INTRODUCTION

Modern anticancer therapies lead to a significant improvement in prognosis in oncological patients. However, both conventional and novel anticancer drugs may cause damage to the heart, ultimately affecting patients’ survival and quality of life.

In the last decades, both due to the longer expectancy of life and higher knowledge of cardiac toxicity of anticancer drugs, a great amount of studies underlined the importance of chemotherapy-induced cardiotoxicity (CTX) [1–3].

In fact, CTX is one of the most severe complications of cancer treatment and represents an adverse event difficult to manage by the oncologists: even minor cardiac damage may lead to a review of the anticancer therapy, with dose reduction or change in administration schedule. This may impact patient outcome.

The most frequent cardiac complication of CTX is the development of a hypokinetic cardiomyopathy. It usually begins with asymptomatic diastolic or systolic dysfunction and may progress to congestive heart failure (HF), possibly leading to death [4]. Onset time of cardiac toxicity is highly variable. Previously, three types of CTX were described: acute, occurring after a single dose, or a single course of anticancer drugs, with the onset of clinical manifestations within 2 weeks from the end of drug administration; early-onset chronic, developing within 1 year; late-onset chronic, developing years after the end of treatment. However, this classification is based on small, retrospective studies performed in childhood cancer survivor populations [5,6]. Instead, recent findings suggest that drug-induced CTX is a continuum that starts with myocardial cell injury, followed by progressive left ventricular dysfunction (LVD), which if disregarded and not treated, leads to overt HF [7].

The phenomenon of CTX is expected to rise because of the increasing number of patients undergoing anticancer chemotherapy, the improved efficacy of anticancer therapies, and prolonged expectancy of.

A consistent number of risk factors for CTX have been identified [8]. Some of them are related to the anticancer strategy adopted, such as cumulative dose, use of chemotherapeutic agents in combination resulting in a synergistic toxicity, and prior or concomitant radiation therapy. In particular, radiation therapy may amplify and accelerate the development of cardiovascular injury, inducing endothelial cell damage and compromising coronary artery blood flow [9]. Other risk factors are patient related: age at the time of first therapy administered, preexisting cardiovascular diseases (coronary artery disease, peripheral vascular disease), well-recognized cardiovascular risk factors (hypertension, dyslipidemia, smoking history), and comorbidities (diabetes, obesity, chronic kidney disease). Notably, young patients, with a longer life expectancy, are more exposed to the risk of developing CTX [10]; on the other hand, older age itself is a risk factor, as extensively demonstrated [11].

At present, there is still no single and proper definition of anticancer drug-induced CTX. In fact, the development of any adverse cardiac events, such as acute coronary syndromes, hypertension, arrhythmias, decreased cardiac contractile function, electrocardiographic changes, and thromboembolic events, can be regarded as expressions of CTX.

International cardiologic societies defined CTX as a decline of the left ventricular ejection fraction (LVEF) greater than 10% points with a final LVEF <50% or as a LVEF reduction greater than 15% points with a final LVEF >50% [1]. More recently, expert consensus from the American Society of Echocardiography and the European Association of Cardiovascular Imaging defines CTX as a decline of LVEF greater than 10% points with a final LVEF <53% [12]. This decrease should be confirmed by repeated cardiac imaging.

Although many aspects of CTX need to be better investigated, the severity and the incidence of this phenomenon...
demand a more accurate prediction of the risk in a preclinical and early clinical stage. This approach would allow the avoidance of restrictions in indications and dose of anticancer agents and drug withdrawal that are recommended when cardiac damage is already clinically evident and moreover to plan closer monitoring.

**ANTICANCER DRUGS AND CARDIAC TOXICITY**

Several chemotherapeutic agents can induce HF or predispose patients to CTX. Traditional chemotherapeutic agents, such as anthracyclines (ACs), have been known to cause cardiovascular morbidities months or years after administration, and new targeted drugs such as monoclonal antibodies and others, have been recently evaluated (Table 7.1).

AC antibiotics, such as doxorubicin, daunorubicin, and epirubicin, are some of the most effective and widespread chemotherapeutic agents used for the treatment of both hematological and solid malignancies. The therapeutic activity of AC is mediated by their intercalation into the DNA of replicating cells, thereby inhibiting polymerases, and disrupting DNA, RNA, and protein synthesis. The mechanism of AC-induced CTX is not fully understood but it is probably multifactorial. The leading pathway is the increase of reactive oxygen species (ROS) within the cardiac myocyte mitochondria; notably, adult myocytes are more susceptible to ROS because they are terminally differentiated and cannot replace cells damaged during treatment [13,14]. Cardiac damage induced by AC is considered irreversible and dose dependent. Other authors explored a possible role for topoisomerase 2β in AC-mediated toxicity. In fact, topoisomerase 2β is required for AC to induce DNA double-strand breaks and changes in the transcriptome, leading to mitochondrial dysfunction and generation of ROS. Deleting topoisomerase 2β from cardiomyocytes prevented the development of anthracycline-induced cardiotoxicity in animal models [15]. On the basis of these molecular observations, Vejpongsa et al. hypothesized that topoisomerase 2β could be regarded as a promising molecular target that can be used to design interventions to prevent AC-induced CTX [16,17].

Trastuzumab is a humanized monoclonal antibody directed against the human epidermal growth factor receptor-2 (ErB2, also called EGFR2 or HER2), very effective for the treatment of HER2-positive breast cancer. Evidence from both in vivo and in vitro studies indicate the importance of the HER2 pathway in the heart as well, suggesting that trastuzumab-induced CTX is related to HER2 blockade with subsequent impairment of cell-protective, growth-promoting, antiapoptotic pathways in the myocardium [18].

Trastuzumab enhances the effect of traditional chemotherapy, leading to an increase of the response to the therapy and an improvement in overall survival [19]. On the other hand, its use results in an unexpected risk of CTX, often manifested by an asymptomatic decrease in LVEF. Of interest, different authors have observed that the incidence of cardiac dysfunction increased among patients who received trastuzumab with AC or trastuzumab with paclitaxel [19].

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**TABLE 7.1 Anticancer Drugs and Cardiovascular Side Effects**

| Chemotherapeutic Agents | Specific Drug | Indications | CV Side Effects |
|-------------------------|--------------|-------------|----------------|
| Anthracycline           | Epirubicin   | Breast cancer, ovarian cancer, sarcoma | Hypokinetic cardiomyopathy |
|                         | Doxorubicin  | Breast cancer, lymphoma                |                            |
|                         | Daunorubicin | Leukemia                                |                            |
| Pyrimidine analogs      | Capecitabine | Breast cancer                            | Coronary spasm             |
|                         | 5-Fluorouracil| Colorectal cancer                       |                            |
| Alkylating agents       | Cyclophosphamide | Breast cancer                | Myocarditis                 |
|                         | Cisplatin    | Urinary tract cancer                   | Thrombosis                  |
| Antimicrotubule agents  | Paclitaxel   | Breast cancer, colorectal cancer        | Bradycardia                 |
| Anti-HER2 agents        | Trastuzumab  | Breast cancer                           | Hypokinetic cardiomyopathy |
|                         | Lapatinib    | Gastric cancer                          |                            |
| Angiogenesis inhibitors | Bevacizumab | Gastric cancer                           | Hypertension                |
|                         | Sunitinib    | Renal-cell cancer                       | Thrombosis                  |
|                         | Sorafenib    | Hepatocellular cancer                   |                            |
| BCR-ABL inhibitors      | Dasatinib    | Gastric cancer                           | QT prolongation and arrhythmias |
DETECTION OF CARDIAC TOXICITY

Current Approach

The detection of drug-induced CTX is based, at present, on regular assessment of cardiac function by LVEF measurement using either transthoracic echocardiography (ECHO) or radionuclide multigated acquisition (MUGA) [3,12,24]. However, evidence-based guidelines specifying how often, by what means, or how long cardiac function should be monitored, are lacking. Moreover, this approach has several limitations [1,25]. LVEF assessment has relatively low sensitivity, because no considerable change occurs until significant myocardial damage is present. In fact, cardiac damage is usually detected only after functional impairment has already occurred, precluding any chance of preventing its development. On the other hand, the evidence of a normal LVEF does not exclude the possibility of a late cardiac deterioration given the low predictive value of LVEF assessment, even when serially repeated. Furthermore, measurement of LVEF by ECHO has further limitations: left ventricular geometric assumptions, inadequate visualization of the true left ventricular apex, lack of consideration of subtle regional wall motion abnormalities, and the inherent variability of measurement. It is also important to consider the load dependency of this measurement. Changes in loading conditions are frequent during chemotherapy and may affect the LVEF value (volume expansion due to the intravenous administration of chemotherapy or volume contraction due to vomiting or diarrhea, changing of arterial pressure values). Moreover, image quality is dependent on the acoustic window, with a high interobserver variability.

Role of Biomarkers

Over the last decades, the use of cardiac biomarkers has been investigated as a possible new tool aimed at early identification, assessment, and monitoring of drug-induced CTX. It is minimally invasive, economical, repeatable, without direct damage for patients, and without interobserver variability. Most of the existing data regarding use of cardiac biomarkers in an oncological setting refer to troponins, related to cardiomyocyte injury, and natriuretic peptides (NPs), released from the heart in response to volume expansion and increased wall stress.

Early identification of patients who are at risk for drug-induced CTX should be a primary goal to plan and to develop individualized therapeutic strategies and intervention in cancer patients.

Troponin

Troponins constitute a regulatory protein complex composed of three subunits, troponin C (TnC), troponin T (TnT), and troponin I (TnI) (Fig. 7.1). Each unit has a specific function in cell contraction, through mediation of actin–myosin interaction. In particular, TnC binds $\text{Ca}^{2+}$ released from the sarcoplasmic reticulum, TnI inhibits the ATPase activity of actomyosin, TnT provides for the binding
of the troponin complex to tropomyosin. TnC is present in all muscle types; on the other hand, three human isoforms have been described for TnT and TnI: one from the cardiac muscle and one from the fast- and the slow-twitch skeletal muscle, respectively. Cardiac troponin is complexed with actin in cardiac myofibrils with an incompletely characterized fraction soluble in the cytoplasm. When an ischemic injury occurs, there is a modification of myocyte membrane integrity, causing rapid depletion of the soluble cytoplasmic pool, followed by larger and more sustained release of troponin into the circulation as the contractile apparatus breaks down.

Cardiac troponins I and T are well-established biomarkers in diagnosis and risk stratification of patients with suspected and proven acute coronary syndromes, according to current guidelines [26]. However, elevation in troponin levels has been observed in other clinical settings, such as left ventricular hypertrophy, HF, acute pulmonary embolism, blunt trauma, sepsis, stroke, renal insufficiency and, more recently, CTX associated with anticancer drugs [27,28].

Studies performed with animal models demonstrated that TnT is released by doxorubicin-damaged myocytes; indeed the serum concentrations of TnT correlated with the dose of drug received as well as the histological degree of myocardial damage [29].

In the clinical setting, a large number of studies performed over the last decades suggest that elevations of cardiac troponin (both TnT and/or TnI) are useful tools in the evaluation of patients receiving potentially cardiotoxic therapy (Table 7.2) [30–50]. Lipshultz first observed an increase in the plasma levels of troponin in about one-third of young patients undergoing chemotherapy, thus suggesting for the first time a possible relationship between myocardial damage and anticancer treatment [30]. In a subsequent study, the same population was followed up for 5 years after the end of treatment; increase in TnT levels occurred during anticancer identified children who would later manifest cardiac abnormalities at ECHO [36].

Similar data were obtained in adult patients. Elevated levels of troponins were founded in patients receiving standard dose of AC, in the days following treatment administration [33,37,38]. In particular, patients with elevated TnT and TnI levels had a significantly greater decrease in LVEF posttreatment than those without elevation [33,37]. TnI has been demonstrated to be a sensitive and specific marker of drug-induced myocardial injury even in patients treated with high-dose AC, able to predict the development of LVD in a very early phase, as well as its severity [31,32]. In fact, in patients showing an increase in TnI, a significant reduction in LVEF after 3 months was observed, and LVEF impairment was still evident at the end of the follow-up; on the other hand patients with normal values of TnI had a transient decrease in LVEF after 3 months, but subsequently recovered to an LVEF greater than 50% (Fig. 7.2) [31]. A larger study performed by the same group confirmed these data: TnI-positive patients had a greater incidence of major adverse cardiac events [35]. In addition, given the very high negative predictive value of the marker, TnI allowed the identification of low-risk patients who will not require further cardiac monitoring, and, on the other hand, the identification of patients at higher risk, requiring closer surveillance.

Recently, the possible role of troponins in the early detection of CTX has also been investigated in patients treated with newer targeted therapies. The role of TnI has been studied in 251 breast cancer patients treated with trastuzumab [41]. It was measured immediately before and immediately after each cycle, and it showed an increase in 14% of the patients. The first TnI increase was observed, in most cases, soon after the first trastuzumab cycle (Fig. 7.3). LVD occurred in 62% of them, and in only 5% of patients with a normal TnI value ($P < 0.001$). HF treatment, including angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers (BB), was promptly initiated, and up-titrated to the maximum-tolerated dose. Patients displaying an increase in TnI during trastuzumab treatment had a threefold lower chance of recovering from cardiac dysfunction and an overall higher incidence of cardiac events, despite optimized HF treatment. These findings suggest that TnI in addition to the early identification of patients at high risk of developing LVD, also allows the identification of patients who will less likely recover from toxicity, possibly distinguishing between reversible and irreversible cardiac injury induced by a sequential treatment with AC and trastuzumab [51].

Further data have also emerged from studies performed in patients with tyrosine-kinase inhibitors. Schmidinger et al. reported an increase in TnT in about 10% of patients with metastatic renal cancer treated with sunitinib or sorafenib, and 90% of them experienced subsequent echocardiographic impairment (decrease in LVEF or regional contraction abnormalities) [40]. Morris showed increased TnI in patients receiving both trastuzumab and lapatinib following AC treatment: of note, the timing of detectable TnI preceded maximum decline in LVEF [42].

**Highly Sensitive Troponin**

A new generation highly sensitive (HS) troponin assay has been recently developed, which is able to detect very low amounts of troponin. [52] This characteristic is of particular interest in the cardioncological setting. In most patients, in fact, troponin values increases are just slightly above the cut-off.

First studies employing HS-troponin assays were conducted by Sawaya group [43,45]. In particular, they evaluated both HS-troponin and ECHO parameters of myocardial deformation in patients receiving AC, taxanes, and trastuzumab. Global and regional myocardial function by tissue Doppler and strain rate imaging, combined
with HS-troponin I, at baseline, and during chemotherapy were evaluated. Decreases in peak longitudinal strain and increases in HS-TnI concentrations, at the end of the AC treatment, were predictive of subsequent occurrence of LVD. In contrast, other tools, such as changes in LVEF, diastolic function, and N-terminal pro-brain natriuretic peptide (NT-proBNP) evaluated at the same time points, were not predictive of later occurrence of LVD. Notably, elevation in HS-TnI or a decrease in longitudinal strain was associated with higher sensitivity and specificity compared to each parameter alone [45].

More recently, other authors evaluated HS-troponin I as predictor of CTX. In particular they observed, in a similar population of cancer patients treated with AC, taxanes, and

| Study (Year) | Patients (n) | Cancer Type | Drugs | Troponin Type | Cut Off | Timing of Assessment |
|--------------|--------------|-------------|-------|---------------|---------|----------------------|
| Lipshultz (1997) [30] | 15a | ALL | AC | T | 0.03 ng/mL | Before CT; 1–3 days after each dose |
| Cardinale (2000) [31] | 201 | Various | HD CT | I | 0.04 ng/mL | 0–12–24–36–72 h after CT |
| Cardinale (2002) [32] | 232 | Breast cancer | HD CT | I | 0.04 ng/mL | 0–12–24–36–72 h after CT |
| Auner (2002) [33] | 30 | Hematological | HD Cycl | T | 0.03 ng/mL | Before CT; 1–14 days after CT |
| Sandri (2003) [34] | 179 | Various | HD CT | I | 0.04 ng/mL | 0–12–24–36–72 h after CT |
| Cardinale (2004) [35] | 703 | Various | HD CT | I | 0.04 ng/mL | 0–12–24–36–72 h after CT |
| Lipshultz (2004) [36] | 158a | ALL | AC | T | 0.01 ng/mL | Before CT; daily after induction; 7 days after a CT single dose; end CT |
| Specchia (2005) [37] | 79 | Hematological | AC | I | 0.15 ng/mL | Before CT; weekly × 4 times |
| Klickap (2005) [38] | 41 | Various | AC | T | 0.10 ng/mL | Before CT; 3–5 days after 1st and last dose |
| Lee (2008) [39] | 86 | Hematological | AC | I | 0.20 ng/mL | Before each dose |
| Schmidinger (2008) [40] | 74 | Renal carcinoma | Sunitinib/soraferinib | I | 0.03 ng/mL | Before CT; bimonthly during CT |
| Cardinale (2010) [41] | 251 | Breast cancer | TRZ | I | 0.04 ng/mL | Before and after each cycle |
| Morris (2011) [42] | 95 | Breast cancer | AC + taxanes + TRZ/LAP | I | 0.30 ng/mL | Every 2 weeks during CT |
| Sawaya (2011) [43] | 43 | Breast cancer | AC + taxanes + TRZ | HS-I | 0.015 ng/mL | Before CT; after 3 and 6 months during CT |
| Lipshultz (2010) [44] | 205a | ALL | AC/AC + dexrazoxane | I/T | Any detectable amount | Before CT; 1–7 days after each dose; end CT |
| Sawaya (2012) [45] | 81 | Breast cancer | AC + taxane + TRZ | HS-I | 30 pg/mL | Before CT; after 3 and 6 months during CT |
| Geiger (2012) [46] | 50 | Various | AC | T | NA | Before CT; after 6 h, 7 days, 3 months |
| Mornos (2013) [47] | 74 | Various | AC | HS-T | NA | Before CT; after 6, 12, 24, 52 weeks |
| Mavinkurve-Groothuis (2013) [48] | 60a | ALL | AC | HS-T | 0.01 ng/mL | Before CT; after 3 and 12 months |
| Ky (2014) [49] | 78 | Breast cancer | AC + taxanes + TRZ | HS-I | NA | Before CT; after 3 and 6 months during CT |
| Putt (2015) [50] | 78 | Breast cancer | AC + taxanes + TRZ | HS-I | NA | Before CT, after 3, 6, 9, 12, 15 months during CT |

AC, Anthracycline-containing chemotherapy; ALL, acute lymphoblastic leukemia; CT, chemotherapy; Cycl, cyclophosphamide; HD, high-dose; HS, ultrasensitive; I, troponin I; LAP, lapatinib; NA, not available; T, troponin T; TRZ, trastuzumab.

*aPediatric population.*
trastuzumab, that LVD was predicted by a significant rise in HS-Troponin I values compared with baseline [49,50]. Of note in these studies, HS-Troponin I was evaluated in a multiple-biomarker approach.

At present, the only study comparing standard troponin assays and HS-assays in the oncological setting was performed by Salvatici et al [53]. Stocked samples of cancer patients, who were previously monitored during and after chemotherapy through troponin assessment and ECHO evaluation, were retested with an HS-troponin assay. A good correlation between standard and high-sensitivity troponin assays was observed, in agreement with other results obtained in other settings (Fig. 7.4) [53].

Taken all together, these observations pointed out that troponin release may identify subclinical cardiac damage in patients treated with both conventional and newer antineoplastic treatments, possibly representing a final event that is common to different mechanisms underlying the cardiotoxic effect. Indeed, troponin measurement is able to detect CTX very early, and to predict LVD—and associated cardiac events—months before their development, both in patients treated with standard dose and high-dose cardioxic drugs, allowing cardiac risk stratification. However, there are still some limitations in the routine employment of troponin in clinical practice. Some studies failed to detect changes in troponin levels during or after anticancer treatments [54,55]. This could be related to different factors: various anticancer protocols employed, varying times of sampling associated with different drug administration schedules, lack of standardization of different assays, cardiac end-points definition and follow-up length [56]. Standardization of routine troponin measurement in the clinical setting to maximize single-time-point assay sensitivity and specificity is needed and should be an important focus for future research.

**Natriuretic Peptides**

Natriuretic peptides (NPs) are hormones produced by cardiomyocytes and released into circulation in response to wall strain and pressure overload. The more widely investigated members of the NP family are atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) and their cosecreted and biologically inactive N-terminal amino acid fragment (NT-proANP and NT-proBNP).

Natriuretic peptides play a pivotal role in the maintenance of cardiovascular homeostasis: in fact they are involved in many physiologic functions including vasodilation,
natriuresis, kaliuresis, inhibition of the renin–angiotensin–aldosterone system and inhibition of sympathetic tone.

BNP and NT-proBNP are gaining acceptance as potentially useful biomarkers in the diagnosis and prognostic stratification of patients with HF [57,58].

In the last decade, great interest has grown about the use of NP in patients with chemotherapy-induced cardiac impairment. Several authors investigated a possible role for BNP and NT-proBNP in particular, in the detection and prediction of CTX. In a very early study performed on 27 patients with hematological malignancy treated with AC, Suzuki observed that persistent elevations of BNP were associated with poor prognosis and reflective of induced diastolic dysfunction, thus suggesting a correlation between NP increase and reduced cardiac tolerance to cardiotoxic agents [59].

After this first report, multiple studies were performed on patients with different malignancies, different ages (both children and adult populations), and different oncologic drugs, and schedules [2,55,60–63]. In most studies persistently elevated levels of posttreatment BNP and/or NT-proBNP correlate with ECHO indexes of myocardial dysfunction [55,63–65]. However, only a few reports indicated NP as strong predictors of LVD after chemotherapy [60,64,65].

In particular, data from Sandri et al [64], showed that persistently elevated levels of NT-proBNP were able to identify patients who would develop an impairment of both diastolic and systolic function 1 year after high-dose chemotherapy for aggressive malignancies. Three distinct patterns of NT-proBNP concentrations were identified. Of the patients, 31% had no change in NT-proBNP concentrations in the 72 h after therapy; 35% of patients experienced a transient increase with normalization within 72 h. In these two groups, no significant echocardiographic abnormalities were founded during the 1-year follow-up. Conversely, 33% of patients with persistently increased NT-proBNP concentrations at 72 h developed a significant worsening of both diastolic and systolic ECHO indexes. In particular, significant increases in mitral deceleration time, isovolumetric relaxation time and in mitral E/A ratio and significant decrease in LVEF mean value were observed.

Other reports confirmed these findings, showing a close relationship between NP and the development of subclinical myocardial injury due to anticancer drugs [60,63,65]. Some studies, however, found no correlation between NT-proBNP increase and development of cardiac dysfunction in patients receiving AC-based chemotherapy [45,61,62].

The role of NPs in the patients treated with new targeted drugs is less understood. A few studies on small...
populations, mainly breast cancer patients treated with trastuzumab, have analyzed the information of NP assay in the setting, leading to conflicting results. In fact, although some authors have identified NT-proBNP as a promising tool in the management of the patients treated with new therapy [66,67], others have failed to reveal any predictive role of the NT-proBNP [45,68].

Therefore, although several data are now available, it is not yet possible to draw definite conclusions or indications because of some important limitations affecting the comparison of results coming from different studies. First, most studies were performed on small and heterogeneous populations with different malignancies at various stages and different therapeutic schedules. Furthermore, different laboratory methods were used, with frequently undeclared cutoffs and an extremely broad range of sampling times. Finally, the follow-up duration of the studies was quite variable and the lack of standardized cardiac endpoints were present. New prospective and multi-center studies, including large populations, using well-standardized methods for dosage and with well-defined timing of sampling and cardiological end-points, are needed to define the appropriate use of NP in this setting.

**Newly Proposed Biomarkers**

Troponins, BNP, and NT-proBNP are the most studied biomarkers for cardiovascular screening in most clinical settings, including the cardioncological setting, for detection and monitoring of CTX, in cancer patients treated with potentially cardiotoxic drugs, as reported above.

In the last decades, however, an increasing number of circulating biomarkers have aroused researchers’ interest in the cardiovascular setting, and more recently even in the cardioncological setting.

Because of the large number of mitochondria in cardiomyocytes and the tight relationship linking oxidative metabolism with myocardial viability, mitochondrial dysfunction is considered as an expression of cardiotoxicity. Therefore, biomarkers related to mitochondrial dysfunction could be studied for monitoring occurrence and extent of cardiac damage; indeed they could be studied in order to prevent mitochondrial cardiotoxic effects of anticancer drugs. Among them, according to current knowledge, cytochrome c, mitochondrial DNA, and oxidized albumin seem to be early and reliable markers of mitochondrial dysfunction [69]. ACs, by generating oxidative stress and alterations in redox status, cause the opening of voltage-dependent channels, leading to mitochondrial membrane permeability changes and the release of proapoptotic proteins from the mitochondria. Cytochrome c is one such protein that can be measured in the circulation as a mitochondrial dysfunction marker, that may anticipate cell necrosis (Fig. 7.5). Preliminary data from an ongoing trial from our institute confirmed that serum cytochrome c may increase during AC-containing chemotherapy (16% of cases, unpublished data) and that its rise temporally precedes the increase of troponin—evidenced in 18% of treated patients. These

![FIGURE 7.5 Molecular pathway of apoptosis that is triggered by doxorubicin. Doxorubicin damages DNA; DNA damage induces cytochrome c release in mitochondria which activates caspases, the effectors of apoptosis.](image-url)
findings suggest that the release of cytochrome c could be a new early marker of CTX, which may precede cell necrosis and the subsequent release of troponin.

Myeloperoxidase (MPO) is an enzyme secreted by polymorphonuclear leucocytes; it has a proatherogenic and prooxidant effect and is considered a marker of oxidative stress, causing lipid peroxidation, scavenging of nitric oxide, and inhibition of nitric oxide synthase. In patients with acute coronary syndromes and HF, elevated levels of MPO are predictive of adverse events [70,71]. Notably, MPO seem to provide an additive value to troponin T [70].

In the cardioncological setting, Ky et al. first observed that early changes in MPO levels are associated with subsequent CTX. This result is of particular interest: in fact oxidative stress has been hypothesized to be an important mechanism in AC-mediated CTX. Another important finding is that MPO and TnI used in combination identify a subgroup of patients at increased risk of CTX. Conversely, no association between CTX and other biomarkers, including high-sensitivity C-reactive protein (CRP), NT-proBNP, growth differentiation factor (GDF)-15, placental growth factor (PIGF), soluble VEGF receptor 1 (sFlt-1), and galactin 3 (Gal-3) was found [49].

Subsequently, the same group confirmed that increased levels of MPO are associated with future development of CTX. Interestingly, the study goes beyond previous observations showing an early rise of MPO: in fact, it indicates that increase in MPO throughout the entire course of therapy is significantly associated with development of CTX. Contrary to the previous findings, in this study GDF-15 and PIGF were shown to be associated with CTX: of note, the independence of these markers in the multivariable model suggests additive utility. No association between CRP, NT-proBNP, sFlt-1, and gal-3 and CTX were observed in this study either [50].

Interestingly, in both studies, among molecules shown to be predictive of CTX, each one was modestly predictive by itself, but their combination allowed for a more confident association with subsequent degree of ventricular dysfunction, thus confirming previous observations that a multimarker approach may better stratify the cardiac risk in oncologic patients [45], allowing for preventive strategies.

Heart-type fatty-acid-binding protein (H-FABP) and glycogen phosphorylase BB (GPBB) have been recently evaluated for the early detection of myocardial ischemia. H-FABP is a relatively small cytoplasmic protein for the oxidation of fatty acids and has a good specificity for cardiac muscle. It is rapidly released from the myocardium into the bloodstream in response to an ischemic injury and returns to normal values within 18–30 h. GPBB is a glycogenolytic enzyme providing glucose for the heart muscle tissue. In ischemic tissue, during glycogenolysis, GPBB is released from the sarcoplasmic reticulum into the cytoplasm and then into the circulation through the damaged cell membrane, returning to normal values within 24–36 h of damage occurrence. In the acute coronary syndrome setting, both markers are regarded as early indicators of cardiac injury due to acute myocardial ischemia [72,73].

The possible roles of H-FABP and GPBB have been investigated in hematological patients receiving AC-based chemotherapy. Whereas El-Ghandour et al. found an association between increased FABP levels and LVEF reduction in patients with cardiac dysfunction [74], Horacek et al. failed to find any association, and reported increases only in GPBB [75]. However, although these markers are highly sensitive and rapidly released after acute myocardial ischemia, they are less specific than troponin for the detection of cardiac damage different from an ischemic insult; further studies on larger number of patients will be needed to better define their potential in the early detection of cardiotoxicity.

**PREVENTION OF CARDIAC TOXICITY**

Patients undergoing a potentially cardiotoxic treatment are considered to be at increased risk of developing LVD [76]. Existing clinical data suggest that programs aimed at preventing the development of LVD appear strategically more effective than interventions aimed at counteracting an already existing LVD, which can be progressive and irreversible in many cases [1,4].

Accordingly, several preventive strategies to reduce the risk of cardiotoxicity have been proposed. To avoid the development of severe LVD, several preventive measures have been proposed as well. They include limitation of cumulative chemotherapy dose, replacement of bolus administration with slow infusion, use of less cardiotoxic AC analogs, addition of cardioprotectants to the chemotherapeutic regimen, and employment of nutritional supplements.

Cardiotoxicity prevention may be a primary prevention, extended to all patients scheduled for potential cardiotoxic therapy, or could be performed in selected high-risk patients showing preclinical signs of cardiotoxicity.

**Primary Prevention**

*Adding Cardioprotectants to Chemotherapy*

Among cardioprotectant agents, dexrazoxane is one of the most extensively studied molecules. Some authors observed an association between dexrazoxane administration and reduction of AC-related CTX both in adult patients with different solid tumors and in children with acute lymphoblastic leukemia and Ewing’s sarcoma [36,44,77,78].

Still there are some limitations in routine dexrazoxane employment in clinical practice. In fact, according to ASCO guidelines [79], it is recommended as a cardioprotectant agent only in selected patients (metastatic breast cancer patients who have already received more than 300 mg/m² of doxorubicin), because of its hypothesized interference
with the anticancer efficacy of AC, implication in the occurrence of second malignancies, and myelosuppression. However, metaanalyzes of antitumor efficacy and of secondary malignancy occurrences did not find a significant difference between patients who were treated with or without dexrazoxane [77,80].

Other cardioprotective agents such as coenzyme Q10, carnitine, N-acetyl-cysteine, the antioxidant vitamins E and C, erythropoietin, the endothelin-1 receptor antagonist bosentan, the lipid-lowering agent probucol, and statins have been investigated. Preliminary evidence shows that these agents may have cardio-protective effects, but their utility in preventing CTX requires further investigation [14,77].

Adding Cardiovascular Agents to Chemotherapy

The cardioprotective effects of many pharmacologic agents have been demonstrated during cancer therapy. However, most of these findings have been obtained from animal models. In the clinical arena four groups of agents—BB, angiotensin antagonists, statins, and aldosterone antagonists—have proven to be cardioprotective, with similar results in patients treated with ACs or trastuzumab (Table 7.3) [81–91].

Carvedilol has shown antioxidant activity that may result in an effective cardioprotective action against doxorubicin. The first evidence showing cardioprotective effects of BB emerged from an in vitro study [92]. This effect was confirmed in a small randomized study in which prophylactic use of the drug prevented LVD and reduced mortality in a population of AC-treated patients [81].

Different studies conducted over the last decades and performed on animal models have shown that, in rats undergoing short- or long-term administration of doxorubicin, coadministration of ACEI completely prevented the decline in cardiac function, as well as the increase in left ventricular weight induced by doxorubicin [93–96]. Furthermore, other authors demonstrated that doxorubicin cannot induce cardiac injury in angiotensin-II type-I receptor gene knockout mice. [97–100]

| Study (Year) | Study Design/ Follow-Up | N | Cancer Type | Drugs | Intervention | Results |
|-------------|--------------------------|---|-------------|-------|--------------|---------|
| ACEI        | RCT/12 months            | 114 | Various HD CT | Enalapril | No LVEF ↓; MACE incidence ↓ |
| ARB         | RCT/7 days               | 40 | NHL | AC Valsartan | No LVEDD↑; no BNP, and ANP↑; no QT↑ |
|             | RCT/18 months            | 49 | Various AC | Telmisartan | No peak strain rate ↓; no interleukin-6 ↑ |
|             | RCT/3–9 months           | 120 | Breast cancer AC, TRZ | Candesartan | No LVEF ↓ |
| Aldosterone antagonists |               |     |     |       |              |         |
| Akpek (2015) [90] | RCT/6 months           | 83 | Breast cancer AC | Spironolactone | No LVEF↓; no TNI and BNP↑ |
| Beta-blockers |               |     |     |       |              |         |
| Kalay (2006) [81] | RCT/6 months           | 50 | Various AC | Carvedilol | No LVEF ↓ |
| Kaya (2012) [87] | RCT/6 months           | 45 | Breast cancer AC | Nebivolol | No LVEF and NT-proBNP↑ |
| ACEI + beta-blockers |               |     |     |       |              |         |
| Bosh (2013) [82] | RCT/6 months           | 90 | Hematological AC | Enalapril + Carvedilol | No LVEF↓; death↓; HF ↓ |
| Statins     | RCT/6 months            | 40 | Hematological AC | Atorvastatin | No LVEF↓ |
| Seicean (2012) [85] | Retrospective/ 5 years | 67 | Breast cancer AC | Statins | HF ↓ |
| Chotenimitkhun (2015) [86] | PO            | 51 | Various AC | Statin | No LVEF↓ |

ACEI, Angiotensin-converting enzyme inhibitor; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; HD CT, high-dose chemotherapy; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; HF, heart failure; MACE, major adverse cardiac events; NHL, non-Hodgkin lymphoma; NT-proBNP, N-terminal-pro-brain natriuretic peptide; QT, QT interval; PO, prospective observational; RCT, randomized controlled trial; TNI, troponin I; TRZ, trastuzumab.
mice [97], thus suggesting that angiotensin II could play a key role in the pathogenesis of doxorubicin-induced CTX.

The efficacy of carvedilol, in combination with enalapril, to prevent chemotherapy-induced LVD was explored in the OVERCOME trial [82]. Patients with various hematologic malignancies receiving intensive high-dose chemotherapy were randomized to the intervention group (enalapril plus carvedilol) or the control group (no intervention). LVEF was evaluated before and after chemotherapy administration. After 6 months, no changes in LVEF were observed in the intervention group, but a significant decrease in the control group was present.

The results of the Prevention of Cardiac Dysfunction during Adjuvant Breast Cancer Therapy (PRADA) [83] trial have demonstrated that candesartan—but not metoprolol—concomitantly administered with adjuvant epirubicin-containing chemotherapy, with or without trastuzumab, provides protection against early decline in LV function, assessed with cardiac magnetic resonance.

Statins have been shown to exert antioxidative, anti-inflammatory, and other pleiotropic effects. In an animal model it has been demonstrated that pretreatment with fluvasatin blunted anthracycline-induced toxicity, reducing oxidative stress, enhancing expression of the antioxidant enzyme mitochondrial superoxide-dismutase2, and limiting cardiac inflammation [98]. In a small clinical trial of 40 patients with normal LVEF undergoing chemotherapy which included AC, the 6-month LVEF value was unchanged among patients treated with atorvastatin compared with an 8% absolute decrease in controls [84]. In a retrospective observational study, 67 breast cancer patients treated with AC, who had already received statins for alternative indications, uninterruptedly statin use was associated with a markedly lower risk for HF and cardiac-related morality over 2.2 ± 1.7 years of follow-up, compared with 134 propensity-matched controls (HR 0.3, CI 95% 0.1–0.9; P < 0.03) [85]. Consistently, Chotenimitkhun et al [86], more recently found in a prospective observational study that individuals already receiving statin therapy for prevention of cardiovascular disease experienced less deterioration in LVEF at 6 months after AC-containing chemotherapy, than individuals not receiving statins. Prospective randomized control trials are needed to further delineate independent effects of statins on clinical outcomes in oncologic patients.

**Role of Biomarkers in Prevention of Cardiac Toxicity**

A primary pharmacologic preventive strategy extended to all cancer patients undergoing chemotherapy would have a very high cost–benefit ratio; moreover, patients could be exposed to fewer side effects.

The possibility of identifying patients at high risk of cardiotoxicity by cardiac biomarkers provides a rationale for targeted preventive pharmacological strategies against cardiac dysfunction and its late complications. The therapeutic strategies needed to be implemented in order to reduce the clinical impact of CTX are: (1) use of specific cardiologic treatments during chemotherapy to prevent, or blunt, the rise of biomarkers indicative of myocardial damage; (2) use of cardiologic treatments given only to a selected cancer patient population, in particular to those patients showing an increase in these markers during and after chemotherapy.

Lipshultz et al. selected TnT as a biomarker for monitoring the cardioprotective effect of dexrazoxane in 206 pediatric patients with acute lymphocytic leukemia: dexrazoxane was associated with less frequent TnT elevations compared with a placebo [36]. More recently, in the same population, followed-up for 5 years after treatment, the authors reported that children with at least one increase in TnT during CT showed significant late cardiac abnormalities at echocardiography [44].

The protective effect of nebivolol against AC-induced cardiomyopathy has been demonstrated in a small randomized study [87]. In 27 breast cancer patients receiving nebivolol during AC-therapy, LVEF and NT-proBNP remained unchanged after 6 months from baseline; conversely, in the placebo group a significantly lower LVEF and a higher NT-proBNP value were observed.

The first study evaluating the role of angiotensin II in the AC-induced CTX in humans was conducted by Nakamae et al. These authors showed that, in a randomized trial enrolling a small number of patients free of cardiac diseases, valsartan, an angiotensin-II receptor blocker, administered at the same time as AC-containing chemotherapy, prevented the increase in ANP and BNP, the acute increase in left ventricular diastolic diameter, and the prolongation and in QTc interval [88].

The possible role of another angiotensin-II receptor blocker, telmisartan, in preventing myocardial damage induced by AC was investigated in a randomized study including patients without prior cardiovascular diseases and treated with epirubicin for different kinds of solid cancers. After an 18-month follow-up, patients starting telmisartan a few days before epirubicin showed no significant reduction in myocardial deformation indexes as evaluated by tissue Doppler echocardiography, nor a significant increase in ROS or in interleukin-6, as found in 24 patients receiving epirubicin alone [89,99].

Aldosterone antagonism has very recently been evaluated in a trial including 83 patients randomized to receive spironolactone, or not, and concomitant AC-containing chemotherapy [90]. After 3 weeks of the end of chemotherapy, spironolactone had prevented a decrease in LVEF, blunted the increase in troponin I and NT-proBNP, and also preserved diastolic function.

The usefulness of biomarkers of myocardial damage, and troponin in particular, in selecting patients for...
prophylactic cardioprotective therapy was investigated in a randomized trial including patients treated with high-dose AC [91]. Among them, 114 patients showed an early increase of TnI; these patients were randomized either to receive enalapril (ACEI group) or not (control group). Treatment with enalapril was started 1 month after chemotherapy and was continued for 1 year. In the ACEI group, LVEF did not change during the follow-up period, whereas, in patients not receiving enalapril, a progressive reduction in LVEF and an increase in ventricle dimensions (both diastolic and systolic) were observed (Table 7.3). Furthermore, patients in the ACEI group had a lower incidence of adverse cardiac events than the other group (Table 7.4).

Similar results were observed in patients treated with developing molecular targeted therapies. In a phase-I trial, Ederhy observed a TnI increase from baseline during treatment with new anti-VEGF monoclonal inhibitors and tyrosine kinase inhibitors in patients with solid metastatic tumors. All patients showing an increase in the marker underwent ECHO, cardiac magnetic resonance, CT scan, and coronary angiography that excluded other possible etiologies of TnI increase. Normalization of TnI values was obtained with BB and aspirin administration. After TnI normalization, all patients were rechallenged with the study drug. No patient experienced any new increase of TnI, and no cardiac events occurred during the following observation period. This study supports previous evidence that troponin may play an important role in the identification of patients at risk for the development of cardiotoxicity who should receive prophylactic treatment, without being excluded from continuing onologic treatment (Table 7.5) [100].

The International Cardioncology Society (ICOS)-ONE trial is the only randomized study to compare a primary prevention approach with prevention in selected high-risk patients, in patients treated with ACs. The primary objective of the ongoing trial is to assess whether enalapril started concomitantly with AC therapy can prevent cardiotoxicity more effectively than when enalapril is prescribed to selected patients showing an increase in troponin (NCT01968200).

**CONCLUSIONS**

Anticancer therapy-induced cardiotoxicity still remains a serious problem, strongly affecting both the quality of life and the overall survival of oncologic patients. The most effective approach for minimizing cardiotoxicity is its

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**TABLE 7.4 Echocardiographic Parameters During the Study Period**

| Parameter | Baseline | Rand. | 3 Months | 6 Months | 12 Months | P Value* |
|-----------|----------|-------|----------|----------|-----------|---------|
| EDV (mL)  |          |       |          |          |           |         |
| ACEI-group| 101.7 ± 27.4 | 100.2 ± 26.1 | 98.1 ± 27.8 | 97.5 ± 24.5 | 101.1 ± 26.4 | 0.045   |
| Controls  | 103.2 ± 20.1 | 103.9 ± 21.0 | 106.4 ± 21.0 | 107.1 ± 23.9 | 104.2 ± 25.6 |         |
| ESV (mL)  |          |       |          |          |           |         |
| ACEI-group| 38.6 ± 10.8  | 38.7 ± 10.4  | 49.8 ± 17.6  | 51.8 ± 16.9  | 44.3 ± 20.1†  | <0.001  |
| Controls  | 38.8 ± 10.2  | 40.5 ± 12.2  | 49.8 ± 17.6  | 51.8 ± 16.9  | 44.3 ± 20.1†  |         |
| LVEF (%)  |          |       |          |          |           |         |
| ACEI-group| 61.9 ± 2.9   | 61.1 ± 3.2   | 61.9 ± 3.3   | 61.6 ± 3.9   | 62.4 ± 3.5   | <0.001  |
| Controls  | 62.8 ± 3.4   | 61.8 ± 4.3   | 54.2 ± 8.1   | 51.9 ± 7.9   | 48.3 ± 9.3†   |         |

*P value for repeated measures analysis of variance. †P < 0.001 versus baseline. EDV, end-diastolic volume; ESV, end-systolic volume; LVEF, left ventricular ejection fraction; Rand., randomization.

Source: Modified from Cardinale D, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation 2006;114:2474-81.

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**TABLE 7.5 Cardiac Events in the Study Groups**

| Event                | Total (n = 114) | ACEI group (n = 56) | Controls (n = 58) | P Value* |
|----------------------|-----------------|---------------------|------------------|---------|
| Sudden death         | 0 (0%)          | 0 (0%)              | 0 (0%)           | 1.0†    |
| Cardiac death        | 2 (2%)          | 0 (0%)              | 2 (3%)           | 0.49*   |
| Acute pulmonary edema| 4 (3%)          | 0 (0%)              | 4 (7%)           | 0.07*   |
| Heart failure        | 14 (12%)        | 0 (0%)              | 14 (24%)         | < 0.001 |
| Arrhythmias requiring treatment | 11 (10%) | 1 (2%) | 10 (17%) | 0.01 |
| Cumulative events    | 31              | 1                   | 30               | < 0.001 |

*By Fisher exact test. ACEI, angiotensin-converting enzyme inhibitor.

Source: Modified from Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation 2006;114:2474-81.
early detection and prompt prophylactic treatment initiation. Measurement of serum cardiac-specific biomarkers has emerged in the last 15 years, resulting in a cost-effective diagnostic tool for early identification of patients more prone to developing cardiotoxicity, in whom a preventive pharmacological strategy and a closer cardiac monitoring are pivotal.

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