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CME

Anthracycline-Induced Cardiomyopathy

Clinical Relevance and Response to Pharmacologic Therapy

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Objectives The purpose of this study was to evaluate the clinical relevance of anthracycline-induced cardiomyopathy (AC-CMP) and its response to heart failure (HF) therapy.

Background The natural history of AC-CMP, as well as its response to modern HF therapy, remains poorly defined. Hence, evidence-based recommendations for management of this form of cardiomyopathy are still lacking.

Methods We included in the study 201 consecutive patients with a left ventricular ejection fraction (LVEF) ≤45% due to AC-CMP. Enalapril and, when possible, carvedilol were promptly initiated after detection of LVEF impairment. LVEF was measured at enrollment, every month for the first 3 months, every 3 months during the first 2 following years, and every 6 months afterward (mean follow-up 36 ± 27 months). Patients were considered responders, partial responders, or nonresponders according to complete, partial, or no recovery in LVEF, respectively. Major adverse cardiac events during follow-up were also evaluated.

Results Eighty-five patients (42%) were responders; 26 patients (13%) were partial responders, and 90 patients (45%) were nonresponders. The percentage of responders progressively decreased as the time from the end of chemotherapy to the start of HF treatment increased; no complete recovery of LVEF was observed after 6 months. Responders showed a lower rate of cumulative cardiac events than partial and nonresponders (5%, 31%, and 29%, respectively; $p < 0.001$).

Conclusions In cancer patients developing AC-CMP, LVEF recovery and cardiac event reduction may be achieved when cardiac dysfunction is detected early and a modern HF treatment is promptly initiated. (J Am Coll Cardiol 2010; 55:213–20) © 2010 by the American College of Cardiology Foundation

Chemotherapy-induced cardiotoxicity is a rapidly evolving area, as well as one of growing interest, due to the increasing number of long-term cancer survivors. The most common clinical presentation of cardiotoxicity is a dose-dependent cardiomyopathy (CMP) leading to chronic heart failure (HF), frequently occurring after administration of chemotherapy including anthracyclines (ACs) (1,2).

Because most studies and registries have not specifically analyzed anthracycline-induced cardiomyopathy (AC-CMP) among the several possible causes of chronic HF, its prevalence is not well known. From among the few studies in which the etiology of HF has been evaluated in detail, a prevalence of 1% of all cases of CMP has been reported (3,4). Data from oncology literature, however, indicate that more than one-half of all patients exposed to AC will show some degree of cardiac dysfunction 10 to 20 years after chemotherapy, and 5% of them will develop overt HF (5). As more than 60,000 patients are treated every year with AC in the U.S., the overall incidence of this complication is probably greatly underestimated (6). The onset of AC-CMP, even asymptomatic, not only negatively impacts the cardiac outcome of cancer patients (7,8), but also seriously limits their therapeutic opportunities. Indeed, patients with poor-prognosis cancer require adjunctive chemotherapy for disease relapse after a first line of chemotherapy in more than 30% to 60% of cases within 5 years (9,10), and the presence of AC-CMP restricts the choice of possible oncologic treatments to those considered less aggressive and, consequently, less effective (1,11–13).

Compared with other more frequent forms of CMP, AC-CMP has been associated with an especially poor prognosis, with a 2-year mortality rate of up to 60% (3,14,15), and is also believed to be refractory to conven-

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Abbreviations and Acronyms

AC = anthracycline
ACEI = angiotensin-converting enzyme inhibitor
CMP = cardiomyopathy
HF = heart failure
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association

tional therapy. Most data concerning the natural history of this disease and its treatment, however, are anecdotal or based on findings reported in old studies, in which standard therapy included only the use of digoxin and diuretics (15,16). The response to modern HF therapy of AC-CMP has never been evaluated in clinical trials, and the effectiveness of angiotensin-converting enzyme inhibitors (ACEIs) and beta-blocking agents in this particular clinical setting can be found in a very few studies that involved small populations. Moreover, data on long-term outcomes of treated and untreated patients with AC-CMP are limited. As a consequence, evidence-based recommendations for the management of cancer patients with asymptomatic and symptomatic AC-CMP are still lacking, and no definite guidelines are currently adopted.

The aim of the present study was to prospectively evaluate a large population of symptomatic and asymptomatic patients with AC-CMP and to examine their response to modern medical HF therapy.

Methods

Study population. This prospective study was conducted at the European Institute of Oncology, University of Milan, between March 1, 2000, and March 1, 2008. Among patients treated with AC in our own institute, as well as those referred to our Cardiology Unit from other oncologic institutes after the detection of cardiotoxicity or for evaluation before new oncologic treatment due to disease relapse, we considered all consecutive patients with echocardiographic evidence of left ventricular systolic dysfunction, regardless of the presence of HF symptoms. Patients were eligible for enrollment if they fulfilled the following inclusion criteria: 1) evidence of left ventricular ejection fraction (LVEF) ≤45%; and 2) absence of any identifiable cause of CMP other than chemotherapy, excluded by clinical history and, in patients with risk factors for coronary artery disease or electrocardiographic abnormalities, by exercise- or pharmacologic-induced provocative tests, coronary angiography, or coronary multislice computed tomography.

All patients younger than 18 years of age, those with contraindication to ACEIs or beta-blockers, already in treatment with these drugs, previously treated with chemotherapy schedules not including AC, with severe (stage 4) renal insufficiency (17), and with an oncologic life expectancy shorter than 12 months were excluded from the study. The investigation conformed with the principles of the Declaration of Helsinki; the study was approved by our institutional review board, and all patients provided written informed consent for clinical research analysis.

Study protocol. All study patients underwent physical examination, electrocardiogram, and echocardiogram, including measurement of LVEF (biplane method according to modified Simpson's rule) (18) at time of enrollment; after 1, 2, and 3 months from the beginning of cardiac therapy; every 3 months during the first 2 years of observation; and every 6 months afterward or whenever required by the clinical situation. In the case of patients who were lost or who died during follow-up, the evaluation performed at the last follow-up check was considered the final measurement.

The primary end point of the study was the LVEF response to HF therapy. During follow-up, patients were considered as responders when LVEF increased up to the normal limit of 50%, as partial responders when LVEF increased at least 10 absolute points but did not reach the limit of 50%, and as nonresponders when LVEF increased fewer than 10 absolute points and did not reach the limit of 50%.

Secondary end points included the occurrence of major adverse cardiac events during follow-up. The following cardiac events were considered: 1) sudden death; 2) death resulting from a cardiac cause; 3) acute pulmonary edema; 4) overt HF requiring hospitalization; 5) life-threatening arrhythmias requiring treatment; and 6) conduction disturbances requiring a permanent pacemaker implantation.

Study treatment. By protocol, in all patients, enalapril was the first initiated treatment at a dose of 2.5 to 5 mg/day (according to baseline systemic arterial pressure), once or twice a day, and gradually up-titrated to 20 mg/day, or to the maximal-tolerated dose. In patients receiving at least 5 mg/day of enalapril, carvedilol was given at an initial dose of 6.25 mg/day (3.125 mg twice a day) and progressively up-titrated to the maximal-tolerated dose or to 50 mg/day.

Additional pharmacologic treatment, including diuretics, anticoagulants, and antiarrhythmic drugs, was given as needed at the discretion of the cardiologist responsible for the patient and on the basis of current standards of care (19).

Statistical analysis. A sample size of 200 patients allowed 90% statistical power to assess as significant, with alpha error of 0.05, and an odds ratio (OR) of 1.6 of the primary end point (partial or nonresponse to treatment) for 1 SD increase in any predictor examined.

Continuous variables are presented as mean (SD) and were compared among groups by 1-way analysis of variance. Categorical data are presented as absolute values and percentages and were compared using the chi-square test or the Fisher exact test, as appropriate. Due to its skewed distribution, the time from the end of chemotherapy to the start of HF treatment (time-to-HF treatment) was presented as median and interquartile range.

Linear regression analysis was used to explore the relationship between LVEF maximal change during the follow-up period and time-to-HF treatment. Time-to-HF treatment was log transformed before analysis.

A multivariable logistic regression model with stepwise selection of variables was used to identify independent predictors of the primary outcome (LVEF recovery). Candidate variables were age, sex, cardiovascular risk factors, cumulative AC dose, time-to-HF treatment, radiotherapy, creatinine clearance, enalapril and carvedilol association, and New York Heart Association (NYHA) functional class. As LVEF at start of HF treatment is strongly associated with final LVEF, and as a consequence, to the primary end point of the study, it was not considered among the potential independent predictors. This variable, however, was forced into the final model in order to confirm the other selected predictors. Adjusted OR and 95% confidence intervals (CIs) were computed.

LVEF recovery was also analyzed as a continuous variable (difference between final and baseline value). In this case, multiple linear regression analysis with stepwise selection of variables was used to obtain the independent predictors of the following LVEF changes.

Kaplan-Meier analysis was used to compare the time-to-event rate among the 3 groups. A p value <0.05 was considered statistically significant.

All tests were 2-sided, and all analyses were performed using SAS software package (version 9.13, SAS Institute, Cary, North Carolina).

Results

Two hundred fifteen consecutive patients were initially enrolled. Fourteen patients were excluded from the analysis because of associated coronary artery disease (n = 3), early (<2 months) death from oncologic disease (n = 2), or lost to follow-up (n = 9). A total of 201 patients (mean age 53 ± 12 years; 149 women) were included in the study. Baseline (before AC therapy) LVEF was available in 148 (74%) patients. On presentation, 148 patients (74%) were in NYHA functional class I or II and 53 (26%) were in class III or IV. In 72 patients (36%), only enalapril was given (mean dose 11 ± 7 mg/day). In these patients, reasons for lack of the addition of carvedilol were symptomatic hypotension (n = 40), critical bradycardia (n = 6), and severe asthenia (n = 26). The remaining 129 patients received the combination of enalapril (mean dose 12 ± 6 mg/day) and carvedilol (mean dose 14 ± 7 mg/day). In 4 patients who referred with cough, enalapril dosage was decreased with symptom resolution.

The median time-to-HF treatment was 4 months (interquartile range 2 to 14 months). The mean follow-up duration after start of HF treatment was 36 ± 27 months (range 12 to 96 months). During this period, 85 patients (42%) normalized their LVEF and were considered responders; 26 patients (13%) were partial responders, and 90 patients (45%) were nonresponders. Neither new electrocardiographic Q waves nor other abnormalities were observed, nor did acute coronary syndromes occur during the follow-up. One hundred seven (53%) patients were given additional chemotherapy, and 62 (31%) died from oncologic disease during the study period.

The clinical characteristics, the HF therapy, and the oncologic treatment before enrollment of the 3 study groups are shown in Table 1 (20,21). There were not significant differences in terms of baseline characteristics, type of oncologic treatment received, or total dose of AC. Responders had a significantly shorter time-to-HF treatment and were more likely to tolerate the combination of enalapril and carvedilol. In these patients, complete reversal of LVEF impairment was observed at 7 ± 4 months from the start of HF therapy. The percentage of responders progressively decreased as the time-to-HF treatment increased. Notably, in no patient was complete LVEF recovery observed after a time-to-HF treatment longer than 6 months (Fig. 1).

Patients with either partial or no LVEF increase after treatment experienced a more complicated clinical course, with a higher rate of cumulative cardiac events, including death, occurring more frequently in these 2 groups (Table 2). The cumulative cardiac event rate as a function of the follow-up time based on Kaplan-Meier estimates in the 3 groups is shown in Figure 2.

Figure 3 shows LVEF changes in response to HF therapy in several subsets of patients, as defined by age, sex, symptom severity, type of HF therapy, time-to-HF treatment, and cumulative AC dose.

At multivariate analysis (logistic regression with stepwise selection of variables in the model, including age, sex, cardiovascular risk factors, cumulative AC dose, time-to-HF treatment, radiotherapy, creatinine clearance, enalapril and carvedilol combination, and NYHA functional class), time-to-HF treatment and NYHA functional class were selected as the only independent predictors of lack of complete LVEF recovery (OR: 3.9; 95% CI: 2.7 to 5.7; $p < 0.0001$ for each doubling in time-to-HF treatment; OR: 8.7; 95% CI: 3.0 to 25; $p < 0.0001$ for NYHA functional class III or IV). When pre-HF treatment LVEF was forced into the final model, time-to-HF treatment and NYHA functional class were still confirmed as significant and independent predictors. When patients with both a time-to-HF treatment <6 months and an NYHA functional class I or II were considered, positive predictive value for complete LVEF recovery was 84%, and negative predictive value was 87% (sensitivity 82%; specificity 89%).

In the entire population, the LVEF maximal change during follow-up, considered a continuous variable, was inversely related to log-time-to-HF treatment (Fig. 4).

Discussion

The major finding of the present study is that, in patients with AC-CMP, an early treatment allows for complete recovery of LVEF and positively impacts cardiac outcome.

Historically, AC-CMP was believed to be refractory to conventional therapy. This opinion, however, was based on findings reported in old studies in which standard therapy

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Table 1 Clinical Characteristics of the 3 Study Groups

	Responders (n = 85)	Partial Responders (n = 26)	Nonresponders (n = 90)	p Value
Age, yrs	52 ± 12	53 ± 10	54 ± 13	0.36
Women	65 (76)	21 (81)	63 (70)	0.48*
Hypertension	27 (32)	6 (23)	24 (27)	0.96
Diabetes	5 (6)	2 (8)	10 (11)	0.49*
Hypercholesterolemia	6 (7)	3 (11)	10 (11)	0.59*
Current or past smokers	32 (38)	10 (38)	33 (37)	0.98
Family history of CAD	11 (13)	5 (19)	10 (11)	0.53*
NYHA functional class III or IV	11 (13)	18 (69)	24 (27)	<0.001
LVEF before AC therapy, %	62 ± 4	60 ± 4	60 ± 4	0.16
LVEF before HF therapy, %	41 ± 5	28 ± 4	38 ± 7	<0.001
LVEF at the end of the study, %	55 ± 3	44 ± 4	38 ± 8	<0.001
Mitral regurgitation grade 3 or 4	4 (5)	1 (4)	8 (9)	0.56*
Creatinine clearance† (ml/min)	110 ± 45	94 ± 26	95 ± 42	0.05
Oncologic disease				0.26‡
Acute lymphatic leukemia	1 (1)	1 (4)	5 (6)	
Breast cancer	52 (61)	16 (62)	39 (43)	
Hodgkin's disease	3 (3)	0 (0)	8 (9)	
Non-Hodgkin's lymphoma	16 (19)	4 (15)	21 (23)	
Other tumors	14 (16)	4 (15)	17 (19)	
Time-to-HF treatment (months)	2 (1–3)	4 (2–6)	17 (8–36)	<0.001
HF therapy				
Enalapril and carvedilol	67 (78)	13 (50)	49 (54)	0.001
Diuretics	21 (25)	18 (69)	45 (50)	<0.001
Amiodarone	0 (0)	4 (9)	8 (9)	0.001*
Anticoagulants	1 (1)	2 (8)	5 (6)	0.15*
Antineoplastic treatment				
Anthracyclines§				
Doxorubicin	37 (44)	11 (42)	40 (44)	0.98
Epirubicin	36 (42)	10 (38)	31 (34)	0.56
Daunorubicin	1 (1)	0 (0)	2 (2)	1.00*
Doxorubicin + epirubicin	2 (2)	1 (4)	4 (4)	0.66*
Doxorubicin + epirubicin + idarubicin	0 (0)	0 (0)	2 (2)	0.61*
Doxorubicin + idarubicin	6 (7)	2 (8)	3 (3)	0.42*
Doxorubicin + idarubicin + mitoxantrone	0 (0)	0 (0)	2 (2)	0.61*
Doxorubicin + mitoxantrone	1 (1)	1 (4)	6 (7)	0.18*
Daunorubicin + idarubicin	1 (1)	1 (4)	0 (0)	0.12*
Liposomal doxorubicin	1 (1)	0 (0)	0 (0)	0.55*
Taxanes in addition to anthracyclines	25 (29)	4 (15)	13 (14)	0.04*
Monoclonal antibodies in addition to anthracyclines				
Trastuzumab	0 (0)	0 (0)	0 (0)	1.00*
Bevacizumab	0 (0)	0 (0)	0 (0)	1.00*
Rituximab	5 (6)	4 (15)	10 (11)	0.25*
Cumulative anthracycline dose‖ (mg/mq)	301 ± 124	341 ± 130	333 ± 150	0.24
Cardioprotective agents				
Dexrazoxane	1 (1)	0 (0)	0 (0)	0.55*
Mediastinum RT¶	6 (7)	1 (4)	12 (13)	0.28*
Chest-wall RT (left)#	24 (28)	9 (34)	15 (17)	0.07
Mean follow-up duration (months)	34 ± 26	46 ± 30	36 ± 27	0.10
Additional CT during follow-up	48 (56)	13 (50)	46 (51)	0.73
Oncologic death during follow-up	23 (27)	9 (35)	30 (33)	0.60

Data are expressed as n (%) or mean ± SD except for time to HF treatment, which is expressed as median (interquartile range). *By Fisher exact test. †Estimated by Cockcroft-Gault formula (20). ‡Cumulative p value. §ACs were given in all cases as a slow intravenous bolus over 15 to 30 min. ‖Cumulative AC dose was calculated by converting different AC agents in terms of doxorubicin equivalents (21). ¶Total dose 30 Gy. #Total dose 60 Gy.

AC = anthracyclines; CAD = coronary heart disease; CT = chemotherapy; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RT = radiotherapy.

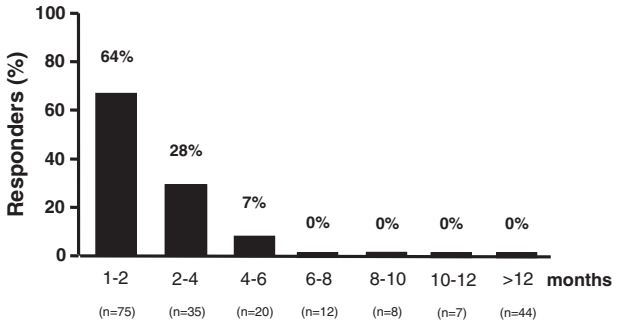

Figure 1 Percentage of Responders According to the Time Elapsed From AC Administration and Start of HF Therapy

AC = anthracyclines; HF = heart failure.

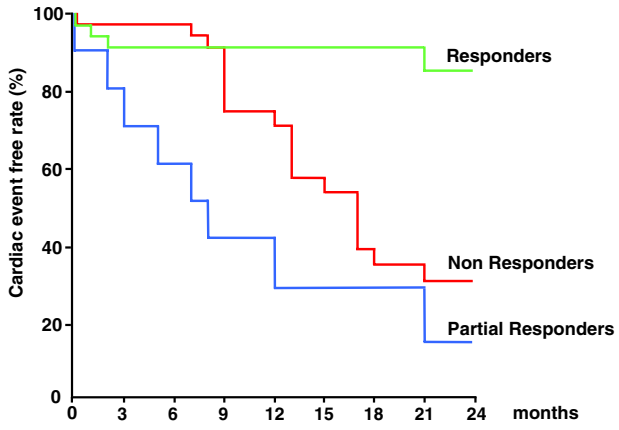

Figure 2 Cumulative Cardiac Event Rate During the Study Follow-Up

2-year Kaplan-Meier analysis for major adverse cardiac events in the 3 study groups. p = 0.0003 (log-rank test).

included only the use of digoxin and diuretics (16,22,23) or in studies with very small sample sizes (14,24–30). The response to modern HF therapy of patients with AC-CMP has never been fully investigated, because typically, these patients have been excluded from large randomized trials evaluating the effectiveness of novel HF therapies.

Due to the different etiology and age distribution of this kind of CMP, when compared with the more frequent ischemic or idiopathic CMPs, there is some concern regarding whether the use of ACEI and beta-blocking agents, recommended by the international cardiologic guidelines, can be directly transferred to this particular clinical setting with similar long-term benefits (6). Moreover, one of the more challenging features of cardiac dysfunction due to AC is the asymptomatic nature of the disease (5). For this reason, many authors have suggested only screening programs to look for overt HF, and current management of AC-CMP mainly focuses on treatment of symptomatic patients (27,29). A crucial issue is whether or not, and eventually how, to treat patients still asymptomatic, in whom left ventricular dysfunction is detected on routine screening examinations. To date, there is no consensus about what (if anything) can be done to curtail the progression of AC-CMP (6). As a consequence, evidence-based recommendations for management of cancer patients with asymptomatic and symptomatic AC-CMP are still lacking.

Predictors of LVEF recovery. In our study, a short time-to-HF treatment and a low NYHA functional class were selected as the only independent predictors of LVEF recovery. In particular, time-to-HF treatment represents the major critical variable in this population. Indeed, an inverse relationship clearly exists between the time elapsed from the end of chemotherapy and the beginning of HF therapy and improvement in LVEF. We found an approximately 4-fold decrease in the chance of complete recovery from cardiac dysfunction for each doubling in time-to-HF treatment. Actually, the percentage of patients with a complete LVEF recovery, among those treated within 2 months after the end of CT, is 64%; after this time limit, however, this percentage gradually decreases, and no complete LVEF recovery is observed after 6 months (Fig. 1). After 12 months, the possibility of obtaining at least a partial LVEF improvement is completely exhausted. Moreover, baseline NYHA functional class III or IV is a strong predictor of lack of response to HF therapy. Therefore, cardiac monitoring exclusively based on symptoms evaluation may miss the opportunity to detect cardiotoxicity early and in a still-reversible stage.

Considering these 2 independent variables together (a time-to-HF treatment <6 months and an NYHA func-

Table 2 Cardiac Events in the 3 Study Groups

	Total (n = 201)	Responders (n = 85)	Partial Responders (n = 26)	Nonresponders (n = 90)
Sudden death	1 (0.5%)	0 (0%)	0 (0%)	1 (1%)
Cardiac death	3 (1.5%)	0 (0%)	0 (0%)	3 (3%)
Acute pulmonary edema	2 (1%)	0 (0%)	1 (2%)	1 (1%)
Heart failure requiring hospitalization	7 (3.5%)	0 (0%)	1 (2%)	6 (7%)
Life-threatening arrhythmias	20 (10%)	4 (3%)	4 (15%)	12 (13%)
Conduction disturbances requiring pacemaker implantation	5 (2.5%)	0 (0%)	2 (8%)	3 (3%)
Cumulative events	38 (19%)	4 (5%)	8 (31%)	26 (29%)*

For each patient, only the first event was considered. *p < 0.001.

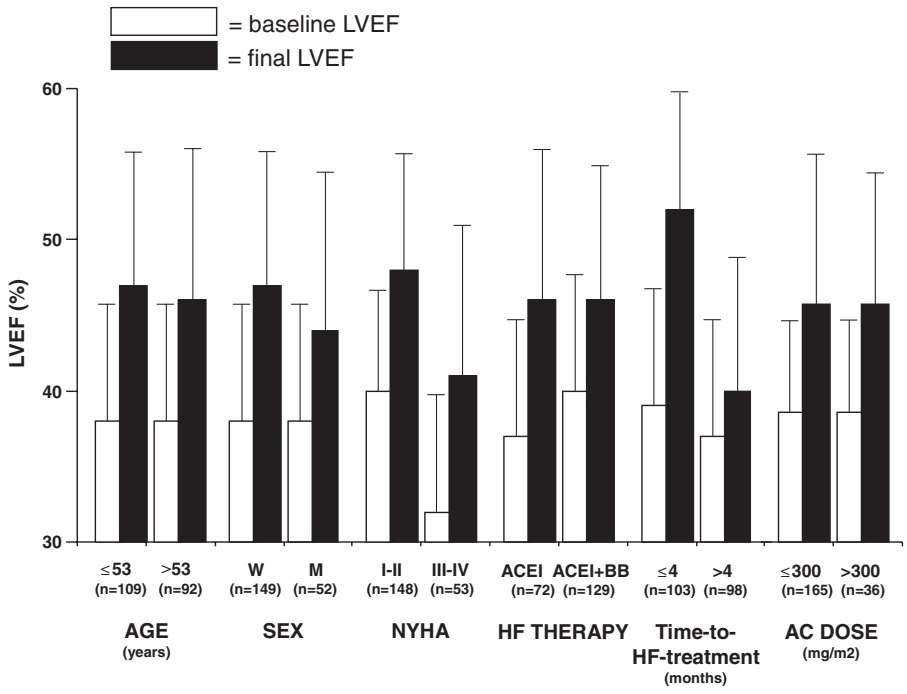

Figure 3 LVEF Changes in Several Subsets of Patients

Left ventricular ejection fraction (LVEF) before (baseline) and after (final) heart failure (HF) therapy in various subgroups of patients. For age, time-to-HF treatment, and anthracycline (AC) dose, patients were stratified according to the median value. $p < 0.001$ for all comparisons. ACEI = angiotensin-converting enzyme inhibitor; BB = beta-blocker; M = men; NYHA = New York Heart Association; W = women.

tional class I or II) as indicators for LVEF recovery at the time of first detection of AC-CMP, we can accurately predict response to therapy, as well as the risk of future cardiac events. This information permits clinicians to better stratify the overall (oncologic and cardiac) risk of cancer patients developing cardiotoxicity and to plan future strategies in case of cancer relapse and need for additional chemotherapy. Notably, in our study, most patients with cancer relapse during follow-up were not treated with AC (particularly doxorubicin, the most cardiotoxic AC) because of cardiac dysfunction.

The importance of an early diagnosis and start of treatment for achieving a reversion of AC-CMP is in agreement with our previous studies, which show that, in AC-treated patients with myocardial cell injury disclosed by a rise of troponin I, enalapril prevents LVEF decrease as well as the occurrence of associated cardiac events (31). This emphasizes the crucial importance of an early detection of cardiotoxicity in order to effectively prevent AC-CMP or to treat patients in a phase in which the disease is still reversible.

Responders more frequently tolerated a combination of enalapril and carvedilol. This underlines the fact that an optimized approach based on the association of these 2 drugs should always be considered, and attempted, in all AC-CMP patients. In our study, by protocol, enalapril was the first initiated treatment in accordance with the international recommendations for chronic HF therapy at the time the study was designed (32) and with the further evidence of the crucial role of the cardiac tissue renin-angiotensin system in the pathogenesis of AC-CMP (33,34). However, given the peculiar characteristics of AC-CMP, often characterized by inap-

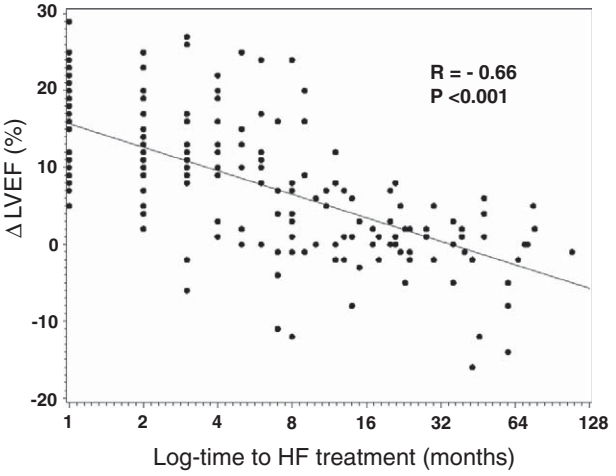

Figure 4 Correlation Between LVEF Changes and Time-to-HF Treatment

Relationship between maximal left ventricular ejection fraction changes (ΔLVEF) during the follow-up period and log time elapsed from chemotherapy and start of treatment (time-to-heart failure [HF] treatment).

propriate sinus tachycardia and hypotension related to the underlying oncologic disease and treatment (30), we cannot exclude that a first treatment with carvedilol could have provided a greater benefit in terms of LVEF recovery and reduction of cardiac events.

Comparison with previous studies. At present, it is very difficult to obtain evidence-based indications for the treatment of AC-CMP from the existing literature. Pooling all the data together, an overall adult population of 108 patients can be derived from a total of 11 previous publications (6 case reports and 5 clinical studies) (14,16,22–30). Only 2 of them, however, were prospective studies (24,27), and only 3 had pre-defined end points (24,27,29). In all patients, treatment was started only when symptoms of HF occurred. Forty-six patients (43%) were treated with digitalis and diuretics, and 32 patients (30%) were treated with different ACEIs (enalapril in most cases); among them, only 13 patients received ACEIs as a first treatment. Finally, only 5 patients (5%) were treated with beta-blockers alone (carvedilol in most cases), and only 25 patients (23%) received a combination of both these classes of drugs. Therefore, no clear evidence can be obtained from these findings in terms of defining the best therapeutic strategy for this CMP. Conversely, the large population we considered, the prospective design, the homogeneous treatment schedule, the long-term follow-up, and the pre-defined functional and clinical end points all represent clear strengths in our study.

In long-term pediatric cancer survivors with AC-CMP, treatment with enalapril slowed the progression of cardiac dysfunction, but did not reverse it (6,35). On the basis of the results of these 2 studies, the routine use of ACEIs is not recommended at present (36). In these 2 studies, however, the mean time-to-HF treatment was 6.9 and 7.2 years, respectively. Considering our findings, it is not surprising that such an approach was doomed to fail.

Although preventing AC-induced cardiotoxicity while treating the malignancy remains the ultimate goal of therapy, cardiac function should also be monitored in patients receiving potentially cardiotoxic chemotherapy in order to detect early cardiac abnormalities while they are still reversible. Indeed, the American College of Cardiology and the American Heart Association recommend routine echocardiography at baseline and recurrent re-evaluation (37). However, in "real world" practice, this recommendation is often disregarded in asymptomatic patients and in those recovered from the oncologic disease. The results of our study highlight the fact that an early treatment is particularly critical in asymptomatic patients. Indeed, most responders were either asymptomatic or had a low NYHA functional class at the time HF therapy was initiated. Oncologists and cardiologists should plan these assessments jointly, as therapy decisions involving the same patients may potentially mean exchanging one fatal disease for another.

Study limitations. First, we included a population admitted to a single center. Second, the possibility that clinical variables or complications other than chemotherapy may have influenced the response to HF therapy cannot be excluded. Similarly, we cannot completely exclude the possibility that diverse forms of AC-CMP (i.e., acute, subacute, or late) may have a different response to HF therapy, or that, as the natural history of AC-CMP has not been well elucidated yet, spontaneous recovery in LVEF may occur in some patients. Third, the poor response to treatment of patients with more symptomatic HF (NYHA functional class III or IV) was possibly influenced by the definition of responders we used. Indeed, although they less frequently reached the criteria for complete recovery of LVEF, their absolute increase in LVEF was greater than that of asymptomatic patients (Fig. 3). Therefore, a high baseline NYHA functional class should not preclude treatment of these patients with an effective HF therapy, particularly when the CMP is detected in an early phase after chemotherapy. Nevertheless, in our study, the incidence of cardiac events was similar in partial and nonresponder patients, despite a significant increase in LVEF in the former group. This highlights the critical importance of normalizing, and not just improving, LVEF in this setting in order to positively impact clinical outcome. Finally, it is possible that LVEF recovery in some patients was blunted and, as a consequence, the number of responders underestimated due to the additional cardiotoxic effect of new chemotherapy administered during follow-up.

Conclusions

In cancer patients treated with AC, the clinical benefit of oncologic treatment may be thwarted by the development of AC-CMP. Our study clearly indicates, however, that a complete LVEF recovery and associated cardiac events reduction may be achieved when cardiac dysfunction is detected early and a treatment with ACEI, possibly in combination with beta-blockers, is promptly initiated.

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