Postgrad Med J 1999;75:265–268 © The Fellowship of Postgraduate Medicine, 1999

Management options

Anthracycline-induced cardiomyopathy

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Summary
Anthracycline cardiomyopathy is less frequently encountered nowadays, due to the well-recognised dose limitations and cardiac monitoring protocols used by chemotherapy centres. However, it is a condition that will persist due to the sensitivity of some patients to these drugs and the necessity for large doses to be used for certain individuals. We have demonstrated the benefit of angiotensin-converting enzyme inhibitor therapy and would consider introducing these compounds at the earliest opportunity. The use of probucol and vitamins as antioxidants capable of preventing the onset of cardiomyopathy in humans appears to require further investigation but may significantly reduce the incidence of this condition in the future.

Keywords: anthracycline; cardiomyopathy

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Accepted 5 November 1998

Anthracycline therapy is known to be potentially cardiotoxic. The effects on the myocardium are predominantly dose-related and the incidence of this condition has declined in recent years, reflecting changing protocols. However, the problem still occurs up to 20 years after treatment[1] and the case report in the box on the next page highlights this condition. The aetiology, epidemiology, detection, prevention and treatment of anthracycline cardiomyopathy is discussed.

Anthracyclines

Anthracyclines (doxorubicin, daunorubicin, epirubicin, aclarubicin and idarubicin) are extremely important in the treatment of lymphomas, breast cancer and soft tissue sarcomas. They were discovered as fermentation products of *Streptococcus verticillus* and exert their cytotoxic activity by their ability to cause DNA fragmentation.

Mechanism of cardiotoxicity

The exact mechanism of cardiac toxicity is not known. However the most accepted mechanism is that of free radical formation and interference with the mitochondrial electron transport chain.[2] The heart is rich in mitochondria and has a relatively poor ability to rid itself of free radicals due to its reliance on the glutathione–glutathione peroxidase cycle[3]; it is therefore particularly vulnerable to free radical attack.

Epidemiology of cardiotoxicity

The incidence of congestive cardiac failure (CCF) with epirubicin is 0.7%, with a median cumulative dose of 660 mg/m^2.[4 5] Doxorubicin is more cardiotoxic than epirubicin and the incidence of CCF ranges from 3–4% with a cumulative dose of 450 mg/m^2 to 18% with a cumulative dose of 700 mg/m^2.[6–8] CCF usually develops within 9–192 days, with a peak incidence 1–3 months after the last dose.[9] Despite these relatively low figures of CCF the incidence of subclinical myocardial damage is much higher, even at lower doses.[10–12] It is difficult to predict which patients are likely to develop CCF and long-term follow-up of all patients is necessary, as the condition has been shown to manifest up to 20 years after treatment.[1]

Formerly, once patients had developed CCF the usual outcome was considered to be fatal in the majority of patients.[8] Subsequent studies have produced more encouraging results, however, indicating that improvement can be seen in up to 80% of patients.[13] In addition, there appears to be continued improvement seen when studies have followed patients in the subsequent four years.[12] These figures compare favourably with idiopathic dilated cardiomyopathy in which progressive deterioration is usually seen, with 75% of patients dying within 5 years.[14]

Detection of cardiotoxicity

Initially an endocardial biopsy was required for detection of anthracycline-induced cardiomyopathy[15] but recent studies using radioactive monoclonal antibodies against cardiac muscle, as well as the MIBG scan, have been able to provide virtually the same degree of information without requiring such invasive investigations.[16 17] However, the use of both of these investigations in daily practice is frequently not feasible, and the ejection fraction tends to be used as a baseline measure of myocardial function prior to treatment, and for early detection of cardiac damage post-treatment. The optimal investigation for measuring the left ventricular ejection fraction (LVEF) is the subject of some debate, with doctors divided between nuclear angiography and

Case report

In 1992, a 54-year-old woman was diagnosed as having stage 4 non-Hodgkin's lymphoma which was initially treated with six cycles of mitoxantrone 12 mg/m^2, chlorambucil, and prednisolone. By 1995 the lymphoma was found to be transforming to a higher grade and she underwent six cycles of cyclophosphamide, adriamycin 50 mg/m^2, vincristine and prednisolone (CHOP). By August 1996 progressive disease was found on computed tomography (CT) and, in preparation for a stem cell mobilisation and harvest, she received dexamethasone, arabinoside and cisplatin (DHAP). Although there was an insufficient yield from the harvest for a stem cell mobilisation there was a decrease in both her lymphadenopathy and systemic symptoms. However, by February 1997, there was clinical and radiological evidence of progressive disease and a further six cycles of CHOP were given. Cardiac ejection fractions prior to the DHAP and second CHOP were recorded as 65% and 56%, respectively. The total dose of anthracycline received was 669 mg/m^2. Following the sixth cycle of CHOP she was admitted with severe left ventricular failure. Her ejection fractions had now dropped to 33%. The failure was initially treated with frusemide but an attempt to introduce captopril resulted in a severe hypotensive episode. The results of the subsequent replacement with perindopril are shown in figure 1, and a comparison of her early and late echocardiograms is given in figure 2.

Despite the gradual improvement in her cardiac function, this patient finally died of her lymphoma in October 1997.

Figure 1 Change in ejection fraction with time as measured by echocardiography

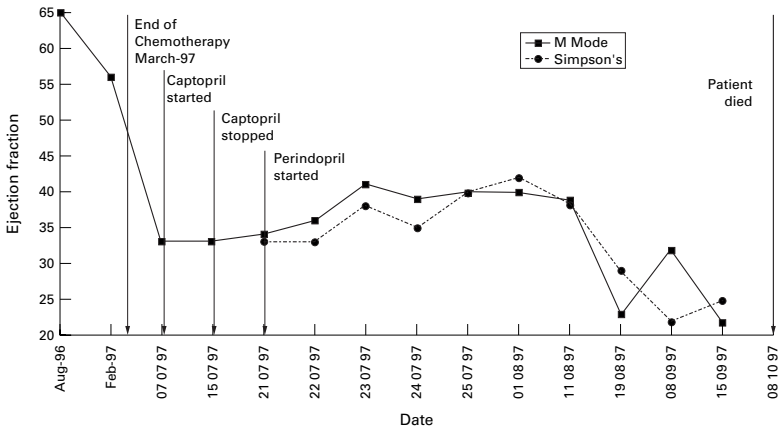
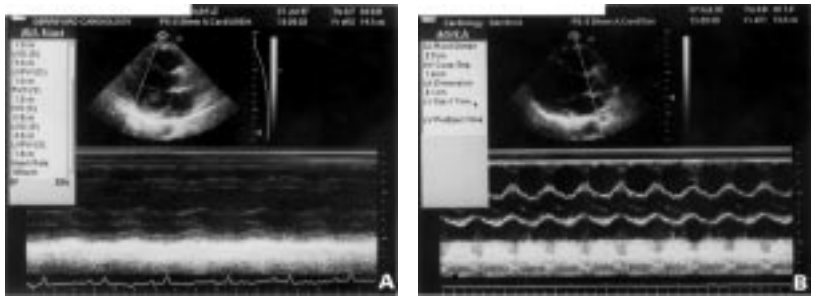


Figure 2 M-Mode echocardiograms taken before (A) and after (B) chemotherapy



Box 1

echocardiography. Two techniques using echocardiography are commonly used, the cubed technique with M-mode and secondly that produced from the use of Simpson's Rule. The cubed technique is the simplest method for measuring ejection fraction and assumes that the left ventricle is an ellipsoid, which is unfortunately frequently not the case in patients with cardiomyopathy. The volume is therefore calculated by cubing the diameter, and the ejection fraction can be calculated by subtracting the systolic volume from the diastolic volume. The computer-based calculation based on Simpson's Rule goes some way to reducing these errors. This assumes that the left ventricular volume is the sum of the volumes of a set of adjacent discs of varying depth and cross-sectional area. Several authors have found that the two correlate quite closely, especially when the echocardiologists used Simpson's technique.[17–19] Also, despite small differences, they show a linear correlation with changing LVEF. The most important factor, regardless of the method chosen, is the consistency of the measuring technique and every effort should be made to ensure that operators and equipment are the same throughout a patient's review period. Particularly important in this patient group is the presence of anaemia, as it is not uncommon for an anaemic patient to drop his LVEF more than 10% when the anaemia is corrected.[20] When these criteria are applied, changes in results due to operator error are kept to a minimum.

Prevention of cardiomyopathy

REDUCTION OF CUMULATIVE ANTHRACYCLINE DOSE

There is little doubt that cardiac damage is related to total cumulative dose, with those receiving more than 400 mg/m^2 being at significant risk.[21] There is also evidence of a cumulative affect with other chemotherapeutic agents, leading to severe and fatal cardiotoxicity even at doses below 400 mg/m^2.[22] Mediastinal irradiation appears to lower the cumulative dose necessary for the development of cardiotoxicity, and hypertension also appears to potentiate the development of adriamycin cardiotoxicity at lower doses.[23] Children are especially susceptible with those under 4 years of age being in greatest danger.[24] There is also evidence that females are more likely to develop late cardiotoxic events[25] and patients over 60 years have been found to have a four-fold greater risk of developing CCF than patients of 39 years.[21]

IRON CHELATORS AND ANTI-OXIDANTS

The iron chelator ICRF-187 has been shown to reduce oxygen free radical production and reduce the severity of cardiomyopathy in dogs but is associated with an increase in haematological toxicity.[26] Vitamins C and E are powerful anti-oxidants and in mice vitamin E offered some early protection against the development of acute cardiotoxicity, although it did not appear to reduce long-term mortality.[27 28] Vitamin C has significantly increased the lives of animals treated with adriamycin[29] and there is likely to be a synergistic benefit when vitamins E and C are given together. Further studies with these vitamins are awaited.

The lipid-lowering drug probucol has now been replaced in this role by the more effective HMG Co-A reductase inhibitors. However, it also has anti-oxidant properties, and in rats it appears to offer complete protection against adriamycin-induced cardiomyopathy without interfering with the drug's anti-tumour properties.[30] No trials in humans have to date been reported.

SERIAL MONITORING OF EJECTION FRACTION

Schwartz *et al* have demonstrated that serial monitoring of resting LVEF using serial radionuclide angiocardiography significantly reduces the incidence of clinical congestive cardiac failure when a few simple rules are applied.[13] In their study, 1487 patients receiving doxorubicin chemotherapy were divided into two groups according to whether their LVEF was above or below 50%. Patients with LVEF below 30% were considered unfit for doxorubicin chemotherapy. The two groups were then treated as shown in box 2. Chemotherapy was stopped when LVEF fell >10% or reached 30%.

There is obviously a need for continued echocardiographic observation in order to detect those patients who go on to develop late onset cardiomyopathy. There are no firm guidelines on the timings of this follow-up, but with the knowledge that the majority of complications will occur in the first year, and are more frequent in those with abnormal echocardiogram results at the end of treatment,[31] a suitable plan can be tailored to individual patients. The time interval between each review should also be adjusted with the knowledge that once the LVEF starts to fall it can do so precipitously.[32]

treatment of cardiomyopathy

The traditional approach to left ventricular failure has been frusemide and digoxin, with the latter being more popular in the US. A recent study has shown that the addition of enalapril or ramipril to this combination in patients with epirubicin-induced cardiomyopathy resulted in an increase of LVEF from 18–30% to near normal.[33] Research is currently investigating the benefit of angiotensin-converting enzyme (ACE) inhibitors immediately after cessation of chemotherapy. The use of ACE inhibitors in conjunction with chemotherapy is yet to be addressed.

Another promising treatment is the selective beta-1 antagonist metoprolol. Okamoto *et al* achieved an increase in LVEF from 33–50% in a patient with daunorubicin-induced cardiomyopathy by titrating the dose from 5 to 40 mg/day over a 2-month period.[34]

If the patient recovers from the malignancy for which the chemotherapy is being given, heart transplantation is a possible option and there are well-documented reports of children and young adults remaining well and in continued remission at least 3 years after transplantation.[35] Transplantation centres will normally expect the patient to have been disease free for at least one year[36] and the importance of improved medical therapy remains, as the majority of patients who are going to develop cardiomyopathy will have done so well within this time scale.

Rules for LVEF measurement in patients receiving doxorubicin chemotherapy

- LVEF > 50%: LVEF repeated 3 weeks after receiving total cumulative dose of 250–300 mg/m^2 and 450 mg/m^2 (400 mg/m in patients with ischaemic heart disease, radiation exposure, abnormal electrocardiogram or previous cyclophosphamide therapy) Thereafter LVEF is repeated prior to each dose
- LVEF < 50%: LVEF is repeated prior to each dose

Box 2

We are grateful to Dr Prentice, Consultant Haematologist, for allowing us to describe his patient in this review.

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