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ORIGINAL ARTICLE

Clinical characterization and natural history of chemotherapy-induced dilated cardiomyopathy

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Abstract

Aims Chemotherapy-induced dilated cardiomyopathy (CI-DCM) is a well-recognized phenotype of non-ischemic dilated cardiomyopathy (DCM), characterized by poor outcomes. However, a detailed comparison between idiopathic DCM (iDCM) and CI-DCM is still lacking.

Methods and results All consecutive DCM patients enrolled in the Trieste Muscle Heart Disease Registry were analysed. CI-DCM and iDCM were defined according to current recommendations. The primary study outcome measure was all-mortality death and secondary outcomes were a) a composite of cardiovascular death/heart-transplantation/ventricular-assist-device implantation, and b) major ventricular arrhythmias. The study included 551 patients (499 iDCM and 52 CI-DCM). At enrolment, compared with iDCM, CI-DCM patients were older (51 ± 14 years vs. 58 ± 3 years, respectively, $P < 0.001$) and had a higher left ventricular ejection fraction (32% ± 9 vs. 35% ± 10, respectively, $P = 0.03$). Over a median follow-up of 90 months (IQR 54–140 months), CI-DCM patients had a higher incidence of all-cause mortality compared with iDCM (36.5% vs. 8.4% in CI-DCM and iDCM respectively, $P < 0.001$), while the incidence of major ventricular arrhythmias was higher in the iDCM group compared with CI-DCM (4% vs. 0%, in CI-DCM and iDCM respectively, $P = 0.03$). The risk of the composite outcome was comparable between the two groups ($P = 0.91$). At Cox multivariable analysis, the diagnosis of CI-DCM emerged as independently associated to primary outcome (HR 6.42, 95% C.I. 2.52–16.31, $P < 0.001$).

Conclusions In a well-selected DCM cohort, patients with a chemotherapy-induced aetiology had a higher incidence of all-cause mortality compared with iDCM. Conversely, the incidence of life-threatening ventricular arrhythmic events was higher among patients with iDCM.

Keywords Chemotherapy induced cardiomyopathy; Dilated cardiomyopathy; Cardiotoxicity; Prognosis; Outcomes

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Introduction

Non-ischemic dilated cardiomyopathy (NI-DCM) is a heterogeneous group of heart muscle diseases caused by a wide range of aetiologies.[1,2] Early etiological characterization might provide useful clinical information, both for the prognostication and optimal management of NI-DCM.[3]

Several factors could be responsible for myocardial impairment in NI-DCM, such as arrhythmias, myocardial inflammation, toxins, systemic autoimmune disorders, peripartum disorders and chemotherapeutic agents.[4] However, in approximately 30% to 40% of DCMs, an external cause of the disease cannot be found and, consequently, these DCM are categorized as idiopathic (iDCM), with a likely genetic or post-inflammatory background.[5,6]

The diagnosis of chemotherapy-induced DCM (CI-DCM) is characterized by left ventricular (LV) systolic dysfunction occurring after specific chemotherapy.[7] Despite early diagnosis and intensive treatments in oncology resulted in improved survival from a cancer perspective, CI-DCM carries

unfavourable outcomes.[8] Indeed, conversely to other forms of DCM, the prognosis of CI-DCM is dictated by the competing risk of cancer-related events rather than by cardiovascular events.[9] This is exacerbated because the incidence of LV systolic dysfunction may lead to chemotherapy down-titration, with possible negative effects on cancer prognosis.[10,11]

Currently, while NI-DCM secondary to aetiologies other than chemotherapy is well characterized,[1,3,12] evidence regarding the clinical characteristics and specific outcomes of CI-DCM is still lacking. We therefore aimed to characterize the clinical characteristics and natural history of a cohort of CI-DCM, compared with iDCM.

Methods

Study population

All consecutive patients with iDCM and CI-DCM enrolled in the Trieste Muscle Heart Disease Registry from 1 January 2005 to 31 December 2019 were included in the present study.[3]

The diagnosis of iDCM was defined by the presence of LV systolic dysfunction (i.e. left ventricular ejection fraction (LVEF) $<$ 50%) after accurate exclusion of other causes that could explain the cardiac dysfunction, including history of significant arterial hypertension, congenital heart diseases, cor pulmonale, tachy-induced cardiomyopathy, chemotherapy, history of alcohol abuse, pericardial diseases and active myocarditis.[3] Coronary artery disease was systematically excluded by coronary angiogram or computed tomography according to the pre-test probability.[13,14]

Cardiotoxicity and, therefore, CI-DCM were defined as a decrease of at least 10% in LVEF to a value below 50% in patients who underwent specific oncologic therapy according to current recommendations.[7]

Patients underwent clinical assessment, blood sampling, electrocardiographic and echocardiographic evaluation at the baseline and during the follow-up. All patients received guidelines directed treatments.[15] The study complied with the Declaration of Helsinki and was approved by our institutional ethics board.

Echocardiographic evaluation

Echocardiography measurements were performed according to current international guidelines.[16]

LVEF was calculated using Simpson's biplane method whenever possible. An LV restrictive filling pattern was defined as an E/A ratio $>$2.[17] LV reverse remodelling (LVRR) was defined as an increase in LVEF of at least 10% from baseline.[18]

Study outcomes

The primary endpoint was all-cause mortality. Secondary endpoints were (i) cardiovascular death; (ii) heart transplantation/ventricular assist device (VAD) implantation; and (iii) survival free from major ventricular arrhythmias. Ventricular arrhythmias were defined as sustained ventricular tachycardia, ventricular fibrillation, tachyarrhythmic death, or appropriate ICD intervention, as previously reported.[3] Information regarding outcome was obtained from official reports, direct contact with patients, their families or general practitioners, queries of regional healthcare data warehouse and registers of death of the municipalities of residence. No patients were lost-to-follow-up with respect to ascertaining outcome.

Statistical analysis

Descriptive statistics are reported as mean and standard deviation (±SD), median and interquartile range [IQR], or counts and percentages, as appropriate. Comparisons between groups were made by the one-way ANOVA test on continuous variables. Categorical variables were compared by the χ^2 or Fisher's exact tests. The Kaplan–Meier method was used to estimate the primary study endpoint, and the log rank test was used to compare the curves. Secondary endpoints were compared considering the presence of competing risks, cumulative incidence curves were estimated and compared using the Fine-Gray's method.[19] Univariable and multivariable Cox regression models were fitted for the primary outcome, treating LVRR as a time-depending variable. To avoid overfitting of the multivariable model, clinical covariates were selected using a backward procedure, using a P value $<$0.10 for model retention. Statistical significance for multivariable, log rank and competing risk analyses was defined as $P < 0.05$ for all analyses. All statistical analyses were performed with the statistical software IBM-SPSS (SBSS Inc., Chicago, IL, USA) version 25 and R statistical packages, library 'cmprsk' (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/).

Results

Baseline characteristics

The study population included 551 patients. Of those, 499 (91%) patients were affected by iDCM and 52 (9%) patients had CI-DCM. Baseline characteristics of the two groups are described in *Table 1*.

Regarding CI-DCM patients, the most frequent tumour was breast cancer (20 patients (40%)) followed by lymphoma (18 patients (36%)). Among anti-neoplastic treatments, 38 (76%)

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Table 1 Baseline characteristics of the study population

Dilated cardiomyopathy (551 patients)	Idiopathic DCM (n = 499)	Chemotherapy-induced DCM (n = 52)	Total	P-value
Demographics				
Age, years (mean ± SD)	51 ± 14	58 ± 13	551	<0.001
Male sex, n (%)	326 (65.3%)	16 (30.8%)	342	<0.001
BMI (mean ± SD)	26.5 ± 5	24.8 ± 3	551	0.02
Systolic BP, mmHg (mean ± SD)	120 ± 17	125 ± 20	543	0.06
NYHA class III–IV, n (%)	106 (21.9%)	17 (32.7%)	123	0.08
Moderate to severe MR, n (%)	159 (33.0%)	12 (26.1%)	171	0.34
Electrocardiogram				
QRS duration, ms (mean ± SD)	124 ± 32	118 ± 31	417	0.29
LBBB, n (%)	136 (27.5%)	17 (33.3%)	153	0.38
Atrial fibrillation, n (%)	35 (8.2%)	0 (0%)	35	0.61
Echocardiography				
LVEF, % (mean ± SD)	32% ± 9	35% ± 10	551	0.03
LVEDD, mm	64 ± 9	58 ± 7	551	<0.001
RFP, n (%)	111 (26.4%)	13 (30.2%)	124	0.59
Left atrial area (mean ± SD)	22 ± 4	21 ± 5	456	<0.001
RV dysfunction (shortening area 35%), n (%)	131 (28.1%)	15 (38.6%)	146	0.74
LVRR, n (%)	78 (24%)	12 (27%)	367	0.42
Medications				
ACEi/ARB/ARNI, n (%)	471 (95.2%)	51 (98.1%)	522	0.49
Beta-blockers, n (%)	459 (92.1%)	45 (86.5%)	504	0.12
MRA, n (%)	275 (55.6%)	21 (40.4%)	296	0.04
Diuretics, n (%)	311 (62.8%)	34 (65.4%)	345	0.76
Ivabradine, n (%)	31 (6.3%)	2 (3.8%)	33	0.76

Moderate or severe MR is defined as MR grade >2. RFP was defined as the presence of E/A ≥ 2. P-values are estimated by χ^2 test for categorical variables with an absolute number >5 and Fisher's exact test for other categorical variables; P-values for continuous variables are estimated by ANOVA.
DCM, dilated cardiomyopathy; BMI, body max index; BP, blood pressure; NYHA, New York Heart Association; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RFP, restrictive filling pattern; RV, right ventricular; LVRR, left ventricular reverse remodelling; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; SD, standard deviation.

patients received anthracyclines, 25 (50%) cyclophosphamide, 13 (26%) taxanes, 7 (14%) trastuzumab, 7 (14%) 5-fluorouracile and 5 (10%) received platinum-derived drugs; 26 (52%) patients were also treated with a neoadjuvant or adjuvant radiotherapy regimen (*Table 2*).

At enrolment, CI-DCM patients were older compared to iDCM (58 ± 13 years vs. 51 ± 14 years respectively, $P < 0.001$) and had a lower prevalence of male sex (31% vs. 65%, $P < 0.001$).

Clinical characteristics were mostly comparable between groups. CI-DCM patients had a slightly higher LVEF compared to iDCM (35% ± 10 vs. 32% ± 9, $P = 0.003$) and a less dilated LV and left atrium.

Most patients were treated with both a renin angiotensin system inhibitor and a beta blocker without differences between CI-DCM and iDCM. Finally, over the first 2 years of follow-up, the incidence of LVRR was not different in the two study groups (24% in the iDCM group vs. 27% in the CI-DCM group, $P = 0.72$).

Table 2 Type of cancer and antineoplastic treatment received in the CI-DCM population

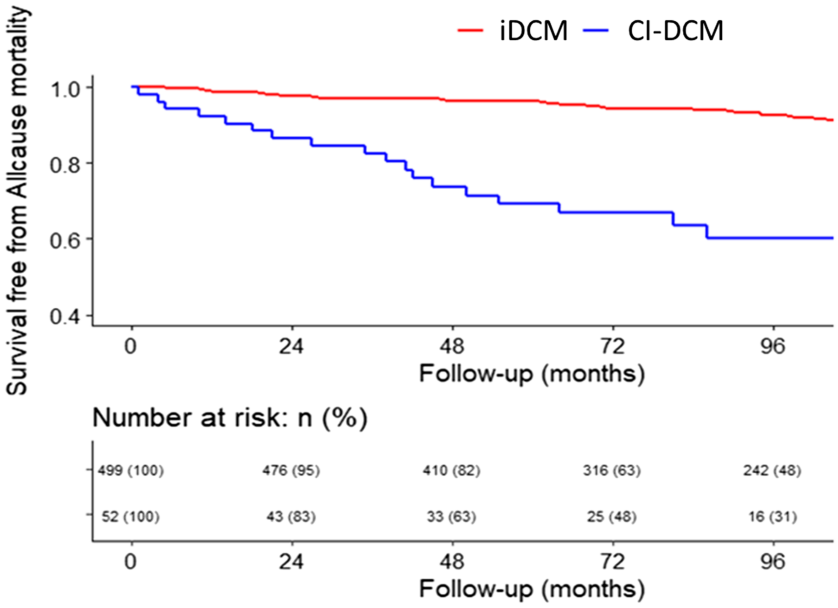
Cancer type*	Total (number)	Total (percentage)
Breast cancer	20	40%
Lymphoma	18	36%
Non-Hodgkin lymphoma	13	83.33%
Hodgkin lymphoma	5	16.67%
Bowel cancer	3	6%
Others	9	18%
Anti-neoplastic treatment* **	**Total (number)**	**Total (percentage)**
Anthracyclines	38	76%
Cyclophosphamide	25	50%
Taxanes	13	26%
Trastuzumab	7	14%
5-fluorouracil	7	14%
Platinum-derived drugs	5	10%
Radiotherapy regimen	26	52%
≥30 Gray (Gy)	10	38.46%
<30 Gray (Gy)	1	3.84%
Data not available	15	57.70%

*Missing data for two patients.
**Missing data for three patients.

Long-term outcomes

Over a median follow-up of 90 months (IQR 54–140 months), 19 CI-DCM (37%) and 42 iDCM (8%) patients died. The cumulative survival in the CI-DCM and iDCM groups at 2 years, 4 years and 8 years was 83%, 63% and 31% versus 95%, 82%, 48%, respectively ($P < 0.001$; *Figure 1*). At multivariable analysis, derived from variables that were significant at

Figure 1 Kaplan–Meier curves for all-cause mortality.



univariable analysis, CI-DCM remained independently associated to all-cause mortality (HR 6.42, 95% Confidence Interval [C.I.] 2.52–16.31, $P < 0.001$), alongside atrial fibrillation (*Table 3*). Concerning the secondary outcomes, the risk of cardiac death/VAD/Heart Transplantation (HTx) was comparable between the two groups (5 [10%] patients in the CI-DCM group vs. 49 [10%] patients in the iDCM group, $P = 0.91$) (*Figure 2*).

A higher risk of life-threatening arrhythmic events was observed in iDCM patients compared to CI-DCM (0% vs. 4%, in

Table 3 Univariable and multivariable analysis for all-cause mortality incidence

Variable	Univariable analysis		Multivariable analysis	
All-cause death	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Chemotherapy-inducedDCM	5.78 (3.35–9.98)	<0.001	5.79 (1.83–18.27)	0.003
Male sex	0.89 (0.53–1.49)	0.65		
Age (per years)	1.04 (1.02–1.06)	<0.001	1.02 (0.99–1.05)	0.23
BMI (per kg/m^2)	0.98 (0.92–1.03)	0.38		
Atrial fibrillation	3.15 (1.56–6.34)	<0.001	5.40 (2.26–12.89)	<0.001
SBP (per mmHg)	0.99 (0.98–1.01)	0.358		
NYHA class III/IV	2.14 (1.28–3.60)	0.004	1.53 (0.71–3.31)	0.27
LBBB	1.13 (0.65–1.95)	0.664		
QRS (per ms)	1.00 (0.99–1.01)	0.561		
Heart rate (per b.p.m.)	1.02 (1.00–1.03)	0.01		
PQ (per ms)	1.00 (0.99–1.01)	0.714		
LAESD (per mm)	0.97 (0.94–1.01)	0.142		
LVEF (per 1%)	0.97 (0.94–0.99)	0.008		
Moderate to severe MR	2.13 (1.27–3.57)	0.004	2.11 (0.89–5.02)	0.091
RFP	1.57 (0.82–2.99)	0.172		
LVRR	0.83 (0.40–1.71)	0.605		
ACEi/ARB/ARNI	1.34 (0.33–5.59)	0.683		
Beta-blockers	0.54 (0.25–1.13)	0.102		
MRA	1.56 (0.93–2.61)	0.089		
Diuretics	3.72 (1.83–7.56)	<0.001		
Ivabradine	0.80 (0.19–3.23)	0.755		

LVRR is treated as a time dependent variable. Moderate or severe MR is defined as MR grade >2. RFP was defined as the presence of E/A ≥ 2.

DCM, dilated cardiomyopathy; BMI, body mass index; SBP, systolic blood pressure; NYHA, New York Heart Association; LBBB, left bundle branch block; LAESD, left atrium end-systolic diameter; LVEF, left ventricular ejection fraction; MR, moderate to severe mitral regurgitation; RFP, restrictive filling pattern; LVRR, left ventricular reverse remodelling; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.

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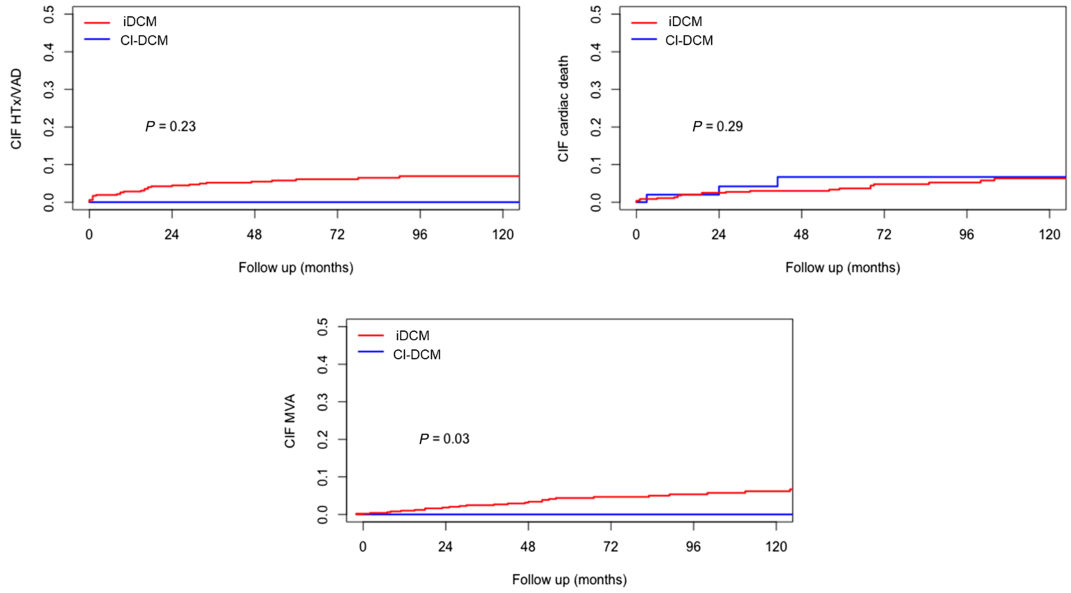
Figure 2 Cumulative Incidence Function for the secondary endpoints of cardiovascular death (Panel A), heart transplantation/VAD implantation (Panel B), or major ventricular arrhythmias (Panel C).



CI-DCM and iDCM respectively, $P = 0.03$) (*Figure 2*). The incidence of specific components of the secondary outcome are depicted in *Table 4*.

Discussion

Despite emerging evidence in the field of CI-DCM, a detailed comparison with iDCM is still lacking. In our study, we found that, despite better baseline cardiac function, CI-DCM emerged as an independent predictor of mortality over long-term follow-up, mostly driven by non-cardiac outcomes. The incidence of life-threatening ventricular arrhythmias was higher in iDCM with no CI-DCM patients experiencing major arrhythmic events.

Table 4 Rates of specific components of outcome measures

	Idiopathic DCM (n = 499)	Chemotherapy-induced DCM (n = 52)
Primary outcome	Number of events (%)	
All-cause death	42 (8.4%)	19 (36.5%)
Secondary outcome	Number of events (%)	
Non-cardiac death	21 (4.2%)	15 (28.8%)
Cardiac death	21 (4.2%)	4 (7.7%)
Heart transplantation	24 (4.8%)	1 (1.9%)
VAD implantation	9 (1.8%)	0 (0.0%)
Major ventricular arrhythmias	22 (4.4%)	0 (0.0%)

DCM, dilated cardiomyopathy; VAD, ventricular assist device.

CI-DCM and iDCM: The same heart disease?

Several factors are commonly considered as disease markers in DCM. We found that patients with CI-DCM had different baseline characteristics compared to iDCM but there was not a clear imbalance with respect to the most frequently occurring prognostic disease markers. While CI-DCM patients were older, they had a higher LVEF and a less remodelled left atrium at baseline. The absence of a severely impaired LV function in most of CI-DCM patients may be linked to the screening of oncology patients to detect clinical and subclinical LV systolic dysfunction.[20] Therefore, although CI-DCM patients are usually sicker due to the co-morbidity burden and the older age, their cardiac phenotype is usually still in a non-advanced stage at the time of diagnosis.

Clinical outcome and mode of death in CI-DCM

CI-DCM is commonly considered a sub-setting of NI-DCM at high risk of adverse outcomes.[3] Previous reports on old series of patients with NI-DCM demonstrated that CI-DCM have a considerably higher risk of all-cause mortality compared to iDCM.[21,22] However, specific causes of death were not previously investigated. From our analysis CI-DCM patients remains a specific subset at high risk of death from any cause. However, this is mainly driven by non-cardiac (i.e. cancer-related) mortality.

We did not find any clinically significant difference in the rate of prescription of HF medications in the two groups. Similarly, the rates of LVRR, which is known to be associated with

favourable outcomes in DCM,[18] were not different between the CI-DCM and groups, confirming previous preliminary findings.[23] Interestingly, we found that the risk of major ventricular arrhythmias in CI-DCM was lower compared to iDCM. In this view, the decision on the indication to primary prevention implanted cardioverter defibrillator in CI-DCM requires particular attention and an accurate risk stratification, possibly with the systematic use of cardiac magnetic resonance. Future, large studies are needed to validate these findings.

Finally, the adverse outcomes among patients with CI-DCM can be explained almost completely by non-cardiac deaths. Although not specifically recorded, it is reasonable to hypothesize that a large proportion of CI-DCM patients with non-cardiac events experience adverse cancer-related outcomes. This issue has a double implication. First, the oncologic disease may be fatal, contributing significantly to the poor prognosis of these patients. Secondly, the incidence of CI-DCM during a chemotherapy treatment may impede cancer treatment by limiting the dose of chemotherapy administrable.[24] It is therefore paramount to avoid LV systolic dysfunction occurrence oncological treatments. So far, most of the cardioactive drugs used have failed to provide significant cardioprotection in this setting. Dexrazoxane, a derivative of ethylenediaminetetraacetic acid; its iron chelator mechanism reduces the generation of oxygen radical species and modifies the structure of topoisomerase II, preventing its binding with anthracycline.[11]

Moreover, liposomal anthracyclines were proven to be effective in the reduction of the risk of CI-DCM incidence compared with traditional anthracyclines in patients treated for breast cancer.[25] This is a relevant point in the prevention of CI-DCM, as the systematic use of these drugs may reduce the burden of cardiotoxicity in these patients. Furthermore, with a different mechanism, the OVERCOME trial demonstrated that patients with malignant haemopathies undergoing haematological chemotherapies had a lower risk of developing left ventricular systolic dysfunction during the course of the chemotherapy when treated with carvedilol and enalapril.[26] Similarly, in patients with early evidence of cardiotoxicity due to high dose anthracycline, treatment with enalapril was able to reduce the incidence of overt cardiac dysfunction.[27] Similarly, beta-blocker and mineralocorticoid receptor antagonists are able to slow the progression of cardiotoxicity and perhaps improve cardiac outcomes in these patients.[28]

Finally, the use of biomarkers may be of interest as they showed relevant clinical implications in different settings.[29,30]

Of note, CI-DCM patients had different distribution between sexes, with a higher proportion of affected women. Although it is well-known that male sex has important prognostic impact in patients with NI-DCM.[31,32] Our results do not allow to draw a conclusion regarding the influence of sex on the outcome, due to the high rate of breast cancers that are proper of female patients.

Clinical implications

The CI-DCM is a particular phenotype in the wide spectrum of NI-DCM, requiring specific care. The outcome of these patients remains poor, but the present study demonstrates that their cardiac phenotype may be less severe than iDCM patients, particularly regarding arrhythmic profile. Cardioactive therapy in CI-DCM should be optimized to prevent severe cardiac manifestations and consequent chemotherapy withdrawal. Small randomized controlled trials showed that targeted therapies may prevent the occurrence of CI-DCM in patients with normal LV function scheduled for chemotherapy.[33,34] Improvements of surveillance and management protocols, early detection of myocardial dysfunction in a subclinical phase through novel and sensitive diagnostic tools (e.g. global longitudinal strain [GLS] or tissue characterization through cardiac magnetic resonance), and the use of the whole HF therapeutic armamentarium, including angiotensin receptor-neprilysin inhibitors (ARNI) and sodium-glucose transport 2 inhibitors (SGLT2-i), could afford further advances in the management of CI-DCM.[35–39]

Limitations

All patients were enrolled in a tertiary referral centre for cardiomyopathies. Therefore, the results of this study should be applied to populations with similar characteristics. Patients with subclinical or mild LV dysfunction might have not been captured in this analysis due to the structure of the referral systems. The proportion of CI-DCM was lower than iDCM, according to the unbalanced epidemiology of the two aetiologies and the difference in the referral system. Biomarkers, especially natriuretic peptides, or advanced imaging characterization were not available for all patients. Furthermore, trajectories of echocardiographic parameters, which has been demonstrated prognostically relevant,[40] were not available for all patients. Limiting the study to those with available data might have introduced selection bias. The relatively low-event rate mandated a long enrollment period to achieve reliable outcome information. Furthermore, the lack of specific cancer related data might have diluted the results. However, the choice of all-cause mortality as the primary outcome allows to capture a wider range of cause of death, partially minimizing this issue. The number of patients receiving novel HF medications (i.e. ARNI and SGLT2-i) is limited due to their recent introduction.

Conclusions

CI-DCM appears to be a specific setting of NI-DCM with a specific clinical and cardiac profile. The risk of all-cause mortality

in CI-DCM is higher compared to iDCM patients, due to the incidence of non-cardiac events. Detailed characterization of patients with CI-DCM is required to optimize medical management and to improve long-term outcomes of these patients, allowing completion of chemotherapy cycles necessary to ameliorate cancer-related outcomes.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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