EDITORIAL

Cardiotoxicity from cytotoxics in the 21st century

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In this issue, Pfeffer *et al.* discuss the impact of anthracycline-related cardiotoxicity and strategies for its treatment and prevention (see pages 85–9). Anthracyclines are not the only widely used class of cytotoxics with the potential to cause cardiotoxicity, but they are the most studied and the effects are well described. The antimetabolites 5-fluorouracil (5FU) and capecitabine, an oral pro-drug of 5FU, can cause an acute and chronic cardiotoxicity[1,2] while vinorelbine, a vinca alkaloid, can cause angina.[3] Paclitaxel, a taxane, has been shown to augment the cardiac side effects of doxorubicin, an anthracycline.[4,5] The potential for cardiotoxicity is therefore, a major consideration when determining appropriate treatment for patients.

Cardiotoxicity and adjuvant anthracycline in early breast cancer

Anthracycline-based polychemotherapy regimens for early-stage breast cancer have demonstrated a superior disease-free and overall survival in comparison to non-anthracycline based regimens.[6] The increasing usage and efficacy of adjuvant chemotherapy is a significant factor contributing to the fall in mortality from breast cancer.[6-9] However, the rising numbers of patients treated with anthracyclines in the adjuvant setting could mean that many women have sustained subclinical cardiac damage that is not yet clinically apparent. A recent analysis has attempted to define the extent of cardiac sequelae following adjuvant treatment for breast cancer.[10] This study reported, reassuringly, that over 13 years of follow-up, exposure to doxorubicin did not increase the likelihood of adverse cardiac effects (arrhythmia, congestive heart failure, angina) and while 9% of patients were recorded to have experienced arrhythmia, none had experienced heart failure or angina within a year of being assessed at eight and 13 years. However, this was a small sample with only 180 of 1,176 potential patients participating. In addition, the dataset to 13 years consisted of only 17 subjects, therefore, the frequency of cardiac damage may have been underestimated. The possible presence of subclinical cardiotoxicity has important implications for the choice of treatment in those who develop metastatic disease. The risk of re-challenge with an anthracycline or exposing the patient to another class of drugs, such as the taxanes, may result in clinical cardiotoxicity.

Trastuzumab-related cardiotoxicity

Trastuzumab is a monoclonal antibody targeting human epidermal growth factor receptor 2 (HER2) that increases survival in early[11,12] and metastatic[13] breast cancer when given in combination with, or sequentially following, chemotherapy. Trastuzumab-associated cardiotoxicity presents a particular problem as it can occur with monotherapy, but importantly, there is an additive risk when administered with anthracyclines or in patients previously exposed to anthracycline, such as those treated adjuvantly for breast cancer. Consequently, the number of patients potentially at risk is significant. Suter *et al.*[14] analysed cardiovascular adverse events in patients treated with trastuzumab monotherapy within the Herceptin Adjuvant (HERA) trial and found that the incidence of trastuzumab discontinuation due to cardiac disorders was 4.3% and that most cardiac dysfunction was reversible within six months of stopping treatment. In the Slamon[15] study the incidence was much higher at 20% and one of the reasons may have been the difference in left ventricular ejection fraction (LVEF) entry criteria between the two trials: the HERA trial required a LVEF of at least 55% while the Slamon trial accepted a value of 50%. Given that the cardiotoxicity from trastuzumab is probably reversible, the question of how much monitoring and how to deal with decreasing function in an asymptomatic patient have become everyday clinical issues.

Cumulative cardiotoxicity is likely to be an increasingly common clinical problem due to the rise in use of anthracycline-containing adjuvant chemotherapy regimens and now long-term treatment with antibodies such as trastuzumab in adjuvant patients (up to one year at present) or indeed long-term treatment in metastatic patients (several years in some cases).

Strategies for management of cytotoxic cardiotoxicity

As Pfeffer *et al*. point out, the observed clinical course of cytotoxic-related cardiotoxicity can be acute, chronic or late, varying according to individual drugs. The authors discuss options for the prevention and management of acute onset adverse cardiac sequelae including dose reduction, anthracycline analogues and use of cardioprotectants such as dexrazoxane. However, there are drawbacks to these options.

In the first instance, adjustments to adjuvant chemotherapy regimens, such as switching to a taxane as in sequential combinations (ACT[16] and FECT[17]), using a less cardiotoxic anthracycline regimen (e.g. FEC 100 x 6,[18] FEC 60 x 8,[19] and shorter courses of anthracycline AC x 4[20]) may help to reduce the anthracycline risk.

Unfortunately, evidence shows that dose reduction of chemotherapy given adjuvantly decreases long-term survival and decreases response rates in metastatic disease.[21-23] In reality, the clinical decision balances the likelihood of long-term morbidity and mortality from possible cardiotoxicity against potentially reduced efficacy due to attenuated dose.

The question of efficacy is also relevant when switching to an alternative drug. Several phase III clinical trials in metastatic breast cancer have shown at least equivalent efficacy when substituting doxorubicin with either a pegylated or non-pegylated liposomal analogue.[24-28] The data are less convincing for the substitution of epirubicin with a liposomal analogue.[27-29] There are no data to recommend this option in the adjuvant setting although, if clinically necessary, the dosing schedule applied in metastatic breast cancer can be used as a guide. In addition, although the risk of cardiac side effects is decreased, there are other acute toxicities such as hand–foot syndrome and stomatitis, which can be unpleasant in the short term.[30]

There is evidence to support the use of dexrazoxane to reduce the incidence of anthracycline-related cardiotoxicity[31,32] but one study showed a lower response rate with dexrazoxane, although overall survival was not reduced.[32] In addition, the mechanism of this effect is unknown, myelosuppression is often enhanced in patients receiving a combination of dexrazoxane and anthracycline, it is expensive and there are no current data on the interaction with trastuzumab. More recently, troponin I used as a biochemical marker in the acute setting to risk-stratify patients in conjunction with assessment of LVEF, has shown promise in the early detection of subclinical cardiac damage. Initial results suggest that persistently elevated troponin I levels have predictive value for those at risk of long-term adverse cardiac outcome secondary to anthracycline treatment.[33] While biochemical markers are a useful adjunct to assessment of LVEF they are not yet sufficiently sensitive to replace echocardiography in determining cardiac risk.

Strategies for prevention of cytotoxic cardiotoxicity

Cardinale *et al*.[34] used troponin positivity as a biomarker to initiate treatment with an angiotensin-converting enzyme (ACE) inhibitor as a cardioprotectant irrespective of LVEF with promising results showing that LVEF was preserved in the group of patients receiving enalapril. ACE inhibitors and beta blockers (e.g. carvedilol) are sometimes used for asymptomatic patients with a drop in LVEF and those who have developed symptomatic chronic cardiotoxicity, although there are inherent risks, such as renal failure, with these drugs and no good prospective data exist.[35,36] A third generation beta blocker, nebivolol, was cardioprotective against anthracycline-induced cardiotoxicity using the model of isolated perfused rat heart.[37] There is no clear evidence that this approach specifically for anthracycline-mediated cardiac damage is more or less effective than the treatment of other causes of heart failure. Further evaluation in randomised clinical trials is needed. Patients with a good prognosis from their cancer who develop chronic cardiac dysfunction can be considered for heart transplantation.

An alternative aspect of prevention is targeting anthracycline exposure more effectively to patients most likely to derive benefit and tolerate it well. For example, the recent meta-analysis by Gennari *et al.*[8] found that in HER2-negative disease (n=3,818 patients), anthracyclines did not improve disease-free (hazard ratio [HR]=1.00; 95% confidence interval [CI]=0.90 to 1.11; p=0.75) or overall (HR=1.03; 95% CI=0.92 to 1.16; p=0.60) survival.

Furthermore, evidence is now available from two clinical trials suggesting that the use of an anthracycline-based regimen can be replaced in most situations by an equally effective non-anthracycline based regimen in breast cancer. The classic AC regimen (doxorubicin and cyclophosphamide) had less favourable disease-free survival in the adjuvant setting than a combination of docetaxel and cyclophosphamide (TC) although there was no significant difference in overall survival at five years.[38] Robert *et al.*[39] showed that TCH (docetaxel, carboplatin and trastuzumab) was equivalent to the anthracycline regimen AC, and neoadjuvant carboplatin and paclitaxel, with or without herceptin, also looks promising.[40,41] It now appears that if we have concerns about potential cardiotoxicity then we can tailor treatment to patients needs by using TC or TCH.

Monitoring patients at risk of cytotoxic cardiotoxicity

Monitoring for cardiotoxicity in clinical practice is somewhat empirical but the guidelines followed in the HERA trial, 12-lead electrocardiogram (ECG) and assessment of LVEF by echocardiography or multi-gated acquisition (MUGA) scanning at baseline and 3, 6, 12, 18, 24, 30, 36 and 60 months of trastuzumab treatment, are now widely applied. No clear consensus yet exists on whether serial echocardiography or MUGA scans are preferable, and the duration of monitoring is also debated, although in practice it is not lifelong. As trastuzumab-related cardiotoxicity is reversible, it is likely intensive, prolonged monitoring is unnecessary for periods of greater than six months. The use of biomarkers is likely to improve monitoring and risk-stratification of patients.

Conclusions

A comprehensive evidence-base is vital for advising patients receiving anthracycline or trastuzumab appropriately and to manage their risks more effectively. For example, should patients exercise or not during treatment or after treatment, what should the advice be if they are found to have a reduced LVEF and how intensive can this exercise be without putting them at risk? What are the guidelines for the duration of treatment with ACE inhibitors or beta blockers? Does subclinical cardiac damage contribute to the fatigue of chemotherapy? Could reduction in levels of oestrogen and progesterone as a result of chemotherapy be contributing to observed cardiotoxicity?

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A greater understanding of mechanism and optimal management (both preventive and treatment) is still required in patients with cancer receiving cardiotoxic drugs with emphasis on research investigating the use of ACE inhibitors, quality of life and health economics

Conflict of interest

RK: none declared. MO'B has participated in clincal trials for liposomal doxorubicin (Caelynx®) and received speaker's and advisory board honoraria from Schering Plough.

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