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ORIGINAL ARTICLE

Real-life incidence of cardiotoxicity and associated risk factors in sarcoma patients receiving doxorubicin

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ABSTRACT

Background: Anthracycline induced cardiotoxicity is well recognized but only few data exist in sarcoma patients. This study retrospectively aimed to analyze sequential Cadmium Zinc Telluride (CZT)-multigated equilibrium radionuclide angiography (ERNA) for monitoring left ventricular ejection fraction (LVEF) and to assess the real-life incidence of cardiotoxicity in sarcoma patients receiving doxorubicin based chemotherapy.

Materials and methods: A retrospective analysis was performed on all sarcoma patients referred to Herlev University Hospital between 2012 and 2015. Cardiotoxicity was defined as a decline in LVEF of $>$ 10% percentage point to a LVEF $<$ 50% as compared to baseline. Early cardiotoxicity was defined as $<$ 1 year and late cardiotoxicity as $\geq$ 1 year. Recovery of cardiotoxicity was defined as a LVEF $\geq$ 50%.

Results: A total of 149 patients were referred, 75 (50%) sarcoma patients were included. The main reason for exclusion was that only one CZT-ERNA had been performed in 50 (68%) of the patients. Twenty-three (31%) of the patients experienced cardiotoxicity, 11 (48%) were female, mean age was 56.9 years. Early cardiotoxicity was observed in 16 (70%) of the patients and 11 (48%) experienced clinical symptoms of cardiotoxicity at diagnosis. Recovery of LVEF was seen in 12 (55%) of the patients and persistent recovery in 10 (45%). The diastolic blood pressure at baseline was positively and significantly associated with a higher risk of developing cardiotoxicity (Relative Risk (RR): 1.039 (95% CI= 1.001 − 1.079; $p = 0.042$)). The median survival was 1.4 years (range 0.5 − 2.2 years) for patients with metastatic disease versus 3.9 years (range 1.5 − 6.4 years) ($p = 0.009$) for localized disease at baseline.

Conclusion: Cardiotoxicity is a relative frequent complication in sarcoma patients treated with doxorubicin based chemotherapy and the diastolic blood pressure at baseline was significantly associated with a higher risk of developing cardiotoxicity.

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KEYWORDS
Sarcoma; cardiotoxicity; anthracycline and doxorubicin

Background

Sarcomas are rare mesenchymal tumors and account for approximately 1−2% of all solid malignancies [1]. Chemotherapy with doxorubicin, an anthracycline, appears to be the most effective drug and is regarded first-line treatment in the metastatic setting with a cumulative response rate of approximately 20% [2].

Anthracyclines are widely used and have been associated with several cardiac toxicities [3], mostly left ventricular (LV) myocardial dysfunction and heart failure [4,5]. The prognosis of anthracycline induced LV myocardial dysfunction is poor, with cardiovascular mortality rates ranging from 9% at 5-years and 24% at 10-years [6]. Known risk factors include life-time cumulative dose, infusion regime, female sex, renal failure, age, radiation therapy and preexisting cardiovascular disease [5].

In this view, it is necessary to ensure cardiac monitoring, which can be assessed by several methods [7,8] including Cadmium Zinc Telluride (CZT)- equilibrium radionuclide angiography (ERNA) [9]. The latest type of cardiac single photon emission computed tomography (SPECT) gamma camera with CZT detectors provides highly reproducible assessments of both left and right ventricular volumes and ejection fractions [10].

To our knowledge only few data exist on the real-life incidence of doxorubicin induced cardiotoxicity in sarcoma patients [11,12] and no studies where cardiac monitoring was performed with CZT-ERNA. As doxorubicin induced cardiotoxicity can result in early cessation of anti-cancer treatment, the need for further evaluation is warranted. The objective of this study aimed to analyze sequential CZT-ERNA for monitoring LVEF to assess the real-life incidence of cardiotoxicity in sarcoma patients receiving doxorubicin based chemotherapy and to identify any preexisting comorbidities that may be associated with cardiotoxicity.

Materials and methods

Study population

A retrospective analysis was performed from October 2012 to August 2015 covering all sarcoma patients referred for

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first-line doxorubicin based chemotherapy at the Department of Oncology at Herlev University Hospital. Approval was granted by the Danish Data Protection Agency (journal number: 2012-58-0004).

Patients were eligible provided they received doxorubicin as part of their initial treatment, $\geq$ 18 years and underwent monitoring with a baseline CZT-ERNA and at least one subsequent CZT-ERNA. Patients were deemed ineligible if they did not have the diagnosis of sarcoma, only had one CZT-ERNA performed, or had received less than three cycles of doxorubicin.

Data collection

Date of referral, gender, performance status (PS), tumor grade, disease status at baseline, doxorubicin cumulative dose, dose reduction, height, weight, blood pressure, heart rate, other anti-cancer treatments, CZT-ERNA results, tobacco, cardiac related comorbidities, concomitant cardiac medications, symptoms at the time of verified cardiotoxicity and referral to a cardio-oncology clinic were identified from the hospital records. Data on blood biomarkers such as cardiac natriuretic peptides, atrial and brain natriuretic peptide or troponin were not collected as these blood samples were not routinely performed. Electrocardiograms (ECGs) was not collected as all the data were not assessable from the hospital records.

Cadmium zinc telluride (CZT)-equilibrium radionuclide angiography (ERNA)

All acquisitions with radionuclide angiographies were performed on a cardiac CZT SPECT gamma camera, GE Discovery 530c (GE Healthcare, Milwaukee, WI) at the Department of Clinical Physiology and Nuclear Medicine at Herlev University Hospital. CZT-ERNA has since October 2012 been the routine method of choice for LVEF assessment and for monitoring potential cardiotoxic side effects of anti-cancer treatments at Herlev University Hospital. Each subject was given an individualized dose of ^{99m}Tc-labeled human serum albumin intravenously or 550 MBq. An acquisition protocol for multigated acquisition, using 16 bins per R-R interval, requesting 600 accepted beats, and a 20% energy window centered on 140 keV was carried out. A Xeleris 3 Imaging workstation reorientation software (GE Healthcare, Milwaukee, WI, USA, version no. 3.0562) and Cedars-Sinai QBS processing software (Cedars-Sinai, Los Angeles, CA, revision 2009.0) was used for image processing. The following variables were registered: LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and LV ejection fraction (LVEF) and converted into *Z*-scores for each variable in order to adjust for age and gender specific variations [13]. The CZT-ERNA was performed routinely before the initiation of doxorubicin and approximately every nine weeks during treatment.

Cardiotoxicity

Numerous cardiology organizations provide various definitions for cardiac toxicity although there is no universally accepted definition [14]. As such, we defined doxorubicin induced cardiotoxicity measured by CZT-ERNA as a decline in LVEF of $>$ 10% percentage point (pp) to a LVEF $<$ 50% as compared to baseline [15,16]. Early cardiotoxicity was defined as $<$ 1 year and late cardiotoxicity as $\geq$ 1 year [5,17]. Recovery of cardiotoxicity was defined as a LVEF $\geq$ 50% [18,19]. Minor/subclinical cardiotoxicity was not investigated. Since 2011 the Department of Cardiology at Herlev University Hospital, has had a cardio-oncology clinic specifically dedicated to patients with cardiac toxicity induced by anti-cancer treatments. At referral an echocardiography (ECHO) and history with physical examinations were performed. Patients with confirmed cardiotoxicity were, since no consensus was decided, offered conventional anti-congestive treatment [20] and followed in the clinic every 1−2 months. Anti-congestive treatment was initiated as an angiotensin converting enzyme inhibitor (ACEi) (ramipril or enalapril) or an angiotensin receptor blocker (ARB) (losartan) and with fast dose titration every 2−3 days to half of target dose. A betablocker (BB) (metoprolol, bisoprolol or carvedilol) was initiated also in a fast titration manner. When half of target of the BB dose was reached, the ACEI/ARB was titrated to full dose if possible, and hereafter the BB to full dose as well. When target dose was not possible the maximal tolerated dose was utilized.

Statistical analysis

Survival curves were constructed according to the method of Kaplan and Meier. Pairwise comparisons for overall survival and time to cardiotoxicity were performed using a Log Rank test (Mantel-Cox) of which those with a p-value $<$ 0.5 were included in a Cox regression model (see below). Comparisons of frequencies were analyzed with a Fisher's exact test. Continuous variables were expressed as means ± standard deviation and categorical variables were expressed as numbers and percentages. A backward stepwise conditional Cox proportional hazards regression analysis on baseline categorical variables was performed (Entry p-value $<$ 0.05; Removal p-value $<$ 0.1) for the assessment of relative risk (RR) for developing cardiotoxicity and overall survival. Selected categorical variables and baseline continuous variables were then entered into a final Cox regression analysis. A p-value $<$ 0.05 was considered significant and a p-value ranging from 0.05 to 0.1 was considered as a trend toward significance. Group comparisons were performed with a t-test. A ROC analysis was performed for assessment of predictive capability of variables with potential for prediction of development of cardiotoxicity. All statistical calculations were performed using the IBM SPSS software package version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results

Study population

A total of 149 patients were referred and 75 sarcoma patients were included. Patient characteristics are summarized in Table 1. The reasons for study exclusion were that: 50 (68%) of the patients had only one CZT-ERNA performed due to either progressive disease, clinical deterioration, or death; 15 (20%) of the patients had their baseline ERNA performed with planar acquisition at another hospital and hence the outcome was not comparable, and 9 (12%) of the patients had never received doxorubicin or did not have a sarcoma.

Cardiotoxicity

Twenty-three (31%) of the patients met the criteriae for cardiotoxicity, 11 (48%) were female, mean age was 56.9 years. Sixteen (70%) of the patients developed early cardiotoxicity

Table 1. Patients characteristics.

	Patients with no cardiotoxicity	*p*-Value	Patients with cardiotoxicity
Number of patients (*n*, %)	52 (69%)		23 (31%)
Age (years) (mean ± *SD*)	51.8 (±17.8)	0.226	56.9 (±14.6)
BMI (mean ± *SD*)	25.0 (±4.6)	0.670	25.9 (±5.0)
BSA (m^2) (mean ± *SD*)	1.87 (±0.23)	0.207	1.95 (±0.27)
Weight (kg) (mean ± *SD*)	74.0 (±16.5)	0.324	79.3 (±19.0)
Height (cm) (mean ± *SD*)	172 (±10)	0.254	175 (±10)
Performance status (*n*, %)		0.188	
0	31 (60%)		18 (78%)
≥1	21 (40%)		5 (22%)
Sex (Male) (*n*, %)	27 (52%)	1.00	12 (52%)
Sex (Female) (*n*, %)	25 (48%)		11 (48%)
Disease status at baseline (*n*, %)		0.442	
Metastatic	30 (58%)		16 (70%)
Localized	22 (42%)		7 (30%)
Cumulative Doxorubicin dose per BSA (mg/m^2) (mean ± *SD*)	344 (±103)	0.131	383 (±96)
LVEDV (*Z*) (mean ± *SD*)	−0.051 (±0.947)	0.482	−0.179 (±0.604)
LVESV (*Z*) (mean ± *SD*)	0.171 (±0.910)	0.818	−0.034 (±0.819)
LVEF (*Z*) (mean ± *SD*)	−0.077 (±0.898)	0.620	−0.194 (±1.017)
Systolic blood pressure (mmHg) (mean ± *SD*)	134 (±21)	0.409	138 (±21)
Diastolic blood pressure (mmHg) (mean ± *SD*)	78 (±11)	0.021	84 (±9)
Heart rate (mean ± *SD*)	74 (±14)	0.330	78 (±13)
Smoking, previous/current (*n*, %)	14 (27%)	0.416	9 (39%)
Oncological schedules (*n*, %)			
Doxorubicin	34 (65%)	NA	16 (70%)
Doxorubicin/Cisplatin	11 (21%)	NA	3 (13%)
Doxorubicin/TH302	1 (2%)	NA	3 (13%)
Vincristine, Ifosfamide, Doxorubicin and Etoposide (VIDE)	3 (6%)	NA	0 (0%)
Vincristine, Actinomycin D, Doxorubicin and Ifosfamide (VAI)	2 (4%)	NA	0 (0%)
Doxorubicin/Ifosfamide	1 (2%)	NA	1 (4%)
Comorbidities (*n*, %)			
Hypertension	12 (23%)	0.396	8 (35%)
Hypercholesterolemia	8 (15%)	1.000	4 (17%)
Ischemic heart disease	1 (2%)	0.522	1 (4%)
Atrial fibrillation	2 (4%)	0.068	4 (17%)
Diabetes	3 (6%)	0.363	3 (13%)
Histological subtypes (*n*,%)			
Synovial sarcoma	5 (10%)	NA	4 (17%)
Leiomyosarcoma	6 (12%)	NA	6 (26%)
Fibromyxoid sarcoma	1 (2%)	NA	2 (9%)
Hemangiosarcoma	0 (0%)	NA	1 (4%)
Liposarcoma	9 (17%)	NA	2 (9%)
Osteosarcoma	11 (21%)	NA	3 (13%)
Myofibroblastic sarcoma	1 (2%)	NA	1 (4%)
Fibrosarcoma	2 (4%)	NA	1 (4%)
Endometrial stromal sarcoma	1 (2%)	NA	2 (9%)
Angiosarcoma	2 (4%)	NA	0 (0%)
Pleomorphic sarcoma	1 (2%)	NA	0 (0%)
Ewing sarcoma	3 (6%)	NA	0 (0%)
MPNST	6 (12%)	NA	1 (4%)
Rhabdomyosarcoma	2 (4%)	NA	0 (0%)
Epithelioid sarcoma	1 (2%)	NA	0 (0%)
Clear cell sarcoma	1 (2%)	NA	0 (0%)

Baseline characteristics of the study population. Continuous variables are given as means ± standard deviation (*SD*), and categorical variables are given as numbers (*n*) and percentages.

LVEF: Left ventricular ejection fraction; LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; BSA: Body surface area; BMI: Body Mass Index; NA: Not applicable; MPNST: Malignant Peripheral Nerve Sheath Tumor and TH302: Hypoxia activated evofosfamide.

LVEF, LVEDV and LVESV are given as *Z*-scores adjusted for age and gender.

and 7 (30%) developed late cardiotoxicity. The median time to confirmed cardiotoxicity as defined by CZT-ERNA or ECHO results was 0.47 years (range 0.21−0.98) (early cardiotoxicity), 2.45 years (range 1.07−4.3) (late cardiotoxicity) and 1.07 years (range 0.21−4.3) (any cardiotoxicity). There was no difference in the mean LVEF at baseline 66.3% (± 9.7) (cardiotoxicity) versus 67.4% (± 9.0) (no cardiotoxicity) ($p = 0.641$). Eleven (48%) of the patients experienced clinical symptoms related to cardiovascular disease at the time of confirmed cardiotoxicity. In one patient the data could not be identified from the hospital record. In 18 (78%) of the patients the cardiotoxicity was confirmed by CZT-ERNA but in 5 (22%) it was confirmed by ECHO which was considered to be sufficient to detect cardiotoxicity [21]. Twenty-two (96%) of the patients with cardiotoxicity were referred to the cardio-oncology clinic in which 19 (86%) initiated anti-congestive treatment. In the 3 patients where anti-congestive treatment at referral was not initiated, the following was identified from the hospital records: Patient 1: The LVEF was 49% at referral to the cardio-oncology clinic but the ECHO showed a LVEF of 60%. The patient was asymptomatic; Patient 2: The LVEF was 40% at referral to the cardio-oncology clinic but the ECHO showed a LVEF of 55%. The patient was asymptomatic and Patient 3: The LVEF was 43% at referral to the cardio-oncology clinic and the ECHO showed a LVEF of 40−45%. The patient was asymptomatic but had significant ventricular bigeminy and was already on treatment with a BB.

In patients with cardiotoxicity the most common treatment given was single agent doxorubicin in 16 (70%) of the patients administered as 75 mg/m^2 by bolus every 3 weeks and the most common histological subtype was leiomyosarcoma in 6 (26%) of the patients . We found no statistically significant association between cardiotoxicity and single agent doxorubicin ($p = 0.231$) but a trend toward an association for leiomyosarcoma ($p = 0.07$).

The median follow-up was 2.9 years (range 0.37−8.1). The 3rd of March 2021 was the last date of follow-up and at that timepoint 19 (83%) of the patients with cardiotoxicity had died. At follow-up, the LVEF remained $<$ 50% in 10 (45%) of the patients, 8 of these initiated anti-congestive treatment; the LVEF increased to $\geq$ 50% and remained $\geq$ 50% in 10 (45%) of the patients, all of these initiated anti-congestive treatment; and the LVEF increased to $\geq$ 50% but subsequently decreased to $<$ 50% in 2 (9%) of the patients, one of these initiated anti-congestive treatment. Overall, recovery of LVEF was seen in 12 (55%) of the patients and persistent recovery in 10 (45%). In one patient the course of the LVEF was unknown.

Three (23%) of the patients had prior to developing late cardiotoxicity, received subsequent treatment with trabectedin which is also considered to be a potentially cardiotoxic agent [22]. Only one patient with cardiotoxicity had received cardio protective treatment with dexrazoxane. Twenty-two (96%) of the patients with cardiotoxicity did not resume treatment with doxorubicin as 17 (74%) had already received the maximum recommended dose. The patient that resumed treatment with doxorubicin had a reduced dose.

Risk factors associated with cardiotoxicity and survival

The diastolic blood pressure at baseline was positively and significantly associated with a higher risk of developing cardiotoxicity (Relative Risk (RR): 1.039 (95% CI= 1.001−1.079; $p = 0.042$)). The mean diastolic blood pressure at baseline was: 78 mmHg (± 11) (no cardiotoxicity), 84 mmHg (± 9) (any cardiotoxicity), 81 mmHg (± 6) (early cardiotoxicity), and 91 mmHg (± 10) (late cardiotoxicity) and correspondingly a significant difference could be demonstrated for no versus late cardiotoxicity ($p = 0.006$). Figure 1 shows a ROC curve for the diastolic blood pressure at baseline with an AUC of 0.664 ($p = 0.024$). No patients with a diastolic blood pressure at baseline below 72 mmHg ($n = 15$ (20%)) developed cardiotoxicity and no patients with a diastolic blood pressure at baseline below 79 mmHg ($n = 33$ (40%)) developed late cardiotoxicity. The cumulative doxorubicin dose per body surface area (BSA) (mg/m^2) showed a trend toward (RR: 1.004 (95% CI= 0.999−1.008; $p = 0.09$)) a higher risk of developing cardiotoxicity.

Metastatic disease (RR: 2.207 (95% CI= 1.221−3.988; $p = 0.009$)), age (RR: 1.028 (95% CI 1.008−1.049; $p = 0.006$)), PSdi (PS $\geq$ 1) (RR: 3.142 (95% CI 1.624−6.015; $p = 0.001$)), LVESV (Z) (RR: 0.672 (95% CI 0.479−0.942; $p = 0.021$)) and hypertension (RR: 3.133 (95% CI 1.360−7.219; $p = 0.007$)) were all significantly associated with a higher risk of death. Heart rate showed a trend toward (RR: 1.020 (95% CI= 0.998−1.043; $p = 0.077$)) a higher risk of death. The median survival was 1.4 years (range 0.5−2.2) for patients with metastatic disease versus 3.9 years (range 1.5−6.4) ($p = 0.009$) for localized disease at baseline. See Figures 2 and 3 for Kaplan Meier plots of overall survival. The multivariate analysis is summarized in Table 2.

Discussion

In this retrospective study of sarcoma patients receiving doxorubicin based chemotherapy, we found a high incidence of cardiotoxicity in 31% of the patients. Other studies display very different incidences of anthracycline induced cardiotoxicity ranging from 9% to 31% [4,15]. In a large review including 22815 patients, anthracycline based chemotherapy was associated with clinically overt cardiotoxicity in 6% of the patients and end-stage heart failure was observed in 2−4% after a median follow-up of 9 years [4]. A real-life report demonstrated, that 298 (31%) of the patients referred for anthracycline based chemotherapy developed LV myocardial dysfunction [17,23]. However another study demonstrated an overall incidence of cardiotoxicity in 226 (9%) of patients [15]. The high incidence found in the present study may be explained by various reasons, one being the long study follow-up resulting in more confirmed cases of late cardiotoxicity (30%). Secondly, prolonged anthracycline infusion schedules have been shown in some studies to be associated with a lower incidence of cardiotoxicity in comparison with a bolus dose [24], though this still remains a controversial issue. All of the patients received doxorubicin as a slow intravenous bolus over 30 min therefore the high incidence may

be partly related to the selected infusion schedule. Finally, the CZT-ERNA has a wider range of LVEF outcome compared to other methods to assess the LVEF [10,13], and using this method may have included more patients with cardiotoxicity.

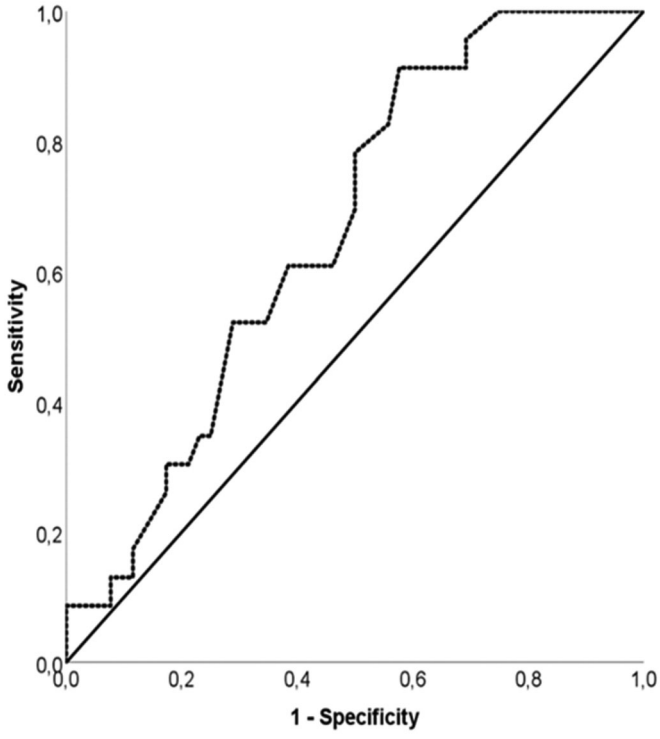

Figure 1. A ROC curve on diastolic blood pressure at baseline as a predictor for cardiotoxicity (AUC = 0.664; $p = 0.024$). Diagonal segments are produced by ties.

It's important to mention that it's difficult to compare the outcome of cardiotoxicity in retrospective studies. The incidence may vary considerably, reflecting the use of different definitions of cardiotoxicity, methods for cardiac monitoring, populations examined, anthracycline regimens, study design, follow-up, and the use of radiation therapy [24].

We found that 16 (70%) of the patients developed early cardiotoxicity, whereas two other studies reported that 53% and 98% of the patients developed cardiotoxicity during the first year [17,23]. This demonstrates that continuous cardiac monitoring remains important especially during the first year after initiation of doxorubicin based chemotherapy. During follow-up we found that recovery of LVEF was seen in 12 (55%) of the patients, persistent recovery in 10 (45%) and no recovery in 10 (45%) of the patients. Other studies have reported that 53% and 87% of the patients displayed an increase in LVEF or improved by at least one congestive heart failure class with anti-congestive treatment [19,25]. In the present study CZT-ERNA was not routinely performed during follow-up in the patients with cardiotoxicity and data on anti-congestive treatment was only collected at baseline and when cardiotoxicity was confirmed, which could both have impacted our results. Furthermore, four patients treated with anti-congestive treatment with no recovery of LVEF had clinical symptoms when cardiotoxicity was confirmed. Initiation of anti-congestive treatment when clinical symptoms are already present have been shown to result in poorer outcomes regarding recovery of cardiac function [23]. Thus, the historical concept that anthracycline induced cardiotoxicity is irreversible has to be reconsidered and the importance of early detection and treatment of cardiotoxicity emphasized.

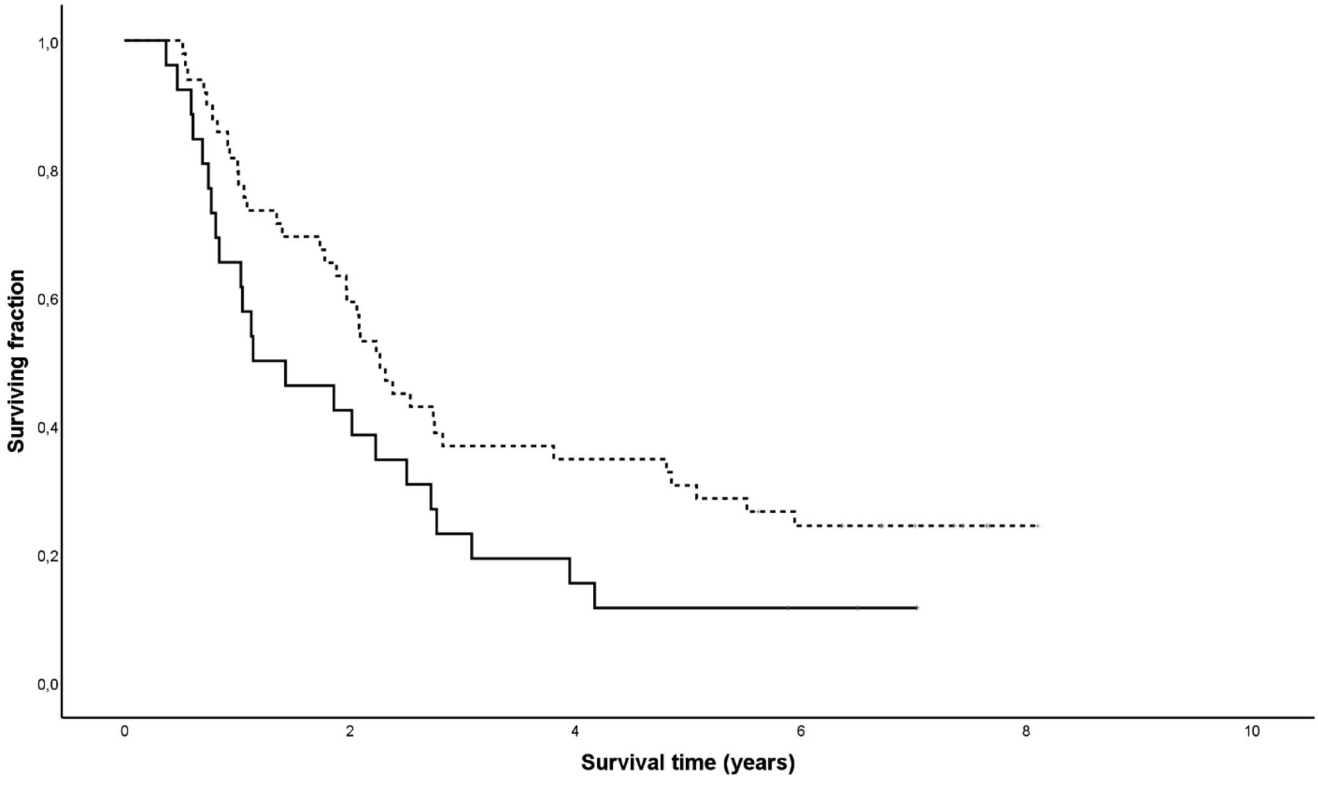

Figure 2. Kaplan Meier plot of overall survival for PS= 0 (dotted line) versus PSdi $\geq$ 1 at baseline (solid line) ($p = 0.044$).

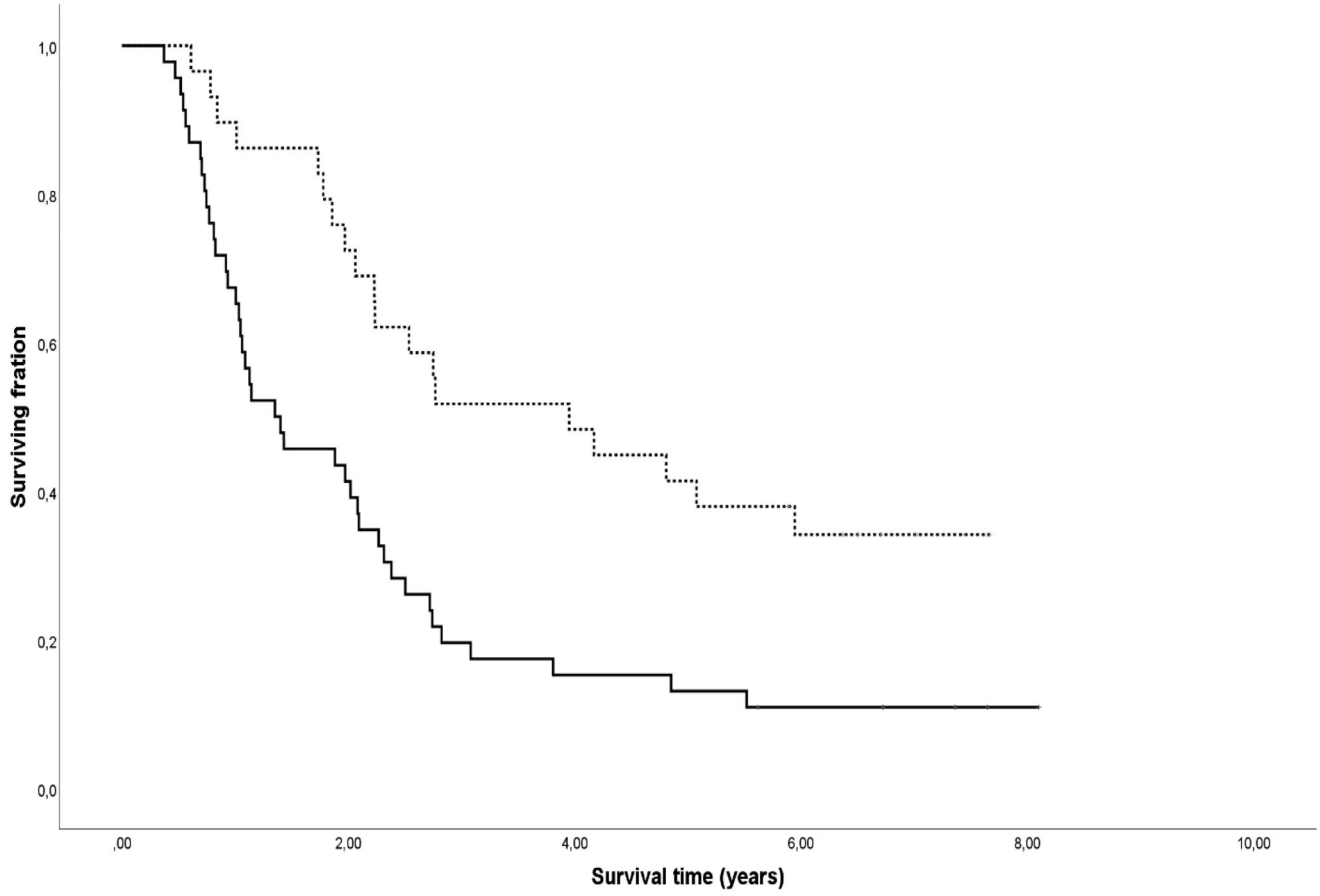

Figure 3. Kaplan Meier plot of overall survival for localized disease (dotted line) versus metastatic disease at baseline (solid line) ($p = 0.001$).

Table 2. Multivariate analysis of potential risk factors associated with the development of cardiotoxicity.

Clinical variable	Relative Risk (95% CI)	*p*-Value
Chemotherapydi	0.903 (0.261–3.123)	0.872
Metastatic disease at baseline	0.901 (0.209–2.772)	0.855
Heart rate	1.006 (0.971–1.043)	0.731
Diabetes	0.702 (0.165–2.991)	0.632
Tobacco	0.798 (0.280–2.271)	0.672
PSdi	1.428 (0.398–5.120)	0.584
Systolic blood pressure	0.987 (0.985–1.016)	0.383
Age	1.020 (0.984–1.058)	0.282
Weight	0.979 (0.946–1.014)	0.238
Height	1.024 (0.984–1.066)	0.249
Hypertension	0.500 (0.200–1.251)	0.139
LVEDV (Z)	5.383 (0.641–45.223)	0.121
LVESV (Z)	0.531 (0.226–1.245)	0.145
LVEF (Z)	0.880 (0.531–1.459)	0.620
Dose per BSA	1.004 (0.999–1.008)	0.090
Diastolic blood pressure	1.039 (1.001–1.079)	0.042

Chemotherapydi: Chemotherapy regime $>$ 1. PSdi: Performance status $\geq$ 1. LVEF: Left ventricular ejection fraction; LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; BSA: Body surface area. *Z*-score: Age and gender adjusted values.

When cardiotoxicity is confirmed during treatment, the maximum cumulative dose of anthracyclines often needs to be limited and as a result the efficacy may be reduced [25]. We found that the majority of cardiotoxic events were detected after 17 (74%) of the patients had already received the maximum recommended dose. Consequently, the cumulative dose and as such the efficacy of doxorubicin was not reduced in most of the patients in the present study, although the development of cardiotoxicity may have had a negative impact on the subsequent anti-cancer treatments given.

Although several guidelines are available, no consensus exists on an optimal monitoring strategy for anthracycline induced cardiotoxicity, as recommendations are either too generic or too strict. The 2016 ESC Position Paper recommends anti-congestive treatment when a decline in LVEF of $>$ 10% to a LVEF of $<$ 50% is observed [5]. A newly published consensus guideline from Journal of the American Heart Association [26] recommends an cardio-oncological risk factor assessment, ECG, biomarkers and imaging before the initiation of an anthracycline in order to estimate the baseline risk of cardiovascular toxicity. We believe this risk assessment is not always feasible as many sarcoma patients may have a poor prognosis and often requires urgent treatment. At our department the patients will have an ECG, CZT-ERNA and physical examination performed before doxorubicin based chemotherapy. If the patient has a pathological ECG, the CZT-ERNA show a LVEF of $<$ 50% and/or has a history of significant cardiac comorbidity, the patient will be discussed with a cardiologist regarding an immediate cardiac protective strategy and if decided referred for a cardio-oncological assessment before treatment initiation. The consensus guideline [26] furthermore recommends that asymptomatic patients, with a decline in LVEF of $>$ 10% pp to a LVEF $<$ 50%, should initiate anti-congestive treatment with an ACEi and BB, and if the LVEF is $>$ 40% they should continue anthracycline. By definite cardiac symptoms the anthracycline

should be put on hold with initiation of anti-congestive treatment [26]. At our department the patients will be referred for a cardio-oncological assessment if they experience a decline in LVEF of $\geq$ 15 pp with a LVEF close to 50%, or if the LVEF decline to $<$ 50% during doxorubicin based chemotherapy. The doxorubicin will be put on hold until the immediate cardio-oncological assessment has been performed. Resumption of doxorubicin will be assessed on a case by case basis and in relation to the results of the assessment, the aggression of the cancer, chemotherapeutic alternatives, and the severity in the LVEF decline. However, it is important to mention that discontinuing doxorubicin should be carefully balanced against the potential anti-cancer benefit but also to keep in mind that cardiotoxicity may be life threatening with severe detrimental side effects.

Combined treatment with Dexrazoxane, an intracellular iron-chelating agent showed in a meta-analysis, including 1619 patients a statistically significant benefit in favor of dexrazoxane for the occurrence of heart failure (RR: 0.29 (95% CI = 0.20−0.41; $p < 0.0001$) and with no difference in response rate between the dexrazoxane group and control group [27]. Another meta-analysis showed that prophylactic treatment with dexrazoxane, beta-blocker, statin or angiotensin antagonists appeared to have similar efficacy for reducing cardiotoxicity [28]. Dexrazoxane is still not routinely used likely because of some concerns surrounding reduced efficacy of anti-cancer treatments. One randomized trial in metastatic breast cancer patients showed a significantly lower response rate in the dexrazoxane arm, but no difference in PFS and OS [29] but a study in patients with osteosarcoma showed that dexrazoxane did not impair the tumor response or increased the risk of secondary malignancy [30]. Based on the results from the meta-analyses and the fact that dexrazoxane has been implemented in some clinical trials with doxorubicin [31,32] the sarcoma patients at our department are currently offered 8 cycles of doxorubicin in combination with dexrazoxane.

Hypertension and the cumulative dose of anthracycline have both previously been described to be associated with the development of cardiotoxicity [33,34]. We found that the diastolic blood pressure at baseline was significantly associated with a higher risk of developing cardiotoxicity and may therefore provide a way to identify patients who are at a particular high risk of developing cardiotoxicity or those who will benefit from prolonged cardiac monitoring. We also found that no patients with a normal diastolic blood pressure at baseline developed cardiotoxicity and therefore this specific subgroup of patients might not benefit from prolonged cardiac monitoring. However, we found that hypertension at baseline (defined as the patient receiving anti-hypertensive treatment at study inclusion) was not associated with a higher risk of developing cardiotoxicity ($p = 0.139$). The explanation for this may be that the blood pressure was already stabilized on anti-hypertensive treatment and therefore hypertension did not correlate with a higher risk of cardiotoxicity. Metastatic disease, age, PSdi, LVESV (Z) and hypertension at baseline were all significantly associated with a decreased overall survival and most of these findings are already well recognized risk factors.

Limitations

First of all, the small cohort of sarcoma patients receiving doxorubicin based chemotherapy displays a somewhat high exclusion rate, but with 50 (68%) of the excluded patients almost initially experiencing grave illness or death, it was limiting but unavoidable. Secondly, the study included both patients with localized and metastatic disease. This has undoubtedly led to a heterogenic population with varying length of survival and, subsequently varying risk of developing late cardiotoxicity. Thirdly, most patients received single agent doxorubicin, but a few patients received other combinations which may have interfered with our results. Still, we find the present population representative and therefore the incidence of cardiotoxicity important to explore. Finally, the lack of additional biomarkers may have reduced our chance to detect cardiotoxic events at an earlier stage which may have delayed initiation of anti-congestive treatment and thus reduced the number of patients recovering from cardiotoxicity.

Conclusion

In conclusion, cardiotoxicity is still a frequent and serious complication in sarcoma patients treated with doxorubicin based chemotherapy. Further optimal risk assessment, treatment and monitoring regarding anthracycline induced cardiotoxicity is still debated and much needed. A future guideline recommendation may consist of individual pre-treatment risk assessment, sequential screening with biomarkers and prophylaxis treatment among others with dexrazoxane. A retrospective study at our department is currently evaluating the incidence of cardiotoxicity in a population-based cohort of sarcoma patients receiving treatment with doxorubicin in combination with dexrazoxane. These future results may help us clarify the use of dexrazoxane as a cardioprotective agent.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

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