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ORIGINAL RESEARCH

Cardiotoxicity and Cardiac Monitoring Among Anthracycline-Treated Cancer Patients: A Retrospective Cohort Study

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Purpose: Cardiotoxicity is a common complication associated with anthracyclines. Little is known regarding the rate of anthracyclines-related acute and chronic cardiotoxicity and adherence to cardiac monitoring recommendations among cancer patients.

Patients and Methods: A single-centre retrospective cohort study was conducted from 2015 to 2018 on patients with cancer, 18 years of age and older, on anthracyclines without a history of cardiovascular diseases. Data on demographic information, comorbidities, cardiovascular events, monitoring parameters, and treatment details were obtained. The primary outcome was the incidence of anthracyclines-related cardiotoxicity both acute and chronic. The secondary outcome was to determine adherence to guideline recommendations for monitoring anthracyclines-related cardiotoxicity based on the American Society of Clinical Oncology clinical practice guidelines. Analyses included descriptive statistics and logistic regression. Institutional review board approval was obtained.

Results: In 235 patients identified, 28.9% developed cardiotoxicity, of which 27.2% were acute, while chronic cardiotoxicity was observed in 8.9% of subjects. Patients who received optimal cardiac monitoring had a statistically significant higher odds of developing cardiotoxicities (odds ratio=2.65, confidence interval=1.32–5.33). The risk of cardiotoxicity was higher in subjects with a history of diabetes mellitus, those using daunorubicin, and concomitant filgrastim use. Adherence to guideline recommendations was only achieved in 25.1% of the population. Echocardiography was the most common monitoring method used.

Conclusion: In this study, there was a high incidence of anthracyclines cardiotoxicity and poor compliance with cardiac monitoring recommendations for cancer patients on anthracyclines, which underscores acute and chronic cardiotoxicity in this population.

Keywords: anthracyclines, anthracyclines-induced cardiotoxicity, cardiac monitoring, cancer

Background

In the last decade, the treatment of many solid and haematological malignancies has advanced significantly. Anthracyclines, such as doxorubicin, epirubicin, and daunorubicin, are commonly used to treat various cancer types.[1] Despite being highly effective, nevertheless, these agents come with a wide range of side effects, specifically cardiovascular toxicity of which some might be permanent.[2–4] The generation of free radicals with anthracyclines use may elevate cardiac biomarkers and decrease left ventricular ejection fraction.[5,6] In the early stages of the left ventricle dysfunction, patients may not have any symptoms. However, it can

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progress to dilated cardiomyopathy and congestive heart failure.[5,6] This problem influences the patient's quality of life, and it could be life-threatening and irreversible.[7,8]

Acute anthracyclines cardiotoxicity is identified during drug administration or soon after and presents mainly as transient arrhythmia, ST/T changes in electrocardiogram (ECG), with a pericarditis-myocarditis syndrome or decompensated acute cardiac failure.[9] These acute effects are usually self-terminating by supportive therapy.[9] On the other hand, chronic anthracyclines cardiotoxicity can occur within a year of therapy or several years after and usually is irreversible and lifelong.[10] Chronic toxicity mainly consists of congestive heart failure with reduced ejection fraction.[11] Studies suggest that subjects with certain risk factors are more susceptible to anthracyclines-induced cardiotoxicity.[12–15] One of the main risk factors is the cumulative dose of anthracyclines, especially doxorubicin, in doses more than 400 mg/m2.[12,13] Other risk factors include age, smoking, obesity (ie, body mass index above 30), and the presence of cardiovascular diseases.[14,15] Previous exposure to cardiotoxic agents or coadministration of chemotherapy that have cardiac adverse effects can also increase the risk of anthracycline-induced cardiotoxicity.[3,16] Most studies on anthracyclines safety report on chronic cardiotoxicity only and little are known on acute cardiotoxicity incidence.[10]

Practice guidelines recommend periodic monitoring for cardiac function even before the first dose of anthracyclines is administered.[17,18] Early detection is more helpful in both treating and preventing cardiotoxicity from progressing.[19] There is little information on cardiac monitoring patterns in subjects receiving anthracyclines, and most available data is focused on subjects with breast cancer, and with the use of trastuzumab.[20,21] Henry et al observed that the rate of chemotherapy-related cardiotoxicity in patients who received anthracycline-based regimens was more likely in those treated with both anthracyclines and trastuzumab.[20] The authors also found that the use of anthracyclines was associated with higher odds of receiving cardiac monitoring adherence to guideline recommendations.[20] One study in subjects with patients with lymphoma receiving anthracycline-based chemotherapy found that only one-third of patients received guideline-recommended cardiac monitoring.[22]

Given the limited data on acute and chronic anthracycline cardiotoxicity, and on adherence rates to cardiac monitoring, globally and specifically in the region, this cohort study aimed to estimate the incidence and determinants of anthracycline-induced cardiotoxicity, both acute and chronic. Also, we determined the rate of adherence to cardiac monitoring recommendations among anthracycline-treated patients and investigated whether this monitoring was associated with the incidence of cardiotoxicity.

Method

Study Design and Setting

This retrospective cohort study was performed at King Saud University Medical City (KSUMC), a tertiary-care teaching hospital, located in Riyadh, Saudi Arabia. Data were collected from medical records starting from June 2015 until May 2018.

Participants

Cancer patients 18 years of age or older were eligible if they received anthracyclines regardless of the type of cancer or malignancy. Patients who already have any cardiovascular dysfunction before the initiation of anthracyclines were excluded. Patients were followed from their cancer diagnosis date until they either died or no longer followed up at KSUMC. The last follow-up date was May 31, 2018. The study was approved by the institutional review board of King Saud University (Institutional review board number E-18-3127).

Data Collection

Demographic characteristics (eg, age, gender, and body mass index [BMI]), clinical (eg, type and stage of cancer and comorbidities), and treatment information (eg, type and doses of anthracycline, use of other medications, and use of radiation therapy) were collected for each eligible subject from the electronic medical record. Also, data were collected on monitoring parameters: echocardiography, radionuclide ventriculography (multiple-gated acquisition [MUGA] scans), ECG, serum cardiac biomarkers (troponin and natriuretic peptides), as well as cardiac magnetic resonance imaging (MRI). Date of medication use and the date of performing any of the monitoring parameters available in the patient electronic medical records were collected.

Definitions

Cardiotoxicity

Patients were categorized according to the presence of cardiotoxicity and the adherence guidelines monitoring

recommendations. Cardiotoxicity was defined as a combination of either acute or chronic cardiotoxicity. Acute cardiotoxicity was defined as new ECG changes occurring after a single dose or a single course, with symptoms within 14 days from the end of treatment. Chronic cardiotoxicity was defined as the incidence of heart failure, either symptomatic or asymptomatic, as reported in medical records at any time after treatment. If left ventricular ejection fraction was reported in the medical records in subjects who developed heart failure that was noted as well. This definition was adapted from that used by others to define cardiac dysfunction associated with cancer therapy.[20]

Adherence to Cardiac Monitoring

Adherence to cardiac monitoring was based on the American Society of Clinical Oncology (ASCO) clinical practice guidelines recommendations.[18] This was defined as a baseline cardiac evaluation before the first dose of anthracyclines and a subsequent follow-up cardiac evaluation during therapy. Baseline cardiac monitoring was defined as a test before any anthracycline dose; follow-up cardiac monitoring was defined as monitoring four months after initiating treatment. Methods for cardiac monitoring included either one or more of the following tests: echocardiograms, ECG, MUGA scans, and cardiac biomarkers. We also collected information on cardiac-MRI.

High-Risk for Cardiotoxicity

According to the American Society of Clinical Oncology Clinical Practice Guidelines definition for high-risk patients, we identified subjects at high risk of cardiovascular toxicity.[18] This criterion includes subjects using high-dose anthracycline (eg, doxorubicin ≥250 mg/m2, epirubicin ≥600 mg/m2). The high-risk criteria also included those receiving lower-dose anthracycline (eg, doxorubicin <250 mg/m2, epirubicin <600 mg/m2) and the presence of multiple cardiovascular risk factors (≥ two risk factors), including smoking, hypertension, diabetes, dyslipidaemia, and obesity, during or after completion of therapy. Those receiving lower-dose anthracycline and older than 60 years of age at cancer treatment were also considered at high risk of cardiotoxicity. Finally, the high-risk definition also included those subjects on lower-dose anthracycline followed by trastuzumab (sequential therapy). The guideline also defines those subjects with compromised cardiac function, such as borderline low left ventricular ejection fraction and history of myocardial infarction and receiving lower-dose anthracycline were deemed as high-risk subjects.[18] However, since we did not include subjects the pre-existing cardiovascular diseases this did not apply to this study population. In addition, the use of high dose radiotherapy (≥30 grays) where the heart is in the treatment field or the use of lower-dose anthracycline in combination with lower-dose radiotherapy (<30 grays) where the heart is in the treatment field puts subjects at high risk of cardiotoxicity, according to the guidelines.[18] Nevertheless, such information on the treatment field for radiotherapy was not available. Therefore, this variable was used in the definition of high risk.

Statistical Analysis

Descriptive statistics were performed to summarize data. Data are shown as a summary for all subjects, and separately for those who developed cardiotoxicity, and also in whom guidelines were followed versus those who did not receive appropriate guideline recommendations. A Chi-square test was used to compare patient characteristics between groups. Univariable and multivariable logistic regressions were used to compare the outcome of having cardiotoxicity and the predictor of following treatment guidelines. Variables associated with cardiotoxicity in univariable models at p-values less than 0.1 were included in the multivariable model. As a sensitivity analysis, we ran the same regression models, including only subjects at high risk of cardiotoxicity. Logistic regression analysis was also performed to identify possible predictors for adherence to monitoring guidelines. Data were analyzed using R statistical program version 4.0.3. All tests are two-tailed, and a p-value of <0.05 was considered significant.

Results

Study Population

A total of 235 patients were included in this study. Subjects were followed up for an average of 1.1 years and a standard deviation of (±0.9) years. The majority were males (54.9%), and 74.5% (175/235) were below the age of 60 years. Sixty percent of participants had a BMI of more than 30 kg/m2. Most study participants were considered at high risk of cardiotoxicity (88.9%). Lymphoma was the most common type of cancer in the study population (56.2%), and the cancer was of new diagnosis in most patients (91.5%). Doxorubicin was the most commonly used anthracycline and most subjects on

high-dose anthracyclines. About half of the subjects received biological therapy, mainly using rituximab, cyclophosphamide, and mesna. Details of the study participants are presented in Table 1.

Cardiotoxicity

In this cohort, 28.9% of subjects developed cardiotoxicity, which included both acute and chronic toxicities. The incidence of chronic (ie, delayed) cardiotoxicity was 8.9%, while acute cardiotoxicity was 27.2%. Subjects who developed cardiotoxicity were more likely to be diabetic (p=0.033). The type of cancer was also different between those who developed and did not develop cardiotoxicity (p=0.001). There was a significant difference in the anthracycline agents used between those with and without cardiotoxicity (p<0.001). Adherence to monitoring recommendations was higher in subjects who developed cardiotoxicity (p=0.014). Other clinical characteristics were similar primarily across the groups. These characteristics are summarized in Table 1. Detailed types of cardiotoxicities observed are presented in Supplementary Table S1.

Univariable and multivariable logistic regression models on the outcome of cardiotoxicity are available in Table 2. After adjusting for possible confounders, the odds ratio for developing cardiotoxicity was 2.73 in subjects who were diabetic versus non-diabetics. The use of daunorubicin was associated with higher odds of cardiotoxicity compared to doxorubicin in multivariable analysis. Also, cardiotoxicity was significantly higher with the concomitant use of filgrastim with anthracyclines. Furthermore, optimal monitoring was associated with higher odds of cardiotoxicity (Table 2). Sensitivity analysis using only subjects at high risk of cardiotoxicity (n=209), the results remained the same, except that the use of filgrastim was no longer associated with higher odds of cardiotoxicity (Supplementary Table S2).

Cardiac Monitoring

Only 25.1% of the study participants received optimal monitoring for cardiotoxicity. Cardiac monitoring was more frequent in subjects who developed cardiotoxicity (36.8%) than those who did not develop any toxicities (20.4%). Subjects who developed cardiotoxicity were more likely to have monitoring tests performed during therapy (57.4% in subjects with cardiotoxicity versus 26.3% in those without toxicities). The most common test performed at baseline was echocardiography (29.8%), followed by ECG (22.1%). On the other hand, at follow-up testing, the most common test performed were cardiac biomarkers (20.9%), followed by ECG (18.3%). Here, MRI testing was only performed on two study subjects during the study period. These results are presented in Table 3.

Study participants' characteristics across those who received optimal cardiac monitoring versus those who received suboptimal monitoring are available in Table 4. There were generally no differences between the groups in terms of clinical and demographic characteristics. However, those who received optimal cardiac monitoring were more likely to be active smokers (16.9%) than those who did not receive optimal cardiac monitoring (6.2%). Cardiotoxicity was more prevalent in those who received optimal cardiac monitoring (42.4%) versus those who did not receive any monitoring (24.4%). We attempted to perform logistic regression analysis on possible predictors for optimal adherence to cardiac monitoring recommendations. However, since only smoking was significantly correlated with cardiac monitoring, multiple logistic regression analysis was not performed. Results of univariable regression analyses are presented in Supplementary Table S3. Although we tried collecting left ventricular ejection fraction information on all study participants, these data were only available on a subset of subjects (n=30). In those participants, the average and standard deviation of the left ventricular ejection fraction were 64.8±6.4 and 56.5±10.7% before and after treatment initiation, respectively.

Discussion

This study found a generally high incidence rate of cardiotoxicity following anthracycline use in subjects with cancer. However, this incidence rate was mostly driven by acute toxicity. There are limited reports on the incidence of acute anthracycline toxicity.[10] Nevertheless, in this cohort, we did observe a high incidence of ECG changes shortly after the initiation of anthracyclines. The rate of chronic or delayed toxicity here was similar to that reported by other studies.[12,19] In a prospective study on cancer patients receiving anthracyclines, the overall incidence of cardiotoxicity was 9%.[19] Another retrospective cohort study on patients with lymphoma compared the incidence of congestive heart failure in patients with anthracycline regimen to non-anthracycline regimen found that 9.4% of patient treated with anthracycline developed heart failure after

Table 1 Characteristics of Study Participants Based on Incidence of Cardiotoxicity

	Overall (N=235)	Cardiotoxicity (N=68)	No-Cardiotoxicity (N=167)	p-value*
Gender				0.228
Male	129 (54.9%)	42 (61.8%)	87 (52.1%)	
Female	106 (45.1%)	26 (38.2%)	80 (47.9%)	
Age				0.481
<60 years	175 (74.5%)	48 (70.6%)	127 (76.0%)	
>60 years	60 (25.5%)	20 (29.4%)	40 (24.0%)	
BMI > 30	141 (60.0%)	40 (58.8%)	101 (60.5%)	0.930
Current Smoking	21 (8.9%)	5 (7.4%)	16 (9.6%)	0.771
History of Hypertension	66 (28.1%)	24 (35.3%)	42 (25.1%)	0.159
History of Dyslipidaemia	38 (16.2%)	15 (22.1%)	23 (13.8%)	0.171
History Diabetes	44 (18.7%)	19 (27.9%)	25 (15.0%)	0.033
High-Risk for Cardiotoxicity	209 (88.9%)	61 (89.7%)	148 (88.6%)	0.991
High dose anthracycline	155 (66.0%)	41 (60.3%)	114 (68.3%)	0.309
Low dose anthracycline and age above 60 years old	26 (11.1%)	18 (10.8%)	8 (11.8%)	0.991
Low dose anthracycline with ≥ two cardiovascular risk factors	18 (7.7%)	9 (5.4%)	9 (13.2%)	0.080
Low dose anthracycline followed by trastuzumab	10 (4.3%)	3 (4.4%)	7 (4.2%)	0.990
Type of Cancer				0.001
Breast	23 (9.8%)	5 (7.4%)	18 (10.8%)	
Lymphoma	132 (56.2%)	29 (42.6%)	103 (61.7%)	
Leukaemia	32 (13.6%)	19 (27.9%)	13 (7.8%)	
Hepatocellular carcinoma	12 (5.1%)	2 (2.9%)	10 (6.0%)	
Others	36 (15.3%)	13 (19.1%)	23 (13.8%)	
Cancer Status				0.234
New	215 (91.5%)	59 (86.8%)	156 (93.4%)	
Recurrent	12 (5.1%)	5 (7.4%)	7 (4.2%)	
Relapse	8 (3.4%)	4 (5.9%)	4 (2.4%)	
Anthracycline type				<0.001
Doxorubcin	193 (82.1%)	43 (63.2%)	150 (89.8%)	
Liposomal doxorubcin	15 (6.4%)	8 (11.8%)	7 (4.2%)	
Danurubicin	27 (11.5%)	17 (25.0%)	10 (6.0%)	
Route of Administration				0.7741
Continuous infusion	90 (38.3%)	27 (39.7%)	63 (37.7%)	
Bolus	75 (31.9%)	23 (33.8%)	52 (31.1%)	
Both	70 (29.8%)	18 (26.5%)	52 (31.1%)	
Radiotherapy	167 (71.1%)	53 (77.9%)	114 (68.3%)	0.185
Biologic Therapy				0.743
Rituximab	109 (46.4%)	32 (47.1%)	77 (46.1%)	
Trastuzumab	10 (4.3%)	3 (4.4%)	7 (4.2%)	
Others	9 (3.8%)	4 (5.9%)	5 (3.0%)	
Not on biologics	107 (45.5%)	29 (42.6%)	78 (46.7%)	
Use of Cyclophosamide	125 (53.2%)	37 (54.4%)	88 (52.7%)	0.924

(*Continued*)

Table 1 (Continued).

	Overall	Cardiotoxicity	No-Cardiotoxicity	p-value*
	(N=235)	(N=68)	(N=167)	
Use of Vincristin	161 (68.5%)	51 (75.0%)	110 (65.9%)	0.226
Use of Mesna	122 (51.9%)	40 (58.8%)	82 (49.1%)	0.227
Use of Filgrastim	99 (42.1%)	35 (51.5%)	64 (38.3%)	0.088

Notes: *Chi-square test was used to compare categorical data. Data presented as number (percent).
Abbreviation: BMI, body mass index.

9-years follow-up compared to 0.8% of patients treated with a non-anthracycline regimen.[12]

Previous studies found a relationship between the cumulative anthracyclines dose, patients age, and the use of radiotherapy with the development of cardiotoxicity.[12–15,19–21] Here we were unable to demonstrate such associations. This could be explained by the fact that almost 90% of study participants were considered at high risk of cardiotoxicity. This indicates being on either high dose anthracyclines, having pre-existing cardiovascular conditions, and above the age of 60, among other risk factors identified here. Interestingly, in a study by Cardinale et al, although they did not include subjects with pre-existing cardiovascular disease, similar to the study here, there was a low number of cardiotoxicities observed.[23] This could be explained by the fact that in this cohort there was a high rate of cardiovascular disease risk factors compared to the study by Cardinale et al.[23] For instance, here 28% of the study subjects had hypertension, and about 19% had diabetes, while in the other study only 3% and 4% of the participants had hypertension or diabetes, respectively.[23] In this cohort, concomitant use of filgrastim was associated with double the odds of developing cardiotoxicity compared to no concomitant use of filgrastim. This could

Table 2 Association Between Cardiotoxicity and Clinical Characteristics Using Logistic Regression Model

	Univariable Regression Analysis for Cardiotoxicity			Multivariable Regression Analysis for Cardiotoxicity		
	OR	95% CI	p-value	OR	95% CI	p-value
History Diabetes	2.20	1.11, 4.34	0.02	2.73	1.27, 5.88	0.01
Type of cancer						
Breast	Ref		<0.001	Ref		
Lymphoma	1.01	0.37, 3.28		1.20	0.41, 4.13	0.80
Leukemia	5.26	1.64, 19.30		2.83	0.59, 14.10	0.20
Hepatocellular carcinoma	0.72	0.09, 4.06		1.22	0.14, 7.97	0.80
Others	2.03	0.64, 7.31		1.87	0.47, 7.83	0.40
Athracycline Agent			<0.001			
Doxorubcin	Ref			Ref		
Liposomal doxorubcin	3.99	1.36, 12.00		2.51	0.66, 10.10	0.20
Danurubicin	5.93	2.57, 14.40		4.51	1.16, 17.90	0.03
Supportive therapy						
Filgrastim	1.71	0.97, 3.02	0.07	2.37	1.23, 4.71	0.01
Outcome						
Adherence to cardiac monitoring	2.27	1.22, 4.23	0.01	2.65	1.32, 5.33	0.01

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 3 Cardiac Monitoring Based on Incidence of Cardiotoxicity

	Overall (N=235)	Cardiotoxicity (N=68)	No-Cardiotoxicity (N=167)	p-value*
Optimal Adherence to Cardiac Monitoring	59 (25.1%)	25 (36.8%)	34 (20.4%)	0.014
Monitoring parameters				
Any test at baseline	125 (53.2%)	43 (63.2%)	82 (49.1%)	0.07
Type of Baseline Test				
Echocardiography	70 (29.8%)	27 (39.7%)	43 (25.7%)	0.05
MUGA scan	48 (20.4%)	13 (19.1%)	35 (21.0%)	0.89
ECG	52 (22.1%)	20 (29.4%)	32 (19.2%)	0.12
Cardiac biomarkers	43 (18.3%)	17 (25.0%)	26 (15.6%)	0.19
Any test at follow-up	83 (35.3%)	39 (57.4%)	44 (26.3%)	<0.001
Type of Follow-Up Test				
Echocardiography	28 (11.9%)	10 (14.7%)	18 (10.8%)	0.54
MUGA scan	19 (8.1%)	7 (10.3%)	12 (7.2%)	0.59
ECG	43 (18.3%)	26 (38.2%)	17 (10.2%)	<0.001
Cardiac biomarkers	49 (20.9%)	21 (30.9%)	28 (16.8%)	0.03
Other tests				
MRI	2 (0.9%)	2 (2.9%)	0 (0.0%)	0.149

Notes: *Chi-square test was used to compare categorical data. Data presented as number (percent).
Abbreviations: ECG, electrocardiogram; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition.

be explained by the fact that these subjects who require the use of filgrastim are more likely to develop adverse events from anthracyclines, whether these adverse events were cardiotoxicity or neutropenia.

Here, there was an association between having diabetes and the development of cardiotoxicity, similar to that reported in previous cohorts.[15] Looking at each anthracycline separately, we observe the highest incidence rate of cardiotoxicity with daunorubicin. However, this association was no longer significant in multivariable regression analysis. There were no differences observed between daunorubicin and idarubicin in terms of cardiotoxicity in a systematic review and meta-analysis.[24]

This study aimed to identify cardiac monitoring parameters performed on patients using anthracycline and compare them with international guideline recommendations. We did observe suboptimal adherence to cardiac monitoring, as only a quarter of subjects received the required monitoring for cardiotoxicity. There are limited data regarding cardiac monitoring in subjects receiving anthracyclines, and most studies focus on cardiac monitoring associated with trastuzumab use, which is reported to be suboptimal.[20] Patients on anthracycline should be monitored closely, even before starting treatment, as early detection helps to treat and prevent cardiotoxicity.[19]

Subjects who developed cardiotoxicity were more likely to receive optimal guideline adherence to cardiac monitoring. However, a higher incidence of cardiotoxicity is expected in those who received optimal monitoring, and the true rate of cardiotoxicity might have been underestimated. Studies show that monitoring patients on anthracyclines will help in the identification of cardiotoxicity.[19] Cardiac monitoring is usually performed with an echocardiogram or with MUGA scans.[25] The following parameters are also recommended for monitoring such as serum natriuretic peptides and cardiac troponins.[17,18,26] For high-risk patients, routine monitoring with an echocardiogram is recommended during treatment.[18] In this study, the most common tests used before the initiation of anthracyclines were echocardiogram and ECG. While during therapy, the most common test performed were cardiac biomarkers, followed by ECG.

Table 4 Characteristics of Study Participants Based on Adherence to Cardiac Monitoring

	Overall (N=235)	Optimal Monitoring (N=59)	Suboptimal Monitoring (N=176)	p-value*
Gender				0.21
Male	129 (54.9%)	37 (62.7%)	92 (52.3%)	
Female	106 (45.1%)	22 (37.3%)	84 (47.7%)	
Age				0.846
<60 years	175 (74.5%)	45 (76.3%)	130 (73.9%)	
>60 years	60 (25.5%)	14 (23.7%)	46 (26.1%)	
BMI > 30	141 (60.0%)	35 (59.3%)	106 (60.2%)	0.902
Active Smoking	21 (8.9%)	10 (16.9%)	11 (6.2%)	0.026
History of Hypertension	66 (28.1%)	15 (25.4%)	51 (29.0%)	0.720
History of Dyslipidaemia	38 (16.2%)	9 (15.3%)	29 (16.5%)	0.987
History Diabetes	44 (18.7%)	10 (16.9%)	34 (19.3%)	0.833
High-Risk for Cardiotoxicity	209 (88.9)	52 (88.1%)	157 (89.2%)	0.990
High dose anthracycline	155 (66.0%)	39 (66.1%)	116 (65.9%)	0.978
Low dose anthracycline and age above 60 years old	26 (11.1%)	20 (11.4%)	6 (10.2%)	0.989
Low dose anthracycline with ≥ two cardiovascular risk factors	18 (7.7%)	11 (6.2%)	7 (11.9%)	0.263
Low dose anthracycline followed by trastuzumab	10 (4.3%)	4 (6.8%)	6 (3.4%)	0.902
Type of cancer				0.442
Breast	23 (9.8%)	8 (13.6%)	15 (8.5%)	
Lymphoma	132 (56.2%)	34 (57.6%)	98 (55.7%)	
Leukaemia	32 (13.6%)	9 (15.3%)	23 (13.1%)	
Hepatocellular carcinoma	12 (5.1%)	1 (1.7%)	11 (6.2%)	
Others	36 (15.3%)	7 (11.9%)	29 (16.5%)	
Cancer Status				0.704
New	215 (91.5%)	55 (93.2%)	160 (90.9%)	
Recurrent	12 (5.1%)	3 (5.1%)	9 (5.1%)	
Relapse	8 (3.4%)	1 (1.7%)	7 (4.0%)	
Anthracycline type				0.738
Doxorubcin	193 (82.1%)	47 (79.7%)	146 (83.0%)	
Liposomal doxorubcin	15 (6.4%)	5 (8.5%)	10 (5.7%)	
Danurubicin	27 (11.5%)	7 (11.9%)	20 (11.4%)	
Route of Administration				0.512
Continuous infusion	90 (38.3%)	20 (33.9%)	70 (39.8%)	
Bolus	75 (31.9%)	18 (30.5%)	57 (32.4%)	
Both	70 (29.8%)	21 (35.6%)	49 (27.8%)	
High Dose of Anthracyclines	155 (66.0%)	39 (66.1%)	116 (65.9%)	0.978
Radiotherapy	167 (71.1%)	42 (71.2%)	125 (71.0%)	0.981
Biological Therapy				0.518

(*Continued*)

Table 4 (Continued).

	Overall (N=235)	Optimal Monitoring (N=59)	Suboptimal Monitoring (N=176)	p-value*
Rituximab	109 (46.4%)	26 (44.1%)	83 (47.2%)	
Trastuzumab	10 (4.3%)	4 (6.8%)	6 (3.4%)	
Others	9 (3.8%)	1 (1.7%)	8 (4.5%)	
Not on biologics	107 (45.5%)	28 (47.5%)	79 (44.9%)	
Use of Cyclophosamide	125 (53.2%)	31 (52.5%)	94 (53.4%)	0.908
Use of Vincristin	161 (68.5%)	39 (66.1%)	122 (69.3%)	0.765
Use of Mesna	122 (51.9%)	30 (50.8%)	92 (52.3%)	0.969
Use of Filgrastim	99 (42.1%)	25 (42.4%)	74 (42.0%)	0.965
Cardiotoxicity	68 (28.9%)	25 (42.4%)	43 (24.4%)	

Notes: *Chi-square test was used to compare categorical data. Data presented as number (percent).
Abbreviation: BMI, body mass index.

There is no consensus in clinical practice guidelines on the preferred mentoring technique, although most recommend echocardiogram or MUGA scans.[27] However, these tests might not be readily available for all patients; therefore, some recommend the use of cardiac biomarkers.[6] One study showed that early changes in troponin levels in subjects using anthracyclines are associated with subsequent cardiotoxicity.[6] The combination of multiple markers may have a common benefit in predicting subsequent cardiotoxicity.[6]

This study has several limitations. First, as a retrospective single-centre study, the sample size was small, with limited generalizability. Second, we did observe poor documentation of the results of cardiac monitoring in the medical records. Third, our patient population mainly had lymphoma. Therefore, the results of this study might not apply to other types of cancer. Fourth, we did not include information on the use of cardiovascular medications in this population, which might have impacted the development of cardiotoxicity. Fifth, baseline data on cardiac function tests, such as left ventricular ejection fraction was not available for all subjects, nevertheless, we did attempt to report the available information when feasible. Sixth, although we attempted to collect follow-up dates for study participants, we were unable to obtain the exact follow-up time for the acute and chronic cardiotoxicity. Lastly, the percentage of chronic cardiotoxicity was underestimated because of the short study period, loss of follow up, and inadequate cardiac monitoring.

Conclusions

To our knowledge, our study is the first of its kind to estimate cardiotoxicity rates and cardiac monitoring in cancer subjects in Saudi Arabia. We did observe a more significant incidence rate of acute cardiotoxicity. However, these results underestimate the true incidence of cardiotoxicity due to the suboptimal adherence to cardiac monitoring. The incidence rate of chronic cardiotoxicity was aligned with that seen in other populations. Future observational studies with prospective follow-up are required to estimate the true incidence of anthracycline-induced acute together with chronic cardiotoxicity.

Abbreviations

ASCO, American Society of Clinical Oncology; BMI, body mass index; ECG, electrocardiogram; KSUMC, King Saud University Medical City; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

The study was approved by the institutional review board of King Saud University (Institutional review board number E-18-3127). All data were anonymized to maintain participant's privacy, and the study was conducted in accordance with the Declaration of Helsinki. In light of

the retrospective and anonymous nature of the study, the Ethics Committee did not require written informed consent provided by participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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