Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-Dose Chemotherapy

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Background—In patients with aggressive malignancies who are undergoing high-dose chemotherapy, even minimal elevation of troponin I (TnI) is associated with late left ventricular dysfunction. The time course of the subclinical myocardial damage and its impact on the clinical outcome have never been investigated previously.

Methods and Results—In 703 cancer patients, we measured TnI soon after chemotherapy (early TnI) and 1 month later (late TnI). Troponin was considered positive for values ≥0.08 ng/mL. Clinical and left ventricular ejection fraction evaluation (echocardiography) were performed before chemotherapy, 1, 3, 6, and 12 months after the end of the treatment, and again every 6 months afterward. Three different TnI patterns were identified, and patients were grouped accordingly. In 495 patients, both early and late TnI values were <0.08 ng/mL (TnI⁻ group); in 145, there was only an early increase (TnI⁺ group); and in 63 patients, both values increased (TnI⁺⁺ group). In the TnI⁻ group, no significant reduction in ejection fraction was observed during the follow-up, and there was a very low incidence of cardiac events (1%). In contrast, a greater incidence of cardiac events occurred in TnI-positive patients, particularly in the TnI⁺⁺ group (84% versus 37% in the TnI⁻ group; P<0.001).

Conclusions—TnI release pattern after high-dose chemotherapy identifies patients at different risks of cardiac events in the 3 years thereafter. This stratification allows us to differentiate the monitoring program and to plan, in selected patients, preventive strategies aimed at improving clinical outcome. (Circulation. 2004;109:2749-2754.)

Key Words: troponin ■ chemotherapy ■ ventricles ■ cardiac toxicity

Cardiotoxicity is a common complication of chemotherapy. The clinical course of the more typical form, chronic cardiotoxicity, can range from transient asymptomatic left ventricular dysfunction to cardiac death.¹⁻³ Its incidence varies according to different clinical definitions but has been reported to be as high as 65%.⁴ The magnitude of the problem is rising as a result of the increasing number of long-term cancer survivors and because of the tendency to use higher doses of anthracyclines (AC), as well as combined treatments with synergistic cardiac toxic effects.¹⁻⁵⁻⁷

Extensive and expensive monitoring programs are usually recommended to identify patients who develop cardiac toxicity.⁶⁻¹¹ However, most methods used in clinical practice (echocardiography, radionuclide angiography, etc), have low sensitivity and poor predictive value or, like endocardial biopsy, have specific technical limitations.²⁻³,⁶⁻¹⁰,¹²,¹³

Troponin I (TnI) is a protein present exclusively in the myocardial cells. The TnI plasma concentration is a well-established specific and sensitive marker of myocardial injury, with both high diagnostic and prognostic value.¹⁴

In previous studies, we observed that in patients with aggressive malignancies, TnI increased in ≈33% of patients soon after high-dose chemotherapy (HDC). This early increment was strongly associated with a reduction in left ventricular ejection fraction (LVEF) that occurred during the following year.¹⁵⁻¹⁶ However, data on TnI behavior after this early increment, as well as on its potential impact on the clinical outcome of cancer patients, are still lacking. Possibly, a prolonged TnI follow-up study can provide us with information on the time course of myocardial damage after HDC and on the stratification of the cardiac risk of these patients.

The present prospective study was undertaken to investigate whether TnI concentration, measured early after HDC as well as 1 month later, is associated with the risk of future cardiac events.

Methods

Study Population

We considered all consecutive cancer patients undergoing HDC in our institute beginning from September 1, 1999. By protocol,
TABLE 1. High-Dose Chemotherapeutic Schedules

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Disease</th>
<th>Drugs</th>
<th>Previous</th>
<th>No. of Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC</td>
<td>B</td>
<td>Epirubicin 200 mg/m²</td>
<td>Cyclophosphamide 4 g/m²</td>
<td>No 3</td>
</tr>
<tr>
<td>TEC</td>
<td>B</td>
<td>Taxotere 85 mg/m²</td>
<td>Epirubicin 200 mg/m²</td>
<td>Cyclophosphamide 4 g/m²</td>
</tr>
<tr>
<td>ICE</td>
<td>B, M, E, G, O, S</td>
<td>Ifosfamide 10 g/m²</td>
<td>Carboplatin 1.2 g/m²</td>
<td>Etoposide 1.2 g/m²</td>
</tr>
<tr>
<td>TICE</td>
<td>B</td>
<td>Taxotere 85 mg/m²</td>
<td>Ifosfamide 10 g/m²</td>
<td>Carboplatin 1.2 g/m²</td>
</tr>
<tr>
<td>BEAM*</td>
<td>HL, NHL</td>
<td>Carmustine 300 mg/m²</td>
<td>Etoposide 0.8 g/m²</td>
<td>Cytarabine 1.6 g/m²</td>
</tr>
<tr>
<td>ESAP*</td>
<td>HL, NHL</td>
<td>Etoposide 1.2 g/m²</td>
<td>Carboplatin 1.2 g/m²</td>
<td>Cytarabine 16 g/m²</td>
</tr>
<tr>
<td>MITOX+MEL*</td>
<td>NHL</td>
<td>Mitoxantrone 60 mg/m²</td>
<td>Melphalan 180 mg/m²</td>
<td>Yes 1</td>
</tr>
<tr>
<td>MEL*</td>
<td>NHL</td>
<td>Melphalan 200 mg/m²</td>
<td>Yes 1–2</td>
<td></td>
</tr>
<tr>
<td>IDA+MEL*</td>
<td>HL, M, E</td>
<td>Idarubicin 45 mg/m²</td>
<td>Melphalan 180 mg/m²</td>
<td>Yes 1–2</td>
</tr>
<tr>
<td>SEQ*</td>
<td>HL, NHL</td>
<td>Methotrexate 8 g/m²</td>
<td>Etoposide 2 g/m²</td>
<td>Idarubicin 45 mg/m²</td>
</tr>
<tr>
<td>CTX</td>
<td>HL, M, E, G</td>
<td>Cyclophosphamide 7 g/m²</td>
<td>Yes 1</td>
<td></td>
</tr>
</tbody>
</table>

EC indicates epirubicin-cyclophosphamide; TEC, taxotere-epirubicin-cyclophosphamide; ICE, ifosfamide-carboplatin-etoposide; TICE, taxotere-isofamide-carboplatin-etoposide; BEAM, BCNU(carmustine)-etoposide-ARA-C(cytarabine)-melphalan; ESAP, etoposide-solodemedrol-ARA-C(cytarabine)-platinum; MITOX, mitoxantrone; MEL, melphalan; IDA, idarubicin; SEQ, sequential; CTX, cyclophosphamide; B, breast cancer; E, Ewing’s sarcoma; G, germ-cell tumors; HL, Hodgkin’s disease; M, myeloma; NHL, non-Hodgkin’s lymphoma; O, ovarian carcinoma; and S, small-cell lung cancer.

†One drug for each cycle.

contraindication for HDC was the presence of ischemic or valvular heart disease, LVEF <50%, age ≥70 years, and abnormal renal or hepatic function. Baseline clinical and echocardiographic evaluations were performed within 1 week before HDC. We also excluded hypertensive patients treated with β-blocking agents and angiotensin-converting enzyme inhibitors because those substances can mask a possible left ventricular impairment. Patients developing acute (<1 week) cardiotoxicity after HDC and those in whom a double TnI evaluation (early and late) was not achieved were also excluded.1 3

A total of 703 patients (487 women; mean age, 47 12 years) fulfilled the inclusion criteria and were enrolled in the study. Clinical indications for HDC were advanced or primary resistant breast cancer (n = 326), high-grade non-Hodgkin’s lymphoma (n = 264), myeloma (n = 44), poor-prognosis Hodgkin’s disease (n = 30), relapsed or refractory ovarian carcinoma (n = 16), small-cell lung cancer (n = 10), germ-cell tumors (n = 8), and Ewing’s sarcoma (n = 5).

All patients received HDC in different drug combinations, according to our institute’s protocols (Table 1). All drugs were administered via central venous catheters. Cycles were delivered at 28-day intervals, and each cycle was supported by reinfusion of autologous blood. Cycles were delivered at 28-day intervals, and each cycle was supported by reinfusion of autologous blood. Cycles were delivered at 28-day intervals, and each cycle was supported by reinfusion of autologous blood.

TnI was also determined 1 month after the last administration of HDC (late troponin; L-TnI). The timing for L-TnI was chosen in a such a way that all patients undergoing radiotherapy had L-TnI determination before beginning radiotherapy to exclude interference caused by a possible radiotherapy-induced cardiac injury.

Cardiac function was evaluated by physical examination, ECG, and measurement of LVEF (biplane method, according to Simpson’s rule) before HDC and 1, 3, 6, and 12 months after the end of HDC and every 6 months thereafter or whenever required by the clinical situation. Patients requiring new chemotherapy for the oncological disease relapse were not considered in the following period of observation. In these patients, as well as in those lost to follow-up or those who died of oncological disease, measurements made at the last follow-up check were considered as final measurements. All patients’ management decisions and measurements were made blindly, without the knowledge of the patient’s TnI results.

The primary end point of the study was the occurrence during the follow-up of one of the following cardiac events: (1) death resulting from a cardiac cause, (2) acute pulmonary edema, (3) overt heart failure, (4) asymptomatic LVEF reduction (≥25% from baseline), or (5) life-threatening tachyarrhythmias and conduction disturbances requiring a permanent pacemaker. All subjects were followed up in our outpatient clinic until March 1, 2003. For each patient, event-free survival was calculated from the end of HDC to the occurrence of the first cardiac event, to the beginning of new chemotherapy for disease relapse, or to the end of the study. When patient information was not directly available, it was obtained from hospital records or from the patient’s general practitioner and relatives.

Laboratory Methods

Blood samples were collected into a Monovette containing a sodium citrate solution (0.106 mol/L) with a dilution ratio after blood collection of 1 to 9 and centrifuged at 1080g for 60 minutes, and the plasma was then separated. TnI concentrations were determined by a fluorometric enzyme immunoassay analyzer (Stratus CS, Dade Behring) with a functional sensitivity of 0.03 μg/L; the cutoff level was 0.08 ng/mL. All positive samples were immediately retested for confirmation.
Three different TnI patterns were identified in our population, and patients were grouped accordingly. In 495 patients (70%), both E-TnI and L-TnI values were <0.08 ng/mL (TnI −/− group). In the remaining 208 patients, E-TnI was ≥0.08 ng/mL (0.16±0.24 ng/mL; range, 0.08 to 1.98 ng/mL). In 145 of them (70%), L-TnI was within the normal range (TnI −/+ group), whereas in 63 patients (30%), L-TnI levels remained ≥0.08 ng/mL, showing, in most cases, a further increase (TnI +/+ group) (Figure 1). The mean E-TnI value was 0.12±0.11 ng/mL (range, 0.08 to 1.05 ng/mL) in the TnI −/− group and 0.25±0.39 ng/mL (range, 0.08 to 1.98 ng/mL) in the TnI −/+ group (P<0.001 versus TnI +/+). A wide overlap between E-TnI values was observed between the 2 groups. Indeed, in only 4 TnI +/+ patients was an E-TnI value >1.05 ng/mL detected. The TnI peak value was observed soon after the end of HDC in 33% of cases, after 12 hours in 22%, after 24 hours in 8%, after 36 hours in 24%, and after 72 hours in 13%. In patients with positive E-TnI values (TnI +/+ and TnI +/− groups; n=208), a relationship was found between E-TnI value and LVEF maximal reduction during follow-up (r=0.78; P<0.0001). This correlation improved when only the TnI +/+ patients (n=63) were considered (r=0.92; P<0.0001).

The clinical characteristics of the 3 groups are reported in Table 2. A greater prevalence of women was observed in the TnI +/+ group, and breast cancer most common in TnI-positive patients. More patients of the TnI −/+ group had previous AC therapy and non-Hodgkin’s lymphoma than in the other 2 groups. Finally, a greater incidence of TnI positivity was observed after epirubicin-cyclophosphamide and taxotere-epirubicin-cyclophosphamide schedules.

The mean follow-up was 20±13 months (range, 1 to 42 months). Fifteen patients were lost to follow-up, and 180 patients started a new chemotherapy for relapse of the oncological disease; among these, 80 subsequently died. No patient died of extracardiac or oncological causes before a new chemotherapy was attempted.

By protocol, in all patients, LVEF was normal at baseline evaluation and was comparable in the 3 groups. A reduction in LVEF was observed in most TnI-positive patients during the follow-up. Figure 2 shows the percentage of patients with different degrees of LVEF reduction in the 3 groups. For each patient, the maximal LVEF reduction during the follow-up was considered.

The incidence of cardiac events in the 3 groups during the follow-up is shown in Table 3. These were significantly more frequent in TnI-positive patients, particularly in the TnI +/+ group. To calculate the positive and negative predictive values of TnI, we defined a true-positive test as cardiac event occurrence during follow-up in patients with both E-TnI and L-TnI values ≥0.08 ng/mL and a true-negative test as the absence of cardiac events in patients with both E-TnI and L-TnI normal value. Positive predictive value was 84%, and negative predictive value was 99%.

The cumulative cardiac events rate, as a function of the follow-up time based on Kaplan-Meier estimates in the 3 groups, is shown in Figure 3. Notably, all cardiac events were registered during the first year of follow-up.

Discussion

Our data clearly show that the TnI pattern after HDC allows us to stratify the risk of cardiac events in cancer patients in the 3 years thereafter.

In previous studies, we demonstrated that TnI is a sensitive and specific marker of myocardial injury after HDC and is able to predict, in a very early phase, the development of future ventricular dysfunction, as well as its severity. In the present study, this observation was extended to a larger population with a longer follow-up in which a wide spectrum of cardiac events was considered. A persistent TnI increase allowed us to identify patients at diverse cardiac risk according to 3 distinct TnI patterns. Patients without TnI elevation after HDC had a good prognosis. Indeed, no significant reduction in LVEF was observed in this group, and a very low incidence of cardiac events (1%) occurred during the follow-up. Hence, in consideration of the high negative predictive value of troponin (99%), we can certainly identify low-risk patients (70%) who do not require close cardiac surveillance.
after HDC. In contrast, TnI-positive patients had a greater incidence of adverse cardiac events. Careful cardiological monitoring is mandatory in these patients, and prophylactic strategies aimed at preventing clinical and subclinical cardiotoxicity should be planned. Among TnI-positive patients, the persistence of the TnI increase 1 month after HDC (TnI†† group) is consistent with a greater cardiac impairment and a higher incidence of cardiac events than in patients showing only a transient increase (TnI† group). Because of the wide overlap of E-TnI value in TnI† and TnI†† patients, a late determination of TnI was necessary to accurately discriminate a patient’s given degree of risk.

Evidence of release of troponins after chemotherapy has been demonstrated previously in animal studies, in children undergoing AC chemotherapy, and in patients with hematological malignancies. More recently, a prolonged rise of troponin in 78 adult patients developing asymptomatic LVEF decrease after chemotherapy has been reported.

Our study is the first that clearly shows, in a wide adult population, that the risk of cardiac events in cancer patients can be predicted by TnI pattern after HDC. Most patients with positive E-TnI values developed a significant LVEF reduction in the first year after HDC. In agreement with our previous observations, a close relationship between the E-TnI peak value and the degree of LVEF reduction during the follow-up was found. In addition to anticipating the development of cardiac dysfunction, TnI is also an important predictor of cardiac events. This finding has important clinical implications and provides an intriguing rationale for the development of pharmacological strategies directed at countering cardiac dysfunction and the occurrence of cardiac complications. The benefit of such an early treatment is expected to be particularly relevant in patients showing an E-TnI rise and in whom the persistence, 1 month later, of a myocardial cell damage, in terms of TnI positivity, is confirmed.

The mechanism of troponin release after chemotherapy needs further definition. We can reasonably exclude a minor necrosis of myocardial cells because of chemotherapy-induced ischemia. The low incidence of coronary risk factors, the absence of coronary artery disease, the lack of any symptoms associated with typical ECG changes, and the similar incidence of anemia and hypotension among the 3 groups are all elements that support a nonischemic pathogenesis. Furthermore, persistence of TnI rise after 1 month suggests that a release pattern different from ischemic injury occurs. Indeed, in acute coronary syndromes, troponin elevation is classically exhausted within 10 days and is usually associated with, not followed by, ventricular dysfunction.

In our study, a greater incidence of TnI positivity in women with breast cancer treated with epirubicin-cyclophosphamide and taxotere-epirubicin-cyclophosphamide could be explained by the presence, in both groups, of epirubicin, an AC with well-known cardiotoxic properties. Conversely, the lower incidence of TnI positivity among patients with non-Hodgkin’s lymphoma and those previously treated with AC could be a result of treatment that did not include ACs at all or that included them at a lower dose.
In our population, the cumulative dose of AC (previous AC dose plus that included in HDC) was similar in the 3 groups (Table 2). However, it must be considered that patients who had received previous AC treatment and developed cardiotoxicity were excluded, by protocol, from HDC. Therefore, patients having a greater propensity to AC-induced cardiotoxicity may have been excluded by the preliminary selection, and the greater incidence of TnI positivity among patients receiving high-dose epirubicin can be explained by the current epirubicin toxicity rather than by an AC cumulative dose-related effect.

In our study, all cardiac events occurred within 1 year after HDC. Consistent with the recent classification of cardiotoxicity, they represent a clinical presentation of "early-onset" chronic cardiotoxicity.\(^2,3\) A longer follow-up may be necessary to detect clinical manifestations of "late-onset" chronic cardiotoxicity, which typically occurs >1 year after chemotherapy. We cannot exclude the possibility that TnI\(^-\) patients, characterized by a very low risk of cardiac events, could experience cardiotoxicity during a longer follow-up.

Subclinical cardiotoxicity has been reported to play an important role in the course of "late-onset" chronic cardiotoxicity.\(^1,4,27,28\) Several studies recommend that patients with subclinical cardiotoxicity be monitored over a long period of time to gain insight into the clinical consequences of this still undefined condition.\(^1,6,29,30\) However, even if many cases of late abnormal cardiac function have been reported, only a small percentage of these patients experienced late clinical events.\(^4,27\)

Several implications and speculations can be assumed from our study. First, TnI, by revealing the presence as well as the persistence of myocardial injury after HDC, is able to discriminate patients at higher risk of developing a clinically relevant cardiotoxicity from those with a good clinical outcome. Second, TnI stratifies cardiac risk in a very early phase, long before impairment in heart function and symptoms develop and when many preventive therapeutic strategies are likely to be effective. Third, TnI could be used to assess as well as to monitor the safety and the effectiveness of different antineoplastic treatments. Finally, we can suppose that cardioprotective therapies that might limit or prevent the TnI rise after chemotherapy, as well as cardiological treatments that interfere with TnI persistence, could improve cardiac prognosis of these patients.\(^20,31\)

### TABLE 3. Cardiac Events in the Study Groups

<table>
<thead>
<tr>
<th>Event</th>
<th>Total (n=703)</th>
<th>TnI(^-) (n=495)</th>
<th>TnI(^+/) (n=145)</th>
<th>TnI(^++) (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death</td>
<td>3 (0.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2 (0.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>3 (0.4)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>47 (7)</td>
<td>1 (0.2)</td>
<td>18 (12)</td>
<td>28 (44)</td>
</tr>
<tr>
<td>Asymptomatic left ventricular dysfunction</td>
<td>37 (5)</td>
<td>2 (0.4)</td>
<td>24 (17)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Life-threatening arrhythmias</td>
<td>17 (2)</td>
<td>2 (0.4)</td>
<td>10 (7)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Conduction disturbances requiring pacemaker implantation</td>
<td>2 (0.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Cumulative events</td>
<td>111 (16)</td>
<td>5 (1)</td>
<td>53 (37)*</td>
<td>53 (84)*†</td>
</tr>
</tbody>
</table>

*Values are given as n (%).

\(^*\)P<0.001 vs TnI\(^-\) group; †P<0.001 vs TnI\(^++\) group.
The TnI peak value was observed at different intervals of time after HDC, so that several samples for each patient were needed to detect it. Furthermore, the best time point beyond which a negative value can assure us that no further TnI release will occur was not identified. These represent possible limitations to the use of this marker in clinical practice. However, it must be emphasized that the cost of TnI assay applies justified and cost-effective when a negative TnI value allows for the exclusion of most patients from a long-term monitoring program with expensive methods such as echocardiography and radionuclide angiocardiography.6–11

In conclusion, the TnI release pattern after HDC identifies patients at different risks of cardiac events. This stratification allows us to differentiate the monitoring program and to plan, in selected patients, preventive strategies aimed at improving clinical outcome.

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References
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