, treat with anti-inflammatory drugs e.g. prednisone, salsalate **Acute MI** Supplemental oxygen, IV morphine sulfate, IV/sublingual nitroglycerin (glyceryl trinitrate), aspirin (aceylsalicylic acid) [160-325 mg/day]; further treatment per institutional and or AHA guidelines	**Monitoring parameters** Serial measurements of ECG, echocardiogram (fractional shortening, LVEF), monitor cumulative dose, 12-lead ECG on signs and symptoms, cardiac enzymes **Prevention** Use of cardioprotectants, e.g. dexrazoxane; use other anthracycline analogues
Epirubicin	Unknown	450-900 mg/m^2	Unknown	Unknown	Unknown	CHF		
Idarubicin	At cumulative dose 150-290 mg/m^2: 5% ≥10% ↓ in LVEF at 150 mg/m^2: 18% ≥15% ↓ in LVEF at 150 mg/m^2: 7%				Unknown	CHF, arrhythmias, angina, MI		
Mitoxantrone	2.2-3.5%; 6% at 60 mg/m^2; 15% at 120 mg/m^2	Cumulative doses of 90-187 mg/m^2	Weeks	Unknown	Cumulative doses, prior anthracycline therapy, pre-existing cardiovascular disorders	Arrhythmias, CHF, MI, ECG changes		

Alkylating agents								
Cyclophosphamide	At >150 mg/kg, 7-25% in adults, 5% in children >1.5 g/m^2/day, 25% incidence	>150 mg/kg over 2-4 days or >1.5 g/m^2/day	1-10 days after the first dose	1-6 days	Total dose/cycle or daily dose, prior anthracycline or mitoxantrone therapy, mediastinal radiation	CHF, chest pain, pleural and pericardial effusions, pericardial friction rub, cardiomegaly, loss of QRS voltage on ECG	**CHF** As for anthracyclines **Chest pain** Supplemental oxygen, IV morphine sulfate, IV/sublingual nitroglycerin; evaluate for ongoing MI	Identify and modify risk factors, cumulative anthracycline and mitoxantrone dose, serial measurements of 12-lead ECG, echocardiogram (LVEF, fractional shortening)
Ifosfamide	17%	Dose-response trend, ≥12.5 g/m^2	Acute onset 6-23 days after the first dose	4-7 days	Total dose	CHF, pleural effusion, re-entrant ventricular tachycardia, pulseless tachycardia, ST or T wave abnormalities, ↓QRS complex	**Re-entrant or pulseless tachycardia, arrhythmias** As for anthracyclines **CHF** As for anthracyclines	Identify and modify risk factors, serial measurements of 12-lead ECG, echocardiogram, fluid intake and output, bodyweight, serum creatinine, electrolytes
Cisplatin	Rare	Unrelated	Acute; within hours of completion of infusion	Unknown	Unknown	Palpitations, left sided chest pain, nausea, vomiting, dyspnoea, hypotension, arrhythmias, interventricular block, MI, ST-T wave changes, T wave inversions	**Arrhythmias and chest pain** As for anthracyclines **Hypotension** IV fluids, inotropes	12-lead ECG on symptoms, cardiac enzymes (CK-MB isozyme), electrolytes, especially magnesium
Mitomycin	10%	Median cumulative dose 60 mg/m^2 (20-80 mg/m^2)	Median of 3 cycles	Unknown	Cumulative dose, prior doxorubicin therapy, chest irradiation	CHF	**CHF** As for anthracyclines	Identify and modify risk factors, echocardiogram (LVEF, fractional shortening), cumulative dose of mitomycin and anthracyclines if left ventricular failure suspected

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Drug	Incidence	Dose	Onset	Duration	Risk factors	Signs and symptoms	Treatment	Monitoring parameters and prevention
Carmustine	Rare	>600 mg/m^2	20-90 min after start of infusion	Unknown	Unknown	Chest pain, hypotension, sinus tachycardia, ECG changes	**Hypotension** IV fluids, inotropes **Chest pain** As for cyclophosphamide **Arrhythmias, ECG changes** As for anthracyclines	Blood pressure, continuous 12-lead ECG, cardiac enzymes if patients exhibit symptoms
Busulfan	Cardiac tamponade 2%	≥7200mg cumulative dose (endocardial fibrosis)	3-9 years (endocardial fibrosis)	Unknown	Unknown	CHF, palpitations, cardiac tamponade, pulmonary congestion, cardiomegaly, pericardial effusion, ECG changes	**CHF** As for anthracyclines **Arrhythmias, ECG changes** As for anthracyclines	Serial echocardiogram (LVEF, fractional shortening) if CHF suspected, continuous 12-lead ECG
Chlormethine	Rare	≥33 mg/m^2	1-3 days	48-72 hours	Unknown	Persistent tachycardia, pulse irregularity, junctional or atrial ectopic beats	**Arrhythmias, ECG changes** As for anthracyclines	No further use of such high dosages
Antimetabolites								
Fluorouracil	1.6-68%	>800 mg/m^2	2-5 days into first course	48 hours	History of cardiovascular disorders, prior mediastinal radiation, concurrent use of other cardiotoxic chemotherapy, rate of administration, higher dose	Angina, MI, hypotension, cardiogenic shock, ECG changes	**Angina and MI** As for anthracyclines **Hypotension** IV fluids, inotropes **Arrhythmias and ECG changes** As for anthracyclines	Identify and modify risk factors, continuous 12-lead ECG, cardiac enzymes if patient experiences symptoms or at high risk
Cytarabine	Unknown	High dose (≥3 g/m^2)	3-28 days following initiation	Several hours (chest pain)	Definitive information unknown, possibly cytarabine dose	Pericarditis with dyspnoea, chest pain, pericardial friction rub, pulsus paradoxus, CHF, pleural, pericardial effusions	**Chest pain** As for cyclophosphamide **Pericarditis** Pericardiocentesis if required, prednisone, salsalate **CHF** As for anthracyclines	Serial echocardiogram (LVEF, fractional shortening), continuous 12-lead ECG and cardiac enzymes if patient becomes symptomatic

Antimicrotubule agents								
Paclitaxel	0.5%	Unrelated	Within 1 hour into infusion to 14 days following paclitaxel therapy	48-72 hours, as short as 4 hours after discontinuation of therapy	Definite information unknown, possibly history of cardiovascular disorders	Sinus bradycardia, atrial and ventricular arrhythmias, MI, supraventricular tachycardia, AV or left bundle branch block	**Arrhythmias, bradycardia, bundle branch block** Observe and treat based on seriousness of clinical signs and symptoms per institutional and/or ECC/AHA guidelines **Acute MI** As for anthracyclines	Continuous 12-lead ECG, cardiac enzymes, in patients with symptoms; no alteration in dosage or schedule of pre-paclitaxel cardiac medications
Etoposide	1-2%	Unrelated	During the infusion in the first or subsequent courses	Several hours (chest pain)	Definite information unknown, possibly history of cardiac disease, mediastinal radiation, prior cardiotoxic chemotherapy	Hypotension, acute MI, ECG changes	**Hypotension** Discontinuation of infusion, IV fluids, slower rate of infusion	Monitor blood pressure during and immediately after the infusion
Teniposide	2% hypotension	Unrelated	During infusion	Unknown	Unknown	Arrhythmia, hypotension	**Hypotension** Related to rate of infusion – discontinue, IV fluids and slower rate of infusion **Arrhythmias** As for anthracyclines	Monitor blood pressure during and immediately after the infusion
Vinca alkaloids	25% (10% clinical manifestations)	Unrelated	Hours to 3 days	2-24 hours	Mediastinal radiation, coexisting ischaemic heart disease	Acute MI, dyspnoea, tachypnoea, pulmonary oedema, ECG changes, T wave inversion, ST segment changes, atrial fibrillation	**Acute MI** As for anthracyclines **Pulmonary oedema** Consider CHF and treat as for anthracyclines **Arrhythmias** same as under anthracyclines	Identify and modify risk factors; continuous 12-lead ECG, cardiac enzymes if patient exhibits symptoms

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Table I. Contd

Drug	Incidence	Dose	Onset	Duration	Risk factors	Signs and symptoms	Treatment	Monitoring parameters and prevention
Miscellaneous								
Amsacrine	1% (chemotherapy naïve)	Unrelated	Within minutes of initiation of therapy to 2 weeks after the course	24 hours	Hypokalaemia, prior anthracycline therapy	Atrial and ventricular tachyarrythmias, CHF, hypotension, cardiopulmonary arrest	**Arrhythmias** As for anthracyclines **Hypotension, cardiopulmonary arrest** IV fluids, inotropes, intubation if required **CHF** As for anthracyclines	Identify and modify risk factors; continuous 12-lead ECG to evaluate arrhythmias, serial echocardiogram (LVEF, fractional shortening) if symptoms of CHF; serum potassium level, cumulative dose of prior anthracycline therapy
Cladribine	Rare	0.1 mg/kg/day × 7 days	17 days after start of treatment	NA	Unknown	CHF	**CHF** As for anthracyclines	Serial echocardiogram (LVEF, fractional shortening) if symptoms of CHF
Asparaginase	Rare	9000 IU/day	11 hours into infusion	Unknown	Unknown	Acute MI, ECG changes	**Acute MI** As for anthracyclines **Arrhythmias, ECG changes** As for anthracyclines	Continuous 12-lead ECG, cardiac enzymes if patient exhibits symptoms
Tretinoin	Arrhythmia 23%, hypotension 14%, hypertension 11%, heart failure 6%	Unknown	Unknown	Unknown	Unknown	Retinoic acid syndrome (fever, respiratory distress, bodyweight gain, peripheral oedema, pleural-pericardial effusions, MI)	**Retinoic acid syndrome** High dosage corticosteroid therapy	Monitor for leucocytosis, disseminated intravascular coagulopathy, thrombotic events
Pentostatin	3-10%	NA	Within a week	8 hours (chest pain)	Definite information unknown, possibly underlying cardiovascular disorders	Angina and MI, CHF, acute arrhythmias	NA	Fluid input, urinary output, CK-MB isozyme

ACTION HF = Advisory Council to Improve Outcomes Nationwide in Heart Failure; **AHA** = American Heart Association; **AV** = atrioventricular; **CHF** = congestive heart failure; **CK-MB** = creatine kinase MB band; **ECC** = Emergency Cardiac Care Committee; **ECG** = electrocardiogram; **IV** = intravenous; **LVEF** = left ventricular ejection fraction; **MI** = myocardial infarction; **NA** = not applicable.

atrial fibrillation, are rare. Subacute cardiotoxicity has resulted in acute failure of the left ventricle, pericarditis or a fatal pericarditis-myocarditis syndrome in some rare cases. The ECG changes or arrhythmias do not seem related to chronic cardiomyopathy.

Early Onset Chronic Progressive Cardiotoxicity

Anthracyclines can also induce early onset progressive chronic cardiotoxicity resulting in cardiomyopathies. This is a more common and clinically important type of cardiotoxicity.[23-25] Chronic anthracycline-induced cardiomyopathy usually presents within a year of treatment. It may persist or progress even after discontinuation of anthracycline therapy, and may evolve into a chronic dilated cardiomyopathy in adult patients and restrictive cardiomyopathy in paediatric patients.[26-28] In a series of more than 3900 patients treated with anthracyclines, CHF secondary to anthracycline-induced chronic cardiomyopathy occurred 0 to 231 days after the completion of anthracycline therapy.[26]

Late Onset Chronic Progressive Cardiotoxicity

Late onset chronic progressive anthracycline cardiotoxicity causes ventricular dysfunction,[29-31] heart failure and arrhythmias[31-33] years to decades after chemotherapy has been completed. This suggests that patients who have received anthracycline chemotherapy and survived their cancer may have undetected increases in morbidity and mortality due to cardiotoxicity. There may be a period of time, after completion of treatment, during which patients may experience no symptoms of left ventricular dysfunction or arrhythmia and cardiac function may appear normal. After the initial acute myocardial insult, there is a progressive decrease in ventricular function leading to late onset decompensation. An increased incidence of severe echocardiographic abnormalities has been seen with increased duration of follow-up. An 18% incidence of reduction in fractional shortening on resting echocardiogram was observed 4 to 10 years after completion of anthracycline therapy.[31] Cumulative doses of doxorubicin as low as 228 mg/m^2 have shown to increase afterload or decrease contractility, or both, in 65% of patients with leukaemia up to 15 years after treatment with anthracyclines.[32]

Late onset arrhythmia and sudden death has occurred more than 15 years after anthracycline treatment.[33-36] This could mean that more anthracycline-induced cardiotoxicity may appear in the future in patients who are presently asymptomatic. Patients may remain in a compensated state for many years until stressors such as acute viral infection[37] or cardiovascular stressors such as weight lifting, pregnancy and surgery[35] could possibly trigger a cardiac event.

1.1.2 Pathogenesis

The cause of anthracycline-induced cardiotoxicity is probably multifactorial. Free radical–mediated myocyte damage is one of the most thoroughly studied mechanisms by which anthracyclines have been proposed to cause cardiotoxicity.[38-42] The quinone form of doxorubicin is reduced to the free radical semiquinone form by cytochrome P450 reductase, particularly in myocardial cells with high levels of flavin centred reductases.[43] The semiquinone free radical is oxidised rapidly to its original quinone form, creating superoxide anions. These superoxide radicals are preferentially converted to oxygen, forming hydrogen peroxide. The myocardium is more susceptible to free radical damage than other tissues because it has comparatively less superoxide dismutase and catalase activity, and its major defence against free radical damage, glutathione peroxidase, is suppressed by doxorubicin.[44] The myocardial cells are therefore unable to eliminate the hydrogen peroxide and it is converted to the superhydroxide free radical by ferrous ion. This ferrous ion, in turn, is converted back to ferric ion for further oxidation of superoxide anions. The superhydroxide free radicals accumulate and cause severe lipid peroxidation, leading to extensive destruction of the mitochondrial membranes, endoplasmic reticulum and nucleic acid. They also crosslink sulfhydryl moieties of normal calcium-release channels, causing extensive efflux of calcium into the cytoplasm, thus depleting the calcium stores in the sarcoplasmic re-

ticulum.[45] Cardiac cells are rich in mitochondria and may therefore be predisposed to free radical toxicity.

Accumulation of doxorubicinol, a toxic metabolite of doxorubicin, in cardiac cells has also been proposed as a mechanism for cardiotoxicity. Doxorubicinol is 50 to 500 times more potent than doxorubicin in decreasing systolic function, and inhibits ion-dependent pumps (calcium and sodium ion exchange pumps) in the mitochondria, sarcoplasmic reticulum and the sarcolemma, leading to production of free oxygen radicals.[46-48]

Circulating proinflammatory cytokines have also been implicated in anthracycline cardiotoxicity. Doxorubicin induces the release of histamine and tumour necrosis factor-α from macrophages and interleukin-2 from monocytes.[49-51] These cytokines have functional receptors on the myocardium and their release may result in dilated cardiomyopathy.[52-54] Adrenergic dysfunction and down-regulation of myocardial histamine and β-adrenergic receptors has also been proposed as a cause for an evolving and established anthracycline–induced ventricular dysfunction.[55]

1.1.3 Risk Factors for Cardiotoxicity

Anthracyclines are well established as highly efficacious antineoplastic agents for various leukaemias, lymphomas and solid tumours. However, chronic cardiotoxicity severely limits their aggressive use. Therefore, measures should be taken to lessen or prevent the cardiotoxicity while maintaining antineoplastic efficacy. This can be achieved by:

- screening for and identifying risk factors before patients start anthracycline chemotherapy
- monitoring patients before, during and after chemotherapy
- modifying the risk factors
- using cardioprotective drugs
- using anthracycline analogues that may be less cardiotoxic.

Some of the risk factors relating to early and late (but not acute) cardiotoxicity have been reported. These include cumulative dose, rate of drug administration, mediastinal radiation, advanced age, younger age, female gender, pre-existing heart disease and hypertension. A multivariate analysis of these factors based on histological evidence of anthracycline-induced cardiac damage concluded that higher rates of administration and previous cardiac irradiation were independent risk factors.[56]

The incidence of CHF secondary to doxorubicin-induced cardiomyopathy depends on the cumulative dose of the drug. At a cumulative total dose of <400 mg/m^2 body surface area, the incidence of CHF was found to be 0.14%. This increased to 7% at a dose of 550 mg/m^2 and to 18% at a dose of 700 mg/m^2.[26] This rapid increase in clinical toxicity at doses of >550 mg/m^2 has made 550 mg/m^2 the empirical maximum dose for minimising doxorubicin-induced cardiac failure. The cumulative dose of doxorubicin has been observed to be the most significant ($p < 0.002$) predictor of left ventricular dysfunction in 57% of paediatric patients after doxorubicin therapy.[32,57] A dose of anthracyclines >550 mg/m^2 was found to be 5 times more likely than lower doses to result in early cardiotoxicity in a study involving 6493 paediatric patients.[58] However, great variability exists in the dose of doxorubicin that may cause cardiotoxicity. Doses >1000 mg/m^2 have been tolerated by patients, whereas others exhibited decrease in left ventricular ejection fraction (LVEF) at doses as low as 300 mg/m^2.[26,59,60] Thus, some patients may exhibit anthracycline-induced cardiac damage at standard doses, whereas others may tolerate cumulative doses twice as large as the conventional limiting dose.

One strategy to prevent anthracycline cardiotoxicity is to alter its administration schedule. Cardiotoxicity due to doxorubicin appears to be related to the peak plasma drug concentration. The antineoplastic activity, however, is dependent on the total systemic exposure or the tissue concentration over time and not on the peak plasma concentration.[61] Doxorubicin appears to be less cardiotoxic when administered as a prolonged, continuous intravenous infusion over more than 48 to 96 hours,[61] or as weekly injections instead of a single

bolus injection every 3 weeks.[62-65] The weekly schedule of doxorubicin caused a significantly lower incidence of drug-induced CHF (0.8%) than the single dose every 3 weeks schedule (2.9%) [p = 0.0001] over an 856-day follow-up period.[26] However, increases in cardiac troponin T levels in blood were observed in patients receiving doxorubicin as continuous as well as bolus infusion, suggesting that cardiac damage may not be prevented by the lower peak doxorubicin concentrations achieved during continuous infusion.[66] Elevations in cardiac troponin T levels have been related to the severity of myocardial damage and may predict subsequent subclinical and clinical cardiac morbidity and mortality. In addition, prolonged exposure to anthracyclines as a result of continuous infusions is of great concern in paediatric patients because, despite reductions in peak anthracycline serum concentrations, continuous infusions could lead to more myocyte exposure time and therefore greater myocardial damage.[57] Further investigation is warranted to clearly understand the effect of anthracycline administration rate.

Both younger and older age have been considered as potential risk factors for developing anthracycline-induced cardiotoxicity.[23,24,67,68] An age of <4 years at the time of exposure has been shown to be a significant risk factor for abnormal cardiac function.[32] Younger age at diagnosis was found to be associated with, and predictive of, ventricular dysfunction in a study of 120 children and adults receiving 244 to 550 mg/m^2 cumulative doses of doxorubicin for the treatment of acute lymphocytic leukaemia or osteosarcoma during childhood.[69] An increasing risk of developing drug-induced CHF with increasing patient age ($p = 0.0027$) was observed.[26] Previous cardiac disease and hypertension may also potentially increase the risk of developing doxorubicin-induced CHF ($p = 0.08$).[26] However, such patients were excluded from the large cooperative group trials of doxorubicin.

Female patients appear to be more vulnerable to the cardiotoxic effects of anthracyclines.[56,70] Significantly greater reduction in ventricular contractility has been observed in female patients receiving anthracyclines, as the difference in ventricular contractility between male and female patients increased with high cumulative doses.[56,58,69]

Concomitant mantle (mediastinum) irradiation is believed to increase the risk of anthracycline-induced cardiotoxicity.[27,71] Severity of histopathological changes evaluated by endomyocardial biopsy were significantly higher ($p < 0.01$) in patients pretreated with radiation therapy before anthracycline therapy compared with those who did not receive radiation therapy.[27] However, evidence linking radiation exposure to enhanced anthracycline cardiotoxicity is anecdotal and inconclusive.

1.1.4 Monitoring

Cardiotoxicity may occur in patients with underlying risk factors even at low anthracycline doses. If reductions in LVEF are not recognised early, additional anthracycline therapy may lead to irreversible severe CHF and death. Therefore, serial and post-therapy cardiac monitoring is necessary to reduce morbidity due to anthracycline-induced cardiotoxicity. Patients should be monitored for clinical signs of cardiomyopathy by physical examination, chest x-rays, ECG, echocardiogram, endomyocardial biopsy and radionuclide angiography before initiation of treatment and at periodic intervals during therapy. Physical examination alone may miss over 50% of cases of early and reversible chemotherapy-induced CHF.[72-74] A 12-lead ECG is a readily available and noninvasive method that can be used for detection of anthracycline-induced ventricular hypertrophy and arrhythmias. Acute ECG changes and arrhythmias following doxorubicin therapy occur in 0 to 14% of patients; however, this method lacks sensitivity and is unable to measure left ventricular function.[28]

Endomyocardial biopsy is considered a moderately sensitive indicator of chronic anthracycline-induced cardiotoxicity; however, its use for routine monitoring cannot be recommended because of its invasive nature.[75] A semiquantitative histological scoring system developed for these biopsy specimens correlated well with the cumulative anthracycline dose.[76] Histopathological examination of

the myocardium has demonstrated myocyte damage characteristic of anthracycline cardiotoxicity (cytoplasmic vacuolisation, abnormal swollen nuclei), acute inflammation of the pericardium and epicardium, and myocardial damage.[59,77] Early myocardial damage can be recognised by myofibrillar lysis and swelling of the cytoplasmic reticulum. Progressive mitochondrial damage and nuclear degeneration may involve >35% of the myocardial cells in the most severe cases. Histological damage to the myocardium was found to be proportional to the total cumulative dose of doxorubicin.[50,78]

There are a number of limitations to using this method. A considerable amount of variability may exist in the degree of morphological changes. Cardiac damage may be underestimated if the cardiomyopathic changes are scattered or if biopsy of the right ventricles is performed when there is predominant left ventricular damage. The expertise needed to perform a biopsy and interpret the findings may not be available at all institutions. Patients at an increased risk for bleeding, infection and impaired wound healing may develop complications as a result of such an invasive method, and therefore, it cannot be recommended as a routine monitoring parameter to detect early cardiac damage.

Serial measurements of LVEF and fractional shortening are the most common indices monitored to assess left ventricular systolic function and cardiotoxicity. This can be achieved by 2-dimensional, M-mode and colour Doppler echocardiographic examination. Echocardiography is less invasive and more sensitive that other methods in detecting abnormalities in left ventricular function. Fractional shortening assessed by echocardiogram has 64% sensitivity and 81% specificity for detecting abnormal contractility or abnormal afterload. It also provides anatomical details and measurements of chamber sizes and wall thickness.

Guidelines for following LVEF in patients undergoing anthracycline chemotherapy have been proposed.[30] A baseline LVEF estimation is recommended before the start of doxorubicin therapy. If LVEF is ≤30%, starting chemotherapy is not recommended. Patients with LVEF ≥30% but <50% can receive doxorubicin, but measurements should be repeated before each dose. For patients with baseline LVEF ≥50%, evaluations should be repeated after a cumulative dose of 250 to 300 mg/m^2 and thereafter at 450 mg/m^2 if they have no risk factors. If patients have known cardiovascular disease, prior radiation treatment to the chest, abnormal ECG changes or concomitant cardiotoxic chemotherapy, LVEF measurement should be repeated at 400 mg/m^2 instead of 450 mg/m^2. It should be monitored with each dose thereafter. Doxorubicin therapy should be stopped if there is a ≥10% absolute drop in the ejection fraction associated with a decrease in LVEF to ≤50% in patients with baseline LVEF ≥50%, and to ≤30% in patients with baseline LVEF <50% but >30%.

Patients should be followed for a long time even after completion of chemotherapy. It is recommended that an echocardiogram examination be performed after 3 to 6 months, after 12 months and then in alternate years after the completion of chemotherapy. Based on these guidelines a 4-fold decrease in CHF was achieved.[30] It is necessary that these guidelines be used with some caution. Both LVEF and fractional shortening are load-dependent indices and may not be specific in assessing left ventricular afterload and cardiomyocyte health,[79] since cardiac loading conditions can alter during conditions such as fever, anaemia, sepsis, volume infusions, renal failure, malnutrition and CNS disease.[57] Early cardiomyopathic changes may not be detected by using LVEF and fractional shortening, since patients with substantial anthracycline-induced cardiac injury may maintain a normal LVEF. A decision to discontinue anthracycline therapy based on these indices should be made knowing that it may affect the possibility of achieving disease remission and result in a relapse. Load-independent parameters such as relationship between rate-corrected velocity of fibre shortening and the end-systolic wall stress are more reliable measures of cardiac contractility that could be monitored during and after anthracycline therapy.[32]

Contrast radionuclide angiography has a specificity of 75% in detecting patients at moderate to high risk of developing CHF after anthracycline therapy.[80] This method has certain limitations. It measures ejection fraction, a load-dependent index; it is a semi-invasive and a moderately expensive method and should be performed at well established, reliable cardiac nuclear medicine centres.[81] Exercise radionuclide studies may increase the detection of early anthracycline cardiotoxicity.[59,82] This test has low specificity unless serial measurements are done, and maximal exercise may be difficult for debilitated patients with cancer.

1.1.5 Cardioprotection

The use of cardioprotective agents is associated with a decrease in cardiotoxicity and facilitates the use of higher cumulative doses of anthracyclines. Dexrazoxane (ICRF-187) is a cardioprotective agent approved by the FDA. It is a bispiperazine, a nonpolar derivative of ethylenediamintetraacetic acid and a water-soluble positive enantiomer of the racemic drug razoxane. It is intracellularly hydrolysed to an active carboxylamine form (ICRF-198). ICRF-198 is similar to ethylenediamintetra-acetic acid and acts as a chelator of heavy metals.[83] It binds to intracellular iron and inhibits the conversion of superoxide anions and hydrogen peroxide to superhydroxide free radicals. It also prevents the conversion of ferrous ion back to ferric ion for use by the superoxide anions.[84] The normal antioxidant mechanisms and the pharmacokinetics of doxorubicin and its metabolites are not affected by dexrazoxane.

In the initial double-blind, placebo-controlled trials, dexrazoxane was used at the ratio by weight of 10 : 1 with doxorubicin (patients who started at a ratio of 20 : 1 were subsequently changed to 10 : 1 because of myelosuppresion and deaths). The patients received 50 mg/m^2 of doxorubicin every 3 weeks along with other chemotherapy agents for advanced metastatic breast cancer or extensive small cell lung cancer.[85] Patients received dexrazoxane after a cumulative dose of 350 mg/m^2 of doxorubicin was reached. LVEF was measured at baseline and at predetermined intervals. The difference between the 2 groups in the mean decrease of LVEF was 6.7, 7.6 and 10.1% at 400, 500 and 550 mg/m^2, respectively. Of the 349 patients treated with doxorubicin, 12 developed CHF, 10 from the placebo group and 2 from the dexrazoxane group. However, a trend towards decreased tumour response was noted in the dexrazoxane group.

In another trial, 150 women with advanced breast cancer were randomised to receive doxorubicin 50 mg/m^2 every 3 weeks with or without dexrazoxane 1000 mg/m^2 over 15 min.[86] The result showed that dexrazoxane was able to provide cardioprotection in the cohort of patients that were studied at the dose employed. There was a marked difference in the incidence of CHF in the 2 groups, with 2 patients in the dexrazoxane group and 20 patients in the control group developing CHF. Patients receiving dexrazoxane were able to tolerate larger doses of doxorubicin for a longer period than the control group. Only 3% of the control group compared with 34% of the dexrazoxane group was able to receive >700 mg/m^2 of doxorubicin. 14% of the dexrazoxane group were able to receive >1000 mg/m^2 of doxorubicin without any evidence of cardiotoxicity. The full cardiac toxicity analysis (clinical, LVEF by multigated radionuclide scans and endomyocardial biopsy) was significantly different between the 2 groups ($p < 0.001$). Though not statistically significant, 37% of the dexrazoxane group experienced complete or partial response compared with 41% of the placebo group. Therefore, there is a concern over decreased efficacy of anthracyclines when used with dexrazoxane.

38 paediatric patients with sarcoma were randomised to receive doxorubicin-containing chemotherapy (70 mg/m^2/cycle over 2 days) with (n = 18) or without (n = 15) dexrazoxane.[87] The incidence of subclinical cardiotoxicity was lower in the dexrazoxane group (22 *vs* 67%, $p < 0.01$). Patients in the dexrazoxane group had a smaller decrease in LVEF per 100 mg/m^2 of doxorubicin (1 *vs* 27%, $p = 0.02$) and were able to receive a higher median cumulative dose of doxorubicin (410 *vs* 310 mg/m^2, $p < 0.05$). There were no significant differences in

the objective responses or in event-free or overall survival of patients. However, the number of patients studied was small and more information is needed to determine if the short term cardioprotective effects of dexrazoxane reduce the incidence of late cardiotoxicity in the survivors of childhood cancer.

Dexrazoxane has shown cardioprotective effects against epirubicin-based chemotherapy.[88] 162 patients with advanced breast cancer receiving epirubicin were randomised to receive dexrazoxane at a ratio of 10 : 1 or not at all. Patients with prior anthracycline therapy received 60 mg/m^2 of epirubicin along with cyclophosphamide and fluorouracil. Patients with no prior anthracycline therapy received 120 mg/m^2 of epirubicin alone. Both chemotherapy treatments were given on day 1 and repeated every 3 weeks. 18 of 38 patients (23.1%) in the control group and 6 out of 82 patients (7.3%) in the dexrazoxane group had cardiotoxicity (clinical signs of CHF, decrease in resting LVEF to ≤45% or a decrease from baseline resting LVEF of ≥20 ejection fraction units). There was no difference in the response rate, disease free survival rates, overall survival rate, and noncardiac toxicities between the 2 groups. The cumulative probability of developing cardiotoxicity was significantly lower in the dexrazoxane group than the control group.

Despite the beneficial effects of dexrazoxane, concerns exist about the lack of information on its effect on late onset progressive cardiomyopathy, the lack of conclusive evidence that it reduces overall morbidity and mortality in paediatric patients, and its possible interference with the antitumour efficacy of anthracyclines.

In addition to dexrazoxane, other cardioprotective drugs have been studied. These include ubidecarenone (coenzyme Q_{10}), carnitine and the antioxidant lipid lowering drug probucol.[89-91] Since anthracyclines are believed to increase the release of catecholamines and histamines, potentiating their cardiotoxicity, pretreatment with antihistamines, antiadrenergics or mast cell stabilisers, such as sodium cromoglycate (cromolyn sodium), might be expected to prevent cardiotoxicity.[92-95]

1.1.6 Other Anthracyclines

Cardiotoxicity of anthracyclines can be minimised by using analogues that may be less cardiotoxic. Compounds such as epirubicin and idarubicin exhibited decreased cardiotoxicity in preclinical trials.

Epirubicin is an epimer of doxorubicin developed to reduce doxorubicin-induced cardiotoxicity.[96] No significant differences in antitumour activity were detected between doxorubicin and epirubicin in animal models or in human solid tumours,[97-101] but a lower potential for cardiotoxicity was observed.[97,99,100] Epirubicin cardiotoxicity occurs at a higher cumulative dose of >900 mg/m^2 versus 550 mg/m^2 for doxorubicin.[102-104] Decrease in LVEF by ≥10% has been observed at a mean cumulative dose of 450 mg/m^2 of epirubicin.

Idarubicin is a semisynthetic derivative of daunorubicin. It is more lipophilic and can be administered orally as well as intravenously. Its main metabolite, idarubicinol, is as active as the parent drug. Idarubicin has shown greater *in vitro* activity and less cardiotoxicity compared with daunorubicin and doxorubicin in preclinical trials.[105] In a retrospective study in patients with acute myelocytic leukaemia and myelodysplasia receiving intravenous idarubicin,[105] a 5% probability of CHF was shown to exist at a cumulative idarubicin dose of 150 to 290 mg/m^2. The probability above a cumulative dose of 290 mg/m^2 was not determined. The probability of mild or greater (≥10% decrease in LVEF to a level of ≤50%) subclinical cardiotoxicity at a cumulative dose of 150 mg/m^2 was 18%, with a 7% probability of moderate or greater (≥15% decrease in LVEF to a final level of ≤45%) subclinical cardiotoxicity at the same cumulative dose. From these results, it was concluded that idarubicin-related cardiotoxicity is uncommon in the dose range generally used in acute myelocytic leukaemia and myelodysplasia at induction and postremission. It was also concluded that cumulative idarubicin doses of at least 150 mg/m^2 are well

tolerated in low risk patients (i.e. normotensive individuals aged <70 years with no prior or sequential exposure to anthraquinones). However, caution should be used when applying these conclusions to practice. Not all patients in the above study received follow-up ventriculograms. Only one dose schedule of idarubicin was used and the total duration of follow-up was limited to a median of 225 days after the last dose of idarubicin.

The cardiotoxic effects of idarubicin have been reported as CHF, serious arrhythmia (including atrial fibrillation), angina, myocardial infarction, asymptomatic decrease in LVEF and cardiomyopathies.[105,106]

1.1.7 Management

Current management of anthracycline-induced CHF consists mainly of symptomatic treatment. Drug therapy should be targeted to correct the anthracycline-induced cardiac abnormalities, such as increased afterload and decreased contractility, that lead to CHF. Treatment modalities including diuresis (diuretics), afterload reduction (ACE inhibitors) and increasing contractility (digoxin) should be initiated according to institutional protocol or to the practice guidelines of the Advisory Council to Improve Outcomes Nationwide in Heart Failure (ACTION HF).[107]

1.2 Mitoxantrone

Mitoxantrone is a non–cell-cycle-specific antitumour agent effective in the treatment of acute lymphocytic leukaemia and acute nonlymphocytic leukaemia.[108,109] It was developed as an anthraquinone derivative, and early animal and clinical studies revealed a lack of cardiotoxicity.[110-112] However, cardiotoxicity, including CHF, has been reported with mitoxantrone in patients who had received no previous doxorubicin therapy.[113-117]

Mitoxantrone has a 2.2 to 3.5% incidence of cardiotoxicity.[118,119] In 801 patients receiving mitoxantrone in 14 phase II Southwest Oncology Group protocols, prior doxorubicin therapy and cumulative dose of mitoxantrone were identified as prognostic variables that may increase mitoxantrone cardiotoxicity.[120] The study projected that patients receiving an average of doxorubicin 134 mg/m^2 and a cumulative dose of 24 mg/m^2 of mitoxantrone by day 442 had a 4% probability of developing cardiotoxicity. This probability was projected to increase with the cumulative dose of mitoxantrone: 6% at a cumulative dose of 60 mg/m^2 and 15% at a cumulative dose of 120 mg/m^2.[120] Cardiac dysfunction appeared to be dose-related in paediatric patients receiving mitoxantrone at cumulative doses of 90 to 187 mg/m^2.[121] Other risk factors such as age, gender or prior mediastinal radiotherapy were not found to predict toxicity.

Among the 801 patients receiving at least 1 course of mitoxantrone, 12 developed CHF (1.5%) and an additional 12 patients (1.5%) exhibited a decrease in their ejection fractions.[120] Two patients (0.25%) with prior doxorubicin therapy developed myocardial infarction. The incidence of CHF significantly increased (>5%) beyond a higher cumulative dose of 160 mg/m^2 of mitoxantrone even when doxorubicin was not administered concurrently.[122]

Cardiac events associated with mitoxantrone include arrhythmias, decreased LVEF, CHF, tachycardia, ECG changes and, infrequently, myocardial infarction.[113-117] ECG changes included sinus tachycardia, nonspecific ST-T wave changes or T wave abnormalities.[113,122] Echocardiogram examination of patients exhibiting mitoxantrone-induced CHF has revealed poor left ventricular function and generalised hypokinesis of the ventricles. Histological examination may reveal tubular swelling, degeneration of mitochondria, minimal chromatin clumping and myofibrillar lysis similar to that seen in doxorubicin-treated myocardial cells.[115] The third highest average mitoxantrone concentration was measured in the myocardial tissue at autopsy, 10 to 272 days after the last dose of mitoxantrone.[123] The highest concentrations were measured in the thyroid and liver. The study, however, was not designed to correlate cardiotoxicity with tissue concentration.

Mitoxantrone was developed to provide broad spectrum antitumour activity, similar to anthracy-

clines, without the cardiotoxicity. However, it has shown potential for cardiotoxicity. Mitoxantrone does not share the same mechanisms of cardiotoxicity as anthracyclines, since it has little propensity for free radical formation and it inhibits lipid peroxidation.[124] The myocardial fibrosis and myopathic changes incurred by mitoxantrone may result in nonhomogenous propagation of conduction, resulting in low amplitude high frequency signals in the terminal portion of the QRS complex and ST segment.[125,126]

Before mitoxantrone is administered, patients should be monitored for risks of cardiotoxicity, such as previous anthracycline therapy and preexisting cardiovascular disorders. Treatment with mitoxantrone in patients with previous anthracycline therapy should be based on known heart failure risk prediction curves for anthracyclines and mitoxantrone. When such a decision is made, practitioners should know that the probability of inducing cardiac failure increases as the cumulative dose increases. Cumulative doses of mitoxantrone should be monitored and ejection fractions and fractional shortening should be assessed before the start of mitoxantrone therapy, as patients progress through therapy and at the completion of therapy. However, there are no specific guidelines to recommend dose reductions based on changes in LVEF or fractional shortening.

CHF caused by mitoxantrone should be treated with suitable agents such as diuretics, ACE inhibitors and digoxin (section 1.1.7).[107] Arrhythmias should be treated only if patients experience serious clinical signs and symptoms, using institutional and/or Emergency Cardiac Care Committee and American Heart Association guidelines for cardiopulmonary resuscitation and cardiac care.[127] Patients experiencing chest pain should immediately receive supplemental oxygen, intravenous morphine sulfate and sublingual or intravenous nitroglycerin as they are being evaluated for an acute myocardial infarction or pericarditis/myocarditis. A continuous 12-lead ECG reading and cardiac enzyme determination should be obtained. A decision on further treatment for myocardial infarction (antithrombolytic therapy or a percutaneous transluminal coronary angioplasty) should be based on the patient's clinical condition, ECG and laboratory tests after confirming an ongoing myocardial infarction by institutional guidelines and/or American College of Cardiology/American Heart Association guidelines for the management of acute myocardial infarction.[128] The decision to continue mitoxantrone therapy should be based on the potential benefit of response versus the risk of developing a fatal cardiac failure.

2. Alkylating Agents

2.1 Cyclophosphamide and Ifosfamide

2.1.1 Cyclophosphamide

Cyclophosphamide is a non–cell-cycle-specific alkylating agent. It is a mainstay of most pretransplant preparative regimens. It is a broadly active antineoplastic and immunosuppressant agent used in combination chemotherapy for non–Hodgkin's lymphoma, leukaemia, Hodgkin's disease, Burkitt's lymphoma, multiple myeloma, endometrial cancer, lung cancer and breast cancer.[129-136] At high dosages, alone or in combination with bone marrow transplant, it is used in the treatment of solid tumours and lymphomas.[135,136]

The incidence of myocarditis caused by high dose cyclophosphamide (>150 mg/kg) is estimated to be 7 to 25% in adults and 5% in children.[73,137-144] When data from 2 studies[73,142] are combined, the incidence of symptomatic cardiomyopathy is 22% and of fatal cardiotoxicity 11%.

The total dose of cyclophosphamide administered during a particular course of chemotherapy has been identified as a reproducible predictive factor of acute cardiotoxicity.[137] A total dose ranging from 180 to 200 mg/kg over 2 to 4 days has been reported to cause symptomatic cardiomyopathy.[137] However, a dose as low as 120 mg/kg may also result in cardiotoxicity. Doses based on body surface area were found to be well correlated with the incidence of cardiotoxicity.[139] Patients receiving >1.5 g/m^2/day had a 25% incidence of cardiotoxicity compared with 3% in those receiving

lower dosages. A lower incidence of cardiotoxicity was observed in paediatric patients. This was attributed to an intrinsic age-related resistance to cyclophosphamide-induced cardiotoxicity and to a relatively lower dosage received by the paediatric patients.[139] Children have a smaller bodyweight to body surface area ratio and therefore receive a relatively lower dosage of cyclophosphamide compared with adults.

It is difficult to identify definite risk factors for the development of cyclophosphamide cardiotoxicity. In addition to total dose, prior anthracycline or mitoxantrone therapy and chest irradiation are proposed as the predisposing factors for cyclophosphamide cardiotoxicity.[142] Cazin et al.[141] did not detect a relationship between cyclophosphamide cardiotoxicity and prior anthracycline therapy; however, Steinherz et al. did.[142] There is little information on the correlation between cumulative cyclophosphamide dose and cardiotoxicity. No cardiotoxicity was observed in 4 patients who received more than 1 bone marrow transplant and 400 mg/kg of total cumulative dose of cyclophosphamide.[139]

Clinically, cyclophosphamide-related cardiotoxicity presents as a syndrome of CHF or myocarditis or both, and may lead to death.[139,145,146] Pericarditis manifests as chest pain, pericardial friction rub and arrhythmias.[146] The onset is acute, with signs and symptoms occurring within 1 to 10 days after the first dose;[137,145] they may last from 1 to 6 days.[147] There were no reports of development of late cardiotoxicity (>3 weeks) in patients who survived the initial event.[73] Loss of QRS voltage associated with significant CHF was observed in at least 50 to 90% of the cases;[73,138,141,144] 25 to 33% may exhibit nonspecific ST segment elevations and T wave inversions.[73,145] These ECG changes occurred within 1 to 3 days of administering cyclophosphamide, were reversible and returned to baseline in 1 to 7 days.[73,145] ECG changes may occur even in the absence of clinical cardiotoxicity. Echocardiogram examination of patients receiving high dose cyclophosphamide therapy has shown a dose-dependent increase in left ventricular mass index and a decrease in the fraction of ventricular wall shortening, resulting in acute reversible decrease in systolic function in >50% of the patients.[73,143,146]

Histopathological examination of the heart of patients experiencing fatal cyclophosphamide-induced cardiotoxicity revealed increased heart weight, noticeable thickening of the left ventricular wall, haemorrhagic myocardial necrosis with interstitial oedema, extravasation of blood, intracapillary microthrombi composed of fibrin and platelets, and vascular endothelial damage.[73,137,139,141,146]

The precise mechanism by which cyclophosphamide induces cardiotoxicity is unknown. One proposed mechanism is damage to the endothelium followed by transudation of the toxic metabolite, resulting in myocyte damage, interstitial haemorrhage and oedema.[140,143] Ischaemic damage caused by intracapillary microthrombi is believed to lead to serious cardiotoxicity. The damage to the endothelium and interstitial transudation may result in decreased electrical activity and decreased QRS complex, thus compromising left ventricular systolic function.[73] Myocardial ischaemia due to coronary artery vasospasm is also proposed to lead to cyclophosphamide-induced cardiotoxicity.

Pharmacokinetic data obtained during the administration of a 4-day infusion of a high dose of cyclophosphamide showed a negative association between the area under the serum concentration-time curve (AUC) for cyclophosphamide and the subsequent development of CHF. Lower AUC for cyclophosphamide meant increased rate of conversion of cyclophosphamide, a prodrug, to its active alkylating metabolites. Increased concentration of the active metabolite led to increased cytotoxicity and end-organ toxicity.[147]

2.1.2 Ifosfamide

Ifosfamide, structurally similar to cyclophosphamide, has activity against soft tissue sarcomas and non–small-cell lung carcinomas.[129,148-150] A retrospective review of patients (n = 52) receiving ifosfamide as combination chemotherapy [ifosfamide, carboplatin, etoposide (n = 19) or vinblastine,

ifosfamide, lomustine (n = 34)] with autologous bone marrow transplantation reported an overall incidence of 17% for significant cardiovascular toxicity such as CHF.[151] A significant dose-response trend was observed for CHF, which was reported in 0 of 6 patients receiving 10 g/m^2, 1 of 12 receiving 12.5 g/m^2, 2 of 20 receiving 15.6 g/m^2, 4 of 12 receiving 16 g/m^2 and 2 of 3 receiving 18 g/m^2. The onset of symptoms occurred at a mean of 12 days (range 6 to 23 days) after the initiation of ifosfamide therapy. Discontinuation of ifosfamide reversed the cardiac abnormalities and these did not recur. The signs and symptoms of CHF resolved in 4 to 7 days after starting supportive care.

In addition to CHF, arrhythmias consisting of pulseless tachycardia requiring lidocaine (lignocaine), re-entrant supraventricular tachycardia treated with procainamide, and ST segment or T wave abnormalities and decreased QRS complex were observed.[151] Cardiac enzymes were normal in these patients and ECG did not show any evidence of myocardial ischaemia. However, a significant correlation was observed between the development of CHF and the doubling of serum creatinine from pre-ifosfamide levels ($p = 0.0001$). Autopsy revealed both gross and histological cardiac abnormalities. These included increased heart weight, small pericardial effusions, fibrinous pericarditis, subendocardial haemorrhages, lymphocytic infiltration of myocardium, petechial lesions in the epicardium, epicardial fibrosis and moderate adipose infiltration of the myocardium.

Ifosfamide is a nephrotoxic antineoplastic agent that reduces glomerular filtration rate and produces renal tubular acidosis and tubular defects.[152,153] Ifosfamide cardiotoxicity may be related to delayed elimination of cardiotoxic metabolites of the drug. This is based on the invariable rise in serum creatinine observed before the onset of CHF. The fluid and sodium loads given with the chemotherapeutic drugs, aided by the tubular defects due to ifosfamide, may result in fluid and acid-base electrolyte disturbances in these patients, resulting in myocardial decompensation. Previous exposure to doxorubicin may also potentiate ifosfamide cardiotoxicity.

2.1.3 Management

Adverse cardiac events such as CHF, arrhythmias and pericarditis/myocarditis should be considered while treating patients with high doses of cyclophosphamide and ifosfamide. There is no specific prophylactic treatment to prevent this toxicity. Patients with previous anthracycline and/or mitoxantrone chemotherapy and mantle irradiation and receiving high doses of cyclophosphamide or ifosfamide should be monitored with a 12-lead ECG and regular echocardiogram. However, patients exhibiting signs and symptoms of clinical cardiotoxicity may not show any changes on ECG and echocardiogram. Studies have failed to find a correlation between pre-cyclophosphamide decreased ejection fraction and clinical cardiotoxicity[147] and even prospective positron emission tomography scans are not predictive of the cardiotoxicity.

Treatment should be initiated immediately, primarily to control the symptoms. CHF may need treatment with diuretics, afterload reducing agents such as ACE inhibitors and digoxin, following institution protocol or ACTION HF practice guidelines.[107] Myocardial infarction should be suspected in patients experiencing chest pain, and should be treated as described in section 1.2. Pericarditis accompanied by large pericardial effusion may benefit from pericardiocentesis, especially if the patient experiences cardiac tamponade.[154] Anti-inflammatory drugs such as corticosteroids and nonsteroidal anti-inflammatory drugs such as salsalate could be used. Arrhythmias and ECG changes should be treated based on the seriousness of clinical signs and symptoms, following institutional or published guidelines.[127]

2.2 Cisplatin

Cisplatin is an alkylating agent with a wide spectrum of antineoplastic activity, e.g. paediatric brain tumours, osteosarcoma, ovarian cancer and head and neck cancer.[155] Cardiotoxicity is a relatively uncommon complication of cisplatin chemotherapy. The earliest reports of cisplatin-induced car-

diac events involve ST segment or T wave changes and CHF[156] and left bundle branch block.[157] It is not clear whether the coronary events were directly related to cisplatin alone, to the other antineoplastic agents (vinblastine, etoposide and bleomycin) that were administered simultaneously, or to the underlying cardiovascular disease state. Men with a history of smoking being treated for smoking-related lung or head and neck cancer are more likely to experience such cardiac events than young women with ovarian cancer, who are less likely to have risk factors for severe coronary disease. However, cisplatin-induced ischaemic vascular complications involving major arteries were not reported frequently in patients with known risk factors for atherosclerosis.[158,159]

The cisplatin-induced cardiac events that have been described include atrial fibrillation, supraventricular tachycardia, intra-ventricular left block and myocardial infarction,[156,157,160,161] and have been correlated with the administration of cisplatin.[162,163] These events, however, do not seem to be dose-related and may occur at any time from hours after the first cisplatin infusion is complete to up to 18 months after the completion of a cycle. Cardiac events occurring 18 months after completion of cisplatin therapy are clearly less likely to be related to cisplatin administration compared with events occurring within hours of cisplatin infusion. Patients may complain of palpitations, substernal chest pain or radiating left sided chest pain, nausea, vomiting, sweating, dyspnoea and hypotension.[162-165] ECG changes may consist of ST segment or T wave changes[163] and T wave inversions.[165] An elevation in cardiac enzymes (creatinine kinase, especially the MB isozyme) can be anticipated.[165] Echocardiogram and chest x-ray may remain normal.[162] There may be a moderate decrease in the ejection fraction and patients may exhibit hypokinesis or akinesis of the myocardium.[163]

The exact mechanism of these events is not known. Several possibilities, including endothelial damage,[158] vascular fibrosis,[166] thrombosis[167] and vasospasm,[168] have been proposed but none have been confirmed. Autonomic dysfunction, heightened α-adrenergic tone and hypomagnesaemia have been frequently associated with cisplatin therapy, and may potentiate arterial vasospasm.[169,170] Magnesium is important for maintenance of vascular smooth muscle tone.[170,171] Its deficiency has been implicated in the triggering of coronary artery vasospasm in dogs and contributing to ischaemic events in humans. Hypoperfusion resulting from arterial vasospasm or thrombosis is probably responsible for the acute ischaemic vascular complications.

Controlled clinical trials are needed to confirm a temporal relationship between administration of cisplatin and occurrence of cardiac events. Arrhythmias and chest pain should be treated as discussed in earlier sections.

2.3 Mitomycin

Mitomycin is an antineoplastic antibiotic from *Streptomyces caespitosus*, and is an alkylating agent with activity against colon and breast cancer.[129,172-176] It may be used in combination with other chemotherapeutic agents in gastric, pancreatic and non–small-cell lung cancer.[177]

The earliest reports of cardiotoxicity caused by mitomycin were between 1971 and 1978.[178-180] Mortality due to cardiac and pulmonary toxicity has been reported to be around 25% of patients developing such toxicities.[181] A study of mitomycin cardiotoxicity in 233 patients found 23 cases, with an incidence of 10%.[182-185] The median cumulative dose among these 23 patients was 60 mg/m^2 (range 20 to 80 mg/m^2). No cardiotoxicity was observed at doses <30 mg/m^2.[186]

The most common cardiac event associated with mitomycin is CHF, which was observed after a median of 3 cycles.[182,185,186] Almost all patients who experienced a cardiac event had received prior doxorubicin therapy. 14 of 91 patients (15.3%) receiving mitomycin after doxorubicin developed CHF compared with 3 of 89 patients not receiving mitomycin as second-line treatment after similar doxorubicin combination chemotherapy.[182] Therefore, delayed cardiomyop-

athy from the previous doxorubicin treatment cannot be excluded. However, the incidence of CHF in the doxorubicin-mitomycin group was significantly higher ($p = 0.01$) than that expected with doxorubicin combination chemotherapy without mitomycin. This strongly suggests that mitomycin probably enhanced the cardiac damage incurred by prior doxorubicin therapy, thus exhibiting a synergistic cardiotoxic effect. Cardiotoxicity due to doxorubicin-mitomycin combination or mitomycin alone after discontinuation of doxorubicin may be seen even at low doxorubicin cumulative doses that are not considered cardiotoxic.

Mitomycin–related cardiac failure is not an acute event; it exhibits a trend towards a cumulative dose effect and occurs weeks after multiple doses of mitomycin. It is believed to occur in well oxygenated organs. Mitomycin undergoes microsomal reduction to a semiquinone radical. Under anaerobic conditions, this radical is subsequently reduced to hydroquinone, finally inducing binding to DNA.[181,187] However, under aerobic conditions, e.g. in the cardiac myocytes, the semiquinone radical is oxidised to the parent compound with the formation of superoxide radicals, which may contribute to mitomycin–induced cardiotoxicity and exacerbate anthracycline-induced cardiotoxicity.[187] Some clinicians have associated this cardiac failure with a mitomycin–induced syndrome of microangiopathy, haemolytic anaemia and azotaemia. The anaemia, associated systemic hypertension and progressive renal impairment are known to contribute to CHF.[188,189]

Left ventricular failure caused by mitomycin should be treated with diuretics, load-reducing agents such as ACE inhibitors and digoxin, following institutional or published[107] guidelines.

2.4 Carmustine

Carmustine (BCNU) is a synthetic nitrosourea derivative. It is an alkylating agent used in the treatment of refractory Hodgkin's disease, non-Hodgkin's lymphoma and multiple myeloma. It is used in high doses (600 mg/m2) in combination with other chemotherapy agents as a preparatory regimen for autologous bone marrow transplantation for breast cancer, neuroblastoma, gliomas, melanoma and sarcoma.[129,190-192]

Carmustine-induced cardiotoxicity is rare, but may cause chest pain, hypotension, and sinus tachycardia.[193] Patients may complain of dyspnoea, nausea and substernal chest pain radiating to both the arms. However, serial ECG and cardiac enzymes may not indicate the presence of an ongoing myocardial infarction. Sinus tachycardia and a 1 to 2mm ST segment depression may be seen on the ECG. Hypotension may manifest during, or a few hours after the end of, the infusion.

Cardiotoxicity due to carmustine should be considered, especially when used in high doses in bone marrow transplant preparatory regimens.[193] The cardiovascular effects of carmustine appeared to be dose-related; however, a correlation between plasma drug concentration and symptoms could not be established.[194] The symptoms persisted even when carmustine was undetectable in the plasma. It is reasonable to question whether these incidents of myocardial ischaemia are solely related to carmustine. Patients experiencing these adverse events had recently received cardiotoxic chemotherapy such as cyclophosphamide and cisplatin. However, patients were relatively young (37 to 41 years) with no cardiovascular risk factors observed on ECG and resting and exercise multigated acquisition cardiac scan. The exact mechanism of carmustine-induced myocardial ischaemia or its incidence is unknown. However, the symptoms are similar to those induced by fluorouracil, and therefore all the mechanisms postulated for fluorouracil could be applied to carmustine. The ECG changes indicated endocardial ischaemia, possibly related to increased oxygen demand, coronary spasm or change in blood flow distribution.

Hypotension should be treated with intravenous fluids and inotropes. Chest pain should be treated as described in section 1.2. Serious signs and symptoms due to sinus tachycardia should be treated following institutional or published guidelines.[127]

2.5 Busulfan

Busulfan is an alkylating agent with limited antitumour activity. At standard doses, it is used in the treatment of chronic myelocytic leukaemia. At high doses, in combination with cyclophosphamide, it is used as a bone marrow transplant preparatory regimen for leukaemia, lymphomas and paediatric solid tumours.[129,195-197]

Pulmonary fibrosis is a well known complication of long term treatment with busulfan. Endocardial fibrosis and cardiac tamponade associated with busulfan are rare, reported only as two case reports, one of which occurred concurrently with pulmonary fibrosis. Endocardial fibrosis was observed after 3 to 9 years of treatment of chronic myelocytic leukaemia and at cumulative doses of 7200mg.[198-200] Patients may present with symptoms of cardiac failure, and radiographic examination may reveal pulmonary congestion and an enlarged heart. Flat T waves or peaked P waves may be observed on ECG. Pericardial effusion and hypokinesis of the ventricular apex may be seen. Myocardial biopsy may reveal focal endocardial fibrosis with thickened and tense pericardium. Cardiac tamponade has been reported and may be fatal.

Since data associating adverse cardiac events with busulfan exist only as case reports, a reasonable question could be raised about their direct correlation. However, myocardial biopsies and resection of the pericardium in both cases indicated fibrosis. The mechanism for endocardial fibrosis is presumably similar to that causing pulmonary fibrosis, either chemical or autoimmune.[201,202]

2.6 Chlormethine

Chlormethine (mechlorethamine, nitrogen mustard), a prototype alkylating agent, is a nitrogen analogue of sulfur mustard. Chlormethine is used primarily in the treatment of Hodgkin's disease and topically for mycosis fungoides and psoriasis.[130,203-205] Cardiotoxicity due to chlormethine is uncommon at normal doses. However, severe cardiotoxicity was observed when it was used at a higher dose of 33 mg/m^2 along with autologous bone marrow transplantation to treat advanced malignant melanoma.[206,207] Cardiotoxicity was manifested as persistent tachycardia, pulse irregularity or junctional or atrial ectopic beats occurring 1 to 3 days after administration of chlormethine, and persisted for 48 to 72 hours. Patients were between 17 and 52 years of age; 2 out of 3 had no cardiovascular risk factors, and chlormethine was the only chemotherapy agent administered. Therefore, these adverse events could be attributed to chlormethine. However, the nature of the effect of chlormethine on the myocardial tissue and the conduction system is unknown. The severity of cardiac and other toxicities prevented further use of this protocol in the treatment of advanced malignant melanoma.

3. Antimetabolites

3.1 Fluorouracil

Fluorouracil is a synthetic pyrimidine antimetabolite. It is relatively S phase–specific, and 5-fluoro-2′-deoxyuridine 5′-monophosphate is the active metabolite. It is widely used as a single agent or in multidrug regimens for varied types of malignancies, including breast, gastrointestinal tract, head and neck, and ovarian carcinoma.[208] Fluorouracil exhibits antitumour activity in a number of different regimens, including daily bolus injection.

Fluorouracil–related cardiac events range from chest pain to massive myocardial infarction culminating in cardiogenic shock and death.[209-211] Typical initial symptoms include retrosternal chest pain, nausea, vomiting, diaphoresis, loss of consciousness, malaise and dyspnoea, with the feeling of imminent death.[211] Cardiotoxicity may manifest as angina pectoris, myocardial infarction, hypotension, symptomatic or asymptomatic arrhythmias (atrial and ventricular) and cardiogenic shock.

A retrospective review of 1083 patients receiving fluorouracil found a 1.6% incidence of clinically apparent cardiotoxicity.[209] Other retrospective studies and anecdotal reports place this incidence at 24 to 68%.[212] Cardiac events in up to

10% of the patients were associated with high dosage fluorouracil therapy (>800 mg/m^2/day).[213] In a prospective study of 367 patients, cardiac events occurred in 7.6% during their first cycle of fluorouracil, resulting in a mortality rate of 2.2%.[211] Similar results have been reported in other studies.[214]

Fluorouracil cardiotoxicity frequently occurs during the first course of fluorouracil, after the second or third dose,[215-217] and is more common after high dose continuous infusion therapy than after bolus doses.[211] The mean onset of fluorouracil-related cardiac symptoms is 3 days (range 2 to 5 days), with the majority of patients experiencing angina within hours of administration.[211,212] The symptoms may resolve at a mean of 48 hours after discontinuation of the infusion, but recur in 90% of cases when infusion is restarted and may be more severe than the previous episode.[218,219] However, no delayed sequelae have been reported.[217]

ECG changes encountered with fluorouracil cardiotoxicity consist of ST segment changes, either elevation or depression, decrease in QRS amplitude, new Q waves suggestive of a myocardial infarction, T waves, peaked T waves, T wave inversions and sinus tachycardia.[210,219] The less common ECG abnormalities include prolongation of the QT interval, atrial fibrillation, ventricular extra systoles, sustained and nonsustained ventricular tachycardia and ventricular fibrillation.[210,220] In most patients, ECG changes returned to normal from within a few hours to 3 days after fluorouracil was discontinued. Left ventricular wall motion abnormalities in the form of segmental or diffuse left ventricular hypokinesia, including global hypokinesia, were observed on M-mode or 2-dimensional echocardiographic analysis. Levels of creatinine kinase may remain normal or increase, but may not be greater than twice normal.[211]

Fluorouracil-associated cardiotoxicity may be more common than previously thought. A number of factors that predispose a patient to fluorouracil cardiotoxicity have been identified. Patients with active or occult ischaemic heart disease, myocardial infarction and serious dysarrhythmias are at a higher risk of fluorouracil–induced cardiotoxicity. In 1083 patients receiving fluorouracil, those with a prior history of cardiac disease were found to be at a significantly increased risk (4.5 *vs* 1.1%) of developing chest pain compared with patients without known heart disease ($p < 0.01$).[209] Prior mediastinal radiation may play a role in fluorouracil cardiotoxicity.[219] Ionising radiation increases the risk of fluorouracil cardiotoxicity by producing small vessel thrombosis.[219,221,222] Concurrent administration of other chemotherapeutic agents may contribute to the development of cardiac symptoms.[211] The fluorouracil administration schedule may also influence the risk of cardiotoxicity. The incidence of cardiotoxicity after bolus administration was lower than with continuous infusion.[209,211,216] Three of 36 patients treated with continuous infusion of fluorouracil developed chest pain.[215] However, no such symptoms occurred in any of the 120 patients who received comparable intravenous bolus doses. The cardiotoxicity of fluorouracil may be associated with higher doses (>800 mg/m^2) but not with cumulative dose.[211,213]

The underlying mechanism of fluorouracil-induced cardiotoxicity is not well understood. Little is known about the accumulation of fluorouracil and its toxic metabolites in the myocardium. One theory proposes that fluorouracil or its metabolites may somehow interfere with myocardial energy metabolism, increase myocardial energy demands and produce a direct toxic effect on the myocardium. The temporal relationship between the classic chest pain and the ECG changes and the recurrence of pain with rechallenge suggests the possibility of coronary ischaemia.[210,212,220] An autoimmune response stimulated by complex formation between fluorouracil and cardiac cells, or damage to the cardiac cells by fluorouracil, has been proposed.[223] Endothelin, a potent vasoconstrictor produced by vascular and endothelial cells, may be a cause of vasoconstriction and ischaemia. Increased plasma concentrations of endothelin have been observed in patients treated with fluorouracil, and were higher in patients experiencing fluorouracil–related cardiac events.[224]

Other theories include stunned myocardium syndrome related to diffuse ischaemia, alteration in the coagulation system, decreased fibrinolytic activity and consequent formation of myocardial thrombus.[225,226] Recently, fluoroacetate, a degradation product of fluorouracil formed in the alkaline medium used to dissolve the drug, was implicated in fluorouracil–induced cardiotoxicity.[227-230] Fluoroacetate, a known cardiotoxic compound,[231] was detected in urine samples from patients receiving continuous infusion therapy.[211,222] However, the aetiological role of fluoroacetate in production of fluorouracil cardiotoxicity in humans is unclear.

Clinicians should be aware of fluorouracil-associated cardiotoxicity and screen patients for predisposing risk factors. Administration of fluorouracil under controlled settings with telemetry and clinical monitoring may be considered in patients at a higher risk of developing cardiotoxicity. If cardiac events occur, fluorouracil administration should be discontinued immediately since prophylaxis or treatment of anginal symptoms with nitrates or calcium antagonists may not be effective.[210,232-234] Prophylactic nitroglycerin 10 to 60 mg/day orally or cutaneously has failed to prevent ECG changes suggestive of ischaemia.[210] Nifedipine 60 mg/day or diltiazem 80 mg/day administered prophylactically with simultaneous intravenous nitroglycerin at therapeutic doses has also failed.[210] Prophylactic use of verapamil 120mg 3 times daily did not change the incidence of ischaemia in patients receiving fluorouracil when compared with a control group who had no prophylactic treatment.

Patients experiencing anginal symptoms should be evaluated and treated for an acute myocardial infarction as discussed in section 1.2. Patients in cardiogenic shock may require vasopressor, inotropic and ventilator support. If further treatment with fluorouracil is warranted based on response, it should be administered in a cardiac unit with appropriate monitoring. The decision to continue treatment with fluorouracil despite life-threatening cardiac events should be based on the benefit obtained by continuing therapy versus the risk of a fatal cardiac outcome.

3.2 Cytarabine

Cytarabine (cytosine arabinoside, Ara-C) is an arabinose nucleoside isolated from *Cryptothethya cypta*. In combination with other chemotherapeutic agents, it is a drug of choice for the treatment of acute nonlymphocytic leukaemia in adults and children. It is also used in the treatment of acute lymphocytic leukaemia and the acute blast phase of chronic myelocytic leukaemia. High dose cytarabine (3 g/m^2) with or without daunorubicin may produced remission in patients refractory to conventional doses of cytarabine.[208]

Cardiopulmonary complications associated with cytarabine are rare. The cardiac events associated with cytarabine include supraventricular and ventricular arrhythmias, pericarditis, acute respiratory distress and recurrent CHF.[235-240] These have most commonly been associated with high dose cytarabine. A 'cytosine arabinoside syndrome' has been associated with cytarabine chemotherapy, characterised by high fever, malaise, joint pain, rash and chest pain.[241] The onset of this syndrome is abrupt, within 12 hours after initiation of therapy. The symptoms tend to resolve within 24 hours after cessation of the drug.

There are only a few published reports of pericarditis and CHF associated with high dose cytarabine. Cytarabine-associated pericarditis can occur between 3 and 28 days following initiation of therapy. It can occur immediately after the first dose or during subsequent doses of the same course or subsequent courses.[235,236] Patients may manifest pericarditis as dyspnoea and a sharp severe substernal chest pain, especially on inspiration, and may subsequently develop a pericardial friction rub observed on physical examination along with a pulsus paradoxus.[242] ECG may remain normal or exhibit ST segment elevations consistent with pericarditis, persisting at least for a week. Echocardiography may reveal global hypokinesis.[236] Chest x-rays may remain normal or show signs of pericardial effusion.[236,242,243] A biopsy

of the endocardium in a patient with cytarabine-induced pericarditis did not exhibit any myocardial cell damage but only focal deposits of granulocytes.[236]

The acute respiratory distress syndrome, also known as noncardiogenic pulmonary oedema, reported with high dose cytarabine may occur within 3 days of cytarabine therapy.[237-240] Elevated levels of tumour necrosis factor and platelet activating factor have been noted in patients developing a capillary leak syndrome after receiving high dose cytarabine.[240] The acute respiratory distress syndrome has been attributed to the inflammatory effect of cytarabine, since symptoms have improved after corticosteroid therapy.

Since cytarabine is frequently used in cancer treatment, clinicians must be alerted of this potential complication and other reported cardiopulmonary complications associated with cytarabine therapy. The exact mechanism of cytarabine-induced cardiac effects is not known. An immune-mediated process or a type of hypersensitivity reaction is suspected.[244]

The episodes of chest pain have been successfully treated with morphine sulfate.[242] Chest pain should be evaluated for an acute myocardial infarction (section 1.2), and patients may receive supplemental oxygen and intravenous morphine sulfate immediately. Prednisone and salsalate have been and can be used for their anti-inflammatory effects in patients with pericarditis. CHF should be treated as discussed in section 1.1.7. Some patients may need pericardiocentesis or pleuracentesis to remove the pleural or pericardial effusion.[232] Arrhythmias should be evaluated and treated based on the seriousness of the clinical signs and symptoms, using institutional or published[127] guidelines.

4. Antimicrotubule Agents

4.1 Paclitaxel

Paclitaxel is a diterpene plant product with antineoplastic activity, derived from the bark of the western yew tree, *Taxus brevifolia*. It is indicated in the treatment of breast and ovarian cancer.[245,246]

During its early phase I trials, paclitaxel caused a high incidence of serious hypersensitivity reactions.[247] These were attributed to Cremophor EL (polyethoxylated castor oil), a vehicle used to dissolve paclitaxel. The administration of paclitaxel over longer duration (24 hours), and premedication with corticosteroids and histamine H_1 and H_2 receptor antagonists resulted in a significant decrease in the frequency and severity of the hypersensitivity reactions. Routine continuous cardiac monitoring in an effort to more effectively evaluate and manage hypersensitivity reactions led to the documentation of cardiac arrhythmias.

The most frequent cardiovascular events reported during paclitaxel administration in the phase II studies were declines in heart rate and blood pressure. Asymptomatic bradycardia was the most frequent cardiac event associated with paclitaxel administration, occurring in approximately 29% of patients undergoing continuous cardiac monitoring during the 24-hour infusion.[248]

The incidence of the various paclitaxel-associated cardiovascular adverse reactions has been determined in over 3400 patients treated with paclitaxel.[249] The data were obtained from a variety of sources including the Cancer Therapy Evaluation Programs (CTEPs), the Adverse Drug Reaction database and the various clinical trials involving use of paclitaxel. A 0.5% incidence of all adverse grade 4 and 5 cardiac events (life threatening reactions and death) was found from CTEPs. The incidence of ventricular tachycardia and ventricular fibrillation was reported to be 0.26%; significant atrial arrhythmias (atrial fibrillation, flutter, supraventricular tachycardia) 0.24%; heart block 0.11%; and grade 4 and 5 ischaemic events 0.29%.

The characteristics of paclitaxel-associated cardiac disturbances that occurred during phase I and phase II clinical trials at the Johns Hopkins oncology centre have been reported.[248,250,251] Ventricular arrhythmias may become evident at a median of 12 hours into the infusion of paclitaxel (range 1 to 24 hours).[249] These may be seen occasionally in the first cycle but most often the second or subsequent

cycles. Atrial arrhythmias have been reported in a median time of 24 hours after initiation of the paclitaxel infusion (range 2.5 hours to 6 days) after a median 1.5 courses of paclitaxel (range 1 to 7).[249] Myocardial infarction and ischaemia were seen during and up to 14 days following paclitaxel therapy. Patients reverted to normal sinus rhythm after discontinuation of paclitaxel. The cardiac disturbances resolved over the next 48 to 72 hours and as early as 4 hours after discontinuation.[248-250] Some patients may continue to exhibit rare and brief episodes of supraventricular tachycardia or rare premature ventricular contractions even 10 days after discontinuing paclitaxel. Cardiac disturbances may be seen even as early as the first course of paclitaxel.

Cardiac rhythm disturbances during paclitaxel administration may be in the form of atrial flutter, atrial fibrillation, supraventricular tachycardia, ventricular tachyarrhythmia, left bundle branch block, atrioventricular conduction block associated with sinus bradycardia, bigeminy, trigeminy and increased premature ventricular contractions. Patients may also experience chest pain indicative of cardiac ischaemia.[248] Sinus bradycardia with heart rates ranging from 30 to 50 beats per minute has been observed in relatively high proportion of patients during paclitaxel infusions.[250,251] These may be asymptomatic without any haemodynamic compromise, but may also progress to higher grades of atrioventricular conduction delay. The cardiac toxicities described in the literature have rarely led to clinically significant sequelae in most patients.[248,249] Paclitaxel cardiotoxicity does not exhibit a cumulative dose effect.

These cardiac disturbances may be multifactorial in aetiology, and other drugs and underlying heart disease may contribute to these disturbances.[248] It is not clear whether paclitaxel or its Cremophor EL formulation vehicle is responsible for these cardiac events. The vehicle is known to induce histamine release, stimulating H_1 and H_2 receptors.[252] Stimulation of these receptors in cardiac tissue can increase myocardial oxygen demand and produce coronary vasoconstriction (H_1) and chronotropic effects (H_2).[248,253-259] Selective activation of histamine receptors in the cardiac tissue may result in the bradycardia, atrioventricular conduction prolongation, bundle branch block, ventricular irritability and even cardiac ischaemia that has been reported in association with paclitaxel treatment.[248] Patients treated with some other drugs containing Cremophor EL, e.g. miconazole (ventricular tachyarrhythmia and cardiac arrests),[260,261] teniposide[262] and cyclosporin,[263] have experienced cardiovascular toxicity, including hypotension. Cardiac arrhythmias with these drugs occur rarely and routine cardiac monitoring is unnecessary. It should be realised, however, that paclitaxel is formulated with the highest concentration of Cremophor EL per dose of all drugs available or utilised clinically.

The cardiovascular reactions reported with paclitaxel could also be related to the administration of premedications such as the H_1 antagonist diphenhydramine and the H_2 antagonist cimetidine. Cardiac rate and rhythm abnormalities, especially bradyarrhythmias, have been reported with the H_2 antagonists cimetidine, ranitidine and famotidine.[264,265] Hypotension, palpitations, tachycardia and extrasystoles have also been reported with diphenhydramine,[260] an H_1 antagonist routinely used as a premedication drug. However, many of the cardiac abnormalities associated with paclitaxel appeared later during the infusion. They were usually self-limited or resolved soon after the discontinuation of the paclitaxel infusion.[248] These findings suggest that the cardiac events reported were more likely to be related to paclitaxel than to the premedications.

Paclitaxel, by virtue of its being an antimicrotubule agent, may mediate cardiac muscle damage by adversely affecting other subcellular organelles.[248] The poisonous properties of yew have been recognised.[266] Taxine, the alkaloid fraction in the plant, contains at least 10 separate alkaloids.[267] The individual components of the alkaloidal fraction 'taxine', which may produce cardiotoxic effects, possess the taxane ring system and some of the substituent positions in common with paclitaxel. Taxines are known to affect automaticity and car-

diac conduction.[266,268-270] Similarities in the symptoms and cardiac effects among cases of yew poisoning, experimental studies with taxine and the clinical observations with paclitaxel cardiotoxicity tend to support the hypothesis that these cardiac abnormalities are caused by paclitaxel.

After the initial reports of cardiac events with paclitaxel infusion, inclusion into study protocols was limited to patients without possible cardiac risk factors. Therefore, it is difficult to identify risk factors that may enhance paclitaxel-induced cardiotoxicity. However, patients with a history of myocardial infarction, angina or CHF; patients at risk for atherosclerosis who are not expected to tolerate bradycardia; those with evidence of altered cardiac conduction (bundle branch block, first-degree atrioventricular block); and those on medications known to alter cardiac conduction (β-blockers, digoxin, calcium antagonists) may be at a higher risk of arrhythmias during paclitaxel therapy. Information about the effect of such predisposing factors on the risk of inducing a cardiac event during paclitaxel administration is not available. Because of the lack of information, however, such patients may require careful cardiac evaluation and continuous monitoring during therapy.

The paclitaxel dose should not be altered or therapy discontinued if patients exhibit asymptomatic sinus bradycardia. Patients who develop severe bradycardia or symptoms of a heart block should be evaluated with a 12-lead ECG and should be monitored thereafter. Those with advanced atrioventricular conduction abnormalities may not be symptomatic and may be controlled with temporary or permanent cardiac pacing. Patients with asymptomatic heart block may also be prophylactically managed with a temporary transvenous pacing. The need for temporary or permanent pacemaker should be based on the severity of the symptoms and the need to continue paclitaxel therapy. Patients receiving any cardiac medications prior to their paclitaxel therapy should be continued on them without alteration in dosage or schedule.

It should be noted that a combination regimen of doxorubicin and a 3-hour schedule of paclitaxel may be associated with an unexpectedly high level of cardiotoxicity, possibly caused by a decrease in doxorubicin clearance by paclitaxel.[271]

4.2 Vinca Alkaloids

The vinca alkaloid class of antineoplastic agents are naturally occurring or semisynthetic compounds found in minute quantities in the periwinkle plant *Catharanthus roseus* C. Don.[272] The class consists of vincristine, vinblastine, vindesine and vinorelbine. Vindesine is a synthetic derivative of vinblastine and vinorelbine is a semisynthetic vinca alkaloid. Vincristine is primarily used for induction therapy in childhood acute lymphocytic leukaemia.[273] It has activity against Hodgkin's and non–Hodgkin's lymphoma, Wilm's tumour, Ewing's sarcoma, neuroblastoma and rhabdomyosarcoma.[272] Vinblastine is used in combination therapy for germ cell cancers of testes, advanced Hodgkin's disease, bladder carcinoma, breast carcinoma and Kaposi's sarcoma. Vindesine is commonly used in combination treatment of non–small-cell lung cancer. Vinorelbine has activity against advanced non–small-cell lung cancer and advanced breast cancer and ovarian cancer.

Autonomic cardioneuropathy has been associated with vincristine.[274] Vincristine can cause abnormal fluctuations in blood pressure because of its toxicity on the autonomic nervous system. Heart rate variability induced by deep breathing was significantly reduced by vincristine. This indicates that vincristine, through its effect on the autonomic nervous system, severely limits the vagal chronotropic control of the heart. Vinca alkaloids caused abnormal variations in heart rate during deep breathing, blood pressure and heart rate on standing in 82, 48 and 48% of patients compared with 30, 10 and 2% of patients not receiving vinca alkaloids, respectively.[274]

The most common cardiac adverse effect associated with all vinca alkaloids is myocardial infarction.[275-284] 25% of the patients studied in a large series of patients with malignant lymphoma had cardiac involvement, but only 10% of these had clinical manifestations.[285] However, myocardial

infarction may be a result of occult and ongoing ischaemic heart disease and not related to the malignancy or the chemotherapy. The signs and symptoms of cardiotoxicity involve severe precordial pain radiating to the back or the neck or shoulder, pulmonary oedema that manifests as shortness of breath, tachypnoea, gallop rhythm and widespread lung crackles.[275-284] Onset of myocardial infarction may range from a few hours to 3 days after the first dose or subsequent doses of the vinca alkaloids. The symptoms may last from 2 to 24 hours. It is usually reversible and may recur on subsequent doses. Myocardial infarction has been reported only with continuous infusion of vindesine.[282]

ECG changes are usually consistent with acute myocardial infarction, consisting of T wave inversions, ST segment depression or elevation depending on the leads, premature ventricular contractions and atrial fibrillation.[275-284] These ECG changes may return to normal within an hour to 10 days after the episode. Blood enzymes, specifically creatinine kinase, lactate dehydrogenase and AST, may be normal or elevated.[275-284]

The definite mechanism by which vinca alkaloids cause this cardiotoxicity is not known. They probably cause changes in a pre-existing atherosclerotic coronary vessel or anoxic myocardium and precipitate an acute myocardial infarction. It is also speculated that these agents may directly affect myocardial cells and increase their sensitivity to hypoxia, leading to an myocardial infarction.[279] A direct effect on the platelets or blood clotting mechanism resulting in coronary artery thrombosis has also been proposed as one of the mechanisms of cardiotoxicity.[279] However, *in vitro* and *in vivo* studies have not revealed any blood clotting abnormalities.[277] Another hypothesis used to explain this effect is the occurrence of an acute coronary artery spasm in response to the vinca alkaloids.[279-282] Release of vasoconstricting substances such as serotonin (5-hydroxytryptamine) from activated platelets has been speculated to be the cause of this event.

More data are needed to conclusively link onset of myocardial infarction to administration of vinca alkaloids and to clearly identify risk factors associated with this cardiotoxicity. A few case reports have proposed previous mediastinal radiation treatment and coexisting ischaemic heart disease as risk factors.[275-278] Patients with a history of an myocardial infarction should be initiated or continued on optimal antianginal medications. If patients experience a myocardial infarction, they should receive immediate care as discussed in sections 1.2.

4.3 Etoposide

Etoposide (VP-16) is a semisynthetic podophyllotoxin derivative effective in the treatment of small cell lung cancer, testicular cancer and lymphoma.[286] Cardiac events, including myocardial ischaemia and infarction, have been reported with the use of a combination regimen of cisplatin, vinblastine, etoposide and bleomycin.[163,278,287] Rapid etoposide infusions have resulted in hypotension in 1 to 2% of patients,[288-290] but can be avoided by infusing the drug over 30 to 60 minutes. If hypotension occurs, infusion should be stopped and fluids should be administered if necessary.

Patients may experience a heavy pressure sensation in the chest, marked hypotension, dyspnoea and chest pain.[291,292] These symptoms may occur during initial or subsequent infusions. ECG changes and elevated cardiac enzymes are consistent with an myocardial infarction. ECG changes may include T wave inversions reflecting acute inferior, posterior and posterolateral myocardial infarction. Echocardiograms performed 2 days after the episode have revealed a posterobasal hypokinesia.[291] Chest pain may last for several hours and cardiac enzymes may remain elevated for several days.

Etoposide-induced myocardial ischaemia has been suggested to be caused by several processes, including coronary artery spasm, direct injury to the myocardium, or an autoimmune response.[287,292] Coronary artery spasm may occur by release of vasoactive substances after administration of etoposide or by direct action of etoposide on the blood vessels. Patients with a history of cardiac disease,

mediastinal radiation or recipients of prior chemotherapy may be at an increased risk.[293] However, no clinical trials or retrospective studies have been conducted to identify such patients. Therefore, it is difficult to identify patients who may experience etoposide-induced cardiotoxicity. Patients should be clinically monitored during and immediately after the infusion. Chest pain should be evaluated for an evolving myocardial infarction and treated as discussed in section 1.2.

4.4 Teniposide

Teniposide (VM-26) is a semisynthetic podophyllotoxin similar to etoposide.[286] Cardiac events associated with teniposide administration include hypotension and arrhythmia.[294] Hypotension is transient and related to the rate of infusion. It may be due to the Cremophor EL component of the vehicle or to teniposide itself.[295] Rapid administration of teniposide has resulted in hypotension in 2% of paediatric patients. Arrhythmia is rare but may result in sudden death.

5. Miscellaneous Drugs

5.1 Amsacrine

Amsacrine (m-AMSA) is a synthetic antineoplastic aminoacridine derivative. Amsacrine has been evaluated in the treatment of numerous types of carcinoma; however, the best results have been obtained against acute nonlymphocytic leukaemia.[296]

Numerous cardiovascular abnormalities have been reported during amsacrine therapy. A detailed review of cardiac abnormalities associated with amsacrine has identified 65 cases of cardiotoxic events among 5340 amsacrine-treated patients.[297] 45 of these patients had received prior anthracycline therapy. The review was based on reports to the National Cancer Institute, Warner Lambert/Parke Davis and other published case reports. Five (0.7%) of the 683 chemotherapy-naïve patients developed arrhythmias and 2 (0.3%) had echocardiographic changes. A total incidence of amsacrine-related cardiotoxicity of 1% was observed in the chemotherapy-naïve patients. However, a number of phase II trials of amsacrine did not report any cardiac adverse events in their patients.[298-304] Therefore, cardiac abnormalities associated with amsacrine may represent a sporadic problem with low incidence.

Amsacrine may exhibit 2 forms of cardiac toxicity.[297] The more common cardiac toxicity is atrial and ventricular tachyarrhythmias and ECG changes. The rarer, but more serious, form is the development of cardiomyopathy and CHF. Cardiotoxicity may manifest as ventricular fibrillation, multiple ventricular extrasystoles, atrial tachycardia, atrial fibrillation resulting in cardiopulmonary arrest, hypotension, bradycardia and sudden death.[305-313] Of the 64 patients reviewed, 31 had serious ventricular arrhythmia, resulting in cardiopulmonary arrest and death of 14 patients.[297] Six of the 18 patients with CHF died.[297] ECG changes consisting of prolongation of the QT interval, nonspecific ST segment or T wave changes, ventricular tachycardia and atrial and ventricular fibrillation changes may occur within minutes to several hours after the administration of amsacrine.[297,305-314] These cardiac abnormalities have been temporally related to the infusion of amsacrine.[285] Cardiac arrests can occur as amsacrine is being infused or within 4 hours after completion of the infusion. Onset of failure may be within 36 hours of receiving amsacrine and up to 2 weeks after the course. These events may occur with the first dose or with the first course or subsequent courses of amsacrine. Therefore, cardiotoxicity due to amsacrine is believed to be acute without a cumulative dose effect. The ECG abnormalities may recur on repeat administration of the drug but are reversible within 24 hours after discontinuation of the infusion. Echocardiography has shown decrease in fractional shortening by an average of 33% compared with baseline.[315] The LVEF may decrease or remain the same.

The exact mechanism of amsacrine-induced cardiac abnormalities is not known. These abnormalities may be subtle and observed only when the patient is on a continuous cardiac monitor during

drug administration. However, since severe life-threatening arrhythmias are rare and may not necessarily occur only during drug infusion, continuous cardiac monitoring during and several hours after amsacrine administration may be unnecessary.

Several factors such as electrolyte abnormalities, mainly hypokalaemia, and previous anthracycline drug exposure can predispose patients to development of amsacrine-induced cardiac disorders. Prior treatment with anthracycline could increase the risk of amsacrine cardiotoxicity, since anthracyclines are a part of the standard treatment of acute leukaemia in patients receiving amsacrine. There is no strong evidence that prior anthracycline therapy increases the susceptibility to amsacrine cardiotoxicity. Some researchers believe that patients with >400 mg/m^2 of previous anthracycline therapy and receiving >200mg of amsacrine within 48 hours and those who have received a total of ≥900 mg/m^2 of anthracyclines and amsacrine may be at the highest risk of developing cardiac abnormalities.[315] However, phase I trials did not observe any cardiac abnormalities in patients who had previously received maximum doses of anthracyclines and were subsequently treated with high doses of amsacrine.[316]

Underlying cardiac disease and gender were not found to be risk factors for amsacrine-associated cardiotoxicity.[297] The number of paediatric patients among the 82 cases of cardiotoxicity due to amsacrine were greater than expected; 39% of the patients among the group having cardiomyopathy were <16 years of age. The number of children treated with amsacrine in relation to the total number of adults was not stated; thus, no definite statement about children being more susceptible to amsacrine can be made. Hypokalaemia has been suspected as a contributing factor for amsacrine-induced arrhythmia; 37% (14 out of 45) with serious abnormalities (frequent ventricular premature contractions, ventricular tachycardia/fibrillation or cardiopulmonary arrest) had hypokalaemia.[308,317] However, 63% (24 out of 45) of the patients with serious abnormalities had normal potassium. Since QT interval prolongation from amsacrine may trigger a potentially fatal arrhythmia in a patient with hypokalaemia, it is imperative that serum potassium be measured before and during amsacrine infusion.

Amsacrine is no longer available in the US since the investigational new drug application for amsacrine was closed by the National Cancer Institute. However, it may still be available in some European countries. There is no information about use of prophylactic agents to prevent amsacrine cardiotoxicity. Continuous cardiac monitoring is not necessary; however, serum potassium levels should be monitored daily before and during amsacrine therapy. Amsacrine-induced CHF should be treated as discussed in section 1.1.7. Arrhythmias should be monitored by a continuous 12-lead ECG and treated immediately following institutional or published[127] guidelines if patients develop serious clinical signs and symptoms.

5.2 Cladribine

Cladribine (2-chlorodeoxyadenosine) is a purine nucleoside antineoplastic agent primarily used in the treatment of hairy cell leukaemia. It rarely causes cardiotoxicity.[318-320]

Cladribine-induced cardiac failure was reported in a patient who received 0.1 mg/kg/day over 7 days for treatment of hairy cell leukaemia.[321] The patient had no family history of cardiac diseases, was a smoker and a moderate drinker, but was not taking any other medications during therapy. 17 days after start of treatment the patient developed acute dyspnoea and mild chest discomfort with rigors and anaemia. Physical examination revealed a new fourth heart sound. Radiography showed pulmonary oedema. Sinus tachycardia and right axis deviation was observed on ECG. A low probability for pulmonary embolism was observed on ventilation-perfusion scan. Global hypokinesis with an ejection fraction of 30% was noted on echocardiogram. The patient exhibited a moderate mitral regurgitation as well as tricuspid and pulmonary insufficiency. Cardiac enzymes were mildly elevated. The patient was treated with digoxin, captopril and diuretics with resolution of signs and symptoms. A

repeat nuclear gate blood pool scan at approximately 1 month revealed an ejection fraction of 54% and the cardiac medications were then stopped.

Viral and endocrine causes of this event were ruled out by performing acute and convalescent Coxsackie A and B titres and thyroid function tests. Alcoholic cardiomyopathy seems unlikely, since the event had an acute onset and resolution over time. Anaemia and fever may have increased stress but did not directly result in cardiotoxicity. Given the acute onset and transient duration, an unusual infectious agent or drug toxicity seem to be the plausible aetiology.

Cladribine cardiotoxicity is a rare acute toxicity only recorded as a single case report, raising questions about the potential of the drug to induce cardiotoxicity. Cladribine is closely related to adenosine. Phosphorylation of troponin I, a protein important in the contractile process of the heart, has been shown to be inhibited by adenosine and its derivative 5′-chloro-5′-deoxyadenosine in rats.[322] Adenosine is also known to inhibit the positive chronotropic and inotropic effect of catecholamines on the heart.[323]

5.3 Asparaginase

Asparaginase is an antineoplastic agent whose active principle is the enzyme L-asparagine amidohydrolase type EC-2, derived from *Escherichia coli*. It is primarily used in the treatment of acute lymphocytic leukaemia in children. It is also used in the treatment of various other types of leukaemia, lymphomas and solid tumours.[324-327]

Asparaginase may produce several haemostatic disorders leading to thrombotic complications. These may include reduction in fibrinogen levels, leading to increased bleeding time, and depletion of antithrombin III, protein C and plasminogen, leading to thrombosis.[328,329] Acute myocardial infarction is rarely associated with asparaginase. In a case report, a 21-year-old patient without any coronary risk factors was treated intravenously with 9000IU of asparaginase/day for acute lymphocytic leukaemia.[330] The patient had received 2 cycles of vincristine and doxorubicin. On day 14 of therapy the patient complained of severe chest tightness 11 hours after the last dose of asparaginase. ECG revealed ST segment elevation in the anterolateral leads consistent with an acute myocardial infarction. The symptoms resolved as the infusion was terminated and there was a marked improvement in the ECG. Creatinine kinase and its MB isoenzyme peaked at 8 hours after the onset of chest pain. The patient received the next cycle of chemotherapy without asparaginase and did not experience any cardiac events. Coronary angiography revealed patent epicordial coronary arteries but hypokinesis of the anterior wall and apex.

The onset of symptoms was temporally related more to administration of asparaginase rather than vincristine and doxorubicin, which were administered 7 days before the event and were administered subsequently without incident. Asparaginase–induced myocardial infarction is a rare event with only a single case reported.

5.4 Pentostatin

Pentostatin (2′-deoxycoformycin) is a purine analogue antineoplastic agent. It is primarily used in the treatment of hairy cell leukaemia and has been used in chronic lymphocytic leukaemia, cutaneous T cell lymphoma and indolent non–Hodgkin's lymphoma.[324,331,332] As the use of pentostatin has increased, more cases of cardiac complications have been observed. The cardiac events reported after the use of pentostatin can be divided into 3 groups: angina and myocardial infarction, CHF and acute arrhythmias.[333] A 3 to 10% incidence of cardiac events has been associated with pentostatin.[334] Cardiac symptoms manifest as chest pain along with nausea and vomiting. Arrhythmias may consist of atrial flutter, atrial fibrillation or extrasystoles. Patients may also experience tachycardia or bradycardia, an atrioventricular block and sinus or ventricular arrest. Cardiac symptoms may manifest within a week of receiving pentostatin and chest pain may last up to 8 hours. ECG changes may be consistent with a myocardial infarction, and creatinine kinase and its MB isoenzyme may be elevated.

There are no controlled trials identifying factors that may predispose patients to pentostatin cardiotoxicity. However, underlying coronary artery disease, CHF, hypertension and pulmonary metastases have been mentioned.[333] Addition of pentostatin to high dosage cyclophosphamide therapy for allogeneic bone marrow transplant may cause increased mortality due to cardiotoxicity.[335]

A specific metabolic pathway is believed to be inhibited by pentostatin. Pentostatin inhibits ATP metabolism by inhibiting adenosine deaminase.[336,337] Since myocytes greatly depend on ATP, pentostatin may induce cardiotoxicity by inhibiting ATP synthesis. Indirect effects, rather than the drug itself, are also suspected to cause cardiotoxicity. Pentostatin is more commonly used in the treatment of hairy cell leukaemia, which frequently occurs in adults with a history of cardiac disease. Administration of pentostatin also requires vigorous pre- and postchemotherapy hydration to prevent acute renal insufficiency and increase renal clearance of the drug. This, however, may lead to fluid overload in patients with decreased cardiac function. Such patients should be closely monitored for their volume status (fluid input and urinary output). Hairy cell leukaemia and chronic lymphocytic leukaemia, both treated by pentostatin, are commonly complicated by anaemia that may induce a cardiac event during treatment. Patients with a history of cardiac disorders and low haemoglobin level should be transfused before initiating pentostatin. Pentostatin-induced nausea and vomiting may contribute to cardiotoxicity and should be prevented.

5.5 Tretinoin

Tretinoin (all-*trans*-retinoic acid, ATRA) is a retinoid derivative of all-*trans*-retinol, a naturally occurring vitamin A_1. When used orally it induces remission in patients diagnosed with acute promyelocytic leukaemia.[338]

A number of cardiac events have been reported in patients receiving tretinoin orally to treat acute promyelocytic leukaemia. These include arrhythmias (23%), flushing (23%), hypotension (14%), hypertension (11%), and heart failure (6%).[339] Cardiac arrest, myocardial infarction, cardiomegaly, heart murmur, ischaemia, stroke, myocarditis, pericarditis, pulmonary hypertension and secondary cardiomyopathy were observed in 3% of this patient population.

'Retinoic acid syndrome' has been associated with tretinoin therapy in the treatment of acute promyelocytic leukaemia. This is most commonly due to tretinoin-induced leucocytosis and is characterised by fever, respiratory distress, bodyweight gain, lower extremity oedema, pleural and pericardial effusions and hypotension.[340] Disseminated intravascular coagulopathy and haemorrhage are the more frequent manifestations of acute promyelocytic leukaemia. It is believed that tretinoin therapy decreases the haemorrhagic tendency of the disseminated intravascular coagulopathy, but the procoagulation activity may remain the same.[341] Major thrombotic events have been reported with tretinoin therapy and the presence of retinoic acid syndrome or leucocytosis may increase the risk of thrombosis. Patients may report chest, flank and shoulder pain due to multiple infarcts in the lungs, liver, spleen and kidneys. They may be hypoxic and chest radiograph may be indicative of infiltrates, usually bilateral and basilar. Patients may develop a myocardial infarction.

Patients may need high dosage corticosteroid therapy to resolve the retinoic acid syndrome. Clinicians should be aware of the thrombotic events associated with acute promyelocytic leukaemia with or without tretinoin.

6. Conclusions

Cardiotoxicity is an adverse event associated with many chemotherapy agents. The potential for cardiotoxic events should be recognised before therapy is started so that measures can be initiated to prevent, monitor and treat such events. A number of risk factors may predispose a patient to certain chemotherapy-induced cardiotoxicities. These can be identified, monitored and possibly modified before initiation of chemotherapy so that cardiotoxicity can be prevented where possible.

This comprehensive review of the manifestations of cardiotoxic events should assist clinicians to monitor signs and symptoms of cardiotoxicity. ECG, echocardiogram, cardiac enzymes and electrolytes can be monitored to assess cardiac function and risk factors before starting the next course of chemotherapy. Various pharmacotherapeutic modalities can be used to treat cardiotoxicity. Cardiac function and the risks versus the benefits of continued use should be assessed to reduce morbidity and mortality associated with a cardiac event. Continuous cardiac monitoring should be considered in high risk patients.

Patients with a history of cardiovascular disorders being treated with cardiac drugs should continue on those medications during their chemotherapy. The drugs or dosages should not be altered during chemotherapy unless clinical signs and symptoms warrant such changes.

Delayed cardiotoxicity (years after completion of chemotherapy) has been seen only after anthracycline therapy. However, patients receiving any cardiotoxic agent should be followed after completion of treatment.

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