Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy

**Running title:** Cardinale et al.; Anthracyclines cardiotoxicity in adults

Daniela Cardinale, MD, PhD, FESC¹; Alessandro Colombo, MD¹; Giulia Bacchiani, MD¹;
Ines Tedeschi, MSc¹; Carlo A. Meroni, MD¹; Fabrizio Veglia, PhD²; Maurizio Civelli, MD¹;
Giuseppina Lamantia, MD¹; Nicola Colombo, MD¹; Giuseppe Curigliano, MD, PhD¹;
Cesare Fiorentini, MD²; Carlo M. Cipolla, MD¹

¹European Institute of Oncology, Milan, Italy; ²Centro Cardiologico Monzino (I.R.C.C.S.), Milan, Italy

**Address for Correspondence:**
Daniela Cardinale, MD, PhD, FESC
Cardioncology Unit
European Institute of Oncology
Via Ripamonti 435
20141 Milan, Italy
Tel:+39 02 57489 539
Fax:+39 02 700 509 829
E-mail: daniela.cardinale@ieo.it

**Journal Subject Codes:** Heart failure:[11] Other heart failure, Treatment:[27] Other treatment
Abstract

Background—Three types of anthracycline-induced cardiotoxicities are currently recognized: acute, early onset chronic, late onset chronic. However, data supporting this classification are lacking. We prospectively evaluated incidence, time of occurrence, clinical correlates, and response to heart failure (HF) 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 afterwards in a heterogeneous cohort of 2625 patients receiving anthracycline-containing therapy (ACT). In case of cardiotoxicity (LVEF decrease >10% units, and below 50%), HF therapy was initiated. Recovery from cardiotoxicity was defined as partial (LVEF increase >5% units and above 50%) or full (LVEF increase to the baseline value). The median follow-up was 5.2 (Q1-Q3 2.6–8.0) years. The overall incidence of cardiotoxicity was 9% (n=226). The median time elapsed between end of chemotherapy and cardiotoxicity development was 3.5 (Q1-Q3 3-6) months. In 98% of cases (n=221), cardiotoxicity occurred within the first year. Twenty-five (11%) patients had full and 160 (71%) patients had partial recovery. At multivariable analysis, end-chemotherapy LVEF (HR 1.37, 95% CI 1.33-1.42 for each percent unit decrement) and cumulative doxorubicin dose (HR 1.09, 95% CI 1.04-1.15 for each 50 mg/mq increment) were independent correlates of cardiotoxicity.

Conclusions—Most cardiotoxicity after ACT 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.

Key words: anthracycline-induced cardiomyopathy, chemotherapy, cardiotoxicity, cardiomyopathy, left ventricular ejection fraction, heart failure, recovery
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.\textsuperscript{1,2} Their clinical effectiveness, however, may be thwarted by the development of cardiotoxicity that negatively affects patients’ outcomes, and seriously limits their oncologic therapeutic opportunities.\textsuperscript{3,4} According to the time of onset, three distinct types of cardiotoxicities have been recognized: 1) “acute”, occurring after a single dose, or a single course, of anthracyclines, with onset of clinical manifestations within two 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 eighties, and it is based on small retrospective studies reporting HF symptoms occurrence in childhood cancer survivor populations.\textsuperscript{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 as, at present, no prospective study has regularly monitored cardiac function in adult patients for more than 3 years.\textsuperscript{4,9} Thus, the questions of whether this classification is based on diagnosis, rather than onset, of cardiotoxicity, and whether it reflects three distinct diseases rather than a single process, remain unanswered. As a result, recommendations for monitoring cancer patients treated with anthracycline-containing chemotherapy (ACT) are still unclear, and often limited to symptomatic patients. Although several guidelines 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, nor how long cardiac function should be monitored after ACT administration; or they are too
restrictive, and not supported by evidence-based data.\textsuperscript{4,10-15} Notably, early detection and treatment of cardiotoxicity, even when asymptomatic, seems to be critical for cardiac function recovery and for reduction of associated adverse cardiac events.\textsuperscript{16}

The present study prospectively evaluated 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.

\textbf{Methods}

\textbf{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-naive patients, scheduled for ACT for various kinds of tumors at first diagnosis, referred to our Cardiology Unit by oncologists. Age <18 years, left ventricular ejection fraction (LVEF) <50\%, valvular heart disease, severe hypertension, life expectancy \textless{}12 weeks were exclusion criteria for enrollment. Patients treated with a “high-dose” protocol,\textsuperscript{17-20} and with anthracycline therapy followed by trastuzumab\textsuperscript{21} were also excluded.

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

\textbf{Study protocol}

All patients underwent an echocardiogram, including measurement of LVEF (biplane method),\textsuperscript{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 afterwards, or whenever required by the clinical
situation. These time points were chosen because corresponding to the scheduled oncologic 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, 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 beta-blockers (patients enrolled after 1999) was promptly initiated, and up-titrated to the maximal tolerated dose. Additional pharmacologic treatment was given when needed, based on current standards of care.23,24

In patients developing LVEF reduction associated with new onset electrocardiographic changes, as well as in those with multiple risk factors for coronary artery disease, 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% units from baseline and below 50%.25,26

The secondary end-point was the recovery from cardiotoxicity after HF treatment initiation, defined either as a LVEF increase greater than 5 percentage points and above 50%, with 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±SD and were compared between groups by t-test or ANOVA as appropriate. Variables not normally distributed are presented as the median (Q1-Q3), and compared by Kruskal-Wallis test. Categorical variables are presented as the n (%) and were compared between groups by Chi-square or Fisher exact test as appropriate. Unadjusted associations with the considered end point (cardiotoxicity) were assessed using a set of univariable Cox proportional hazard regressions. Independent correlates of cardiotoxicity were identified by multivariable Cox regression model with forward stepwise selection of variables. Candidate variables were age, gender, 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, North Carolina).

**Results**

Two-thousand-six-hundred-seventy-one consecutive patients were initially enrolled. Forty-six of them were excluded because of death from oncologic disease during chemotherapy. A total of 2625 patients (mean age 50±13 years; 74% women; 51% breast cancer and 28% non-Hodgkin’s lymphoma) were included in the study. The median follow-up after the last dose of ACT was 5.2 (IQR 2.6–8.0) years (range 4 months to 19 years). For 1417 (54%) patients the follow-up was >5
years, for 451 (17%) >10 years, and for 51 (2%) >15 years. At last contact, 812 (31%) patients
had died: in 792 (97%) of them, death was due 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 multi-gated
equilibrium radionuclide ventriculography (MUGA), contrast echocardiography (from 2006) or
magnetic resonance imaging. Overall, 131 (5%) patients skipped one LVEF assessment; no
patient skipped more than one LVEF assessment.

Cardiotoxicity occurred in 226 (9%) patients (9.7% in patients with breast cancer and
6.2% in those with non-Hodgkin’s disease). One-hundred-eighty-three (81%) of them, were in
New York Heart Association (NYHA) class I-II, and 43 (19%) in class III-IV. In nine 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 1.²

The median time elapsed between the last dose of anthracyclines and the development of
cardiotoxicity was 3.5 months (Q1-Q3 3-6). In 221 (98%) cases, 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 of them had a positive stress test at the time of LVEF
reduction: coronary CT scan or angiography documented the presence of coronary artery disease
in 4 patients, which was critical in two. The last patient had a negative stress test and had
received additional left chest brachytherapy (45 Gys in a single shot), for local relapse of breast
cancer 1 year before detection of LVEF reduction.

In all patients developing cardiotoxicity HF therapy was initiated. In 40 (17%) patients, enalapril was given (mean dose 10±6 mg/day). In them, reasons for lack of the addition of beta-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/day) and carvedilol (n=112; 16±9 mg/day) or bisoprolol (n=91; 2±1 mg/day). In 3 patients who referred 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 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 didn’t develop cardiotoxicity (from 64±4% to 61±4%; p<0.001). 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 NYHA class, and were less likely to tolerate the association of enalapril and beta-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 (HR 1.37, 95% 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 gender (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/mq 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 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 two 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 pre-clinical myocardial cell damage, using a biomarker, like troponin for instance, 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 three distinct diseases.

To our knowledge, ours is the first study that included a large, non-selected, population of cancer patients undergoing prospective measurement of LVEF for a long time. Notably, in a very recent study including 1491 breast cancer survivors, prospectively followed for ten years, evaluation of LVEF during the first 5 year follow-up was performed only in patients with HF symptoms. In the past, only 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 increased dramatically. It has been estimated that there are >13 million cancer survivors in the US, at present. This number is expected to reach 18 million by 2022. When we consider that about 50-60% of childhood cancer survivors have been treated with anthracyclines, a long-term cardiac surveillance extended to all these potential patients is hardly proposable because of logistic and economic reasons. Our data, however, indicate that a close monitoring limited to the first 12 months
allows for 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 very late detection of LVEF reduction observed in 5 of our patients remains uncertain, given its atypical behavior (sudden onset and prompt recovery), when compared to 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 al. 19 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 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 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 anthracyclines-related cardiac effects. Accordingly, prolonged ACT infusion schedules have been shown to be associated with a lower incidence of cardiotoxicity, when compared to bolus therapy. However, this remains a controversial issue. If, on one hand, continuous infusion limits peak anthracyclines 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.\textsuperscript{34,35} In our study all patients received anthracycline as a slow i.v. bolus over 15–30 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 utilized.

In agreement with the current classification, both forms of chronic cardiotoxicity are considered to be irreversible, refractory to standard HF therapy, and, associated with a poor prognosis.\textsuperscript{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, i.e. at a still reversible phase. Consistently with our previous data, a greater improvement in cardiac function was observed in patients receiving a combination of ACEI and beta-blockers.\textsuperscript{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.\textsuperscript{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.\textsuperscript{39}

Previous data demonstrated that time is a crucial factor for obtaining complete recovery from cardiac dysfunction in patients with anthracycline-induced cardiomyopathy.\textsuperscript{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, as well as in anthracycline-induced cardiomyopathy.\textsuperscript{16,39-43} Several studies have clearly demonstrated increased morbidity and mortality rates in patients with reduced LVEF, even when asymptomatic.\textsuperscript{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.\textsuperscript{19} Conversely, LVEF recovery has been associated with a parallel reduction in cardiac events.\textsuperscript{16} In agreement with previous data, in our study, patients who recovered from cardiac dysfunction had a lower incidence of adverse cardiac events, when compared to those who didn’t normalize LVEF. However, as 97\% of the patients who died did so for oncologic 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 two diseases (earlier for cancer, later for cardiac disease) in the natural history of cancer patients treated with ACT. Considering the good tolerability of HF therapy and its high effectiveness, particularly in patients receiving a combination of enalapril and beta-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 oncologic 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-
occuring toxicity. Third, the incidences of cardiotoxicity and of recovery were likely
underestimated and overestimated, respectively, in our study, due to the definitions we used.
Indeed, a reduction in LVEF was also observed in some patients who didn’t 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, as
well as which extent of LVEF recovery, 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 generalizability of our findings to the entire cancer population; however, gender
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 cardiac dysfunction
detection, we cannot exclude that spontaneous LVEF recovery could have occurred in some
cases.

Conclusions
Cardiotoxicity is a relatively frequent complication in adult cancer patients 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.

Funding Sources: The study was funded by the European Institute of Oncology.

Conflict of Interest Disclosures: None.

References:
1. Yang F, Teves SS, Kemp CJ, Henikoff S. Doxorubicin, DNA torsion, and chromatin
dynamics. _Biochim Biophys Acta_. 2014;1845:84-89.

of anthracycline agents for the treatment of cancer: Systematic review and meta-analysys of
randomized controlled trials. _BMC Cancer_. 2010;10:337.

3. Van Dalen EC, Caron HB, Kremer LCM. Prevention of anthracycline-induced cardiotoxicity I

Vaughn DJ. American Society of Clinical Oncology clinical evidence review on the ongoing
care of adult cancer survivors: cardiac and pulmonary late effects. _J Clin Oncol_. 2007;25:3991-
4008.


22. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005;18:1440-1463.


Table 1. Clinical characteristics of patients developing or not anthracycline-induced cardiotoxicity.

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

Data are expressed as numbers (percent) or mean±SD; P values were computed by univariable Cox regression analysis. Hazard Ratios are computed for 1 unit increase, except for age and cumulative dose (each 5-year and each 50 mg, respectively); AC = doxorubicin, cyclophosphamide; ACOD = doxorubicin, cyclophosphamide, vincristine, dexamethasone; CAD = coronary artery diseases; CEF = cyclophosphamide, epirubicin, 5-fluorouracil; ChlVPP/ABVVP = chlorambucil, vinblastine, procarbazine, doxorubicin, bleomycin, vincristine, etoposide; LVEF = left ventricular ejection fraction; R-ACOD = rituximab, doxorubicin, cyclophosphamide, vincristine, dexamethasone; RT = radiotherapy; VAD = vincristine, doxorubicin, dexamethasone. † total dose 60 Gy; ‡ total dose 30 Gy; § cumulative anthracycline dose was calculated by converting different anthracycline agents in terms of doxorubicin equivalents; AC were given in all cases as a slow i.v. bolus over 15-30 minutes; † calculated by Cockcroft-Gault formula. * by Fisher exact test.
Table 2. Clinical characteristics and cardiac events during follow-up of patients with full, partial, and no recovery from cardiac dysfunction.

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

Data are expressed as numbers (percent) or mean±SD except for time to HF treatment expressed as median (Q1-Q3). HF = heart failure; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association. *estimated by Cockcroft-Gault formula; †cumulative anthracyclines dose was calculated by converting different anthracycline agents in terms of doxorubicin equivalents; ‡total dose 30 Gy; §by Fisher exact text.
Figure Legends:

**Figure 1.** Kaplan-Meier curve showing the cumulative incidence of cardiotoxicity in the study population.

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

**Figure 3.** Left ventricular ejection fraction (LVEF) in patients with cardiotoxicity and with partial (red line) or full (blue line) recovery with heart failure therapy. Data are mean±SD. CT = chemotherapy; HF = heart failure.
Proportion Event-free Patients

Time since end of chemotherapy (years)

Pts.at risk (n)

2625 2266 1958 1716 1437 1291 1010 784 608 461 174 116 68 49 25 16 7 0

Figure 1
Figure 2

LVEF (%) over time with 95% CI.
Figure 3
Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy
Daniela Cardinale, Alessandro Colombo, Giulia Bacchiani, Ines Tedeschi, Carlo A. Meroni, Fabrizio Veglia, Maurizio Civelli, Giuseppina Lamantia, Nicola Colombo, Giuseppe Curigliano, Cesare Fiorentini and Carlo M. Cipolla

Circulation. published online May 6, 2015;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2015/05/05/CIRCULATIONAHA.114.013777

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/