Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

Daniela Cardinale, MD; Alessandro Colombo, MD; Maria T. Sandri, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Maurizio Civelli, MD; Giovanni Martinelli, MD; Fabrizio Veglia, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

**Background**—An increase in troponin I soon after high-dose chemotherapy (HDC) is a strong predictor of poor cardiological outcome in cancer patients. This finding has important clinical implications and provides a rationale for the development of prophylactic strategies for preventing cardiotoxicity. Angiotensin-converting enzyme inhibitors slow the progression of left ventricular dysfunction in different clinical settings, but their role in the prevention of cardiotoxicity has never been investigated.

**Methods and Results**—Of the 473 cancer patients evaluated, 114 (72 women; mean age, 45±12 years) who showed a troponin I increase soon after HDC were randomized to receive (angiotensin-converting enzyme inhibitor group; 20 mg/d; n=56) or not to receive (control subjects; n=58) enalapril. Treatment was started 1 month after HDC and continued for 1 year. Cardiological evaluation was performed at baseline and at 1, 3, 6, and 12 months after HDC. The primary end point was an absolute decrease >10 percent units in left ventricular ejection fraction, with a decline below the normal limit value. A significant reduction in left ventricular ejection fraction and an increase in end-diastolic and end-systolic volumes were observed only in untreated patients. According to the Kaplan-Meier analysis, the incidence of the primary end point was significantly higher in control subjects than in the angiotensin-converting enzyme inhibitor group (43% versus 0%; P<0.001).

**Conclusions**—In high-risk, HDC-treated patients, defined by an increased troponin I value, early treatment with enalapril seems to prevent the development of late cardiotoxicity. (Circulation. 2006;114:2474-2481.)

Key Words: angiotensin-converting enzyme inhibitors | cardiotoxicity | chemotherapy | heart failure | left ventricular dysfunction | troponin

The survival rate of cancer patients has greatly increased over the last 20 years.1,2 However, to achieve this result, a considerable price has been paid in terms of the side effects associated with the intensive anticancer treatment. In particular, chronic cardiotoxicity may compromise the clinical effectiveness of chemotherapy, affecting the patient’s survival and quality of life independently of the oncological prognosis. As a result of the increasing number of long-term cancer survivors and of the tendency to use higher doses of anthracyclines and combined treatments with synergistic cardiotoxic effects, the magnitude of this problem is growing.

International oncological guidelines define cardiotoxicity as an absolute decrease in left ventricular ejection fraction (LVEF) >10 percent units associated with a decline below its normal limit of 50%. Notably, this definition is used as a strict criterion for discontinuing chemotherapy.3,4 Therefore, the onset of cardiac dysfunction, even asymptomatic, not only negatively affects cancer patients’ cardiac outcomes5,6 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 >30% to 60% of cases within 5 years.7,8

**Editorial p 2432**

**Clinical Perspective p 2481**

We previously demonstrated that the increase in troponin I (TnI) soon after high-dose chemotherapy (HDC) is a strong predictor of left ventricular dysfunction and poor cardiac outcome, particularly in patients showing a persistent TnI increase.5,6 This finding has important clinical implications and allows the identification of patients at high risk of future cardiotoxicity in whom preventive measures are warranted.
Angiotensin-converting enzyme (ACE) inhibitors (ACEIs) have been shown to slow the progression of left ventricular dysfunction in several different clinical settings, including anthracycline-induced cardiomyopathy.9–12 Furthermore, data referring to experimental models suggest that the cardiac renin-angiotensin system (RAS) plays an important role in the development of anthracycline-induced cardiomyopathy and that treatment with ACEIs protects against chemotherapy-induced cardiotoxicity.13–19 Hence, it is likely that a prophylactic strategy based on the use of ACEIs in selected high-risk patients could prevent cardiotoxicity.

We performed a prospective, randomized clinical study to evaluate the effect of enalapril treatment on the prevention of cardiotoxicity in cancer patients undergoing HDC that is followed by an increase in TnI.

### Study Protocol

Plasma TnI concentration was measured before and soon after each cycle of HDC (early TnI). Determination of early TnI consisted of a curve of assays: baseline, immediately after, and 12, 24, 36, and 72 hours after the end of chemotherapy infusion. This sequence was repeated after each cycle of therapy. For each patient, the highest TnI value was considered. All patients with an early TnI value >0.07 ng/mL were considered for enrollment and were randomly assigned in a 1:1 ratio to receive (ACEI group) or not to receive (control subjects) enalapril. Randomization was based on numbers generated by an electronic computer. Treatment allocations were kept in numbered envelopes to be opened only at the moment that patients actually were assigned to a specific group. No dropouts occurred between enrollment and the beginning of treatment. In ACEI group patients, enalapril was started 1 month after the end of the last cycle of HDC to achieve the patient’s clinical stability, and treatment was continued for 1 year. TnI value also was determined at randomization (late TnI), before enalapril administration in ACEI group, and 2, 3, 6, and 12 months later. Enalapril was administered at an initial dose of 2.5 mg once daily and was increased gradually through 3 steps to 20 mg once daily (5, 10, and 20 mg, respectively). In the case of persistent hypotension, the dose was reduced to the lowest level.

Clinical assessment was done weekly during enalapril titration. Cardiac function was evaluated by physical examination, ECG, and measurement of left ventricular volumes and LVEF by echocardiography (biplane method according to Simpson’s rule)24 at baseline; or whenever required by the clinical situation. Cardiologists performing echocardiographic evaluations were blinded to the patients’ treatment assignments. If a relapse of the oncological disease occurred or new chemotherapy was required, patients were not considered in the subsequent period. In these patients and in those lost to follow-up or dead from oncological disease, the evaluation performed at the last follow-up check was considered the final measurement. All subjects were followed up in our outpatient clinic until December 31, 2005.

The primary end point of the study was the occurrence of cardiotoxicity in the 2 groups, defined as an absolute decrease >10 percent units in rest LVEF associated with a decline below the normal limit value (50%).3,4 Secondary end points included the effect of enalapril on LVEF and the occurrence of adverse cardiac events during the 1-year follow-up. The following cardiac events were considered: sudden death, death

### Methods

#### Study Population

All consecutive cancer patients undergoing HDC in our institute from January 1, 2002, to December 31, 2004, were considered. Clinical indications for HDC were advanced or primary resistant breast cancer, acute myeloid leukemia, relapsed or refractory poor-prognosis Hodgkin’s disease, high-grade non-Hodgkin’s lymphoma, myeloma, and Ewing’s sarcoma. By protocol, contraindication for HDC was the presence of ischemic, valvular, and hypertensive heart disease; uncontrolled hypertension; LVEF <40%; age ≥65 years; and abnormal renal or hepatic functions. All patients received HDC in different drug combinations, according to the oncological protocols of our institute (Table 1). Patients previously treated with anthracyclines were assigned to schemes either not containing or containing only low doses of these agents to maintain the cumulative amount of anthracyclines below dosages associated with a high risk of cardiotoxicity.4,20 All drugs were administered via central venous catheters. Reinfusion of autologous peripheral blood progenitor cells, with or without pretreatment with high-dose cyclophosphamide, was performed to accelerate hematopoietic recovery and to reduce the requirements for supportive care.21 Additional exclusion criteria were intolerance or contraindication to ACEIs; ongoing therapy with β-blocking agents, ACEIs, and angiotensin II receptors blockers; and systolic blood pressure <90 mm Hg. Patients developing acute (<2 weeks) cardiotoxicity after chemotherapy also were excluded.4,22,23 The investigation conformed to the principles of the Declaration of Helsinki. The local ethics committee approved the protocol, and written informed consent was obtained from all patients.
resulting from a cardiac cause, acute pulmonary edema, overt heart failure, and life-threatening arrhythmias requiring treatment. A combined end point including LVEF reduction or cardiac events also was considered.

TnI Measurement
Blood samples for TnI measurement were collected into a Monovette (Sarstedt AG & Co., Nümbrecht, Germany) containing a sodium citrate solution (0.106 mol/L) with a dilution ratio after blood collection of 1:9 (1 part citrate to 9 parts blood) and then centrifuged at 1080g for 60 minutes. The plasma was then separated. TnI concentration was determined by a fluorometric enzyme immunosay analyzer (Stratus CS, Dade Behring, Miami, Fla) with a functional sensitivity of 0.03 μg/L; the cutoff level was 0.08 ng/mL.29 All positive samples were immediately retested to confirm the result obtained.

Statistical Analysis
A sample size of 54 patients per group was planned to assess as statistically significant a reduction in the combined event rate (decrease >10 percent units in rest LVEF associated with a decline below 10% from 35% to 10% with a 0.05 type I error and 90% power.4 At baseline, categorical variables were compared between treatments by χ² or Fisher’s exact test as appropriate; quantitative variables were compared by 2-sample t test.

The primary, secondary, and combined end points were compared between treatments by the Kaplan-Meier survival analysis, and differences between groups were assessed by the log-rank test. To correct for baseline imbalances in potential confounders, we used multivariate Cox proportional-hazard regression analysis with a discrete time variable adjusting for age, gender, hypertension, diabetes, radiotherapy (yes/no), total dose of anthracyclines, and number of chemotherapeutic agents administered. The time course of ventricular volumes and of LVEF in the 2 groups was compared by repeated-measures analysis of variance with adjustment for baseline values. Data are expressed as mean±SD. A value of P<0.05 was considered statistically significant. All analyses were performed with the SAS software package (version 8.02; SAS Institute Inc, Cary, NC).

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results
Of the 473 consecutive patients undergoing HDC who were considered, 114 (24%; 72 women; mean age, 45±12 years) showed increased TnI values soon after HDC and were enrolled in the study. Fifty-six patients were randomly assigned to the treatment arm (ACEI group), and 58 patients were assigned to the no-treatment arm (control subjects). The clinical characteristics of the 2 groups are reported in Table 2.26 The 2 populations were similar with regard to age, gender, cumulative dose of anthracyclines therapy and radiotherapy, cardiac risk factors, acute in-hospital complications, kind of oncological disease, and HDC schedule. The average early TnI values also were similar in the 2 groups. Of the entire population, 50 patients (44%) showed a persistently high TnI at 1 month (45% in ACEI group, 43% in control subjects; P=NS). Enalapril was well tolerated in most patients; in only 1 patient who developed a cough, the enalapril dosage was decreased and the symptom resolved. The maximal tolerated dose of enalapril in ACEI group was 16±6 mg/d.

By protocol, LVEF was normal in all patients at baseline evaluation and comparable in the 2 groups. Similarly, LVEF was not statistically different in the 2 groups at the time of randomization. In the subsequent months, a different behavior of LVEF was observed in the 2 groups, with a progressive reduction in LVEF and an increase in end-diastolic and end-systolic volumes in control subjects only (Table 3). Twenty-five control subjects (43%) and no patients in the ACEI group showed a decrease in LVEF >10 percent units from baseline associated with a decline below the normal limit value of 50% (P<0.001). Three patients started a new chemotherapy for relapse of the oncological disease; 2 of them, 1 in each group, subsequently died. Overall, 31 cardiac events occurred during follow-up. However, their incidence was significantly higher in control subjects than in the ACEI group (Table 4). Among patients showing normal TnI values after HDC (n=359), none experienced cardiac events during the 1-year follow-up; 6 of them (2%) died of the oncological disease.

For each group, LVEF also was analyzed separately in patients with and without persistent TnI increase. In control subjects, a greater LVEF reduction was observed in patients with a persistently high TnI increase than in those with only a transient TnI increase (Figure 1, left). No difference was observed in the 2 ACE-treated subgroups (Figure 1, right). Notably, the percentage of patients showing an increased TnI value during follow-up and a mean TnI value at each step was higher in control subjects than in the ACEI group (Figure 2).

According to Kaplan-Meier analysis, the incidence of the primary end point was significantly lower in the ACEI group (log-rank χ²=30.5; P<0.001). Because no events occurred in this group, the Cox multivariate analysis was not applicable, and the adjusted hazard ratio could not be computed. The log-rank test, applied to the secondary and combined end points, also was very significant (P<0.001 in both cases). At multivariate analysis, with adjustment for age, gender, hypertension, diabetes, radiotherapy (yes/no), total dose of anthracyclines, and number of chemotherapeutic agents administered, the hazard ratio in treated patients for the combined end point was 0.015 (95% confidence interval, 0.002 to 0.11; P<0.001). Moreover, when oncological death and relapse were included in the combined end point, the results were minimally affected: the log-rank χ² was 37.7 (P<0.001), and the adjusted hazard ratio was 0.032 (95% confidence interval, 0.01 to 0.14; P<0.001).

Discussion
The main finding of this study is that early treatment with enalapril in patients with evidence of myocardial cell injury (TnI increase) after HDC seems to prevent the development of cardiotoxicity and the occurrence of associated adverse clinical events.

In previous studies, we demonstrated that the increase in TnI soon after HDC is a strong predictor of cardiotoxicity and poor cardiological outcome, with the highest risk observed in patients showing a persistent (1 month) TnI increase.5,6 Identifying such a high-risk patient subset highlights the opportunity for targeted preventive measures. The results of the present study confirm the prog-
nostic role of TnI and show that high-risk patients, defined on the basis of an early TnI increase after HDC, have an improved cardiological outcome and a preserved left ventricular function when prophylactic therapy with enalapril is carried out. Indeed, in the ACEI group, neither LVEF nor left ventricular volumes changed during the treatment period, and a lower incidence of adverse cardiac events was observed than in untreated patients.

It has been reported that more than half of all patients exposed to anthracyclines and evaluated after 10 to 20 years from initial oncological diagnosis show cardiac abnormalities, the incidence of which increases over time.

TABLE 2. Clinical Characteristics of the Study Population According to Treatment

<table>
<thead>
<tr>
<th></th>
<th>ACEI Group (n=56)</th>
<th>Control Subjects (n=58)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>47±11</td>
<td>44±13</td>
<td>0.30</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>33 (60)</td>
<td>39 (67)</td>
<td>0.47</td>
</tr>
<tr>
<td>Baseline LVEF, %</td>
<td>62±3</td>
<td>63±3</td>
<td>0.17</td>
</tr>
<tr>
<td>Early TnI, ng/mL</td>
<td>0.18±0.38</td>
<td>0.22±0.44</td>
<td>0.59</td>
</tr>
<tr>
<td>Previous anthracycline therapy, n (%)</td>
<td>44 (78)</td>
<td>43 (74)</td>
<td>0.74</td>
</tr>
<tr>
<td>Previous mediastinum radiotherapy, n (%)*</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0.51†</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>3 (5)</td>
<td>4 (7)</td>
<td>0.52†</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0.74†</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>2 (4)</td>
<td>2 (3)</td>
<td>0.68†</td>
</tr>
<tr>
<td>In-hospital acute post-HDC complications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia requiring blood transfusion</td>
<td>45 (80)</td>
<td>48 (83)</td>
<td>0.93</td>
</tr>
<tr>
<td>Hyperpyrexia (&gt;38.5°C)</td>
<td>44 (78)</td>
<td>50 (86)</td>
<td>0.41</td>
</tr>
<tr>
<td>Oncological disease, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>6 (11)</td>
<td>9 (15)</td>
<td>0.63</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>14 (25)</td>
<td>15 (26)</td>
<td>0.91</td>
</tr>
<tr>
<td>Ewing's sarcoma</td>
<td>2 (4)</td>
<td>2 (3)</td>
<td>0.68†</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>5 (9)</td>
<td>5 (9)</td>
<td>0.78</td>
</tr>
<tr>
<td>Myeloma</td>
<td>10 (18)</td>
<td>7 (12)</td>
<td>0.55</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>19 (34)</td>
<td>20 (34)</td>
<td>0.89</td>
</tr>
<tr>
<td>Antineoplastic treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEAM</td>
<td>12 (21)</td>
<td>9 (16)</td>
<td>0.57</td>
</tr>
<tr>
<td>DAUNO +ARAC</td>
<td>6 (11)</td>
<td>9 (15)</td>
<td>0.63</td>
</tr>
<tr>
<td>ESAP</td>
<td>4 (7)</td>
<td>3 (5)</td>
<td>0.48†</td>
</tr>
<tr>
<td>ESAP+BEAM</td>
<td>1 (2)</td>
<td>3 (5)</td>
<td>0.32†</td>
</tr>
<tr>
<td>ICE</td>
<td>2 (4)</td>
<td>2 (3)</td>
<td>0.68†</td>
</tr>
<tr>
<td>ICE+IDA+MEL</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0.51†</td>
</tr>
<tr>
<td>MEL</td>
<td>4 (7)</td>
<td>2 (3)</td>
<td>0.32†</td>
</tr>
<tr>
<td>MEL+IDA</td>
<td>6 (11)</td>
<td>5 (9)</td>
<td>0.95</td>
</tr>
<tr>
<td>MITOX +MEL</td>
<td>2 (4)</td>
<td>4 (7)</td>
<td>0.36†</td>
</tr>
<tr>
<td>SEQ</td>
<td>3 (5)</td>
<td>6 (10)</td>
<td>0.52</td>
</tr>
<tr>
<td>TEC</td>
<td>11 (20)</td>
<td>13 (22)</td>
<td>0.89</td>
</tr>
<tr>
<td>TICE</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td>0.30†</td>
</tr>
<tr>
<td>Chest-wall radiotherapy (left), n (%)</td>
<td>9 (16)</td>
<td>7 (12)</td>
<td>0.73</td>
</tr>
<tr>
<td>Chest-wall radiotherapy (right), n (%)</td>
<td>3 (5)</td>
<td>5 (9)</td>
<td>0.38†</td>
</tr>
<tr>
<td>Mediastinum radiotherapy, n (%)§</td>
<td>7 (12)</td>
<td>6 (10)</td>
<td>0.95</td>
</tr>
<tr>
<td>Cumulative anthracycline dose, mg/m2</td>
<td>332±191</td>
<td>338±167</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. Data are expressed as numbers (percent) or mean±SD.
*Total dose=30 Gy.
†Fisher exact test.
‡Total dose=60 Gy.
§Total dose=40 Gy.
Cumulative anthracycline dose was calculated by adding the prior anthracycline treatment to the anthracycline dose included in HDC and by converting different anthracycline agents in terms of doxorubicin equivalents.
Of these patients, possibly 5% develop congestive heart failure. Arrhythmias also have been found to occur in ≈40% of patients within 20 years after diagnosis.27 In addition to anthracyclines, many other chemotherapeutic agents have been shown to cause cardiotoxicity.28 In particular, most drugs included in HDC have been reported to have cardiotoxic effects when administered either singly or in combination.29

The development of cardiotoxicity, even asymptomatic, not only negatively affects patients’ cardiological outcome but also seriously limits their therapeutic opportunities when adjunctive chemotherapy for relapse is required.7,8 Indeed, the presence of impaired cardiac function restricts the choice of possible oncological treatments to those considered less aggressive and consequently less effective.4,30–32

The benefits of and clinical indications for ACEIs have been clearly defined in many cardiovascular conditions such as chronic heart failure, asymptomatic left ventricular dysfunction, acute myocardial infarction, and hypertension and in patients at increased risk of cardiovascular events.8–10 In cardiomyopathy, because of anthracycline-induced cardiotoxicity, the use of enalapril has been proved to be beneficial in prolonging survival and in preventing further deterioration of cardiac function.12

Although the mechanisms by which ACEIs improve outcome in patients with systolic dysfunction are not completely understood, induction of a more favorable hemodynamic condition and counteraction of RAS activation most likely play important roles. ACEIs reduce afterload and systolic ventricular wall stress, increase cardiac output, improve ventricular geometry, prevent the growth effects of angiotensin II on myocytes, attenuate aldosterone-induced cardiac fibrosis, and reduce apoptosis of cardiac cells.11 In all these responses, local inhibition of RAS plays an important role in the development of anthracycline-induced cardiomyopathy. In these models, cardiac ACE activity was found to be increased after chemotherapy compared with control subjects. Notably, treatment with lisinopril started after chemotherapy significantly inhibited cardiac ACE activity and improved mortality, cardiac remodeling, and cardiac dysfunction in an animal model.13 Moreover, in rats treated with temocapril, collagen accumulation was inhibited and fibrosis was avoided in the cardiac interstitium.14 These findings suggest that beneficial effects of ACEIs in anthracycline-treated animals depend on inhibition of cardiac ACE and that its activation plays a pivotal role in the development of this kind of cardiomyopathy.

ACEIs have been shown to be potent scavengers of free radicals, and they exert antioxidant effects.16 Then again, an increased oxidative stress has been indicated as a possible primary mechanism in the development of anthracycline-

### TABLE 3. Echocardiographic Parameters During the Study Period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Randomization</th>
<th>3 mo</th>
<th>6 mo</th>
<th>12 mo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV, mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI group</td>
<td>101.7±27.4</td>
<td>100.2±26.1</td>
<td>98.1±27.8</td>
<td>97.5±24.5</td>
<td>101.1±26.4</td>
<td>0.045</td>
</tr>
<tr>
<td>Control subjects</td>
<td>103.2±20.1</td>
<td>103.9±21.0</td>
<td>106.4±21.0</td>
<td>107.1±23.9</td>
<td>104.2±25.6</td>
<td></td>
</tr>
<tr>
<td>ESV, mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI group</td>
<td>38.6±10.8</td>
<td>38.7±10.4</td>
<td>37.3±10.9</td>
<td>37.4±10.3</td>
<td>38.5±11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control subjects</td>
<td>38.8±10.2</td>
<td>40.5±12.2</td>
<td>49.8±17.6</td>
<td>51.8±16.9</td>
<td>54.4±20.1</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI group</td>
<td>61.9±2.9</td>
<td>61.1±3.2</td>
<td>61.9±3.3</td>
<td>61.6±3.9</td>
<td>62.4±3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control subjects</td>
<td>62.8±3.4</td>
<td>61.8±4.3</td>
<td>54.2±8.1</td>
<td>51.9±7.9</td>
<td>48.3±9.3</td>
<td></td>
</tr>
</tbody>
</table>

EDV indicates end-diastolic volume; ESV, end-systolic volume.

*Probability value for repeated-measures analysis of variance.
†P<0.001 vs baseline.

### TABLE 4. Cardiac Events in the Study Groups

<table>
<thead>
<tr>
<th>Event</th>
<th>Total (n=114), n (%)</th>
<th>ACEI Group (n=56), n (%)</th>
<th>Control Subjects (n=58), n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>0.49*</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td>4 (7)</td>
<td>0.07*</td>
</tr>
<tr>
<td>Heart failure</td>
<td>14 (12)</td>
<td>0 (0)</td>
<td>14 (24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arrhythmias requiring treatment</td>
<td>11 (10)</td>
<td>1 (2)</td>
<td>10 (17)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cumulative events</td>
<td>31</td>
<td>1</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Fisher exact test.
induced cardiac toxicity. In several studies, both sulfhydryl-
and non–sulfhydryl-containing ACEIs have been shown to be
effective free radical scavengers, having an antioxidant effect
on Adriamycin-induced cardiotoxicity.18,33

The mechanism by which enalapril prevents the develop-
ment of cardiotoxicity remains uncertain. Hemodynamic
abnormalities and systemic activation of RAS probably
were not present in our population, given the normal LVEF
observed at the time of patient randomization. Conversely,
it is more likely that other effects such as cardiac tissue
RAS activation and oxidative stress might be involved in
the development and progression of HDC-induced myo-
cardial injury in this preclinical phase and that, by coun-
teracting these mechanisms with enalapril, the develop-
ment of a clinically relevant dysfunction and of the
associated cardiac events may be prevented.

Untreated patients showing a persistent TnI increase 1
month after the end of HDC had a greater long-term LVEF
reduction than patients with a transient TnI increase, in
agreement with our previous findings (Figure 1).6 Notably,
the benefit of enalapril treatment was present in both
subgroups, suggesting that patients with a persistent TnI
increase may particularly benefit from this preventive
therapy.

The different TnI patterns observed during follow-up in
the 2 groups support this hypothesis. Persistence of in-
creased levels of TnI, also several months after HDC, was
observed more frequently in control subjects than in ACEI
group patients. This finding suggests that cardiac damage
induced by HDC elicits an ongoing phenomenon charac-
terized by a progressive loss of myocytes whose late
cumulative effect is reflected by LVEF impairment. How-
ever, whatever the mechanism involved, our data seem to
indicate that enalapril is able to turn off TnI release and to
prevent cardiac dysfunction. Interestingly, in both control
subjects and ACEI group, all but 2 patients had normalized
TnI value within 12 months. We previously observed that
most of the clinical events occur during this period.6
Therefore, we can speculate that enalapril may not be
required after this time and could be withdrawn safely after
1 year from the end of HDC. This hypothesis should be
addressed in future studies on a longer follow-up.

Enalapril was very well tolerated in all patients. A very
slow and careful drug titration may have contributed to this
result, particularly in these types of patients, often char-
acterized by a poor performance status as a result of recent
chemotherapy.

Several different strategies have been devised in an
attempt to prevent or to reduce cardiac toxicity. Among
these, changes in chemotherapy administration schedule,
limitation of cumulative anthracyclines dose, use of an-
thracycline analogues and cardioprotectants (antioxidant
agents, dexrazoxane, erythropoietin, etc),34,35 and close
monitoring of cardiac function have been proposed. How-
ever, each of these approaches has some limitations such
as the possible compromise of chemotherapy clinical
success, high costs, and poor predictive value. Finally,
the most critical limitation, common to all these strategies,
is that all cancer patients receiving chemotherapy must be
indiscriminately considered, with a very high cost-to-
benefit ratio. In contrast, an extremely important aspect of
our approach is that TnI allows us to select patients more
prone to develop late cardiotoxicity (24% of our popula-
tion) for which a preventive therapy can be planned. We
previously reported a very high negative predictive value
of TnI after HDC (99%); this allows us to exclude most
patients from a prophylactic treatment.

Study Limitations
Although our trial was designed as a prospective, random-
ized, controlled study, the lack of placebo administration, not
permitted by our ethics committee, and the open-label
follow-up were potential limitations for our study. Further
limitations were the lack of prespecified and rigorously
defined clinical end points and the several oncological dis-
eases and chemotherapeutic regimens included in the study.
However, in this regard, it must be emphasized that the
percentage of patients treated with schedules, including
anthracyclines, and the anthracycline cumulative doses were well balanced in the 2 groups. Therefore, a different risk of cardiotoxicity in control subjects and in ACEI group patients is unlikely.

Conclusion

The findings of our study suggest that, in high-risk HDC-treated patients, early treatment with enalapril seems to be an effective approach both to prevent cardiotoxicity and to improve cardiological outcome.

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Disclosures

None.

References

26. Bearman SI, Petersen FB, Schor RA, Denney JD, Fisher LD, Appelbaum FR, Buckner CD. Radionuclide ejection fractions in the evaluation of...


**CLINICAL PERSPECTIVE**

Occurrence of chemotherapy-induced cardiotoxicity not only negatively affects a patient’s cardiological outcome but also seriously limits his or her therapeutic opportunities. In cancer patients, an increase in troponin I soon after high-dose chemotherapy is a strong predictor of late cardiotoxicity and poor cardiological outcome. This finding has important clinical implications and provides a rationale for the development of prophylactic strategies against cardiotoxicity. Angiotensin-converting enzyme inhibitors preserve left ventricular function in different clinical settings, but their role in the prevention of cardiotoxicity has never been investigated. We evaluated 473 cancer patients; of them, 114 (24%) showed an increase in troponin I soon after high-dose chemotherapy and were randomized to receive or not to receive enalapril. Treatment was started 1 month after high-dose chemotherapy and continued for 1 year. Our data indicate that early treatment with enalapril prevents the development of left ventricular dysfunction and the occurrence of adverse cardiological events. Several strategies have been devised such as limitation of cumulative anthracyclines dose, use of anthracyclines analogues and cardioprotectants, and close monitoring of cardiac function in attempts to prevent or reduce cardiotoxicity. However, each of these approaches has limitations, such as the possible compromise of chemotherapy success, high costs, and poor predictive value. Moreover, for all these preventive approaches, all patients receiving chemotherapy must be indiscriminately considered, with a very high cost-to-benefit ratio. Conversely, troponin I allows us to select patients at high risk of developing cardiotoxicity, thus excluding most patients, namely those at low risk, who are unlikely to derive benefit from a prophylactic treatment.
Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

Daniela Cardinale, Alessandro Colombo, Maria T. Sandri, Giuseppina Lamantia, Nicola Colombo, Maurizio Civelli, Giovanni Martinelli, Fabrizio Veglia, Cesare Fiorentini and Carlo M. Cipolla

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