

Cardiovascular Topics

The effect of anthracyclines on myocardial function in 50 long-term survivors of childhood cancer

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Summary

Anthracyclines, which are effective in the treatment of childhood cancer, are known for their cardiotoxicity. In this study, with a mean follow-up of 116 months, the adverse effects of anthracyclines on conduction and myocardial function were evaluated by means of electrocardiography and echocardiography. ECG abnormalities, present in 2 patients, were nonspecific ST-segment and T-wave changes; cardiac function was normal. Echocardiographic abnormalities were present in 1 patient. He had a shortening fraction of less than 25% and presented in cardiac failure.

Cardiotoxic effects of anthracyclines used in doses according to standard treatment protocols were minimal in this long-term follow-up study. Routine ECG and echocardiography in asymptomatic patients during long-term follow-up are not indicated when an anthracycline dose of less than 450 mg/m² has been used and concomitant radiotherapy has not been administered.

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Anthracyclines are glycoside antibiotics¹ used as effective antineoplastic agents in many childhood malignant diseases including acute lymphoblastic leukaemia.² Their antineoplastic action is exerted by inhibition of nucleic acid synthesis, preventing normal function of RNA and DNA polymerases.¹

One of the main side-effects of anthracyclines is cardiotoxicity.³ These toxic effects manifest as nonspecific electrocardiographic abnormalities (ST-segment and T-wave changes), arrhythmias^{4,5} and cardiac failure due to the development of dilated cardiomyopathy.^{6,9} The toxic effects can be dose-dependent or independent of dose and are classified as early or late.^{4,7} Early toxicity which affects the myocardium is usually dose-dependent, and is characterised by left ventricular diastolic dysfunction followed by left ventricular systolic dysfunction. In time progressive left ventricular free wall thinning and dilatation occur with loss of ventricular function (cardiomyopathy).^{6,9} These effects may only manifest long after cessation of treatment. Cyclophosphamide and radiation therapy may also damage the myocardium and potentiate the toxicity of anthracyclines.¹⁰

The aim of this study was to evaluate the possible adverse effects of anthracyclines on myocardial function in long-term survivors of childhood cancer in southern Africa.

Patients and methods

The patients were part of a prospective study to measure late effects of treatment in 108 long-term (> 5 years) survivors

of childhood cancer. All had been treated at Tygerberg Hospital between 1973 and 1992 by authors P.B.H. and G.W. All 50 children who had received anthracyclines for various neoplastic conditions were included in the study. The diagnosis, age, weight and height at diagnosis, age at follow-up, cumulative anthracycline dose and presence of ECG and echocardiographic changes were recorded. Myocardial function was evaluated with M-mode and two-dimensional echocardiography. Measurements recorded included left ventricular end-diastolic diameter (LVED), free wall thickness, the shortening fraction (SF) and the ejection fraction (EF). The LVED is an expression of ventricular dilatation, while the SF and EF are parameters of function. No exercise testing was performed.

All children had received standard international treatment protocols. These include BFM protocols for acute lymphoblastic leukaemia (ALL)¹¹ and acute myeloid leukaemia (AML),¹² CLVPP, MOPP and/or ABVD with low-dose involved field radiotherapy in Hodgkin's disease (HD),^{13,14} LSA2-L2 in lymphoblastic lymphoma,¹⁵ COMP in B-cell and other non-Hodgkin's lymphoma (NHL),¹⁵ surgery and radiotherapy for brain tumours, NTWS 3¹⁶ and later SIOP 9 in Wilms' tumour,¹⁷ and a St Jude protocol in neuroblastoma.¹⁸

Results

The male/female ratio was 1.4:1.1. The mean duration of follow-up of the 50 patients was 116 months (range 60 - 268

months). The average cumulative dose of anthracyclines for the whole group was 266 mg/m² (range 60 - 480 mg). The mean cumulative anthracycline dose for each specific treatment group (e.g. leukaemia), mean age at diagnosis, mean age at evaluation, and number of abnormal ECGs and echocardiograms are summarised in Table I.

An ECG was done in 46 patients (92%). ECG abnormalities were present in 2 male patients. One had nonspecific flattening of the T waves in leads V4 - V6 (Fig. 1) and the other nonspecific ST-segment flattening and T-wave inversion in the inferolateral leads (Fig. 2). These patients had received a cumulative anthracycline dose of 240 mg/m² and 360 mg/m², respectively.

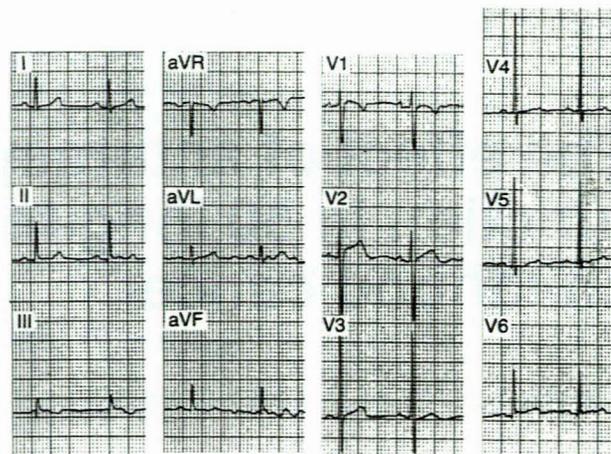


Fig. 1. ECG shows flattening of the T waves in V4 - V6.

TABLE I. DIAGNOSTIC GROUPS WITH ANTHRACYCLINE CUMULATIVE DOSE, AGE AT DIAGNOSIS AND MEAN AGE AT FOLLOW-UP

Diagnosis	No.	Mean cumulative anthracycline dose (mg/m ²) (range)	Mean age at diagnosis (mo.) (range)	Mean age at follow-up (mo.) (range)	ECG changes (46 patients)	Echocardiographic changes (50 patients)
ALL	22	225.2 (60 - 240)	66.7 (19 - 74)	189 (92 - 314)	1	0
Neuroblastoma	8	218.8 (210 - 280)	23.9 (5 - 55)	125 (67 - 167)	0	0
Hodgkin's disease	6	300	127.8 (56-175)	242.7 (177 - 299)	0	1
NHL	3	274.3 (223 - 300)	95.3 (33 - 154)	233 (217 - 268)	0	0
AML	2	400	120 (92 - 148)	200 (169 - 231)	0	0
Liver cancer	2	360	71.5 (19 - 124)	147 (85 - 209)	1	0
PNET	2	365 (280 - 450)	90 (6 - 174)	197 (118 - 276)	0	0
Wilms' tumour	1	250	44	108	0	0
Germ-cell tumour	1	480	168	320	0	0
Nasophar. carcinoma	1	336	129	196	0	0
Osteosarcoma	1	360	105	253	0	0
Rhabdo-myosarcoma	1	300	27	293	0	0

PNET = primitive neuro-ectodermal tumour.

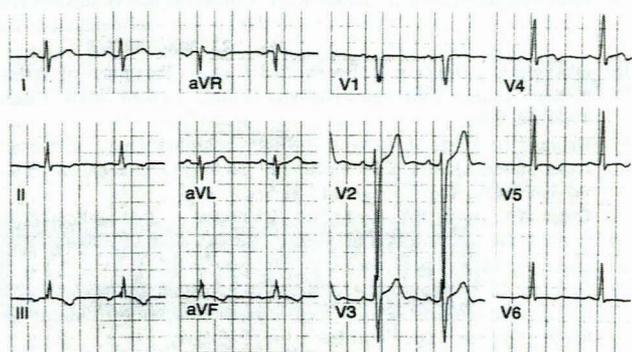


Fig. 2. ECG shows nonspecific intraventricular conduction delay, ST-segment flattening and T-wave inversion in leads II, III, aVF and V4-V5.

Echocardiography was performed in all patients. One boy had an SF of less than 25%. He had received anthracycline 300 mg/m² (ABVD) and abdominal irradiation (40 gy) for primary treatment of Hodgkin's disease. He relapsed and received additional non-anthracycline-containing chemotherapy and mediastinal irradiation (34 gy). He is currently on treatment for cardiac failure.

Thirty-two per cent of the children had a weight-for-height index (body mass index) below the 5th percentile before the start of treatment, while only 10% had a body mass index below the 5th percentile at follow-up.¹⁹ The 3 children with ECG and echocardiographic abnormalities were above the 5th percentile for weight at diagnosis. The boy with the EF of 45% was below the 5th percentile for weight at follow-up.

Discussion

To understand anthracycline-induced cardiotoxicity, a basic knowledge of cardiac development and function is necessary. Cardiac development begins in the 3rd week of fetal gestation. By the postnatal age of 6 months, the total adult number of myocytes are present and growth subsequently only occurs by an increase in size of the existing myocytes. After the age of 6 months myocytes that die are replaced through fibrosis. Synchronised contraction of the myocytes is caused by the interaction of electrical impulses which create the action potential necessary to release calcium from the sarcoplasmic reticulum so that cross-bridging, and therefore contraction, can take place. After contraction has taken place the myocytes must return to their resting state in order for the cycle to repeat itself.¹⁰

Cardiomyopathies caused by anthracyclines and irradiation impede the return of myocytes to the resting state, and therefore decrease diastolic compliance.¹⁰ Anthracyclines also interfere with calcium homeostasis by injuring the mitochondria, sarcoplasmic reticulum and sarcolemma. These events lead to death of the myocyte, which is replaced by fibrosis, while the non-affected myocytes undergo hypertrophy to maintain cardiac output.¹⁰

The effects of anthracycline cardiotoxicity can be divided into three groups: (i) direct damage to the myocardium; (ii) arrhythmias; and (iii) effects on the con-

duction tissue. These may occur during (early effects) or after (late effects) treatment with anthracyclines. Some of the adverse effects are dose-dependent and others are not. Von Hoff *et al.*²⁰ reported that early congestive cardiac failure developed in about 30% of patients who received anthracyclines at a cumulative dose of over 550 mg/m² and in only 0.01 - 0.27% of patients who received less than 550 mg/m². Four hundred and fifty milligrams per square metre body surface is therefore recommended as a safe upper limit.^{21,22}

Lipshultz *et al.*⁹ found slightly elevated age-adjusted afterload in 17% of patients who received a single 45 mg/m² dose of doxorubicin. Cardiac functional abnormalities were present in 23% of survivors of acute lymphoblastic leukaemia who had received more than 228 mg/m² doxorubicin.²³ Smaller doses of anthracyclines can lead to cardiac dysfunction which can only be elicited by exercise.^{24,25} The toxic effects of anthracyclines may be potentiated by cyclophosphamide and thoracic irradiation.¹⁰

In a prospective study of 201 patients treated with anthracyclines, Steinherz²⁵ found that none of his patients had an SF of less than 20% at 4 - 6-year follow-up, but at 10-year follow-up 33% of patients had an SF below 20% and over 50% an SF of below 25%. None of our patients had an SF below 20%, and only 1 patient an SF below 25%. The only patient who presented with cardiac failure (EF 45%) had received a cumulative anthracycline dose of 300 mg/m² and abdominal irradiation (40 gy) for primary treatment of Hodgkin's disease. He suffered a relapse which was successfully treated with non-anthracycline-containing chemotherapy and 34 gy mantlefield irradiation.

Conclusion

The cumulative dose of anthracyclines given during standard treatment protocols caused minimal long-term effects in South African children. One-third of the children tested were poorly nourished, with a low body mass index at diagnosis. The only child with definite cardiac decompensation had received additional chemotherapy and mediastinal irradiation when his Hodgkin's disease had relapsed.

Jakacki *et al.*²⁶ proposed an algorithm based on an abnormal electrocardiographic shortening fraction, ECG and history in order to determine which children need radionuclide imaging of the heart to identify cardiac damage following anthracycline therapy. The only child in this study who would qualify for further investigation would be the boy who already had obvious cardiac damage and severe exercise intolerance. It is possible that sophisticated investigations might have detected more subtle evidence of cardiac damage.²⁷

Our data do not support the routine performance of ECG and echocardiography during long-term follow-up in asymptomatic patients who have received a cumulative anthracycline dose of less than 450 mg/m². Regular assessment of cardiac status is, however, warranted in children who have received both anthracyclines and radiotherapy to the chest.

The use of expensive newly developed cardioprotective drugs such as ICRF187 and liposomal daunorubicin is difficult to justify in poor countries when anthracyclines are used within the recommended safe dosage limits.²⁸⁻³⁰

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