LEADING ARTICLE

Drug Safety 2002; 25 (5): 301-311
0114-5916/02/0005-0301/$25.00/0

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Predicting Cancer Therapy–Induced Cardiotoxicity

The Role of Troponins and Other Markers

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Abstract

Several anticancer drugs have been associated with cardiac toxicity, especially the anthracyclines and trastuzumab. The pathogenesis of anthracycline-associated toxicity has been well described, whereas the mechanism of trastuzumab-associated toxicity is unknown. Although routine cardiac imaging studies (e.g. echocardiogram or multiple gated acquisition scans) may identify subclinical evidence of myocardial dysfunction, available data do not support their routine use for monitoring asymptomatic patients undergoing cancer therapy. Other modalities such as nuclear medicine scintigraphy with indium-111-antimyosin antibody and endomyocardial biopsy have been shown to be useful in identifying early cardiac damage, but their routine use is limited by practical considerations such as feasibility and cost. Consequently, there is significant interest in developing simple and reproducible methods for identifying patients at risk for treatment-induced myocardial damage. Available data suggest that circulating markers such as troponins and natriuretic peptides could potentially be useful for this purpose. Measurement of plasma troponin levels are commonly used in clinical practice in order to provide diagnostic and prognostic information in patients with myocardial ischaemia. Elevated levels may likewise correlate with anthracycline-induced cardiac damage, although plasma levels are only minimally elevated (well below that associated with ischaemia), and elevations may persist for weeks or months after anthracycline exposure. Clinical trials are currently evaluating the role of these markers in predicting both early and late, clinical and subclinical damage associated with anthracyclines and trastuzumab.

Several anticancer drugs have been associated with cardiac toxicity, including the cytotoxic agents (e.g. anthracyclines, anthracenediones, fluorouracil, cyclophosphamide, mitomycin), biological agents (e.g. interferons, interleukin-2), and monoclonal antibodies (e.g. trastuzumab). The agents that are most commonly associated with this complication and that are frequently used include the anthracyclines (e.g. doxorubicin, epirubicin, and daunorubicin) and trastuzumab. The anthracyclines are frequently used with curative intent in patients with acute leukaemia, lymphoma, and

breast cancer. Trastuzumab is regularly used for the treatment of metastatic breast cancer that over expresses human epidermal growth factor receptor 2 (Her2)/neu; it is currently being evaluated in patients with early stage breast cancer.

This review will focus on employing serum or plasma markers that may be predictive for cardiac toxicity associated with cancer therapy.

1. Anthracyclines

The anthracyclines play an important role in the treatment of early stage and metastatic breast cancer. Doxorubicin-based regimens are associated with about a 10% reduction in the risk of relapse and death when used in patients with early stage breast cancer compared with similar regimens that do not include doxorubicin.[1] Other studies have also demonstrated similar results for epirubicin-based adjuvant therapy and provide evidence for a dose-response relationship.[2,3] Several studies have likewise suggested similar benefit in patients with metastatic disease. A pooled analysis of five randomised trials that included a total of 1088 patients with metastatic breast cancer indicated that doxorubicin-based regimens were associated with a significantly lower hazard rate (HR) for treatment failure [HR 0.69; 95% confidence intervals (CI) 0.59 to 0.81] and death (HR 0.78; 95% CI 0.67 to 0.90).[4] In a subsequent meta-analysis that included 30 randomised trials and 5241 patients, anthracycline-containing regimens were associated with a significantly higher response rate (51 *vs* 45%); there was a modest reduction rate in the hazard rate for death (HR 0.89; 95% CI 0.82 to 0.97) if the comparison regimen did not contain prednisone, whereas there was a disadvantage for anthracyclines (HR 1.16; 95% CI 1.02 to 1.32) if the regimen contained prednisone.[5]

1.1 Cardiac Toxicity of Anthracyclines

The anthracyclines mediate their cardiac effects via reactive free-radical intermediates (e.g. superoxide, hydrogen peroxide, and hydroxyl radical) that are produced by chemical reduction via iron-catalysed pathways.[6] The resulting damage to myocardial cells leads to the release of toxic cellular metabolites, generation of inflammatory cytokines, calcium overload, and adrenergic dysfunction, all of which contribute to myocardial cell damage.[7] Typical histological changes include myofibril loss, vacuolar swelling of the sarcoplasmic reticulum, loss of contractile elements and organelles, and mitochondrial and nuclear degeneration.[8] The toxic hydrogen peroxide molecule is inactivated by catalase (which converts it to water and oxygen) and glutathione peroxidase (which uses glutathione to reduce hydrogen peroxide to water and oxidised glutathione). Possible explanations for why cardiac muscle is prone to doxorubicin-induced injury include its relative deficiency of catalase, and doxorubicin-induced depletion of glutathione peroxidase in cardiac muscle.[9] Agents that chelate iron (e.g. dexrazoxane) prevent generation of oxygen free radicals and protect against anthracycline-induced cardiomyopathy.[10]

The incidence of chronic cardiomyopathy (that occurs within one year of treatment) is minimised by restricting the cumulative doxorubicin dose less than 400 mg/m^2, a dose that is generally not exceeded when doxorubicin is used as adjuvant therapy for breast cancer or curative therapy for lymphoma. However, this evidence is based upon retrospective chart review, which may underestimate the true incidence of cardiac dysfunction.[11] In fact, some evidence suggests some patients treated below this threshold may experience subclinical or clinical toxicity during or many years after therapy if they are carefully monitored. For example, the incidence of congestive heart failure was substantially higher in patients prospectively monitored by Swain and colleagues[12,13] compared with the retrospective analysis reported by Von Hoff et al.[11] (table I). Furthermore, with regard to late toxicity, Steinherz et al.[14] reported that the incidence of echocardiographically detected abnormal systolic function was 14% after 4 to 6 years, 24% after 7 to 9 years, and 38% after more than 10 years following exposure to anthracyclines in childhood. Moreover, the incidence of

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Table I. Incidence of congestive heart failure in patients treated with doxorubicin

Cumulative doxorubicin dose (mg/m^2)	Retrospective analysis (%)[a] [11]	Prospective evaluation (%)[12,13]
200	<1	2
400	<1	7
450	3	9
500	5	25
600	12	38
800	33	55

a Data provided represents estimates from visual inspection of Kaplan-Meier curve.

severe cardiac dysfunction (fractional shortening <20%) was 0% at 4 to 6 years, 8% after 7 to 9 years, and 15% after 10 years. It is noteworthy the incidence of cardiac dysfunction was similar in adolescents (more than 15 years of age) and children, suggesting that similar findings may occur in adults. Likewise, Zambetti et al.[15] reported a higher incidence of subclinical cardiac dysfunction in breast cancer survivors treated with adjuvant doxorubicin (8 *vs* 3%) after a median follow-up of about 11 years compared with those not treated with doxorubicin, although cumulative cardiac mortality was only minimally increased (0.4 *vs* 0%).

2. Trastuzumab

Trastuzumab is a humanised version of the murine monoclonal antibody 4D5 that was formulated by inserting the complementarity-determining regions of 4D5 into the framework of a consensus human immunoglobulin (Ig) G.[16] It binds to the extracellular domain of HER2, which is overexpressed by approximately 20 to 30% of human breast cancer. The HERs consist of a family of proteins that play an important role in cellular growth, differentiation, and survival. There are currently four known members of this family, including epidermal growth factor receptor (also known as HER1, erbB1), HER2 (erbB2), HER3 (erbB3), and HER4 (erB4).[17] The receptors may become activated by forming homodimers or heterodimers, or by ligand binding.[18,19] Breast cancers that have HER2 gene amplification and protein over expression exhibit greater metastatagenecity (are more likely to metastasise) and virulence (relapse sooner).[20]

Trastuzumab has been shown to improve response rate, response duration, and survival of patients with HER2-overexpressing metastatic breast cancer treated with chemotherapy.[21] Clinical investigators are currently designing a new generation of trials that will evaluate the role of this drug in improving the curability of patients with early stage disease.[22] This effort has been complicated by the unexpected observation of cardiac toxicity in patients treated with trastuzumab.

2.1 Cardiac Dysfunction Associated with Trastuzumab

An unexpected adverse effect of trastuzumab that was noted during the course of the pivotal trial and subsequently observed in other studies was cardiac dysfunction (table II). Factors associated with an increased risk of cardiac toxicity include current anthracycline use, past anthracycline use, and age more than 60 years.[23] The majority of patients who developed class III or IV congestive heart failure improved with medical therapy, suggesting a better prognosis for patients with trastuzumab-associated cardiac toxicity than anthracycline-associated cardiac toxicity.[24] Cardiac dysfunction has also been noted with single agent trastuzumab therapy, although it usually occurs in patients who have previously been exposed to anthracyclines.

The pathogenesis of cardiac dysfunction associated with trastuzumab is unknown. However, it does not seem to have the histological characteristics associated with doxorubicin-associated cardiotoxicity, and there is no evidence for a pharmacokinetic interaction between trastuzumab and doxorubicin. However, some evidence suggests that the epidermal growth factor family (and some of their ligands) play an important role in myocardial cell physiology and development.[25] For

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Table II. Incidence of cardiac toxicity with trastuzumab[a]

Treatment	Setting	Prior anthracycline therapy (%)	No. of patients	Cardiac dysfunction (%)	Class III/IV CHF (%)
Pivotal trial (648G)					
Doxorubicin/cyclophosphamide	First-line	0	135	8	3
Doxorubicin/cyclophosphamide plus trastuzumab			143	27	16
Paclitaxel	First-line	100	95	1	1
Paclitaxel plus trastuzumab			91	13	2
Trastuzumab alone (650G)	First-line	51	113	0.8	0
Trastuzumab (649G)	Second-line	94	213	7	5

a Study identification number shown in parentheses.

CHF = congestive heart failure.

example, mice with loss of function mutations of neuregulin-1 (NRG)-1or of either of its receptors (erbB2 and erbB4) die during midembryogenesis due to aborted development of myocardial trabeculae in ventricular muscle, and exhibit abnormal development of the neural crest, stomach, pancreas, and other organs.[26] ErbB3 knockouts exhibit cardiac cushion abnormalities leading to defective heart valves and have impaired development of the midbrain/hindbrain region.[27] ErbB4 is the predominant NRG1 receptor in postnatal rat ventricular muscle, and declines after midembryogenesis, after which its expression is limited to cardiac myocytes.[28]

3. Noninvasive Predictors of Cardiac Toxicity

Although routine cardiac imaging studies (e.g. echocardiogram or nuclear scans) may identify subclinical evidence of myocardial dysfunction, available data do not support their routine use for monitoring asymptomatic patients undergoing anthracycline therapy.[29] Although other modalities such as nuclear medicine scintigraphy with indium-111-antimyosin antibody[30,31] and endomyocardial biopsy[32-34] have been shown to be useful in identifying early cardiac damage, their routine use is limited by practical considerations such as feasibility and cost. Consequently, there is significant interest in developing simple and reproducible methods with strong predictive value that are useful in identifying patients at risk for therapy-induced myocardial damage. Available data suggest that circulating markers such as troponins and natriuretic peptides could potentially serve as such monitoring tools.

4. Biology of Troponins

The major function of myocardial cells is contraction and relaxation. These processes require the highly regulated interaction of the two primary contractile proteins, actin and myosin. Two actin units intertwine as a helix mounted upon a backbone of tropomyosin to form the thin filaments. The myosin molecule contains a head that interacts with the thin filaments during muscle contraction and relaxation. Such crossbridge cycling requires constantly changing concentrations of calcium ions in the myocardial cytosol. The troponin complex consists of three protein subunits (troponin C, I, and T) found at regular intervals along the thin filament that regulates the calcium-mediated contractile process of striated muscle.[35] Troponin C binds calcium ions released in large amounts from the sarcoplasmic reticulum – this initiates the process of crossbridge formation between actin and myosin. As calcium interacts with troponin C, troponin I (TnI) is disinhibited, thus promoting crossbridge formation and muscle contraction. When troponin C is not activated by calcium, TnI binds actin and inhibits actin-myosin interactions.

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Troponin T (TnT) attaches the troponin complex to the thin filament by binding to tropomyosin.

5. Troponins as Markers of Ischaemic Myocardial Injury

Although both TnT and TnI are present in cardiac and skeletal muscle, different genes encode them resulting in tissue-specific isoforms with different amino acid sequences.[36] These differences have permitted the development of quantitative monoclonal antibody-based assays specific for cardiac forms of TnT (cTnT) and TnI (cTnI). Such assays have been approved for clinical use by the US Food and Drug Administration to detect myocardial injury. Prior to the availability of troponin assays, the cardiac specific isoform of creatine kinase (CK-MB) was considered the gold standard for the biochemical detection of myocardial necrosis.[37] However, several features of troponin biology make them potentially a superior marker of necrosis (table III). CK and CK-MB exhibit a release pattern during myocardial infarction characteristic of a functionally unbound, cytosolic protein; it is therefore strongly dependent on perfusion of the infarct zone to be detected in serum.[38] In contrast, cTnT and cTnI are predominantly bound to the thin filament via the troponin complex; only about 3 to 6% are found in the cytosol, resulting in release kinetics characteristic of both structurally bound and cytosolic molecules.[39,40] Necrosis of a relatively small amount of myocardium, therefore, results in an early release of the cytosolic pool followed by a later release of bound proteins. These release kinetics result in a continuous release of troponin to a diagnostic threshold that is strongly correlated with adverse outcomes. CK-MB is less abundant in the myocardium than cTnT or cTnI but is cleared more rapidly. Furthermore, whereas troponins are generally not measured in the circulation in the absence of myocardial injury, low levels of CK-MB may be detected in the blood in the absence of myocardial damage. Thus, during an episode of minor myocardial necrosis, the CK-MB level may rise but the increase may not be detectable above the baseline amount of CK-MB in the blood because of the rapid clearance of this molecule. On the other hand, troponins, because they have a negligible baseline value and are cleared much more slowly, tend to accumulate in the circulation allowing a diagnosis of myocardial injury, even when CK-MB is normal. Both cTnT and cTnI are released within 4 to 12 hours following an episode of myocardial necrosis with a peak value 12 to 48 hours following the injury. Troponin values return to baseline in 5 to 15 days whereas CK-MB levels normalise in approximately 3 days. The sensitivity of cTnT for detection of myocardial infarction is 98.2% when measured 12 hours after symptom onset.[41] However, the sensitivity of troponin sampling is only 33 to 49% when measured within 4 hours of symptom onset. Thus, in order to achieve optimum sensitivity, serial sampling at least 12 hours following symptom onset is recommended. Because of its enhanced sensitivity for myocardial necrosis, elevation in troponin is not as specific for infarction as CK-MB. However, autopsy studies have verified that small amounts of myocardial necrosis may not be reflected in premortem CK measurement.[42,43] In recognition of the value of troponin testing, the European Society

Table III. Characteristics of biochemical markers in acute myocardial infarction

Marker	Localisation	Molecular weight (Da)	Time to first increase after infarction (h)	Time to peak (h)	Return to baseline (d)
CK-MB	Cytosol	86 000	3-10	10-24	3
Troponin T	6% cytosol; 94% bound	37 000	4-12	12-48	5-15
Troponin I	3% cytosol; 97% bound	24 000	4-12	10-24	5-10

CK-MB = cardiac specific isoform of creatine kinase.

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of Cardiology and the American College of Cardiology have issued a consensus document which includes the typical rise and gradual fall of troponin levels as one of the clinical criteria for diagnosis of acute, evolving or recent myocardial infarction. Additional criteria include at least one of the following: ischaemic symptoms, development of pathological Q-waves, ST-segment elevation or depression on electrocardiography or a coronary artery intervention.[44]

In addition to being a sensitive marker of myocardial infarction, troponin measurements have provided insight into the prognosis of patients with other ischaemic syndromes. Unstable angina is a syndrome characterised by accelerating chest pain, normal CK-MB levels and an electrocardiogram without ST-segment elevation. The demonstration of elevated troponin levels in these patients is an important predictor of prognosis. Patients with unstable angina who have an elevated troponin level have a 3- to 4-fold increase in the risk of death or myocardial infarction at 30-day follow-up.[45]

Troponin measurement has proved valuable in triage of patients presenting to emergency departments with complains of chest pain. Patients who present with acute chest pain to emergency departments are a heterogeneous group. Many have symptoms compatible with myocardial infarction but have low clinical likelihood of significant coronary artery disease. From this population it is important to identify the small number of high-risk patients with an ischaemic aetiology of their symptoms for admission to the hospital. These patients may be risk-stratified according to their troponin levels. Elevated troponin levels in these patients is associated with an 80% increase in the risk of major cardiac events within the next 72 hours.[46] Thus, troponin levels may help determine the level of care required for a patient admitted to the hospital for evaluation of suspected ischaemic chest pain.

In the absence of myocardial infarction, elevation in troponin levels in patients with acute ischaemic syndromes is likely a marker of microscopic necrosis caused by platelet activation and aggregation at the site of a ruptured atherosclerotic plaque in a coronary artery with subsequent distal embolisation of thrombi leading to necrosis. Thus the prognostic ability of an elevated troponin value is unlikely to be related to detection of the small area of downstream necrosis. Rather an elevated troponin has prognostic value because it indicates the presence of an upstream recently ruptured unstable plaque in an epicardial coronary artery.

Although release of troponins is indicative of myocardial necrosis, it is not synonymous with an ischaemic mechanism of injury. Troponin elevation has been documented in other clinical syndromes (table IV). Thus, an elevated troponin value in the absence of clinical evidence of ischaemia should initiate a search for other aetiologies of myocardial damage. The myocardial necrosis induced by cardiac surgery,[47] coronary angioplasty,[48] defibrillation,[49] catheter ablation[50]or myocardial contusion[51] has been associated with troponin elevation. Elevated troponins have been reported in patients with congestive heart failure[52] and pulmonary embolism.[53] The common pathophysiology in these syndromes may be subendocardial injury due to increases in wall stress of the left or right ventricle. In addition, abnormal troponin levels have been found some cases of myocarditis,[54] cardiac allograft rejection[55] and

Table IV. Causes of elevated serum levels of troponins

Definite myocardial necrosis	Possible myocardial necrosis	Questionable myocardial necrosis
Myocardial infarction	Myocarditis	Renal failure
Cardiac surgery	Congestive heart failure	Haemodialysis
Coronary angioplasty	Heart transplant rejection	Rhabdomyolysis
Defibrillation	Cardiac contusion	
Catheter ablation	Sepsis	
Resuscitation		

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vasodilatory shock,[56] possibly reflecting an immune mechanism-mediated myocardial injury.

6. Biology of Natriuretic Peptides

The family of natriuretic peptides includes several members with potent natriuretic, diuretic, and vasodilatory effects that could be used for therapeutic intervention, and also for the diagnosis and monitoring of cardiovascular diseases. They are one component of a homeostatic vasodilator/natriuretic system that also includes prostaglandins, nitric oxide, and the parasympathetic nervous system. In patients with congestive heart failure or subclinical evidence of left ventricular dysfunction, they play an important role in counteracting the vasoconstrictor/anti-natriuretic effects of the renin-angiotensin-aldosterone system, anti-diuretic hormone, and the sympathetic nervous system.

The natriuretic peptides are small peptides (22 to 32 amino acids) with a common core amino acid composition and a disulphide linkage between the two cysteine residues at positions 105 and 121. This linkage is essential for their pharmacological activity, which is mediated through transmembrane receptors with protein kinase activity.[57] The first identified member of this family was the atrial natriuretic peptide (ANP). ANP is secreted by atrial myocytes in response to local load-induced wall stretch. Two other related peptides were subsequently identified, including brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). BNP is a misnomer, as higher concentrations of this peptide are found in ventricular myocytes than in the brain. It is formed after cleavage of proBNP, which yields the hormonally active BNP and the inactive N-terminal-proBNP (NT-proBNP). Plasma BNP levels increase rapidly (within four hours) in response to acute ventricular overload, which is mediated through rapid induction of BNP mRNA expression in cardiac ventricles.[58] One group reported that infants who exhibited fetal heart rate abnormalities during delivery had a significant elevation in umbilical artery mean N-terminal pro-BNP level but not TnI level, suggesting that elevated pro-BNP may be increased by myocardial stress without necrosis.[59] Immunoassays under development for detecting both BNP and NT-proBNP should facilitate their routine measurement in clinical pathology laboratories.[60,61]

Evidence suggests that BNP and other peptides are strong predictors for mortality in patients with acute ischaemic events.[62] They are potentially useful in the risk stratification of patients with either symptomatic or subclinical left ventricular dysfunction,[63] as an adjunct to clinical evaluation in the initial assessment of patients presenting with dyspnoea[64] and in patients with heart failure.[65] Preliminary data suggest that high plasma levels of BNP and NT-proBNP are associated with a higher risk of left ventricular dysfunction and heart failure, and could identify patients that would benefit from aggressive therapy with ACE inhibitors and β-blockers.[66-68]

7. Circulating Markers for Myocardial Injury Related to Anticancer Therapy

7.1 Cardiac Troponin T

Preclinical studies have demonstrated cTnT to be a reliable marker of early myocardial injury in a spontaneously hypertensive rat model given repeated doses of doxorubicin;[69] histological sections showed decreased cTnT staining without significant histological alteration in myocytes, whereas circulating levels were elevated.

Much of the initial clinical data comes from paediatric studies. Fink et al. failed to show any significant changes in either CK-MB mass or cTnT levels up to 72 hours after anthracycline therapy.[70] However, Lipshultz et al.[71] showed that elevation of blood cTnT in children treated with anthracyclines predicted for subsequent cardiac morbidity and mortality. They also showed that minimal elevation of cTnT (above 0.025 ng/ml) was a marker for active myocardial injury in children with acute lymphoblastic leukaemia treated with doxorubicin-containing therapy, and that cTnT elevation persisted for up to 5 months after therapy, indicating persistent cardiac myocyte in-

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jury.[72] It is noteworthy that these seemingly trivial elevations of cTnT are well below those observed in patients with myocardial infarction (20 to 100 ng/ml) or myocardial ischaemia without infarction (2 to 10 ng/ml).

The potential usefulness of cTnT as a marker has been tested in adults. Hughes-Davis et al.[73] found no changes in serum cTnT levels in early stage breast cancer patients before and after radiation therapy to the whole breast as part of breast-conserving surgery. Auner et al.[74] showed that plasma cTnT level peaked at around 18 days after anthracycline therapy, and that an elevated level was associated with significantly greater decrease in left ventricular ejection fraction (10 *vs* 2%, p = 0.017) compared with those who did not have an elevation. Nag et al.[75] measured cTnT levels for up to 7 days following treatment with fluorouracil for colorectal cancer and reported elevated levels in 16%.

7.2 Cardiac Troponin I

There is less information regarding cTnI. Although it appears to be a prognostic marker in children with severe acute illness or cardiac trauma,[76] its potential role as a predictive factor in monitoring anthracycline therapy is less clear. Mathew et al.[77] published preliminary prospective data from several Children's Cancer Group protocols showing that while left ventricular ejection fraction and shortening fraction decreased with cumulative anthracycline therapy, all children remained asymptomatic and none showed an increase in cTnI levels. In adults, several studies have also been reported. Sedky et al.[78] reported a correlation between cTnI level changes and cumulative doxorubicin exposure with breast cancer. Cardinale et al.[79] showed its potential use as a predictive factor in a study with 204 patients treated with high-dose chemotherapy for aggressive malignancies.Plasma cTnI levels were measured for up to 72 hours after every chemotherapy cycle (which included anthracyclines), with repeated echocardiographic examination for up to 7 months after therapy. Patients with normal cTnI levels (<0.4 ng/ml) had a small median drop in left ventricular ejection fraction at 3 months (5%) which subsequently normalised, whereas those with high cTnI levels (>0.4 ng/ml) had a greater decrease in left ventricular ejection fraction (16%) which was still evident at later follow-up. On the other hand, Benvenutto et al.[80] reported no evidence of cardiac impairment or increase in cTnI levels in 16 breast cancer patients treated with high-dose cyclophosphamide.

7.3 Natriuretic Peptides

Natriuretic peptides appear sufficiently sensitive to identify subclinical changes in plasma volume and myocardial load resulting from anthracycline therapy, which may correlate with long-term outcome. Nousiainen et al.[81] described a gradual increase in plasma levels of ANP and BNP with each new cycle of idarubicin in the absence of electrocardiogram changes or arrhythmias, and plasma BNP levels correlated with an increase in left ventricular end-diastolic diameter. Their data in patients with non-Hodgkin's lymphoma treated with doxorubicin-containing chemotherapy also showed similar correlation with subclinical left ventricular dysfunction (median NT-proBNP increased from 3.3 to 8.5 pmol/L while left ventricular ejection fraction decreased from 58 to 49.6%), though serial measurements were not useful to predict subsequent impairment.[82] However, Suzuki et al.[83] showed a potential correlation between persistent elevation of BNP following anthracycline administration and future risk of ventricular dysfunction, as compared with patients with transient elevation. A similar pattern was observed by Okumura et al.[84] following treatment with daunorubicin. Hayakawa et al.[85] screened 34 children previously treated with anthracyclines and found a correlation between ANP and BNP levels and cardiac systolic (but not diastolic) function. Overall, existing data suggest a strong correlation between natriuretic peptide measurements and myocardial dysfunction, but their potential use as a predictive tool remains investigational. There is currently no information regarding natriuretic peptides in patients treated with trastuzumab.

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8. Ongoing Studies

The studies described above confirm a correlation between direct (troponins) and indirect (natriuretic peptides) markers of myocardial injury and functional studies (cardiac imaging). However, their role as a predictive marker for the early identification of individuals at risk for subsequent development of symptomatic or asymptomatic myocardial damage is under active investigation, and is the subject of ongoing studies. For example, several studies are evaluating the safety of combining anthracyclines with trastuzumab in operable breast cancer (National Surgical Adjuvant Breast Cancer protocol B-31; North American Intergroup study N9831). Cardiac safety is a major endpoint in both studies, and ancillary studies will examine any potential correlations of clinical endpoints (imaging studies and cardiac symptoms) with troponins, natriuretic peptides, and inflammatory cytokines [e.g. interleukin (IL)-1, IL-6, and tumour necrosis factor-α]. Other studies are evaluating circulating markers in patients receiving liposomal anthracyclines (which are less cardiotoxic than conventional anthracyclines[86]) used alone in conjunction with trastuzumab. Studies evaluating circulating markers as predictors of late cardiac toxicity in the paediatric setting have been completed and the data are maturing. Further studies and analyses of completed studies will be necessary to define their role.

Acknowledgements

The authors have received no funding for the preparation of this manuscript, nor have any conflicts of interest directly relevant to the contents of this manuscript.

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