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RESEARCH ARTICLE

Comparison of long-term outcome in anthracycline-related versus idiopathic dilated cardiomyopathy: a single centre experience

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Aims Cardiac dysfunction is a severe complication of anthracycline-containing anticancer therapy. The outcome of anthracycline-induced cardiomyopathy (AICM) compared with other non-ischaemic causes of heart failure (HF), such as idiopathic dilated cardiomyopathy (IDCM), is unresolved. The aim of this study was to compare the survival of AICM patients with an IDCM cohort followed at our centre from 1990 to 2016.

Methods and results We included 67 patients (67% female, 50 ± 15 years) with AICM, defined as onset of otherwise unexplained left ventricular ejection fraction (LVEF) ≤50% following anthracycline therapy, and 488 IDCM patients (28% female, 55 ± 12 years). Patients were followed with constantly optimized HF therapy, for 7.6 ± 5.5 and 8.1 ± 5.5 years, respectively. In both cohorts, 25% of patients reached the combined endpoint of death/heart transplantation. Overall survival rates at 5 and 10 years were similar (AICM: 86% and 61%, IDCM: 88% and 75%; $P = 0.61$), and so was cardiovascular survival (AICM: 91% and 76%, IDCM: 91% and 80%; $P = 0.373$), also after 1:1 propensity matching ($P = 0.27$) and adjusting for age, LVEF and left ventricular size. A trend toward higher all-cause mortality was present in AICM patients [hazard ratio (HR) 1.67, 95% confidence interval (CI) 0.95–2.92, $P = 0.076$]. No differences were observed between AICM and IDCM with regard to pharmacological HF therapy, but AICM patients were less likely to receive devices (13% vs. 41.8% in IDCM, $P < 0.001$).

Conclusion Cardiovascular mortality in patients with AICM did not differ from that of a matched IDCM cohort, despite cancer-related morbidity and less prevalent use of devices. These data suggest that patients with AICM should be treated with appropriate guideline-directed medical therapies similar to other non-ischaemic dilated cardiomyopathies.

Keywords Cardio-oncology • Anthracycline cardiotoxicity • Anthracycline cardiomyopathy • Left ventricular dysfunction • Heart failure • Prognosis

Introduction

Earlier diagnosis and novel, effective treatments have led to a remarkable increase in the number of cancer survivors, presently estimated at 14.5 million in the USA[1] and expected to reach 18 million by the year 2022.[2] In many of these individuals, long-term outcome is determined by cardiovascular (CV) morbidity associated with cancer therapy-related toxicity.[3] In the last decade, the field of cardio-oncology has rapidly gained clinical relevance and the resulting, widespread awareness has led to the

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adoption of preventive measures such as low-dose chemotherapy regimens and early cardioprotective treatment.[4] Yet, surprisingly little information is known about the contemporary outcome of chemotherapy-related heart diseases, including its most prevalent form: anthracycline-induced cardiomyopathy (AICM).[5–9] AICM, defined as a > 10% reduction in left ventricular ejection fraction (LVEF), to levels <50%, compared with pre-treatment values, is associated with rates of heart failure (HF) that range from 5% to almost 26%, depending on the population and duration of follow-up.[8] AICM is common also in paediatric populations with haematological and solid malignancies, and often presents as dilated cardiomyopathy progressing to a restrictive phenotype.[10,11]

Despite a remarkable increase in the number of publications on cardiotoxicity, limited data are available regarding the long-term prognosis of cancer patients developing left ventricular (LV) systolic dysfunction. When compared with other forms of cardiomyopathy, AICM has been associated with a particularly poor prognosis, with up to 60% of patients dying within 2 years of diagnosis.[12] Of note, the 4-year mortality reported by Felker *et al.* in 2000 for doxorubicin-induced cardiomyopathy was 3.5-fold higher than that of idiopathic dilated cardiomyopathy (IDCM).[12] Following this seminal study, progress has been limited and the long-term outcome of AICM largely remains an open research and clinical issue. Specifically, it is unclear whether the prognosis of AICM is comparable with other non-ischaemic forms of cardiac dysfunction, such as IDCM and therefore simply determined by the severity of functional impairment, or whether its peculiar pathogenesis is associated with an incremental prognostic impact. The present retrospective analysis is aimed at comparing the characteristics, risk factors and survival of two cohorts of AICM and IDCM patients, systematically followed at our centre with the same management strategies over the last 25 years.[13]

Methods

Study population

We retrospectively compared 67 patients with AICM, and 488 patients with IDCM consecutively included in a systematic follow-up programme at our centre from 1990 to 2016. The IDCM patients were part of a previously described cohort.[13] The clinical setting and management strategies adopted at out centre over this period have been detailed in a previous publication.[13] During the follow-up period, three senior cardiologists with specific interest in primary cardiomyopathies and HF have been in charge of the patients. There is no dedicated cardio-oncology unit at our centre, although a tight cooperation has progressively developed over the years, as awareness of cardio-oncologic issues developed in the cardiological community.

Definitions

AICM was defined as a not-otherwise-explained LV systolic dysfunction, i.e. LVEF ≤50%, with or without dilatation, following anthracycline administration and occurring in the absence of prior symptoms or clinical and instrumental signs of heart disease.[14] Specifically, each patient had a demonstration of normal LVEF at screening evaluations prior to anthracycline exposure, confirmed by at least two echocardiograms ≥6 months apart. All patients had a negative/inconclusive coronary angiogram following diagnosis of AICM.

IDCM was defined by the presence of LV or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions (hypertension, valvular disease) or coronary artery disease (CAD).[14] In total, among 747 patients evaluated during the same period, 259 were excluded from the analysis because the LV dysfunction was deemed secondary to CAD ($n = 125$), hypertensive heart disease ($n = 77$), valvular heart disease ($n = 24$), alcohol abuse ($n = 11$), tachycardiomyopathy ($n = 7$), tricyclic antidepressant toxicity ($n = 6$), myocarditis ($n = 3$), acquired immuno-deficiency syndrome ($n = 3$), connective tissue disease ($n = 1$), Tako-tsubo cardiomyopathy ($n = 1$), and Lyme disease ($n = 1$). Nine patients with mild elevation of arterial pressure (World Health Organization grade I hypertension) were included.

Follow-up

Follow-up data were obtained from charts recorded during outpatient controls that were programmed at 6-month intervals, unless more frequently indicated. Clinical history, physical examination, 12-lead electrocardiograms (ECG), standard chest X-ray, routine laboratory tests, 24-h Holter ECG, and M-mode, 2D and Doppler echocardiography were recorded at baseline and over the follow-up. For the purpose of the present analysis, follow-up was closed on 21 April 2016. For patients who died or underwent orthotopic heart transplant (OHT), these events were considered as the end of the follow-up, while last clinical evaluation or telephone contact was taken into account for patients lost to follow-up (i.e. not traceable by 21 April 2016). Deaths were adjudicated by consensus between two senior investigators based on the evaluation of institutional documents and clinical records. Use of drugs, implantable cardioverter defibrillator (ICD), biventricular pacing for cardiac resynchronization therapy (CRT) or ventricular assist device (VAD), was also recorded. Pharmacological treatment was optimized following existing guidelines to maximal tolerated doses of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), beta-blockers (BB) and mineralocorticoid receptor antagonists (MRA). Oral anticoagulation with warfarin or, more recently, direct inhibitors, was initiated for cardioembolic prevention in patients with paroxysmal or permanent atrial fibrillation.

Echocardiography

M-mode, 2D, and Doppler variables were measured in all patients according to international guidelines[15]: left ventricular end-diastolic (LVEDD) and left ventricular end-systolic diameters (LVESD) were measured in M-mode, while volumes and LVEF were calculated by 2D images from an apical four-chamber view, using the biplane method. End-systolic left atrial dimension (LAD) was measured in the antero-posterior linear diameter from the parasternal long-axis view. All 2D echocardiographic parameters were indexed for body surface area.[16]

Study endpoints

All-cause and CV deaths were considered as endpoints. For the purpose of the study, OHT was considered as a CV death-equivalent and included in the endpoint. Cancer-related death was defined as any case in which a definite correlation between primitive cancer and death was identified.

Statistical analysis

Student's *t*-test was used to compare continuous variables. Categorical variables were compared by χ^2 test or Fisher's exact test, as appropriate. Mann–Whitney U test was used to compare numerical variables with non-normal distribution, with prior normality assessment by means of Shapiro–Wilk test. Wilcoxon signed-rank test was used for paired comparisons (e.g. measurements on the same patients before/after follow-up). The univariable survival estimates were obtained using the Kaplan–Meier method. To avoid possible bias due to unbalanced numbers of patients in the two cohorts, a 1:1 based propensity score matching was done. A non-parsimonious logistic regression model was built in order to detect two subgroups of patients, according to type of cardiomyopathy, with comparable baseline data. Candidate matching variables were: age, sex, New York Heart Association (NYHA) functional class, LVEDD, indexed LVEDD (iLVEDD), indexed LAD (iLAD) and LVEF. With these two subgroups, each including 67 patients, survival analyses were performed for all-cause and CV death. Proportional risk multivariable Cox regression analysis was used to evaluate the relationship between clinical and instrumental baseline data and long-term all-cause or CV mortality. Age, LVEF and iLVEDD were included in the regression model as independent variables. Risk proportionality was graphically assessed; candidate predictors which did not met proportionality (namely, age) were previously log-transformed. A *P*-value <0.05 was considered statistically significant. All analyses were performed with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

The mean follow-up from first diagnosis was 7.6 ± 5.5 years in the AICM cohort and 8.1 ± 5.5 years in the IDCM cohort. The mean age was 50 ± 15 years in the AICM and 55 ± 12 years for the IDCM group (*Table 1*). Non-Hodgkin's (*n* = 39; 58.2%) and Hodgkin's lymphoma (*n* = 9; 13.4%) accounted for most indications to anthracycline therapy in the 67 AICM patients. Nine patients (13.4%) had mild (grade I) hypertension, five (7.5%) diabetes, six (9.0%) hypercholesterolaemia and six (9.0%) were active or previous smokers. By definition, a diagnosis of IDCM at our centre implied the exclusion of coronary, hypertensive heart disease (with the exception of the above mentioned nine mild grade hypertensive patients) and diabetes. With regard to dyslipidaemia and smoking, a similar prevalence to the AICM cohort was observed (*n* = 76/15.6%, *P* = 0.128 and *n* = 80/16.4%, *P* = 0.97, respectively). Fourteen patients (21.2%) had already received anticancer chemotherapy prior to the most recent anthracycline exposure and 29 (43.9%) received additional mediastinal or thoracic radiotherapy. Time interval between last chemotherapy and AICM diagnosis ranged from less than 1 month to 23 years (median 10 years, interquartile range 3–48 years), with most cases diagnosed within 2 years of exposure (*Figure 1*). Almost three-quarters (70%) of AICM patients developed CV complications (*Table 1*), including HF (*n* = 43, 64%), thromboembolism (*n* = 11, 16%), moderate-to-severe valve disease (*n* = 4; 6%, mainly mitral regurgitation), or atrial fibrillation (*n* = 1; 1.5%). Two patients developed radiation-induced pulmonary fibrosis (3%). Of note, 14 (21%) patients presented two or more of these complications during follow-up.

Table 1 Baseline characteristics

	AICM (*n* = 67)	IDCM (*n* = 488)	*P*-value
Follow-up, years	7.6 ± 5.5	8.1 ± 5.5	0.408
Age at diagnosis, years	50 ± 15	55 ± 12	0.027
Male gender, *n* (%)	22 (32.8)	353 (72.3)	<0.001
NYHA class I–II, *n* (%)	37 (55.2)	270 (55.3)	0.599
NYHA class III–IV, *n* (%)	30 (44.8)	218 (44.7)	
LVEDD (mm)	56 ± 7	65 ± 8	<0.001
iLVEDD (mm/m^2)	32 ± 5	35 ± 5	<0.001
iLAD (mm/m^2)	22 ± 3	23 ± 4	0.128
LVEF (%)	39 ± 10	33 ± 9	<0.001
AICM characteristics			
Time from last CT to diagnosis, years	3.5 ± 5.6	–	–
History of prior CT[a], *n* (%)	14 (21.2)	–	–
Mediastinum/chest RT, *n* (%)	29 (43.9)	–	–
Oncological diseases			
Non-Hodgkin's lymphoma, *n* (%)	39 (58.2)	–	–
Hodgkin's disease, *n* (%)	9 (13.4)	–	–
Leukaemia (lymphoblastic), *n* (%)	3 (4.5)	–	–
Breast cancer, *n* (%)	6 (8.9)	–	–
Other[b], *n* (%)	10 (15)		
Cardiovascular and other complications			
Heart failure, *n* (%)	43 (64.2)	–	–
Valve disease, *n* (%)	4 (6.2)	–	–
Arrhythmia (atrial fibrillation), *n* (%)	1 (1.5)	–	–
Thromboembolism, *n* (%)	11 (16.4)	–	–
Radiation-induced pulmonary fibrosis, *n* (%)	2 (3.1)	–	–
No other complications, *n* (%)	18 (26.9)	–	–
Two or more complications, *n* (%)	14 (20.9)	–	–
Cardiological treatment during follow-up			
ACEI, *n* (%)	45 (67.2)	409 (83.8)	0.003
ARB, *n* (%)	11 (16,4)	128 (26.2)	0.098
BB, *n* (%)	61 (91,0)	390 (79.9)	0.01
ACEI/ARB + BB, *n* (%)	52 (78.8)	381 (78.1)	0.896
MRA, *n* (%)	28 (42.4)	188 (38.5)	0.591
CRT, *n* (%)	4 (6.0)	89 (18,2)	0.009
ICD, *n* (%)	5 (7.5)	115 (23.6)	0.001
VAD, *n* (%)	0 (0.0)	2 (0.4)	1.000
Status and causes of death			
Death (all causes), *n* (%)	13 (19.4)	100 (20.5)	–
Cardiac (refractory HF), *n* (%)	7 (53.8)	29 (29.0)	–
Cardiac (sudden death), *n* (%)	0 (0.0)	60 (60.0)	–
Cancer related, *n* (%)	4 (30.8)	6 (6.0)	–
Other[c], *n* (%)	2 (15.4)	5 (5.0)	–
OHT, *n* (%)	4 (6.0)	21 (4.3)	–
Lost at follow-up, *n* (%)	11 (16.4)	40 (8.2)	–
Alive, *n* (%)	40 (59.7)	327 (67.0)	–

AICM, anthracycline-induced cardiomyopathy; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CT, chemotherapy; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; IDCM, idiopathic dilated cardiomyopathy; iLAD, indexed left atrial diameter; iLVEDD, indexed left ventricular end-diastolic diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; OHT, orthotopic heart transplant; RT, radiotherapy; VAD, ventricular assist device.

[a]For the same or for a different disease.

[b]Endometrial (uterine) cancer (*n* = 3), osteosarcoma (*n* = 3), hepatocellular carcinoma (*n* = 2), neuroblastoma (*n* = 2).

[c]Non-cardiac, non-cancer-related deaths.

Chemotherapy regimens

Typical anthracycline regimens, in most cases for haematological cancers, are summarized in *Table 2*. On average, a cumulative doxorubicin dose of 273 mg/m^2 (range 160 to 300 mg/m^2) was administered. The initial exposure to previous anthracycline-containing regimens was not included in the dose related to AICM onset.

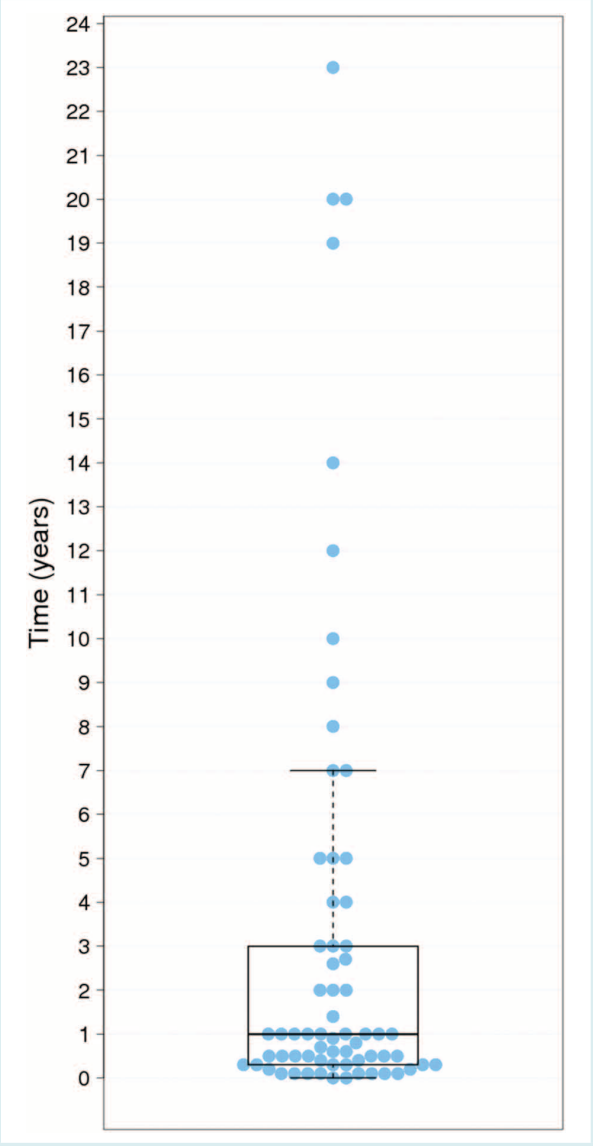


Figure 1 Time from last anthracycline-containing regimen administration to diagnosis of anthracycline-induced cardiomyopathy (AICM) (years).

Comparison with the idiopathic dilated cardiomyopathy cohort

The AICM and IDCM cohorts had comparable follow-up and baseline functional status. However, AICM patients were younger (50 ± 15 vs. 55 ± 12, $P = 0.027$), predominantly females (67%, vs. 28%, $P < 0.001$), and had less severe LV dilatation and dysfunction (*Table 1*). Indeed, they had lower baseline LVEDD and iLVEDD, and higher LVEF than IDCM patients. Such differences disappeared after 1:1 propensity score matching based on age, sex, NYHA functional class and echocardiographic parameters (*Table 3*).

Although BB were prescribed more often than ACEI to AICM patients, there was no difference between the two groups in the use of ACEI/ARB combined with BB (78.8% and 78.1% in AICM and IDCM, respectively, $P = 0.896$), nor of MRA (42.4% and 38.5% in AICM and IDCM, respectively, $P = 0.591$). Devices were more often implanted in IDCM than in AICM patients (18.2% vs 6%, for CRT, $P = 0.009$; 23.6% vs. 7.5%, for ICD, $P = 0.001$, 0 vs. 0.4%, for VAD, $P = 1$; *Table 1*). Evolution of HF therapies in AICM patients over follow-up is described in *Figure 2*. The same data for IDCM were found previously.[13]

Of note, LVEF significantly improved over follow-up in both matched cohorts (AICM: from $39 \pm 10\%$ to $46 \pm 10\%$, $P < 0.001$; IDCM: from $39 \pm 9\%$ to $44 \pm 10\%$, $P < 0.001$). Other relevant echocardiographic parameters remained stable in AICM patients (LVEDD: 56 ± 7.1 mm vs. 56 ± 7.0 mm, $P = 0.601$; iLVEDD: 32 ± 4.6 mm/m^2 vs. 32 ± 3.9 mm/m^2, $P = 0.531$; iLAD 22 ± 3.0 mm/m^2 vs. 23 ± 3.3 mm/m^2, $P = 0.104$), whereas they worsened significantly in those with IDCM (LVEDD: 58 ± 6.6 mm to 59 ± 6.9 mm, $P = 0.009$; iLVEDD: 32 ± 4.4 to 34 ± 5.2 mm/m^2, $P = 0.004$; iLAD 23 ± 5.0 to 24 ± 4.7 mm/m^2, $P = 0.008$; *Figure 3*).

Outcome

Of the 67 AICM patients, 11 (16%) were lost to follow-up after attending clinic visits for a mean of 2.9 years, while 13 (19%) died over a total of 509 patient/years. Of these, seven died of cardiac causes, four of cancer-related complications, and two of other causes. No arrhythmic or coronary deaths occurred in AICM patients; 4 (6%) underwent OHT, 4.3 ± 4 years after the diagnosis of AICM, and were subsequently followed for 14.1 ± 3 years. One of the OHT recipients died of refractory HF 9.5 years after transplant. At 5 and 10 years, CV mortality-free survival was 91% and 76%, while overall survival was 86% and 61%, respectively.

Of the 488 IDCM patients, 40 (8%) were lost to follow-up after attending outpatient visits for a mean of 6.6 years. Over 3950 patient/years, 100 patients (20%) died of sudden cardiac death ($n = 60$), refractory HF ($n = 29$), cancer ($n = 6$), other non-cardiac causes ($n = 5$). Twenty-one (4%) underwent OHT. At 5 and 10 years, CV mortality-free survival was 91% and 80%, while overall survival was 88% and 75%, respectively.

Survival analysis

Survival rates in AICM and IDCM patients were comparable, both for CV (log-rank χ^2 test 0.78, $P = 0.373$) and all-cause mortality (log-rank χ^2 test 0.25, $P = 0.616$). At multivariable analysis, age, iLVEDD and LVEF at diagnosis were significant predictors of CV death, whereas the primary diagnosis was not (HR for AICM vs. IDCM 1.22, 95% CI 0.62–2.40, $P = 0.558$; *Table 4*). There was no difference in the outcome between AICM patients that received concomitant radiation therapy and those who did not ($P = 0.34$). There was a trend toward higher all-cause mortality in the AICM cohort [hazard ratio (HR) vs. IDCM 1.67, 95% confidence interval (CI) 0.95–2.92, $P = 0.076$; *Table 4*]. Survival free of CV death remained comparable after 1:1 propensity score matching (log-rank χ^2 test 1.08, $P = 0.271$; *Figure 4*).

Table 2 Chemotherapy regimens

Schemes	Composition	*n*
Fi2/89	Epirubicin 75 mg/m^2 (day 1), Vincristine 1.4 mg/m^2 (day 2;9) – Bleomycin 10 mg/m^2 (day 2–3, 8–10) – Cyclophosphamide 300 mg/m^2 (day 4–5, 11–12) + Prednisone 40 mg/m^2 (day 1–12)	4
BAVEC–MiMA	BCNU (carmustine) 100 mg/m^2 (day 1) – Doxorubicin 40 mg/m^2 (day 1) – Etoposide 60 mg/m^2 (day 1–4) – Vincristine 1.4 mg/m^2 (day 2) – Cyclophosphamide 600 mg/m^2 (day 3–4), Cytarabine 300 mg/m^2 (day 18), Methotrexate 150 mg/m^2 (day 19) + Prednisone	4[a]
R–CHOP	Rituximab 375 mg/m^2 – Cyclophosphamide 750 mg/m^2 (day 1) – Adriablastin 50 mg/m^2 (day 1) – Vincristine 1.4 mg/m^2 (day 1) + Prednisone	9[b]
CHOP	Cyclophosphamide 750 mg/m^2 (day 1) – Adriablastin 50 mg/m^2 (day 1) – Vincristine 1.4 mg/m^2 (day 1) + Prednisone	15[c]
R–MACOP B	Rituximab 375 mg/m^2 (weeks 1, 3, 5, 7, 9, 11) – Cyclophosphamide 350 mg/m^2 alternated to Adriablastin 50 mg/m^2 (weeks 1, 3, 5, 7, 9, 11) – Methotrexate 400 mg/m^2 (weeks 2, 6, 10)– Vincristine 1.4 mg/m^2/Bleomycin 10 mg/m^2 (weeks 4, 8, 12)	5
MEGA CHOP	Cyclophosphamide 1200 mg/m^2 (day 1) – Adriablastin 70 mg/m^2 (day 1) – Vincristine 1.4 mg/m^2 (day 1) + Prednisone	7
ABVD	Adriablastin 25 mg/m^2 (day 1–14) – Bleomycin 10 mg/m^2 (day 1–14) – Vinblastine 6 mg/m^2 (day 1–14) – Dacarbazine mg/m^2 (day 1–14)	7
Other	Typical doses of Doxorubicin (in the context of various regimens) for breast cancer, ovarian cancer, osteosarcoma and neuroblastoma: 40 to 60 mg/m^2 every 21 to 28 days; hepatocellular carcinoma: 75 mg/m^2 every 21 days	16

[a]One patient received BAVEC–MiMA + mitoxantrone 10 mg/m^2.
[b]Two patients received liposomal doxorubicin instead of adriablastin.
[c]Six patients received CHOP + sequential rituximab.

Table 3 Idiopathic dilated cardiomyopathy baseline characteristics in the 1:1 propensity score matched cohort

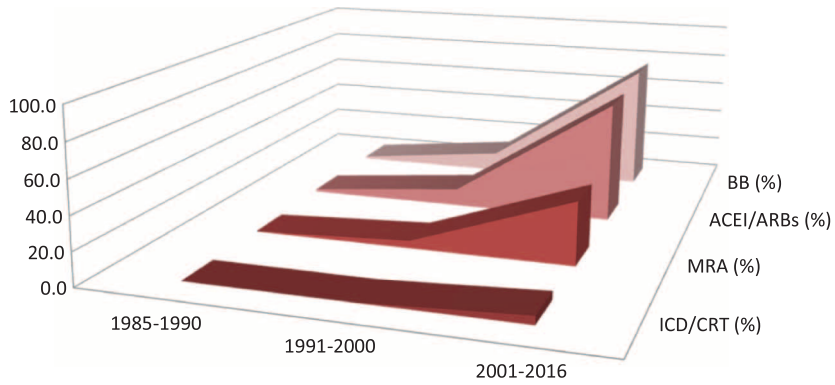
	AICM (*n* = 67)	IDCM (*n* = 488)	IDCM cohort after 1:1 propensity score matching[a]
Follow-up, years	7.6 ± 5.5	8.1 ± 5.5	7.7 ± 5.3
Age at diagnosis, years	50 ± 15*	55 ± 12*	51 ± 14
Male gender, *n* (%)	22 (32.8)*	353 (72.3)*	26 (38.8)
NYHA class I–II, *n* (%)	37 (55.2)	270 (55.3)	37 (55.2)
NYHA class III–IV, *n* (%)	30 (44.8)	218 (44.7)	30 (44.8)
LVEDD (mm)	56 ± 7*	65 ± 8*	57 ± 6
iLVEDD (mm/m^2)	32 ± 5*	35 ± 5*	32 ± 5
iLAD (mm/m^2)	22 ± 3	23 ± 4	23 ± 5
LVEF (%)	39 ± 10*	33 ± 9*	39 ± 8

AICM, anthracycline-induced cardiomyopathy; IDCM, idiopathic dilated cardiomyopathy; iLAD, indexed left atrial diameter; iLVEDD, indexed left ventricular end-diastolic diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
[a]Candidate matching variables were: age, sex, NYHA functional class, LVEDD, iLVEDD, iLAD, and LVEF.
*$P < 0.05$ before 1:1 propensity score matching.

Discussion

The present retrospective study was based on a well characterized cohort of 67 patients with AICM systematically followed over a mean of 7.6 years with optimized HF therapy, compared with IDCM patients managed in the same setting and by the same team of cardiologists with specific interest in primary cardiomyopathies and HF. In line with the seminal report by Cardinale *et al.*,[9] our data show that AICM may be occasionally diagnosed decades after the last anthracycline administration, but is largely recognized in the first 2 years. As previously described[17] and in contrast with the well known preponderance of males in IDCM,[13] we found a higher baseline prevalence of females among AICM patients. Compared with our IDCM patients, those with AICM showed higher LVEF with smaller LV dimensions at diagnosis, in keeping with previous reports indicating lesser degrees of LV dilatation as characteristic of chemotherapy-induced cardiomyopathies.[5,18,19]

In our experience, AICM and IDCM patients showed similar improvement in LVEF in response to optimized pharmacological treatment, which was generally well tolerated (almost 80% of our patients were treated with ACEI/ARB and BB). Moreover, we observed a comparable outcome for CV mortality in the two groups, confirmed by 1:1 propensity score matching analysis (adjusted for demographic, functional and echocardiographic



	1985-1990	1991-2000	2001-2016
ICD/CRT (%)	0.0	0.0	5.0
MRA (%)	0.0	4.5	37.8
ACEI/ARBs (%)	1.5	10.6	72.7
BB (%)	1.5	11.9	76.1

Figure 2 Evolution in pharmacological and device therapy of the anthracycline-induced cardiomyopathy group from initial evaluation to end of follow-up based on enrolment period. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist.

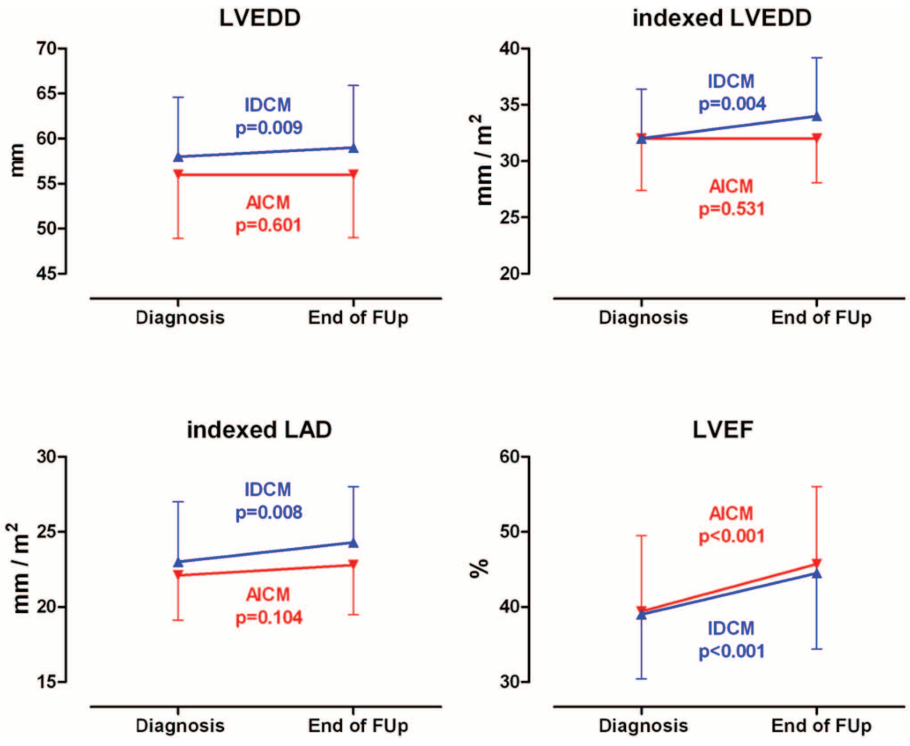


Figure 3 Changes in echocardiographic features over time in anthracycline-induced cardiomyopathy (AICM) and idiopathic dilated cardiomyopathy (IDCM) patients. FUp, follow-up; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

Table 4 Multivariable Cox regression analysis

	Adjusted HR	95% CI	*P*-value
Overall death			
AICM vs. IDCM	1.67	0.95–2.92	0.076
Age (1 year increase)	1.02	1.01–1.03	0.007
iLVEDD (1 mm/m^2 increase)	1.06	1.02–1.09	0.004
LVEF (1% increase)	0.98	0.96–1.00	0.059
Cardiovascular death			
AICM vs. IDCM	1.22	0.62–2.40	0.558
Age (1 year increase)	1.01	0.99–1.03	0.086
iLVEDD (1 mm/m^2 increase)	1.07	1.03–1.11	<0.001
LVEF (1% increase)	0.98	0.96–0.99	0.041

AICM, anthracycline-induced cardiomyopathy; CI, confidence interval; HR, hazard ratio; IDCM, idiopathic dilated cardiomyopathy; iLVEDD, indexed left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

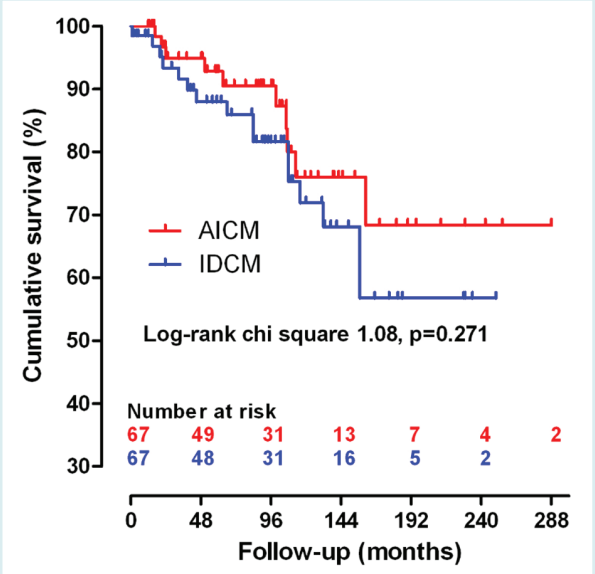


Figure 4 Kaplan–Meier curves for cardiovascular mortality in the anthracycline-induced cardiomyopathy (AICM) and idiopathic dilated cardiomyopathy (IDCM) 1:1 matched populations.

parameters), despite an expected trend toward higher all-cause mortality in AICM. Notably, the 5-year overall survival rate in our AICM cohort (86%) appeared considerably better than that reported by Felker *et al.* 17 years ago (<50%)[12] and was substantially equivalent to the 86.5% rate recently reported by Mazur *et al.* in a small, but well characterized cohort of long-term adult cancer survivors with AICM, followed for up to 8.5 years after CRT/ICD implantation.[20] This finding is even more remarkable considering that a significant proportion of our AICM patients received thoracic radiotherapy and/or additional anticancer chemotherapy prior to the most recent anthracycline exposure, and that use of the less toxic liposomal anthracyclines was limited.

Of note, a striking 64% of our AICM patients experienced signs and/or symptoms of HF, despite constant surveillance and an optimized treatment. In addition, almost three-quarters (73%) experienced other CV events or non-CV-related complications likely related to cancer therapies (see *Table 1*). This finding corroborates the recognition that CV toxicity in AICM patients extends beyond LV dysfunction and HF, to include a variety of complications including vascular disease, thromboembolism and arrhythmias.[21]

While the main mechanisms mediating anthracycline-mediated cardiotoxicity are known,[22,23] factors triggering individual predisposition to AICM are unresolved. In some patients, the cardiotoxic effect of antineoplastic drugs is likely enhanced by co-morbidities and traditional CV risk factors (i.e. diabetes, dyslipidaemia, obesity, smoking, hypertension, and CAD), suggesting an intrinsic frailty of cancer survivors.[24] Furthermore, a degree of individual genetic predisposition appears likely, reflecting non-specific myocardial susceptibility to acquired disease. This view is supported by recent evidence that rare truncating variants in the titin gene, not pathogenic *per se*, are involved in peri-partum cardiomyopathy[25] and that a common deletion in MYBPC3 is associated with development of HF in South Asian populations.[26] Studies exploiting the potential of next generation sequencing genetic techniques are warranted to further investigate these issues.

The improved survival rate of AICM over time likely reflects a more extensive use of potent HF therapies, aggressively pursued at our centre in the last two decades[13] and a greater awareness and earlier recognition of AICM among specialists dedicated to an increasingly close collaboration with the oncology teams. The favorable response to neurohormonal blockade is in line with previous reports on the effects of carvedilol and enalapril in AICM patients with LVEF ≤45%, showing a 42% rate of responders at 3 years (i.e. patients with LVEF recovery to values ≥50%),[27] and with the more recent finding of a recovery rate > 80% in patients treated with cardioprotective medications soon after detection of AICM,[9] confuting the dogma of the irreversibility of anthracycline-induced myocardial damage.[5] Of note, in the former study,[27] the proportion of responders was inversely related to the delay between the end of chemotherapy and initiation of HF treatment, and LVEF failed to recover whenever treatment was delayed >6 months. Consistently, cardiac event rates were lower in responders than in partial or non-responders.[27]

In this perspective, advanced treatment options such as CRT/ICD as well as VAD implantation or OHT, on top of an optimized pharmacological HF therapy, represent reasonable strategies for AICM patients and should be implemented when appropriate according to international guidelines. This is an important clinical message as aggressive management is often denied to cancer survivors: for instance, we observed a lower use of implantable devices in our AICM compared with our IDCM cohort (significant for CRT/ICD). This may reflect, at least in part, a potentially erroneous assumption of reduced life expectancy in cancer patients, even when they are potentially cured. Of note, none of the AICM patients died suddenly, suggesting anyway that less frequent ICD implantation did not negatively affect their outcome: this finding is in line with recent published literature[9] and corroborates the recent findings by Mazur *et al.* about the similar burden of

arrhythmias in AICM patients with CRT/ICD, compared with both cancer and non-cancer patients suffering from ischaemic LV dysfunction or IDCM[20]: interestingly, in this recent report, clinical outcomes, including device therapy, OHT, and overall mortality, did not differ between groups, as previously described.[5,28,29] A recent retrospective study also showed comparable outcome of VAD and/or OHT in 17 patients with end-stage AICM vs. 51 patients with IDCM matched for co-morbidities and severity of LV dysfunction, although a greater proportion of patients in the AICM group developed recurrent or new primary cancer.[30]

We have acknowledged a number of limitations from this study, starting with its retrospective nature, and the relatively small cohort of AICM patients, this being only partly compensated by the homogeneity of follow-up strategies and extended follow-up. In addition, patients have been referred to our clinic over the years following the detection of AICM, rather than during systematic screening for cardiotoxicity (the latter having been implemented only recently at our Institution). Thus, intervals between end of chemotherapy and diagnosis of LV dysfunction were variable and may have influenced the final results. Finally, we acknowledge the fact that a control cohort of cancer survivors with non-anthracycline-related cardiomyopathy, would have been desirable, following the experience of Mazur *et al.*[20]

To date, the definition of chemotherapy-related LV dysfunction is much debated. The definition of AICM used in our study (a LVEF $\leq$50% given at least two previous measurements of LVEF >50%) differs somewhat from the current widely accepted definition of a LVEF drop of 10% or higher to a value below 50%.[31] While most of our AICM patients likely fulfilled both criteria, we recognize that the two definitions may not be fully comparable.

From the observations we made, there were no differences in the AICM patients' outcome between those receiving chemotherapy and none receiving chemotherapy plus radiotherapy patients. However, owing to the relatively small sample size, our results should be interpreted with caution. Moreover, information about radiation doses were not systematically collected as the study was based on a historical cohort followed over decades. In the same way the analysis of the prognostic impact of anthracycline dose was attempted, but the study was definitely not powered to assess differences among groups receiving diverse cumulative doses.

Finally, although patients with a history of significant CAD, valvular disease or hypertensive heart disease were excluded from the analysis, a substantial percentage of AICM patients showed CV risk factors (i.e. mild hypertension and diabetes) that may have influenced the natural history of the disease, potentially impacting the correlation between cancer therapies and LV dysfunction in our patients.

In conclusion, CV-related and overall mortality in patients with AICM receiving optimized HF therapy did not differ from that of a matched IDCM cohort, despite significant cancer-related morbidity. These findings argue against the assumption of reduced life expectancy in cardio-oncologic cohorts, compared with other cardiac conditions, and support the implementation of dedicated cardiological outpatient resources for cancer survivors. Given similar prognosis of AICM with other non-ischaemic dilated forms of cardiomyopathy, these patients should be treated aggressively and appropriately guided by contemporary HF clinical practice guidelines. Larger, multicentre registry studies are needed to define the clinical course and prognosis of AICM in the background of modern chemotherapy regimens.

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