Title : Chemotherapy related cardiotoxicity – Are Australian practitioners missing the point?

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Abstract

Background It has long been established that cardiotoxicity occurs as a result of exposure to certain chemotherapeutics, particularly anthracyclines. Historically, clinicians equate cardiotoxicity with a poor prognosis, in a small percentage of patients and deem long-term surveillance as optional. Emerging evidence suggests that anthracycline cardiotoxicity (ACT) is a life-long risk with an incidence approaching 20%.

Methods Participants were identified via the Haematology-Oncology (HO) database at the Royal Children's Hospital, Melbourne. Patients were identified from a retrospective audit of outpatient attendances between January 2008 - December 2015. Patients with a cancer diagnosis exposed to anthracyclines were eligible for the study. Patient demographics and echocardiogram findings were recorded with patients subcategorized according to degree of ACT. More significant ACT defined as fractional shortening < 24% and less significant if FS 24-28% or a decline in baseline ejection fraction of > 10%.

Results : 286 of a total 481 identified patients were eligible for study inclusion. Twenty patients displayed significant ACT with FS < 24 %. Ten patients had a FS 24-28 % and 25 patients with a decline in EF from baseline of >10 %. Overall, 6.6% demonstrated significant cardiac complications, whilst 19.6 % demonstrated some degree of ACT and decline in myocardial function. When stratified for cumulative anthracycline dose, the incidence of severe cardiac dysfunction was 5.1 % (< 250 mg/m^2) and 25 % (>250mg/m^2)

Conclusion This study demonstrates, in keeping with modern literature, the higher incidence of anthracycline associated cardiac toxicity and a need for better surveillance and follow-up.

Key Words Anthracycline cardiotoxicity, cancer, childhood cancer, echocardiography, late-onset cardiotoxicity, cardio-oncology, adolescent and young adults

Chemotherapy related cardiotoxicity – Are Australian practitioners missing the point?

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Introduction

It has long been established that cardiotoxicity can occur as a direct result of exposure to chemotherapy. Although many chemotherapeutic agents are cardiotoxic, most of the research to date has focused upon anthracyclines.[1] Despite being extremely effective, this drug class carries a significant risk of cardiomyopathy. In trial settings, symptomatic heart failure occurs in 2-5 % of patients treated with anthracyclines, whilst heart failure incidence may be as high as 20 % less controlled patient populations over extended extended follow-up[2]. Anthracycline-induced cardiomyopathy is associated with a particularly poor prognosis, with a two year mortality approaching 60 %.[3] Clinicians worldwide have generally accepted the need to protect against anthracycline cardiotoxicity (ACT) by limiting dose exposure, extending infusion time, or using prophylactic therapies such as angiotensin converting enzyme inhibitors, beta blockers or dexrazoxane.

As cancer survivorship has improved with advancing therapies, late cardiovascular (CV) side effects have become an important management issue, particularly in childhood cancers, lymphoma, leukaemia and breast cancer. For example, CV disease is now the major cause of mortality in patients diagnosed with early stage breast cancer, as these patients have longer cancer free survival, are older at diagnosis and develop chemotherapy specific side effects.[4] The impact of a higher incidence of ACT within the paediatric cancer cohort of survivors is profound given the increasing success of therapy within the age group and large survivorship numbers.

However, for many clinician's cardiotoxicity is thought to portend a poor prognosis in only a small percentage of patients and surveillance for ACT is not necessarily routine for cancer survivors, particularly if there is no documented cardiotoxicity at the completion of chemotherapy. We performed a retrospective cohort study of paediatric cancer patients exposed to anthracycline at our tertiary paediatric institute, to compare the incidence of ACT at our institute with previously published data.

Methods

Study Protocol: Study participants were identified via the Haematology-Oncology (HO) database at the Royal Children's Hospital, Melbourne. Patients were identified from a retrospective audit of outpatient attendances between January 2008 - December 2015. To be eligible for the study, patients had to be diagnosed with a paediatric cancer and exposed to anthracyclines. Patients with pre-existing cardiac abnormalities were excluded from the study, as were patients without a baseline echocardiogram. Patients deceased at the time of the audit were also excluded.

Once the cohort was identified, patients were screened for ACT by recording left ventricular function as measured by echocardiogram. Ejection fraction was measured using the biplane Simpson's method. Guidelines at our institute suggest baseline echocardiogram for all patients exposed to anthracyclines. Follow up is according to protocols or if not enrolled on protocols performed at clinician discretion. To exclude transient acute cardiotoxicity, only echocardiograms obtained 21 days or more after a dose were used. Demographics were recorded for each patient. Cumulative anthracycline doses were calculated using doxorubicin equivalents.[5] This study was approved by the ethics committee of the involved institute (HREC 35102D)

Endpoints: The main study endpoint was ACT. ACT was grouped according to fractional shortening with more significant ACT defined as (FS) was < 24 %. Further, less significant ACT, was defined as either a FS 24-28 % or a drop in baseline left ventricular ejection fraction (LVEF) of > 10 %. Patients without ACT (non-ACT) were those defined as having normal echocardiogram findings (FS > 28 % and without decline of > 10 % EF from baseline).

Statistical Analysis

Statistical analysis was performed using Stata 14.1. Age at survey, cumulative equivalent anthracycline dose and follow-up were not normally distributed: Wilcoxon-Mann-Whitney test was used. For gender, anthracycline type, tumour type and radiotherapy involving heart Pearson Chi squared test was used if the expected value in all cells was greater than 5, otherwise Fisher's exact test was used.

Results

Patient characteristics

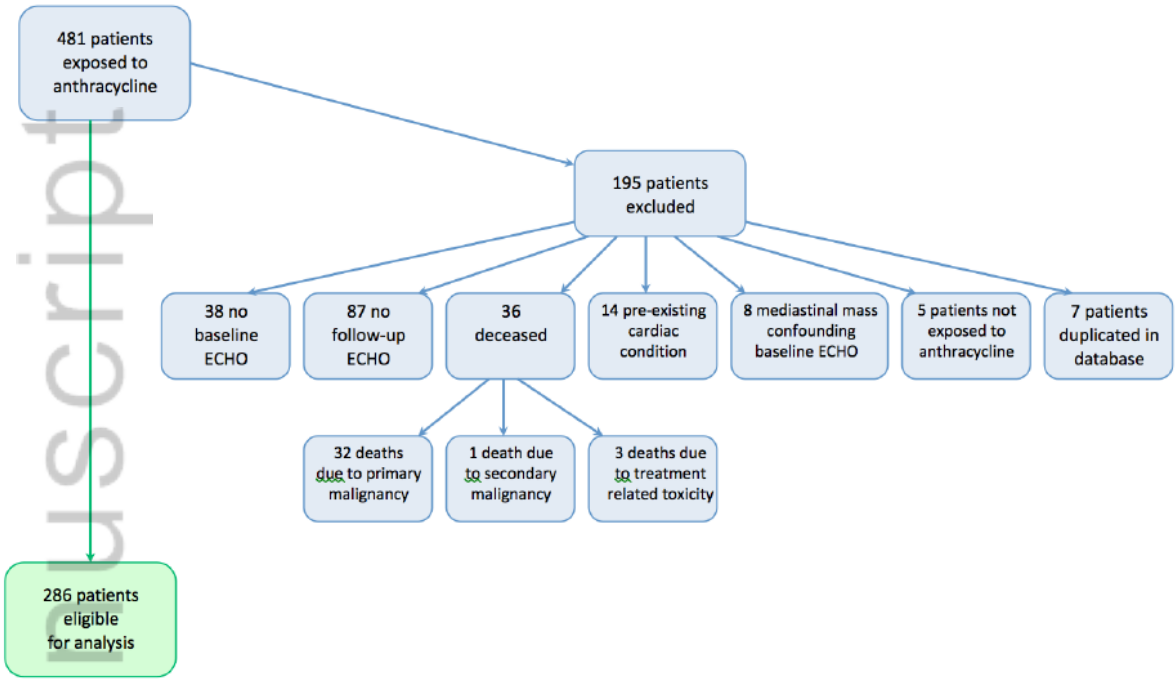

Figure 1: A total of 481 patients were identified from the HO database to have been exposed to anthracycline as a result of a cancer diagnosis. Of these patients, 38 (7.9 %) were excluded as no baseline echocardiogram (ECHO) had been performed. A further 87 (18.1 %) patients were excluded as no follow-up ECHO had been performed at the time of the audit. Eight (1.6%) patients were excluded because of pre-existing heart conditions. Fourteen (2.9 %) patients were excluded because the initial ECHO provided a poor baseline attributable to a mediastinal mass. There were 36 (7.5 %) patients deceased at the time of the audit and therefore excluded from study. Of these 36 deceased patients, 32 deaths were attributable to the primary malignancy, 1 to a secondary malignancy and 3 patients died as a result of treatment-related toxicity. In addition, 5 (1%) patients were excluded because they had not been exposed to anthracycline and 7 (1.5 %) were excluded due to duplication on the database. Therefore, a total of 286 patients were eligible for analysis.

Demographics for each patient were recorded along with their echocardiogram results. Patients with evidence of cardiotoxicity (ACT) and without cardiotoxicity (non-ACT) are compared in Table 1. Female patients were disproportionately represented amongst the ACT group (52% female and 48% male in ACT vs. 43% female and 57% male in the non-ACT group, p=0.224). Leukaemia, both acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL), were the most common diagnoses in both cohorts (69.8 % controls, 63.1% cases). In the ACT group there was a higher number

of patients with Ewing's Sarcoma (8.8 % v 2.1 %), Non Hodgkin lymphoma (7.0 % v 4.3 %) and AML (15.7 % v 2.6 %). The cumulative anthracycline dose was significantly higher in the ACT group (median 180.25 mg/m^2) compared with controls (129.9 mg/m^2, p = 0.004). The most common anthracycline exposure was doxorubicin in both the controls (68.1 %) and cases (46.5 %). The combination of doxorubicin plus daunorubicin, seen frequently in the ALL treatment, was distributed evenly between ACT (29.8 %) and non-ACT (21.4%). There was also a difference in radiotherapy involving the heart between ACT (8.9 %) and non-ACT (2.6 %) although this did not meet statistical significance (p = 0.66) Follow up, since completion of therapy was 48.5 months (cases) and 37.3 months (controls) with ranges of 11-138 months and 5-117 months respectively.

Anthracycline Cardiotoxicity

The echocardiographic findings according to cumulative dose anthracycline are summarized in Table 2. A total of 20 ACT displayed a FS < 24 %. Furthermore, 10 ACT patients had a FS 24-28 % and a further 27 patients had a decline in EF from baseline of >10 %. Overall, 6.9 % of the entire cohort demonstrated a FS < 24%, whilst 19.9 % had a FS < 28%. Of the ACT patients 21 (37%) had a decline in LVEF to < 50%. When stratified for cumulative anthracycline dose, the incidence of more significant cardiac dysfunction (FS <24%) was 5.1 % for those patients with cumulative anthracycline exposure < 250 mg/m^2 and 25 % for patients with cumulative anthracycline exposure 250 mg/m2 - 400 mg/m^2 (data not shown). Only 4 patients had exposures of > 400 mg/m^2 of which one (25%) had a FS < 24% . A total of 4 patients commenced protective cardiac medications including ace-inhibitors and beta blockers of which 3 were symptomatic of their cardiotoxicity.

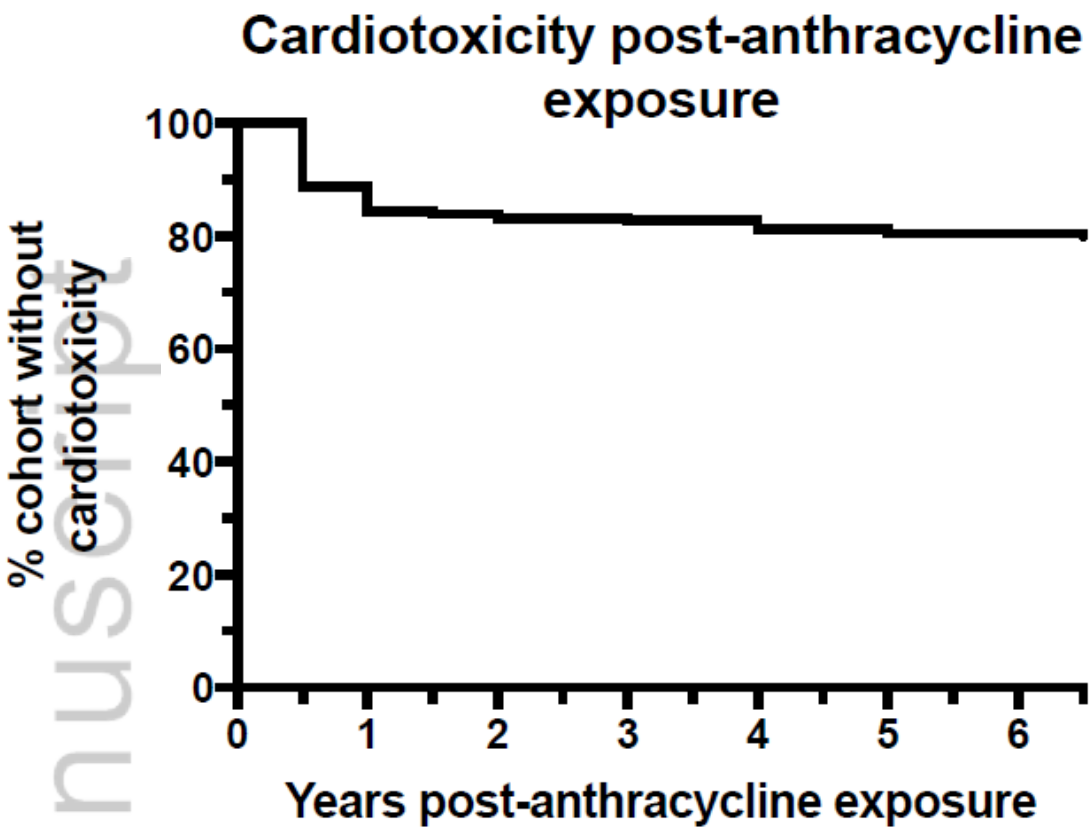

Figure 2 - Timing to development of cardiotoxicity post-anthracycline exposure. At 6.5 years following anthracycline exposure 57 (19.9 %) patients out of the cohort of 286 had developed ACT with abnormal findings on ECHO and 229 (80.1 %) remained without any abnormal findings on ECHO. Within 6 months of anthracycline exposure 32 (11.2 %) patients had developed ACT. Therefore, more than half of the 57 cases developed ACT in the short term with the other half arising over the course of 6 years. The rapidity of onset of ACT did not correlate with the severity of ACT.

Discussion

The findings of this study demonstrate that, in keeping with some of the more contemporary adult literature, the incidence of cardiotoxicity in anthracycline exposed patients is significantly higher than originally thought, with nearly one in five patients demonstrating evidence of cardiotoxicity. This incidence may be under-reported given that 7.9 % of the original cohort was excluded for lack of baseline echocardiogram and a further 18.1 % were excluded due to inadequate imaging at the time the data was audited.

The initial large retrospective studies in the late 1970's (n=4000) reported a 2.2 % incidence of clinical heart failure[2] and identified risks associated with cardiotoxicity including cumulative dose and radiation therapy. Additional risk factors noted at the time included younger age, short infusion times, and female

sex.[6] Subsequent reports found that up to 50 % of patients exposed to anthracyclines will show some degree of cardiac dysfunction 10-20 years after chemotherapy with 5% of them developing overt heart failure.[7] Contemporary evidence provided by the Surveillance, Epidemiology and End Results (SEER) Medical Database in the USA, reflecting a cancer cohort treated between 2002-2007, reports a heart failure incidence rate of 18 %.[8] Overall childhood cancer survivors are at a 15-fold[9] increased risk of developing congestive heart failure and of concern are 7 times more likely to have a premature death secondary to these cardiac causes.[2,10]

Cumulative anthracycline dose has previously been shown to be a strong independent risk factor for ACT. Our study has shown some evidence of dose dependence with the median cumulative anthracycline dose in the ACT group being greater than that in the non-ACT group (180 mg/m^2 vs. 129.9 mg/m^2, p = 0.004.). This finding is in keeping with a recent study that revealed exposures of 250 mg/m^2 or more have higher rates of cardiomyopathy.[11] Previous studies have reported the incidence of congestive heart failure to be 5 % for cumulative anthracycline doses < 250 mg/m^2, 10 % for 250 – 600 mg/m^2 and 30 % for doses > 600 mg/m^2.[9,12-14] In our study, the incidence of more significant cardiac dysfunction with fractional shortening < 24 % was 5.1 % for those patients with cumulative anthracycline exposure < 250 mg/m^2 and 25 % for those patients > 250 mg/m^2. The higher reported incidence of significant cardiac abnormalities may reflect the relatively small cohort size, but warrants further investigation.

For paediatric patients an increased incidence of ACT is particularly important. Paediatric patients diagnosed with cancer at < 15 years of age have an overall survival of 80 %.[8] This statistic is reflected in the 325,000 survivors of childhood cancer currently in the United States. Recent studies from the Children's Oncology Group report an incidence of symptomatic heart failure of 7%.[13] The majority of these patients have been treated with anthracyclines, leading to permanent or irreversible cardiac damage.[13] Beyond symptomatic cardiac failure is a large proportion of patients who are asymptomatic of their cardiac morbidity. The true incidence of asymptomatic cardiac complications is not well documented and the appropriate screening method for this group undetermined.[10] Our findings are consistent with those of Lipshultz *et al* who observed left ventricular dysfunction in 6.8 % of cancer survivors within 6 years of follow-up.[12] In addition, a recent study from St Judes Research Hospital with 1853 adult survivors of childhood cancer exposed to anthracycline therapy at least 10 years prior demonstrated 7.4 % of patients had cardiomyopathy with nearly all patients being asymptomatic of disease.[11]

The observed rates of cardiac dysfunction and heart failure amongst childhood cancer survivors highlights the need for focused cardiovascular surveillance. Physicians need to be aware of cardiac

complications and their incidence in light of modern therapy. It has been reported that physicians' understanding of late-effects of therapy for patients is not always accurate and often poorly communicated to patients. Currently, the recommendations in our institute are to follow the Children's Oncology Group's (COG) Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers.[16] These guidelines were developed from an expert clinical consensus incorporating best medical evidence at the time of their collation. These guidelines support screening LVEF function with imaging every 1-5 years which has been found recently to be cost effective across a range of modalities.[17] More recently, a harmonisation of the COG, Dutch Children Oncology Group (DCOG), Scottish Intercollegiate Guidelines Network (SIGN) and United Kingdom Children's Cancer and Leukaemia Group (UKCCLG) has been published.[18] These guidelines recommend screening within 2 years of the last anthracycline exposure and then, at a minimum, every 5 years thereafter. The rationale for screening is that early instigation of heart failure therapies (ACE inhibitors and beta-blockers) can delay the onset of congestive heart failure.[19] The recommendations are for life-long screening.

Despite the reported incidence of cardiac abnormalities, the adherence to follow up recommendations only occurs in ~28 % of childhood cancer survivors enrolled upon trial in the United States.[20] This poor adherence to follow up can reflect a lack of understanding of a patient's individual risk and the need for periodic screening.[21] The lack of recognition amongst treating physicians may relate to the tools used for screening. Adult physicians often use MUGA scans to assess LVEF, and current MUGA techniques may not be as effective as in the initial trials.[17] Of importance, MUGA scans have a significant radiation exposure (up to 8 mSv) and do not report upon atrial pressures, right ventricular measurements or the pericardium.

Anthracyclines are the best documented cardiotoxins but other agents have been associated with acute and delayed heart failure as well as other cardiac abnormalities. Bradycardia has been cited with paclitaxel with incidences ranging from 0.1-30%.[22] Arrhythmias and QT prolongation have been reported with amsacrine,[23] arsenic trioxide (26-94 %),[24] alkylating agents,[25] tyrosine kinase inhibitors (TKI) dasatinib, imatinib, nilotinib[26] and anthracyclines.[27,28] Myocardial ischaemia has been reported with anti-metabolites (5-FU), paclitaxel and newer agents such as monoclonal antibody bevacizumab,[29] sorafenib[30] and erlotinib.[31] Left ventricular dysfunction has been reported with anthracyclines along with TKI imatinib,[32] sunitinib[33] and sorafenib. In breast cancer patients the humanised monoclonal antibody Trastuzumab has been heavily linked to cardiac toxicity[34] although this is less relevant to the paediatric population. The varied and unpredictable cardiac side-effects of novel targeted therapies highlights the need for cardiac surveillance during the treatment of cancer.

Conclusions

This is the first reported Australian cohort of paediatric cancer survivors regarding anthracycline cardiotoxicity. There are however a few limitations to note, including a retrospective approach and small study numbers. Furthermore the method of assessment of LVEF, using fractional shortening, lacks sensitivity. To build upon our findings we propose to analyse a prospective cohort of paediatric cancer survivors exposed to anthracyclines using more advanced imaging techniques including echo derived measures of global longitudinal strain, cardiac magnetic resonance imaging, and cardio-pulmonary exercise testing.

Many questions remain to be answered in regards to anthracycline cardiotoxicity and cardiotoxicity in general. Given the increasing incidence of anthracycline cardiotoxicity and newer agents carrying their own cardiovascular risk profile, it is imperative for physicians to monitor closely during therapy and following therapy for toxicity. Traditional cardiovascular risk factors should be screened for (diabetes, hypertension, smoking) and modified accordingly. Monitoring and early detection of cardiotoxicity should assess LVEF.

The role of pharmacogenetics and individual patient pharmacokinetic profiles has recently gained attention. Identifying genetically susceptible patients through screening for single polynucleotide polymorphisms may advance the field, allowing physicians to identify upfront, patients at risk of this co-morbidity. Ideally patients would be screened at diagnosis for single nucleotide polymorphisms associated with cardiotoxicity. Following identification of the at-risk population a decision could be made by the treating clinician about whether to use cardio-protectant medication against ACT or heart failure. Recent guidelines have been released to help clinicians navigate this further, but, in essence, further prospective trials are required. Finally, the optimum screening tool for accurately accessing cardiotoxicity and documenting how the spectrum of disease alters as patients progress from childhood to adolescence and through to adulthood is yet to be determined and warrants further investigation.

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Patient demographics and Clinical characteristics					
	n = 286				
	Cardiotoxicity (n= 57)		Control (n= 229)		p-value
Characteristics	**No.**	**%**	**No.**	**%**	
Age at survey, years					**0.0008**[1]
Median	12		8.0		
Range	2.0 – 22.0		1.0 – 20		
Sex					0.224[2]
Female	30	52	101	43	

Male	27	48	133	57	
Dose (mg/m^2)					**0.0004**[1]
Median	180.25		129.9		
Range	22 - 437		20 – 417.6		
Anthracycline type					
Doxorubicin	26	45.6	156	68.1	0.16[2]
Daunorubicin	9	15.7	14	6.1	0.34[3]
Idarubicin	0	0	4	1.6	1.00[3]
Doxorubicin plus Daunorubicin	17	29.8	49	21.4	0.41[2]
Doxorubicin plus other †	0	0	1	0.4	1.00[3]
Daunorubicin plus other†	3	5.3	2	0.8	0.52[3]
Doxorubicin plus Daunorubicin plus other †	1	1.8	4	1.6	1.00[3]
Mitoxantrone	1	1.8	0	0	1.00[3]
Tumour type					
ALL	27	47.4	154	67.2	**0.017**[3]
AML	9	15.7	6	2.6	0.12[3]
APML	0	0	5	2.1	1.00[3]
Hodgkin's lymphoma	3	5.3	10	4.3	1.00[3]
Non-Hodgkin's lymphoma	4	7.0	10	4.3	1.00[3]
Osteosarcoma	3	5.3	8	3.5	1.00[3]
Rhabdomyosarcoma	1	1.7	6	2.6	1.00[3]
Ewing's sarcoma	5	8.8	5	2.1	0.35[3]
Desmoplastic small round cell tumour	0	0	1	0.4	
Neuroblastoma	2	3.5	18	7.9	0.407[3]
Nephroblastoma	3	5.3	3	1.3	1.00[3]
Other solid cancer	0	0	4	1.7	1.00[3]
Radiotherapy involving heart	5	8.9	6	2.6	0.66[3]
Follow up (months)					0.0594[1]
Mean	48.53		37.3		
Range	11-138		5-117		

Table 1:**Characteristics of retrospective cohort population:** AML; Acute Myeloid Leukaemia, ALL; Acute Lymphoblastic Leukaemia, APML; Acute promyelocytic leukaemia. Statistical analysis was performed using Stata 14.1. Age at survey, cumulative equivalent anthracycline dose and follow-up were not normally distributed: Wilcoxon-Mann-Whitney test was used. For gender, anthracycline type, tumour type and radiotherapy involving heart Pearson Chi squared test was used if the expected value in all cells was greater than 5, otherwise Fisher's exact test was used. Cumulative anthracycline dose in doxorubicin isotoxic equivalent doses. † Other anthracyclines include idarubicin, epirubicin, mitoxantrone. Bold value indicates $P < 0.05$

Cardiac dysfunction	Cumulative anthracycline dose (mg/m^2)							
	0-150 mg/m^2		150-250 mg/m^2		250-400 mg/m^2		> 400 mg/m^2	
	Total	Age > 12	Total	Age > 12	Total	Age >12	Total	Age > 12
FS < 24%	6	1	8	4	5	3	1	1
FS 24-28%	7	0	3	3	0	0	0	0
EF > 10%	10	4	10	7	4	3	3	3
Total (n)	23	5	21	14	9	6	4	4

Table 2: **Summary of ACT.** Summary of echocardiogram results for ACT (n=57) according to cumulative equivalent anthracycline dose and LVEF findings.

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