

Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy

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Background—Three types of anthracycline-induced cardiotoxicities are currently recognized: acute, early-onset chronic, and late-onset chronic. However, data supporting this classification are lacking. We prospectively evaluated incidence, time of occurrence, clinical correlates, and response to heart failure therapy of cardiotoxicity.

Methods and Results—We assessed left ventricular ejection fraction (LVEF), at baseline, every 3 months during chemotherapy and for the following year, every 6 months over the following 4 years, and yearly afterward in a heterogeneous cohort of 2625 patients receiving anthracycline-containing therapy. In case of cardiotoxicity (LVEF decrease >10 absolute points, and <50%), heart failure therapy was initiated. Recovery from cardiotoxicity was defined as partial (LVEF increase >5 absolute points and >50%) or full (LVEF increase to the baseline value). The median follow-up was 5.2 (quartile 1 to quartile 3, 2.6–8.0) years. The overall incidence of cardiotoxicity was 9% (n=226). The median time elapsed between the end of chemotherapy and cardiotoxicity development was 3.5 (quartile 1 to quartile 3, 3–6) months. In 98% of cases (n=221), cardiotoxicity occurred within the first year. Twenty-five (11%) patients had full recovery, and 160 (71%) patients had partial recovery. At multivariable analysis, end-chemotherapy LVEF (hazard ratio, 1.37; 95% confidence interval, 1.33–1.42 for each percent unit decrement) and cumulative doxorubicin dose (hazard ratio, 1.09; 95% confidence interval, 1.04–1.15 for each 50 mg/m² increment) were independent correlates of cardiotoxicity.

Conclusions—Most cardiotoxicity after anthracycline-containing therapy occurs within the first year and is associated with anthracycline dose and LVEF at the end of treatment. Early detection and prompt therapy of cardiotoxicity appear crucial for substantial recovery of cardiac function. (*Circulation*. 2015;131:1981-1988. DOI: 10.1161/CIRCULATIONAHA.114.013777.)

Key Words: anthracyclines ■ cardiomyopathies ■ cardiotoxicity ■ drug therapy ■ heart failure ■ recovery of function

Anthracyclines are among the most widely used chemotherapeutic agents and have been shown to be effective in a wide range of tumors, in particular, breast cancer and lymphoma.^{1,2} Their clinical effectiveness, however, may be thwarted by the development of cardiotoxicity that negatively affects patients' outcomes and seriously limits their oncological therapeutic opportunities.^{3,4} According to the time of onset, 3 distinct types of cardiotoxicities have been recognized: (1) acute, occurring after a single dose, or a single course, of anthracyclines, with the onset of clinical manifestations within 2 weeks from the end of treatment; (2) early-onset chronic, developing within 1 year. This is the most frequent and clinically relevant form of cardiotoxicity, usually presenting as a dilated and hypokinetic cardiomyopathy leading to heart failure (HF); (3) late-onset chronic, developing years, or even decades, after the end of chemotherapy. This classification dates back to the early 1980s, and it is based on small

Editorial see p 1946 Clinical Perspective on p 1988

retrospective studies reporting the occurrence of HF symptoms in childhood cancer survivor populations.^{5–8} The clinical relevance of such a classification, however, is unclear, particularly when applied to adult populations. Actually, the timing of anthracycline-induced cardiotoxicity is not well defined, because, at present, no prospective study has regularly monitored cardiac function in adult patients for >3 years.^{4,9} Thus, the questions of whether this classification is based on diagnosis, rather than onset, of cardiotoxicity, and whether it reflects 3 distinct diseases rather than a single process, remain unanswered. As a result, recommendations for monitoring patients with cancer who are treated with anthracycline-containing chemotherapy (ACT) are still unclear, and often limited to symptomatic patients. Although several guidelines

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are available, no consensus exists on an optimal monitoring strategy scheme for anthracycline-induced cardiotoxicity. Indeed, recommendations are either too generic, not specifying how often or how long cardiac function should be monitored after ACT administration, or they are too restrictive, and not supported by evidence-based data.^{4,10–15} It is noteworthy that the early detection and treatment of cardiotoxicity, even when asymptomatic, seems to be critical for cardiac function recovery and for the reduction of associated adverse cardiac events.¹⁶

The present study prospectively evaluated the incidence, timing of occurrence, clinical correlates, and response to HF therapy of cardiotoxicity in a large population of anthracycline-treated patients, followed up by clinical and echocardiographic monitoring.

Methods

Study Population

This prospective study was conducted at the European Institute of Oncology, Milan, between June 1, 1995, and May 31, 2014. We considered all consecutive chemotherapy-naïve patients, scheduled for ACT for various kinds of tumors at first diagnosis, referred to our Cardiology Unit by oncologists. Patients were excluded if they were <18 years of age and if they had a left ventricular ejection fraction (LVEF) <50%, valvular heart disease, severe hypertension, and a life expectancy of ≤12 weeks. Patients treated with a high-dose protocol^{17–20} and with anthracycline therapy followed by trastuzumab²¹ were also excluded.

The study was approved by our Ethical Committee, and all patients provided written informed consent.

Study Protocol

All patients underwent an echocardiogram, including measurement of LVEF (biplane method),²² before starting ACT (baseline), every 3 months during chemotherapy, at the end of treatment (within 1 month), every 3 months during the first year after chemotherapy, every 6 months during the following 4 years, and yearly afterward, or whenever required by the clinical situation. These time points were chosen because they corresponded to the scheduled oncological controls. All LVEF measurements were evaluated by 2 independent cardiologists. Disagreement between the 2 readers (difference in LVEF >5 absolute points) was solved by consensus reached with subsequent joint evaluation of the echocardiographic findings.

In the case of patients who were lost to follow-up, who died, or who had to receive additional cardiotoxic chemotherapy for cancer relapse, the evaluation performed at the last follow-up check was considered as the final measurement.

In the case of cardiotoxicity, treatment with enalapril alone (patients enrolled before 1999) or with enalapril and β-blockers (patients enrolled after 1999) was promptly initiated and up-titrated to the maximal tolerated dose. Additional pharmacological treatment was given when needed, based on current standards of care.^{23,24}

In patients developing LVEF reduction associated with new-onset electrocardiographic changes, and in those with multiple risk factors for coronary artery disease, as well, further evaluation (electrocardiographic or stress tests, and, more recently, coronary computed tomography) was performed to exclude a possible concomitant, ischemic origin.

Study End Points

The primary end point of the study was the time of occurrence of cardiotoxicity. Cardiotoxicity was defined as a reduction in LVEF >10 percentage points from baseline and <50%.^{25,26}

The secondary end point was the recovery from cardiotoxicity after the initiation of HF treatment, defined either as a LVEF increase >5

absolute points and >50%, with the absence of HF symptoms (partial recovery) or as a LVEF increase to the baseline value (full recovery). The following cardiac events were also considered as secondary end points: cardiac death, acute coronary syndromes, acute pulmonary edema, overt HF, and life-threatening arrhythmias.

Statistical Analysis

Continuous variables are presented as the mean±standard deviation and were compared between groups by *t* test or analysis of variance as appropriate. Variables not normally distributed are presented as the median (quartile 1 to quartile 3) and compared by the Kruskal-Wallis test. Categorical variables are presented as the n (%) and were compared between groups by χ^2 or Fisher exact tests as appropriate. Unadjusted associations with the considered end point (cardiotoxicity) were assessed by using a set of univariable Cox proportional hazards regressions. Independent correlates of cardiotoxicity were identified by a multivariable Cox regression model with forward stepwise selection of variables. Candidate variables were age, sex, cardiovascular risk factors, cumulative anthracycline dose, mediastinal radiotherapy, left chest radiotherapy, body mass index, year of recruitment, and baseline and final (at the end of chemotherapy) LVEF. To avoid spurious selection of the correlates, because the model was built and tested on the same sample, a 2-split cross-validation procedure was used. We considered a correlate validated when it was selected and confirmed ≥70% of times. All calculations were computed by SAS software package, version 9.2 (SAS Institute, Cary, NC).

Results

Two thousand six hundred seventy-one consecutive patients were initially enrolled. Forty-six of them were excluded because of death from oncological disease during chemotherapy. A total of 2625 patients (mean age, 50±13 years; 74% women; 51% breast cancer and 28% non-Hodgkin lymphoma) were included in the study. The median follow-up after the last dose of ACT was 5.2 (interquartile range, 2.6–8.0) years (range, 4 months to 19 years). For 1417 (54%) patients, the follow-up was >5 years, for 451 (17%) patients the follow-up was >10 years, and for 51 (2%) patients the follow-up was >15 years. At last contact, 812 (31%) patients had died: in 792 (97%) of them, death was owing to tumor-related causes, in 20 (2.5%) to other causes, including cardiac death in 6 (0.7%) cases. Two hundred twenty-five (9%) patients were lost to follow-up. In 118 (4%) patients, the assessment of LVEF was technically difficult because of the presence of left breast prosthesis. In these patients, LVEF was assessed by multigated equilibrium radionuclide ventriculography, contrast echocardiography (from 2006) or MRI. Overall, 131 (5%) patients skipped 1 LVEF assessment; no patient skipped >1 LVEF assessment.

Cardiotoxicity occurred in 226 (9%) patients (9.7% in patients with breast cancer and 6.2% in those with non-Hodgkin disease). One hundred eighty-three (81%) patients, were in New York Heart Association class I to II, and 43 (19%) were in class III to IV. In 9 patients, cardiotoxicity was detected during hospitalization for acute decompensated HF. Six of them subsequently died. In the remaining 217 patients developing cardiotoxicity, no hospitalization was needed. The clinical characteristics of patients with and without cardiotoxicity are shown in Table 1.²⁷

The median time that elapsed between the last dose of anthracyclines and the development of cardiotoxicity was 3.5 months (quartile 1 to quartile 3, 3–6). In 221 (98%) cases,

Table 1. Clinical Characteristics of Patients Developing or Not Developing Anthracycline-Induced Cardiotoxicity

	Cardiotoxicity (n=226)	No Cardiotoxicity (n=2399)	P Value
Age, y	51±13	49±13	0.02
Female sex, n (%)	170 (75)	1779 (74)	0.83
Hypertension, n (%)	59 (26)	508 (21)	0.08
Diabetes mellitus, n (%)	13 (6)	68 (3)	0.012
Hypercholesterolemia, n (%)	20 (9)	142 (6)	0.10
Current or past smokers, n (%)	36 (16)	483 (20)	0.14
Coronary artery disease, n (%)	8 (4)	50 (2)	0.09
Family history of CAD, n (%)	20 (9)	123 (5)	0.01
Baseline LVEF, %	61±3.6	63±3.7	<0.001
End-chemotherapy LVEF, %	55±4.6	61±4.0	<0.001
Chest wall RT (left),* n (%)	49 (27)	392 (16)	0.06
Mediastinum radiotherapy, † n (%)	16 (7)	154 (6)	0.65
Oncological disease, n (%)			<0.001‡
Breast cancer	131 (58)	1213 (51)	
Hodgkin disease	10 (4)	113 (5)	
Non-Hodgkin lymphoma	46 (20)	695 (29)	
Myeloma	8 (4)	144 (6)	
Ovarian	2 (1)	67 (3)	
Other hemato-oncologic diseases	10 (4)	76 (3)	
Other solid tumors	19 (8)	91 (4)	
Cumulative anthracycline dose, § mg/m ²	359±172	299±144	<0.001
Oncological schedules, n (%)			
AC	64 (28)	637 (27)	0.69
EC	35 (21)	320 (18)	0.52
CEF	11 (6)	88 (4)	0.43
ACOD	13 (6)	191 (8)	0.38
R-ACOD	18 (8)	216 (10)	0.75
VAD	8 (4)	120 (5)	0.41
ChIVPP/ABVVP	10 (5)	92 (4)	0.73
Body mass index, kg/m ²	24.3±4	24.8±10	0.65
Creatinine clearance, ¶ mL/min	105±34	114±36	0.09

Data are expressed as numbers (%) or mean±SD; P values were computed by univariable Cox regression analysis. Hazard ratios are computed for 1 U increase, except for age and cumulative dose (each 5-year and each 50 mg, respectively). AC indicates doxorubicin, cyclophosphamide; ACOD, doxorubicin, cyclophosphamide, vincristine, dexamethasone; CAD, coronary artery diseases; CEF, cyclophosphamide, epirubicin, 5-fluorouracil; ChIVPP/ABVVP, chlorambucil, vinblastine, procarbazine, doxorubicin, bleomycin, vincristine, etoposide; LVEF, left ventricular ejection fraction; R-ACOD, rituximab, doxorubicin, cyclophosphamide, vincristine, dexamethasone; RT, radiotherapy; SD, standard deviation; and VAD, vincristine, doxorubicin, dexamethasone.

*Total dose 60 Gy.

†Total dose 30 Gy.

‡By Fisher exact test.

§Cumulative anthracycline dose was calculated by converting different anthracycline agents in terms of doxorubicin equivalents.²⁷

||AC were given in all cases as a slow intravenous bolus over 15 to 30 min.

¶Calculated by Cockcroft-Gault formula.

cardiotoxicity occurred within the first year of follow-up (Figure 1). Figure 2 shows the LVEF behavior in patients developing cardiotoxicity during the first year. In 5 patients the echocardiographic criteria for cardiotoxicity were reached after at least 5.5 years. Four patients had a positive stress test at the time of LVEF reduction: coronary computed tomography scan or angiography documented the presence of coronary artery disease in 4 patients, which was critical in 2. The last patient had a negative stress test and had received additional left chest brachytherapy (45 Gy in a single shot) for local relapse of breast cancer 1 year before the detection of LVEF reduction.

HF therapy was initiated in all patients developing cardiotoxicity. In 40 (17%) patients, enalapril was given (mean dose, 10±6 mg/d). In them, the reasons for lack of the addition of β -blockers were enrollment before 1999 (n = 22),^{11,12} hypotension (n=12), critical bradycardia (n=2), and severe asthenia (n=4). The remaining 186 patients received enalapril (9±6 mg/d) and carvedilol (n=112; 16±9 mg/d) or bisoprolol (n=91; 2±1 mg/d). In 3 patients who developed a cough, enalapril dosage was decreased with symptom resolution. Intravenous diuretics were required only in patients hospitalized for acute HF. Oral diuretics were added to the therapy in 43 (20%) cases. Medications were continued throughout the study, also in the case of partial or full recovery.

One hundred eighty-five (82%) patients recovered from cardiotoxicity (mean time to recovery, 8±5 months). Of those, 25 (11%) had full recovery, and 160 (71%) had partial recovery (Figure 3). The 5 patients showing a very late LVEF decrease had a shorter time of recovery (<3 months). At the end of follow-up, a lower LVEF than baseline was also observed in patients who did not develop cardiotoxicity (from 64±4% to 61±4%; $P<0.001$). The clinical characteristics of patients who partially or fully recovered from cardiotoxicity and of those who did not recover are shown in Table 2. Patients who did not recover had a higher New York Heart Association class and were less likely to tolerate the association of enalapril and β -blockers. Notably, patients who did not recover from cardiotoxicity had a higher incidence of adverse cardiac events.

Multivariable Analysis

At multivariable analysis, end-chemotherapy LVEF (hazard ratio [HR], 1.37; 95% confidence interval [CI], 1.33–1.42 for each percent unit decrease), age (HR, 1.07; 95% CI, 1.02–1.13 for each 5-year increase), female sex (HR, 1.61; 95% CI, 1.17–2.17), family history of coronary artery disease (HR, 1.67; 95% CI, 1.05–2.64), and cumulative anthracycline dose (HR, 1.09; 95% CI, 1.04–1.15 for each 50 mg/m² increase) were selected as independent correlates of cardiotoxicity. Only end-chemotherapy LVEF and cumulative anthracycline dose, however, were reconfirmed as independent correlates at cross-validation analysis (99% and 71% reconfirmation rate, respectively).

Discussion

The most important results of the present study were that anthracycline-induced cardiotoxicity occurred in 9% of adult treated patients, it was dose dependent, and its highest incidence was observed during the first year after the completion

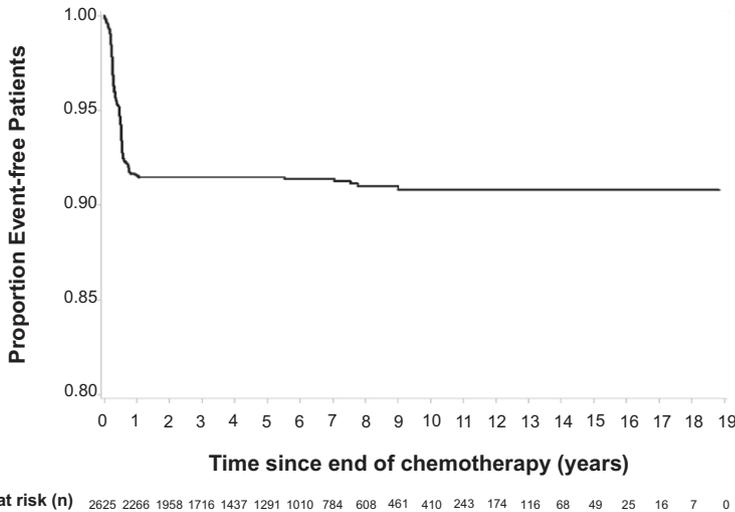


Figure 1. Kaplan–Meier curve showing the cumulative incidence of cardiotoxicity in the study population. Pts. indicates patients.

of chemotherapy. Another important finding was that close monitoring of cardiac function during this period allowed early detection and treatment of cardiotoxicity, with major LVEF improvement in most cases.

The results of our study were not consistent with the current classification of chronic cardiotoxicity that considers early and late cardiotoxicity as 2 distinct entities. This classification is based on retrospective studies in which LVEF decline was detected either after HF development, or on random evaluations in pediatric cancer patients presumed to have no other cardiac complications.^{5–8,28,29} However, HF may be preceded by asymptomatic LVEF depression that is characterized by early onset with a slow and progressive deterioration that may continue for months or years after the end of chemotherapy. Indeed, in our study, most patients experiencing cardiotoxicity were asymptomatic and LVEF reduction was detected by scheduled echocardiographic controls.

In previous retrospective studies, the diagnosis of cardiotoxicity was made years after the end of chemotherapy but, possibly, reflected the late diagnosis of an early developed disease, rather than one of late onset. Anthracycline-induced cardiotoxicity is most likely a unique and continuous phenomenon that starts with myocardial cell injury, and is followed by progressive LVEF decline that, if disregarded and not treated,

progressively leads to overt HF. The distinction between different forms of cardiotoxicity depends, therefore, on the definition we give to it and on our ability to identify early subclinical cardiac damage. So, if we look at HF symptoms, our diagnosis may take several years, and we will define this cardiotoxicity as late. If we look at LVEF reduction, it may take months and we will designate it as early. Finally, if we look at preclinical myocardial cell damage, using a biomarker, like troponin for instance,^{17–19,30} we will identify cardiotoxicity during or soon after chemotherapy, and we will define it as acute. In other words, we are possibly observing different stages of evolution of the same phenomenon and not 3 distinct diseases.

To our knowledge, ours is the first study that included a large, nonselected, population of patients with cancer undergoing prospective measurement of LVEF for a long time. Notably, in a very recent study including 1491 breast cancer survivors, prospectively followed for 10 years, the evaluation of LVEF during the first 5-year follow-up was performed only in patients with HF symptoms.³¹

In the past, only a relatively few patients survived long enough to experience potential late cardiac events. Today, as a result of improved early malignancies detection and effective treatment, the number of long-term cancer survivors has

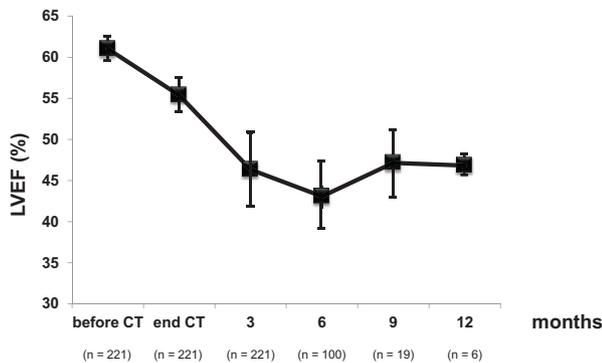


Figure 2. Left ventricular ejection fraction (LVEF; mean±SD) behavior in patients developing cardiotoxicity in the first year, from baseline (before starting chemotherapy) to the initiation of heart failure therapy. CT indicates chemotherapy; and SD, standard deviation.

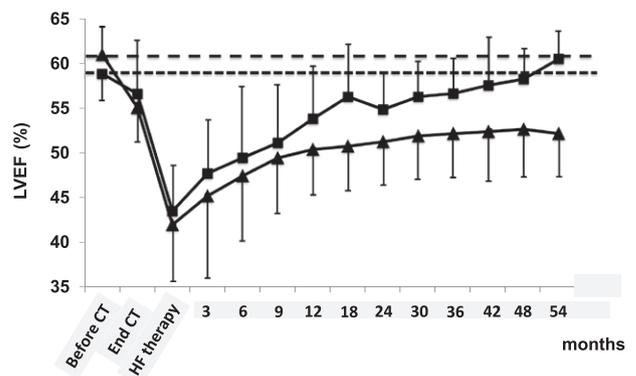


Figure 3. Left ventricular ejection fraction (LVEF) in patients with cardiotoxicity and with partial (triangle) or full (square) recovery with heart failure therapy. Data are mean±SD. CT indicates chemotherapy; HF, heart failure; and SD, standard deviation.

Table 2. Clinical Characteristics and Cardiac Events During Follow-Up of Patients With Full, Partial, and No Recovery From Cardiac Dysfunction

	Full Recovery (n=25)	Partial Recovery (n=160)	No Recovery (n=41)	P Value
Age, y	52±11	50±13	53±14	0.22
Women, n (%)	23 (92)	124 (77)	27 (65)	<0.001
Hypertension, n (%)	6 (24)	44 (27)	10 (24)	0.99
Diabetes mellitus, n (%)	3 (12)	7 (4)	4 (10)	0.13*
Coronary artery disease, n (%)	2 (8)	4 (3)	2 (5)	0.18*
Hypercholesterolemia, n (%)	3 (12)	14 (9)	4 (10)	0.81*
NYHA class III–IV, n (%)	2 (8)	27 (17)	14 (34)	0.02*
Creatinine clearance, † mL/min	97±34	104±29	116±51	0.56
Cumulative AC dose, ‡ mg/m ²	283±94	314±129	346±150	0.12
Mediastinum RT, § n (%)	1 (4)	12 (7)	3 (7)	1.00*
Body mass index, kg/m ²	25±5	24±4	25±5	0.73
LVEF before ACT, %	59±3	61±4	61±4	0.002
LVEF at the end of ACT, %	57±6	56±5	55±4	0.06
LVEF before HF therapy, %	42±8	41±7	33±9	<0.001
LVEF at the end of the study, %	61±4	54±3	38±9	by definition
Time to HF treatment, mo	4.0 (3–6)	3.5 (3–6)	3.6 (2–6)	0.76
Mean enalapril dose, mg	10±6	10±6	8±5	0.24
Mean carvedilol dose, mg	16±7	17±10	14±6	0.42
Mean bisoprolol dose, mg	2.1±0.8	2.3±1.4	2.4±1.4	0.81
Enalapril only, n (%)	0 (0)	12 (7)	6 (15)	0.12*
β-Blocker only, n (%)	0 (0)	3 (2)	0 (0)	1.00*
Enalapril + β-blocker, n (%)	25 (100)	145 (91)	31(75)	0.004
Cumulative events, n (%)	2 (8)	27 (17)	19 (46)	0.001*
Sudden death	0 (0)	1 (0.5)	0 (1)	
Cardiac death	0 (0)	2 (1)	4 (10)	
Acute pulmonary edema	0 (0)	2 (1)	3 (7)	
HF requiring hospitalization	0 (0)	1 (0.5)	3 (7)	
Acute coronary syndrome	0 (0)	4 (2.5)	2 (5)	
Life-threatening arrhythmias	2 (3)	14 (8)	5 (12)	
ICD implantation	0 (0)	0 (0)	(0)	
Conduction disturbances requiring pacemaker implantation	0 (0)	3 (2)	2 (5)	

Data are expressed as numbers (%) or mean±SD except for time to HF treatment expressed as median (Q1–Q3). HF indicates heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and SD, standard deviation.

*By Fisher exact test.

†Estimated by Cockcroft-Gault formula.

‡Cumulative anthracycline dose was calculated by converting different anthracycline agents in terms of doxorubicin equivalents.²³

§Total dose 30 Gy.

have been treated with anthracyclines,^{2,3} a long-term cardiac surveillance extended to all these potential patients is hardly proposable because of logistic and economic reasons.³³ Our data, however, indicate that a close monitoring limited to the first 12 months allows for the identification of almost all cases of cardiotoxicity, with a favorable cost-effectiveness ratio. Possibly, all cases of cardiotoxicity occurred within 1 year. Indeed, the causal relationship between ACT and the very late detection of LVEF reduction observed in 5 of our patients remains uncertain, given its atypical behavior (sudden onset and prompt recovery), in comparison with the classic picture of cardiotoxicity. In addition, the association with coronary artery disease and the previous left chest exposure to high doses of radiation further contribute to make such a relationship unlikely.

We identified some independent correlates of cardiotoxicity that were confirmed by cross-analysis validation; in particular, cumulative anthracycline dose and end-chemotherapy LVEF were associated with cardiotoxicity occurrence. Although the relationship between anthracycline dose and cardiotoxicity risk is well recognized, the association between end-chemotherapy LVEF and cardiotoxicity development in adult patients has never been reported, thus far. Only Steinherz et al²⁸ reported an association between early cardiac dysfunction and long-term further functional deterioration in a small population of pediatric cancer patients. However, as in their study baseline (reference) echocardiographic parameters were measured during the first year after the end of chemotherapy, when possibly many cases of LVEF impairment had already occurred, these cardiac abnormalities likely reflected early detection rather than the prediction of cardiotoxicity.

Mediastinal irradiation may cause inflammation and fibrosis leading to progressive diastolic dysfunction and restrictive hemodynamics. These effects seem to be facilitated by associated ACT.⁴ Thus, mediastinal exposure to radiation might influence the development of and recovery from cardiotoxicity. However, no difference between irradiated and not irradiated patients was observed in our study.

Because a clear relationship between the peak levels of anthracyclines and cardiotoxicity exists, administering anthracyclines via continuous infusion rather than as a bolus dose has been proposed to limit peak dose levels and reduce anthracycline-related cardiac effects. Accordingly, prolonged ACT infusion schedules have been shown to be associated with a lower incidence of cardiotoxicity, in comparison with bolus therapy. However, this remains a controversial issue. If, on one hand, continuous infusion limits peak anthracycline levels, on the other, it prolongs patients' exposure to the drug's toxic effects. Experimentally, a longer exposure time has been shown to counteract functional recovery of the cardiomyocytes damaged by anthracyclines.^{34,35} In our study, all patients received anthracycline as a slow intravenous bolus over 15 to 30 minutes; hence, we cannot exclude that the incidence of cardiotoxicity could be lower and the percentage of patients recovering higher, if a prolonged infusion schedule would have been used.

In agreement with the current classification, both forms of chronic cardiotoxicity are considered to be irreversible, refractory to standard HF therapy, and associated with

increased dramatically. It has been estimated that there are >13 million cancer survivors in the United States, at present. This number is expected to reach 18 million by 2022.³² When we consider that ≈50% to 60% of childhood cancer survivors

a poor prognosis.^{27,36} In our study, however, early detection of the disease allowed for recovery of LVEF, in response to HF therapy, in most patients, possibly because treatment was started soon after detection of left ventricular impairment, ie, at a still reversible phase. Consistently with our previous data, a greater improvement in cardiac function was observed in patients receiving a combination of angiotensin-converting enzyme inhibitors and β -blockers.¹⁶ Conversely, in a recently published study that retrospectively evaluated 366 patients with cancer therapy–induced cardiac dysfunction, recovery did not appear to be determined by the use of HF medications.³⁷ However, this study included patients treated with various kind of anticancer drugs, such as vascular endothelial growth factor inhibitors and trastuzumab, that may induce cardiac injury with mechanisms different from those of anthracyclines, and in which cardiac damage has been shown to be reversible in many cases.³⁸

Previous data demonstrated that time is a crucial factor for obtaining complete recovery from cardiac dysfunction in patients with anthracycline-induced cardiomyopathy.¹⁶ As a result, cardiac surveillance, exclusively based on symptoms, might miss early detection and effective treatment of cardiotoxicity. Worthy of note, LVEF is the most important independent predictor of short- and long-term mortality in different cardiac conditions, including myocardial infarction, cardiac surgery, ischemic and idiopathic cardiomyopathy, and in anthracycline-induced cardiomyopathy, as well.^{16,39–43} Several studies have clearly demonstrated increased morbidity and mortality rates in patients with reduced LVEF, even when they are asymptomatic.^{39–43} In particular, asymptomatic LVEF reduction in ACT patients has been shown to be associated with a higher incidence of adverse cardiac events at a 3.5-year follow-up.¹⁹ Conversely, LVEF recovery has been associated with a parallel reduction in cardiac events.¹⁶ In agreement with previous data, in our study, patients who recovered from cardiac dysfunction had a lower incidence of adverse cardiac events, in comparison with those who did not normalize LVEF. However, because 97% of the patients who died did so for oncological reasons, a reduction in anthracycline dose cannot be recommended. On the other hand, the low cardiac mortality observed in our study could be due to our strategy of a very early HF treatment. Moreover, we cannot exclude a different temporal impact of mortality of the 2 diseases (earlier for cancer, later for cardiac disease) in the natural history of patients with cancer treated with ACT. Considering the good tolerability of HF therapy and its high effectiveness, particularly in patients receiving a combination of enalapril and β -blockers, early identification of cardiotoxicity and prompt pharmacological treatment initiation appear to be justified.

According to our results, the old definition of cardiotoxicity should be revised for future use in clinical practice: early preclinical cardiac injury should be looked for soon after anthracycline treatment to effectively treat this disorder from its onset, before its overt clinical expression.

Study Limitations

Several limitations warrant mention. First, we included a population admitted to a single center. Second, although the oncological diagnosis was a first diagnosis for all patients, the study

population included both patients with early and advanced cancer disease. This could have influenced different lengths of survival and, consequently, different opportunities to develop late-occurring toxicity. Third, the incidences of cardiotoxicity and of recovery were likely underestimated and overestimated, respectively, in our study, because of the definitions we used. Indeed, a reduction in LVEF was also observed in some patients who did not fulfill both criteria for cardiotoxicity, and patients with more important LVEF impairment were less likely to satisfy our definition of recovery. Future studies should investigate which degree of LVEF reduction, and which extent of LVEF recovery, as well, should be considered for clinical relevance. Fourth, the lack of additional and more sophisticated echocardiographic parameters, other than LVEF, and of biomarkers, in particular troponin, may have reduced our chance to detect cardiotoxicity at an earlier stage. This may have delayed HF therapy initiation and reduced the number of patients recovering from cardiotoxicity. Fifth, the high prevalence of women in our study population (74%) may limit the generalizability of our findings to the entire cancer population; however, sex was not among the variables validated at the cross-analysis, thus showing a limited influence on the results. Sixth, we cannot exclude that patients with asymptomatic cardiotoxicity, when not treated, may have not developed overt HF. Thus, the association between asymptomatic LVEF decline and later development of symptomatic HF, remains, at least in part, speculative. Finally, because in our population we promptly started HF therapy soon after the detection of cardiac dysfunction, we cannot exclude that spontaneous LVEF recovery could have occurred in some cases.

Conclusions

Cardiotoxicity is a relatively frequent complication in adult patients with cancer treated with ATC, occurring in almost all cases in the first year after the end of treatment. End-chemotherapy LVEF and cumulative anthracycline dose are independent correlates of its occurrence. Early cardiotoxicity detection and its prompt treatment seem to be crucial for major improvement in cardiac function.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Cardiac dysfunction due to anthracycline cardiotoxicity not only negatively affects patients' cardiac outcome, but also seriously limits their oncological therapeutic opportunities. According to the time of onset, 3 distinct types of cardiotoxicities have been recognized: acute, early-onset chronic, and late-onset chronic. In our study, anthracycline-induced cardiotoxicity occurred in 9% of treated patients, in most cases (98%) during the first year after the completion of chemotherapy. Close monitoring of cardiac function during this period allowed early detection and treatment of cardiotoxicity, with major improvement in cardiac function in most cases, particularly in patients receiving a combination of angiotensin-converting enzyme inhibitors and β -blockers. Our study results are not consistent with the current classification of cardiotoxicity that considers early and late chronic cardiotoxicity as 2 distinct, frequently irreversible, entities. Conversely, anthracycline-induced cardiotoxicity is most likely a unique and continuous phenomenon characterized by progressive left ventricular ejection fraction decline that, if disregarded and not treated, may progressively lead to overt heart failure. As a result, cardiac surveillance, exclusively based on symptoms, might miss the early detection that is crucial for prompt treatment and recovery from cardiac dysfunction.

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Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy

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