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Cardiovascular complications of conventional and targeted adjuvant breast cancer therapy

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Adjuvant therapy has improved the survival of women with early breast cancer (BC). Meta-analyses suggest that anthracycline-based regimens reduced the annual BC death rate by ~40% in women below the age of 50 and 20% in older women. Novel agents designed to modulate abnormal growth factor signaling in and around the BC cell further increase patients' chances of survival. However, both conventional chemotherapeutic agents as well as some of the novel signaling inhibitors can induce important cardiovascular side-effects, potentially attenuating the progress made in recent years. The mechanism of cancer drug-induced cardiovascular complications varies greatly with some compounds inducing irreversible myocardial cell damage, while others lead to temporary cell dysfunction. The challenge of the future will be to prospectively discriminate between irreversible damage which can lead to progressive cardiovascular disease and reversible cardiovascular dysfunctions without further prognostic implications. Since adjuvant therapy for BC is potentially curative, emphasis must be placed on finding treatments combining maximum efficacy with the minimum of long-term side-effects in order to achieve survival with preserved quality of life.
Key words: anthracyclines, breast cancer, cardio-oncology, cardiotoxicity, trastuzumab, tyrosine kinase inhibitors

introduction

The introduction of adjuvant anticancer therapy [anthracyclines, taxanes and, for patients with human epidermal growth factor receptor 2 (HER2)-positive disease, trastuzumab and lapatinib] considerably improved both disease-free survival (DFS) and overall survival (OS) in women with operable early breast cancer (EBC) [1–4]. Early detection is thought to have contributed roughly equally to the evident steady reduction in age-standardized BC death rates over the past two decades [5]. In the UK, mortality fell 40% from 1989 to 2006 [6], and in the United States, by 28% from 1990 to 2000 [5]. Age-adjusted 5-year survival among European women diagnosed with BC from 2000 to 2002 is now 79% [7].

methods

Despite the fact that growing patient numbers are cured with modern adjuvant therapy, disease relapse and death, as well as short- and long-term toxic effects including treatment-related malignancies and heart failure (HF) still occur. Minimizing delayed toxic effects is of crucial importance in potentially curative treatment. Therefore, the search for more effective and less toxic adjuvant regimens continues. With increasing understanding of BC, individualization of therapy based on specific tumor characteristics is warranted.

Experience from metastatic trials raised concerns that were rapidly incorporated into design of adjuvant trials. One important insight was that targeted agents needed to be used in combination with conventional agents or, alternatively, with other novel agents. Table 1 summarizes current novel agent adjuvant phase III trials [8]. In addition, pertuzumab and other multi-targeted compounds already in registration studies for use in first-line metastatic BC are likely to be investigated in the adjuvant setting soon.

Some of these newer agents have inherent cardiac and/or cardiovascular toxicity. Certain pathways targeted in the tumor cell (such as HER2) are also present in the heart [9]. Preclinical work suggests that the HER2/erbB2 system may modulate the effects of oxidative stress in the cardiac myocyte; these agents therefore require further study with regard to implications of cardiotoxicity [10, 11]. This paper describes the known cardiovascular side-effects of cytotoxic and targeted drugs used in adjuvant BC therapy. Our understanding of risk factors for cardiotoxicity and developments in imaging and biomarkers which may prove helpful in identifying and managing these problems in our patients will also be addressed.

unique myocardial characteristics

The heart is a post-mitotic organ and has only limited ability to recover cell loss. Additionally, myocardial tissue lacks

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Table 1. Current phase III adjuvant and neoadjuvant trials in breast cancer involving novel agents

Acronym	Population	Regimens
BETH (NSABP)	N+ or high-risk N−	TCH or T-FEC followed by trastuzumab to 1 year versus above plus bevacizumab for 1 year
SOLD (Finnish Breast Cancer Group)	N+ or high-risk N−	T-FEC with 9 weeks trastuzumab during T versus above plus post-FEC trastuzumab to 1 year
ALTTO (BIG–TCBI)		Anthracycline-taxane-based chemotherapy plus one of four options: trastuzumab 1 year versus lapatinib 1 year versus trastuzumab then lapatinib versus trastuzumab plus lapatinib
BEATRICE (Roche)	Triple negative	Anthracycline plus/minus taxane or taxane only versus above plus bevacizumab for 1 year
ECOG 5103 (ECOG)	N+ or high-risk N−	AC followed by paclitaxel versus AC plus bevacizumab followed by paclitaxel plus bevacizumab ×4 versus treatment as in second arm followed by bevacizumab ×10
USO 06090	Various, depending on ER/PR status	TC versus TAC versus TC–bevacizumab
Gepar Quinto (GBG)	HER2-negative	EC with or without bevacizumab followed in responders by T plus/minus bevacizumab and in nonresponders by paclitaxel plus/minus everolimus (RAD 001)
	HER2-positive	EC-T trastuzumab versus lapatinib, followed by postoperative adjuvant trastuzumab for 1 year
Neo-ALTTO (BIG–TCBI)	HER2-positive	Lapatinib 1500 mg versus trastuzumab versus lapatinib 1000 mg plus trastuzumab, all plus paclitaxel, and with further randomization post surgery
NSABP B41	HER2-positive	AC followed by wP plus lapatinib versus wP plus trastuzumab versus wP plus lapatinib plus trastuzumab followed by 1 year trastuzumab after surgery
CALGB 40601	HER2-positive	wP plus lapatinib versus wP plus trastuzumab versus wP plus lapatinib plus trastuzumab followed after surgery by dose-dense AC and then 1 year trastuzumab

N+/−, node positive/negative; TCH; docetaxel plus carboplatin plus trastuzumab; T, docetaxel; FEC, fluorouracil, epirubicin, cyclophosphamide; AC, doxorubicin plus cyclophosphamide; ER, estrogen receptor; PR, progesterone receptor; C, carboplatin; HER2, human epidermal growth factor receptor 2; wP, weekly paclitaxel.

the enzyme catalase and thus demonstrates reduced capacity to handle oxidative stress, as may be caused or furthered by anthracyclines, hypertension or other cardiac conditions that may be considered cardiac risk factors. Oxidative stress changes the equilibrium between protein degradation and synthesis and, when pronounced, also activates caspases that induce myocyte apoptosis or necrosis [12].

The heart, however, has extensive reserves and can accommodate considerable myocyte loss. When clinically relevant cardiac dysfunction is observed, cardiac reserves are substantially exhausted; clinical deterioration from that point may be in an accelerated phase, and deterioration may be precipitous. Since decreased left ventricular ejection fraction (LVEF) ensues only after full compensation is no longer achieved, maintained LV function as measured by cardiac ultrasound or nuclear techniques should be considered neither as an indicator of normal myocardium nor as an evidence of an absence of cardiotoxicity [13]. Early damage may not be recognized by these parameters, and biomarkers have not yet been incorporated into the routine clinical setting but may have considerable potential.

targeted anticancer agents may also target the heart

Activation of the HER2 signaling pathways in cardiomyocytes appears to modulate cell adaptation with regard to environmental stressors and to promote cell survival [14]. Mice with ventricle-restricted deletion of the HER2 gene demonstrate spontaneous LV failure as the mature respond poorly to additional stress and to have myocytes that are particularly susceptible to anthracycline toxicity [9]. While there is little evidence, the idea that HER2 inhibition can potentiate the effects of oxidative stressors could explain, at least in part, the synergy between the cardiotoxic effects of trastuzumab and anthracyclines first apparent with their concurrent use in the metastatic setting [15].

LV dysfunction associated with specific therapies

anthracyclines

Anthracyclines are highly effective in the treatment of a variety of solid and hematologic malignancies, and they remain

a frequently utilized group of drugs in BC treatment in both the metastatic and the adjuvant setting. Of continuing concern, however, is that specter of cardiotoxicity, especially in the adjuvant setting, where many of the patients have been made disease free as a result of their prior treatment [13, 16, 17].

Anthracycline cardiotoxicity is a form of irreversible non-ischemic toxic cardiomyopathy. In the most extreme form, the entity leads to severe LV systolic dysfunction and HF, which may be progressive, which carries a poor long-term prognosis and which can result in cardiac death. Acute manifestations that appear at the time of exposure may include troponin elevation, electrocardiogram changes, dysrhythmia and, occasionally, myopericarditis. Biopsy specimens in this period confirm early myocyte damage despite preserved LVEF [18]. More typically, anthracycline cardiotoxicity presents as LV dysfunction months or years after exposure; analogous to other forms of progressive HF, it is assumed that considerable remodeling and compensatory mechanisms have been invoked. When severe, even late anthracycline cardiotoxicity may progress to advanced HF and end-stage heart disease.

Anthracycline cardiotoxicity is related to the cumulative dose administered. Initially, in case of doxorubicin, it was estimated that a cumulative dose of ~500 mg/m^2 correlated with a likelihood of developing HF of ~5%. [19] More recent retrospective analyses suggest that doxorubicin cardiotoxicity occurred at cumulative dosages considerably lower than first appreciated and that the cumulative dosage that correlated with a 5% incidence of HF ranged between 400 and 450 mg/m^2 [20]. Lower cumulative dosages are used in the adjuvant setting and the fact that women without preexisting heart disease were entered into these trials yielded an estimated HF likelihood of ~2.2%. Long-term effects of adjuvant anthracycline treatment are still being explored, and the final incidence may be somewhat higher than these estimations. Long-term follow-up in Belgian patients treated with adjuvant epirubicin demonstrates that higher anthracycline dosages result in better oncologic event-free survival, but at the cost of additional cardiotoxicity; the overall oncologic effectiveness was equivalent to that seen in the combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil regimens [21]. The French Adjuvant Study Group found a possible association between a higher dose of fluorouracil, epirubicin and cyclophosphamide (FEC) (100 versus 50 mg epirubicin) with HF and asymptomatic LV dysfunction, but the oncologic survival benefit probably outweighed the risks [22]. A recent Cochrane meta-analysis of five trials with doxorubicin and epirubicin found a nonsignificant difference in the clinical HF in favor of epirubicin [relative risk (RR) 0.36, 95% confidence interval (CI) 0.12–1.11] [23].

Since the 1980s, a marked decrease in cumulative anthracycline exposure has taken place and has reduced the incidence of associated cardiotoxicity. Nevertheless, some myocyte damage occurs even at low dosages and renders patients more susceptible to the development of HF when sequential stresses are encountered [13]. Recent evidence from the SEER database on routine use in >40 000 women suggests an ongoing appreciable problem, at least in more elderly patients [24]. Among women aged 66–70 years diagnosed with stages I–III BC from 1992 to 2002, the adjusted hazard ratio (HR) for HF in patients treated with adjuvant anthracyclines compared with non-anthracyclines was 1.26 (95% CI 1.12–1.42). Cumulative HF incidence at 10 years was 38% after anthracyclines, 32.5% after non-anthracyclines and 29% without chemotherapy. These differences become more pronounced with longer follow-up. HF rate was higher in patients who received anthracyclines, even after excluding elderly and those with significant comorbidities, than was the case when other agents were utilized. Age is a well-known risk factor for anthracyclines, and, not surprisingly, the likelihood of HF almost doubled with each 10-year increase in age. Other significant baseline predictors of increased risk were peripheral and coronary artery disease (HRs 1.31 and 1.58, respectively), diabetes (HR 1.74), hypertension (HR 1.45) as well as emphysema and chronic bronchitis (HR 1.68). Trastuzumab, given in <3% of those treated with chemotherapy, was significantly associated with HF risk (HR 1.44); however many of these patients recover cardiac function. Left-sided irradiation of the chest was not a risk factor, probably reflecting improved techniques minimizing cardiac radiation dose. Two recent comparable studies reported an increased risk of HF and valve dysfunction in irradiated BC patients as well as higher rates of myocardial infarction and coronary artery disease associated with radiation involving the left hemithorax [25, 26].

trastuzumab

The addition of trastuzumab to adjuvant therapy reduces the risk of BC recurrence at 3 years nearly by half and improves survival by around a third [2–4, 27]. However, major trials consistently show an increased relative risk of New York Heart Association (NYHA) class III–IV HF, with incidence ranging from 0 to 3.9% [28]. The risk of cardiac dysfunction increases at lower levels of baseline LVEF, with higher cumulative dose of anthracyclines given before trastuzumab, and at advanced age; the incidence is also increased with current or previous use of antihypertensive agents and a higher body mass index [14]. Interestingly, much of the cardiotoxicity associated with trastuzumab when given following an anthracycline is reversible.

Cardiotoxicity is relatively rare with trastuzumab as monotherapy [29]. The toxicity is unrelated to cumulative dose and largely reversible. In the HERA trial with sequential chemotherapy and trastuzumab, the majority of patients with cardiac dysfunction recovered within 6 months [30]. Longer term follow-up of these patients showed that trastuzumab-associated cardiac dysfunction predominantly occurs during trastuzumab treatment (in contrast to anthracycline cardiac toxicity which frequently becomes manifest months to years after the initial treatment) [31]. Furthermore, reexposure to trastuzumab after recovery from LV dysfunction is generally well tolerated [32]. In the major adjuvant BC trials, which included >10 000 patients randomly assigned to receive trastuzumab, only one cardiac death was reported compared with two in the control arms. Based on growing evidence, a distinction can be made between Type I and Type II cardiotoxicity, whereby Type I reflects the scenario of damage associated with myocyte death; Type II is more benign and is associated with cell hibernation or myocardial stunning (Table 2).

Table 2. Clinical features distinguishing Type I and Type II cardiotoxicity [33]

Type I (e.g. doxorubicin)	Type II (e.g. trastuzumab)
Predominant cell death	Cell dysfunction
Typical anthracycline biopsy	No anthracycline-like changes on biopsy
Cumulative and dose related	Not cumulative or dose related
Permanent damage	Generally reversible

There is certainly an additive and possibly synergistic interaction between anthracyclines and trastuzumab. It is likely that despite preserved LVEF after anthracycline therapy, some degree of cardiac damage has occurred and compensatory mechanisms have been recruited. Trastuzumab then constitutes a form of sequential stress on an already compromised heart. Alternatively, trastuzumab could prevent the myocyte's adaptive response to or repair of the anthracycline injury, further compounding the oxidative damage [34]. This mechanism could explain the distinctly higher incidence of cardiotoxicity in concurrent use of trastuzumab and anthracyclines [35]. Taken together, data from metastatic and adjuvant trastuzumab trials suggest that a longer interval between anthracycline treatment and trastuzumab reduces the risk of cardiomyopathy, but this has not been evaluated prospectively [27]. Concurrent use of anthracyclines and trastuzumab should therefore be preferably confined to clinical trials [14].

lapatinib

Lapatinib inhibits both EGFR and HER2 kinases. Perez et al. [36] prospectively evaluated LVEF in 3689 patients (69% in BC) who received lapatinib (alone or in combination) in the course of 44 phase I–III studies. No cardiac deaths were attributed to lapatinib; significant HF occurred in 0.2% of patients and 1.4% had an asymptomatic decline in LVEF of >20 percentage points. This less stringent criteria for cardiac impairment suggests that the incidence may have been underestimated; lack of standardization of cardiotoxicity criteria makes comparison of outcome across studies more difficult. Notwithstanding these concerns, of the patients with cardiac events, 88% recovered to some degree, suggesting that lapatinib is an agent exhibiting the Type II form of cardiac impairment.

In this series, cardiac events were not substantially influenced by prior therapy; overall cardiac event rate was 1.6%, in 2.2% of patients with prior anthracyclines exposure and in 1.7% of patients who had received trastuzumab. It should be noted, however, that the population treated with lapatinib may have included patients who tolerated trastuzumab. Additionally, a relatively long interval between anthracycline and subsequent lapatinib treatment may have allowed further recovery of the anthracycline injury. Data from 274 patients who received lapatinib for >6 months do not suggest cumulative, dose-related cardiotoxicity, but longer follow-up is needed. The ongoing adjuvant phase III ALLTO trial comparing the efficacy and safety of lapatinib, trastuzumab and both will provide more definitive information on relative cardiotoxicity.

In a second study, patients with advanced HER2-positive BC and normal LVEF were randomly assigned to receive lapatinib plus capecitabine or capecitabine alone [37]. All had previously been exposed to an anthracycline, a taxane and trastuzumab. There was no symptomatic LVEF in either group.

bevacizumab

In metastatic BC, an anti-angiogenic strategy is proven to be beneficial [38, 39]. At least five major ongoing adjuvant or neoadjuvant trials in BC (three in HER2-negative disease) now include bevacizumab. Cardiovascular monitoring is a crucial element in these studies given evidence that hypertension, arterial thromboembolism and HF are among the potentially serious toxic effects of bevacizumab [40]. Early data from a phase II trial on feasibility of incorporating bevacizumab into an adjuvant regimen of dose-dense doxorubicin and cyclophosphamide followed by paclitaxel suggest that ~10% of patients experience a >10% decline in LVEF after eight cycles [41]. Hypertension with secondary LV dysfunction, rather than primary myocardial toxicity, may play a part in this decline, and further study is required to clarify the relative contribution of these factors.

sunitinib and sorafenib

The multi-targeted tyrosine kinase inhibitors (TKIs) sunitinib and sorafenib, which inhibit both angiogenesis and tumor growth pathways, have been extensively used in advanced BC trials. Whereas the sunitinib phase III SUN program in BC has recently been stopped due to futility of reaching the primary end point in several trials, sorafenib is still under development. Recently, a phase IIb study evaluating sorafenib combined with capecitabine in patients with locally advanced BC reported no unexpected side-effects [42]. In a study of sunitinib in a series of 75 patients with gastrointestinal stromal tumors, 28% had an absolute LVEF reduction of at least 10% and 8% developed HF [43]. Schmidinger et al. [44] reported symptomatic cardiotoxicity in 18% of 74 renal cancer patients treated with sunitinib or sorafenib. Prompt treatment led to recovery in all cases and allowed anticancer treatment to continue. The reversibility of the cardiotoxicity suggests that sunitinib and sorafenib are Type II agents. However, cardiotoxicity in routine practice (particularly with sunitinib) may be more frequent than is reported in clinical trials [44, 45]. In a recent review, the data for placebo and sunitinib arms were reviewed and demonstrated elevation of blood pressure in the sunitinib group with partial resolution between cycles. Fifteen instances of hypertensive crises were noted among 243 patents in the treatment arms, while no instances of hypertensive crises were seen in the 118 patients on the placebo arms [46].

other cardiovascular toxic effects

hypertension

BC and hypertension are often comorbid conditions, as both more commonly affect older populations. Underlying

hypertension and/or antihypertensive therapy increases risk for anthracycline- and trastuzumab-related LV systolic dysfunction (see below). The anti-angiogenic agents bevacizumab, sunitinib and sorafenib also are associated with significant systemic hypertension with a reported incidence as high as one-third of the patients and considered partly responsible for the modest risk of LV dysfunction [43, 47, 48]. The mechanism is thought to involve VEGF inhibition [49]. Serious complications such as stroke are rare but have been reported.

ischemia

A number of anticancer agents are associated with myocardial ischemia and rarely infarction. Among those commonly used are 5-fluorouracil [50, 51] and the pro-drug capecitabine. Myocardial ischemia, however, is more prevalent with continuous infusions of 5-fluorouracil rather than with the bolus administration which forms part of adjuvant BC chemotherapy and as such is very rarely a problem in clinical practice. These agents probably induce ischemia through coronary artery spasm, and ischemia is more frequently encountered in those with preexisting coronary artery disease. Other agents that may be associated with cardiac ischemia include paclitaxel and docetaxel, but ischemia is rare following the use of these agents. Bevacizumab has been associated with systemic arterial thrombotic events, with a reported incidence of 3.8%; these have included predominantly myocardial infarction, angina, stroke and transient ischemic attack. Risk factors included prior arterial thromboembolic events and age >65 years [52].

dysrhythmia

Paclitaxel has been associated with sinus bradycardia and various degrees of heart block; these episodes are self-limited and usually do not require alteration of the therapeutic regimen; no malignant arrhythmias have yet been reported [53]. Arsenic trioxide has been associated with QT prolongation, and patients on that agent should be monitored; other drugs that may further prolong the QT interval, including certain antiemetics and antimicrobials, should be used with increased caution and with consideration of serial monitoring of the QTc.

assessing cardiac risk and monitoring for toxicity

history and physical examination: when should alarm bells ring?

A detailed clinical assessment is essential in identifying individuals at risk for cardiovascular complications of cancer treatment (see Table 3). In addition, a careful assessment of current functional capacity, volume status and blood pressure is required. Patients at particular risk of cardiotoxicity should have cardiac evaluation that should be carried out in conjunction with the oncologist so that the choice of therapy may be optimized. Risk factors to be considered are included in Table 3, but other factors that could contribute to cardiac stress should not be ignored. Whenever possible, risk factors should be modified or reduced by treating elevated blood pressure, normalizing lipids, encouraging weight reduction and smoking cessation.

Table 3. Risk factors for cardiomyopathy

Established risk factors for anthracycline cardiomyopathy include
Prior anthracycline exposure regardless of agent or administration regimen
Mediastinal radiation
Age >65 years or very young
Hypertension
Exposure to other cardiotoxic agents such as cyclophosphamide, taxanes or trastuzumab
Established risk factors for trastuzumab-related cardiac dysfunction include
Exposure to anthracyclines (worse with higher cumulative dose) and taxanes
Age >50 years
Antihypertensive medications
Borderline left ventricular ejection fraction
Increased body mass index

imaging

Echocardiography is widely available and relatively inexpensive and hence is often the initial investigation of choice for evaluating systolic function. Reproducibility has generally improved over the last decade. Several relatively small studies with conflicting results have looked at various echocardiographic parameters to evaluate earlier and more sensitive indicators of chemotherapy-related cardiomyopathy. These included the Tei index [54], tissue Doppler measurements [55], myocardial strain [56] and dobutamine stress echocardiography [57]. Further validation of these techniques is required before incorporating them into monitoring algorithms.

Alternatively, radionuclide ventriculography or Multiple Gated Acquisition scan (MUGA) is frequently used and is less subject to observer variability; it involves exposure to radiation and is associated with higher cost. Nuclear imaging is difficult in patients with arrhythmias. Choice between echocardiography versus MUGA can be individualized but is often based on provider preference or regional practice patterns. As the two measurements are not interchangeable, the same technique should be used for serial measurements in a given patient whenever possible.

biomarkers

A rise in troponin I, a marker of cell death, may precede measurable changes in LVEF, and B-type natriuretic peptide (BNP), associated with myocardial stretch, is a marker for volume overload. BNP can increase when filling pressures rise even with normal LVEF. Despite inconsistent evidence, both markers seem potentially sensitive indicators of treatment-related cardiac disease. There is some evidence that early release of troponin I predicts later LV dysfunction following anthracycline chemotherapy [58]. Follow-up of patients treated for childhood cancers has established that levels of plasma N-terminal brain natriuretic peptide (NT pro-BNP) are abnormally raised in some asymptomatic survivors [59]. Elevated levels were related to cumulative anthracycline exposure and to end-diastolic LV diameter. Ongoing trials that

incorporate these markers should help place their clinical application in better perspective [13].

tools for reducing risk of cardiotoxicity

cardioprotection

There has been considerable interest in dexrazoxane as a potential means of reducing anthracycline cardiotoxicity. However, based on a review of current evidence, the American Society of Clinical Oncology advises against routine use of dexrazoxane in adjuvant BC therapy [60]. There is also a clear rationale for liposomal formulations of doxorubicin based on more favorable pharmacokinetics and tissue distribution as well as evidence from the metastatic setting that cardiotoxicity is reduced while antitumor efficacy is maintained [61, 62].

limiting anthracycline exposure

Given the risk of cardiotoxicity associated with anthracyclines, treatment regimens reducing exposure to these agents are being actively debated. Modern adjuvant treatment regimens generally limit the cumulative doxorubicin dose to 300 mg/m^2 and several recent trials are addressing non-anthracycline regimens in the adjuvant setting. Other strategies included identification of patient subsets responding more or less favorably to anthracyclines in order to individualize therapy. In a retrospective analysis, Gennari et al. [63] demonstrated that the benefits of anthracycline-containing adjuvant chemotherapy are confined to the minority of women whose tumors overexpress or amplify HER2. Pooled data from eight studies involving >3000 women with HER2-negative disease showed that DFS and OS were almost identical with anthracycline- and non-anthracycline-based regimens. Anthracycline sensitivity of HER2-positive disease may therefore be not due to HER2 *per se* but to amplification of the topoisomerase (topo) IIa gene located nearby on chromosome 17 [64].

More recent data, however, do not support this hypothesis. A meta-analysis using data from randomized trials of ~2000 patients showed that HER2 and topo IIa genes were of clinically modest and statistically borderline value in predicting sensitivity to anthracyclines. In a recent analysis of a large randomized trial, no association between HER2 or topo IIa status and efficacy of adjuvant anthracycline-based treatment was found. Furthermore, data from the neoadjuvant setting suggest that high rates of pathological complete response can be achieved by standard anthracycline-based regimens in patients with triple negative disease, i.e. in the absence of HER2 positivity [65]. Given current uncertainties, the recommendation to use HER2 or topoisomerase IIa as a predictive tool is premature.

In the PACS 01 trial, a sequential regimen of three cycles FEC followed by three cycles docetaxel achieved a significantly higher rate of 5-year DFS and OS than six cycles FEC in women with node-positive EBC [66]. The taxane-containing regimen was associated with significantly fewer severe cardiac adverse events (0.4% vs 1.3% in the FEC ×6 arm). The most recent follow-up of USO trial 9735 demonstrated an OS of 87% with four cycles of adjuvant docetaxel plus cyclophosphamide (TC) versus 82% with doxorubicin plus cyclophosphamide (AC) at 7 years [67]. The non-anthracycline regimen also achieved a significantly higher DFS. These intriguing data (not yet confirmed) represent a shift in management as they show potential benefit for TC in all relevant subgroups. Yet, comparative trials of TC against state-of-the-art three-drug anthracycline-containing combinations (e.g. USO trial 06090 in the United States, PlanB or SUCCESS C trials in Germany) are still ongoing.

Given these data, docetaxel/cyclophosphamide can be considered for women at risk for cardiotoxicity and in HER2-positive patients when chemotherapy is to be followed by trastuzumab. In a combined analysis of the pivotal B31/NCCTG data, 6.7% of the patients treated with anthracyclines experienced a large enough drop in LVEF to preclude planned trastuzumab treatment [2]. The BCIRG 006 trial compared anthracycline plus cyclophosphamide followed by docetaxel plus trastuzumab (AC-TH) against docetaxel plus carboplatin plus trastuzumab (TCH). At the third interim analysis, both regimens had comparable DFS (84% versus 81%) and OS rates (92% and 91%) at 5 years [68]. Compared with TCH, AC-TH was associated with four to five times more NYHA class III–IV HF and twice >10% drop in LVEF. This greater LVEF reduction was evident even after 4 years. The final report of this important trial is eagerly awaited.

screening, monitoring and avoidance of other risk factors

There is still no established consensus about cardiac monitoring during anthracycline chemotherapy. An approach, based on the preferences of the authors, is provided in Table 4. Uncertainties related to cardiotoxicity are reflected in current guidelines and prescribing information generally based on protocols in the major trastuzumab trials [27,69–72]. It is recommended that LVEF be assessed before starting an anthracycline, before starting trastuzumab, every 3–6 months during therapy and

Table 4. Proposal/recommendations for cardiac monitoring

Thorough cardiac assessment including baseline LVEF, before starting treatment
Reassessment after 300 mg/m^2 of doxorubicin or equivalent; after every one to two cycles if additional anthracycline is given
Follow-up LVEF measurements: 3–6 months following completion of therapy and then yearly for 5 years
Higher risk individuals, especially if LVEF has decreased >15% from baseline or to <45%, may be monitored more frequently
In case of anthracycline-related cardiomyopathy at any time during or following treatment, further anthracycline should be avoided (or after careful consideration of the risks)
In patients with comorbidities or diagnostic findings at risk for cardiotoxicity, anthracycline-free adjuvant chemotherapy can be considered, particularly if additional therapy with targeted agents is planned
If potentially cardiotoxic treatment is indicated, all other sources of oxidative stress should, whenever possible, be avoided and volume status optimized

LVEF, left ventricular ejection fraction.

every 6–12 months for at least 2 years following cessation. If trastuzumab is withheld because of a decline in ventricular function, LVEF should be assessed more frequently. When trastuzumab is used without an anthracycline, less intensive monitoring is acceptable. In case of other agents and regimens, protocols are less clear. For a summary of reported incidences of cardiotoxicities for breast cancer drugs refer to Table 5.

treatment of cardiovascular dysfunction

The treatment of asymptomatic LV dysfunction and HF caused by cancer treatment has not been adequately studied. When the causative agent is associated with cell death, treatment should be similar to that utilized in managing the traditional forms of HF. Initially a β-adrenergic blocker and/or an angiotensine converting enzyme (ACE) inhibitor may be employed if the LVEF is <45%; judicious use of diuretics and dietary sodium restriction to maintain euvolemia and careful control of risk factors such as hypertension should be incorporated into the treatment plan. Pharmacotherapy should be long term to prevent LV remodeling and progressive HF.

When the reduced LVEF is likely to be reversible, it should be reevaluated after 1 month free of the agent. LVEF remaining <45% should be considered for treatment, although data on long-term benefit of such intervention are not available.

interruption and resumption of anticancer treatment

Trastuzumab should be suspended if LVEF drops >15 percentage points from baseline or >10 percentage points to a value below the lower limit of normal. The measurement should be repeated after 4–6 weeks. If LVEF improves or rises above the lower limit of normal, restarting trastuzumab may be considered. The policy on rechallenge should be adjusted according to the individual patient's risk of relapse; in cases of HER2-positive disease, adjuvant trastuzumab substantially increases the chance of cure and, therefore, the threshold for stopping it permanently should be high. If substantial anthracycline-associated cardiotoxicity occurs, these agents should not be resumed. Long-term cardiac follow-up by will depend on the individual patient's cardiac risk. A distinction can be made between agents with a demonstrated long-term risk of HF and those with unknown long-term risk.

Table 5. Incidence of cardiotoxicities with breast cancer drugs[a]

	Left ventricular dysfunction	Ischemia
Doxorubicin	5[b]	Nr
Epirubicin	0.9%–3.3%	Nr
Paclitaxel	Nr	<1%–5%
Docetaxel	2.3%–8%	1.7%
Trastuzumab	2%–28%	Nr
Bevacizumab	1.7%–3%	0.6%–1.5%
Sunitinib	2.7%–11%	Nr

[a]Adapted from Yeh et al. [73].
[b]At a cumulative dose of 400–450 mg/m^2; considerably higher at larger cumulative dosages.
Nr, not reported.

discussion

Anticancer drugs have a range of potential cardiotoxicities. Of greatest concern in adjuvant BC therapy are anthracyclines and trastuzumab with fundamental differences regarding pathologic findings, clinical features and prognosis. Noteworthy is that established risks are based on data from clinical trials conducted in very select populations. The true problem of cardiotoxicity in routine clinical practice may therefore be underestimated.

The challenge presently is maintaining the efficacy of BC treatment while considering cardiac risk varying between patients and with different treatment options. Gianni et al. [14] estimate that up to 2 million women in the United States have been treated with anthracyclines and are at risk of developing delayed cardiac damage. HF with anthracycline regimens can occur long after treatment ends. Moreover, even very common adjuvant endocrine therapies, particularly in postmenopausal women may also contribute to the expression of underlying cardiovascular disease or expose the heart to additional toxic effects [74]. Minimizing long-term toxicity is important given the rising number of patients whose life expectancy is approaching that of those without BC. For the afflicted patient, HF is a devastating and sometimes fatal event. For society, it is a significant additional drain on health resources. Nevertheless, exaggerated concern for cardiotoxicity should not lead to inappropriate withdrawal of valuable therapy.

Our greater understanding of BC is increasing, and cardiologists are distinguishing between the seemingly irreversible cardiotoxicity due to cumulative exposure to anthracyclines, and the reversible, non-dose-related toxicity seen with trastuzumab. New cardiac imaging techniques and biomarkers should enable more accurate monitoring of the short-term treatment-related cardiac effects. Cardiac care in the future is likely to become more complex. The combined effects of a multiplicity of oncology interventions, longer durations of treatment using targeted agents, and an aging population mean that the number of cancer patients with cardiac problems will increase. Optimizing cardiac health requires oncologists, cardiologists and family doctors to promote lifestyle changes such as smoking cessation, weight loss, healthy diet and regular exercise.

Cardiologists and oncologists have a shared interest in ensuring that today's cancer survivors do not become tomorrow's heart patients, and the two specialties are already cooperating in developing guidelines (e.g. proposed by the Canadian Trastuzumab Working Group) [28]. Cardiologists stand ready to help in advising on treatment, in monitoring its effects, in dealing with cardiac problems that arise and in deciding when treatment constitutes a substantially increased cardiac risk. They need encouragement to develop expertise in the area. Whether there is a need for a formal subspecialty of cardio-oncology remains an open question. But there is no doubt that a key to effective management will be communication and collaboration between oncologists and cardiologists within a multidisciplinary cancer team.

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