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Anthracycline cardiotoxicity in breast cancer patients: synergism with trastuzumab and taxanes

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Abstract Doxorubicin is known to cause cardiomyopathy and congestive heart failure (CHF) upon chronic administration. A major obstacle to doxorubicin-containing multiagent therapies pertains to the possible development of cardiomyopathy and CHF at lower than expected cumulative doses of doxorubicin. For example, the cardiac toxicity of doxorubicin is aggravated by the anti-HER2 antibody Trastuzumab or by the tubulin-active taxane paclitaxel; however, the mechanisms by which Trastuzumab and paclitaxel aggravate doxorubicin-induced cardiotoxicity are mechanistically distinct: Trastuzumab interferes with cardiac-specific survival factors that help the heart to withstand stressor agents like anthracyclines, while paclitaxel acts by stimulating the formation of anthracycline metabolites that play a key role in the mechanism of cardiac failure. Here, we briefly review the molecular mechanisms of the cardiotoxic synergism of Trastuzumab or paclitaxel with doxorubicin, and we attempt to briefly outline how the mechanistic know-how translates into the clinical strategies for improving the safety of anthracycline-based multiagent therapies.

Keywords Anthracyclines · Cardiotoxicity · Toxic synergism · Trastuzumab · Taxanes

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Introduction

Chronic anthracycline regimens are limited by the possible development of cardiomyopathy and congestive heart failure (CHF). In general, the incidence of CHF increases disproportionally at cumulative doses >500–550 mg of doxorubicin (DOX)/m^2; however, CHF may occur at lower cumulative doses if DOX is combined with other agents. Several studies of women receiving DOX for the treatment of breast cancer show that trastuzumab and taxanes are highly active at aggravating the cardiac toxicity induced by DOX. Here, we review the pharmacological mechanisms and clinical readouts of the cardiotoxic synergism between such agents and DOX.

Molecular basis of the cardiotoxic synergism between trastuzumab and doxorubicin

p185HER2, product of the protooncogene HER2 (also known as *c*-erbB-2 or *neu*), is a transmembrane receptor tyrosine kinase belonging to the epidermal growth factor (EGF) family. HER2 is amplified and the p185HER2 protein overexpressed in 20–25% of human breast cancers, and such alterations associate with a poor prognosis. Trastuzumab, an antiHER2 humanized monoclonal antibody, represents the most significant improvement for treating women with breast cancer characterized by increased expression of the HER2 receptor, as originally reported in a study of chemotherapy with or without the antibody for women with metastatic breast cancer [1]. The outstanding results of that pivotal study were also associated with a high incidence of cardiac events that mainly occurred with the concomitant use of anthracyclines. More precisely, the authors reported symptomatic or asymp-

tomatic cardiac dysfunction in 27% of patients receiving an anthracycline containing chemotherapy regimen, while the rate of cardiac events was 4.7%, or 13% when Trastuzumab was administered alone or with the tubulin-active taxane paclitaxel, respectively [1, 2].

The mechanism(s) responsible for the toxic interaction(s) of Trastuzumab with the heart have not been fully elucidated; an attractive hypothesis calls into question the interference(s) of Trastuzumab with cardiac tissue repair mechanisms mediated by HER2, primarily in the form of an HER2:HER4 heterodimer [1, 3–5]. Indeed, gene-targeting studies in mice show that HER2 is essential for cardiac development [6]; moreover, conditional deletion of HER2 leads to a dilated cardiomyopathy [7]. Either observation indicates that the HER2 receptor and associated intracellular signaling are important determinants of normal cardiac structure and function. The link between the physiological function of HER2 in the heart and the enhancement of DOX-induced cardiotoxicity was recently outlined by studies with mice knocked-out (KO) for neuregulin-1 (NRG-1), a well-defined ligand for the HER2:-HER4 heterodimer [8]. These studies showed that under normal conditions the wild-type and KO mice exhibit comparable total levels of HER2 in the left ventricle; however, DOX administration caused much more HER2 phosphorylation in wild-type mice as compared with KO mice, consistent with the hypothesis that an NRG-1 modulation of HER2 activation represents an important adaptive response to the stress induced by anthracyclines [8]. In other terms, the NRG-1/HER2 signaling is cardioprotective in the presence of cardiac injury such as that caused by an anthracycline treatment (Fig. 1).

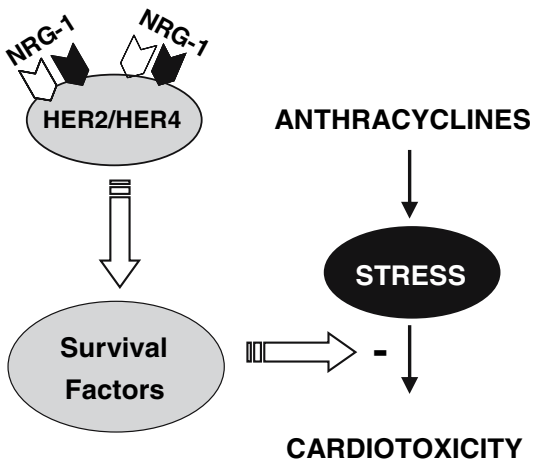

Fig. 1 Role of the NGR-1/HER2 signaling in the defense of the heart against anthracycline-induced stress. Ligand-binding interactions of NGR-1 (neuregulin-1) with HER/HER4 heterodimers are coupled with activation of cardiac survival factors that counteract stress conditions such as that induced by anthracyclines. See text for explanations

Given that Trastuzumab downregulates the HER2 receptor and competes for the NRG-1 signaling, any pre-existing cardiac sub-clinical problem (including that caused by prior anthracyclines) may be worsened by the administration of the antibody and cause the development of symptomatic dysfunction at lower than expected cumulative dose of e.g., DOX. On the other hand, the mechanistic considerations done so far point to a detrimental cardiac effect of single agent Trastuzumab that is totally different and probably more benign than that of anthracyclines, and can be simplified as the contribution to accelerating cardiac dysfunction and CHF due to exacerbation of heart injury by other causes (including anthracyclines).

Clinical readouts of the cardiotoxicity of trastuzumab as single agent or in combination with anthracyclines

On clinical grounds, the immediate consequence of the cardiotoxicity described in the pivotal study of Trastuzumab with chemotherapy [1] has been the search for schedules that combined Trastuzumab with anthracyclines less cardiotoxic than DOX; these schedules were hoped to exhibit the same activity as that of Trastuzumab-DOX schedules, while also introducing a less severe risk of symptomatic cardiac events. Clinical studies therefore investigated the efficacy and safety of Trastuzumab in combination with epirubicin (EPI) or liposomal formulations of DOX. The available studies (phase II studies of Trastuzumab with pegylated liposomal DOX, and phase I and II studies of Trastuzumab with uncoated liposomal DOX and PTX) attest to the promising activity and safety of all such schedules [9–11].

In the past 2 years the initial results of the application of Trastuzumab in the adjuvant setting became available and indicated a strong beneficial effect of the antibody in ameliorating the disease-free survival of patients with operable HER2-positive breast cancer [12–15]. Although the results of all the studies showed that cardiac toxicity was acceptable and always within an upper limit of ~4% incidence [12], caution on this aspect is still necessary and longer follow-up is certainly needed [12–17]. In keeping with the different mechanisms outlined before, it is important to stress that Trastuzumab-induced cardiotoxicity was usually reversible after discontinuation of therapy and responsive to standard treatments [18]. Among the different trials of Trastuzumab as an adjuvant therapy, the NSABP B31 is the only study designed to specifically address the issue of Trastuzumab-associated cardiotoxicity. Relevant to the topic of the feasibility and wide applica-

bility of Trastuzumab adjuvant treatment, an important point emerging from the B31 trial (the one with the longest follow-up) is that there appears to be a plateau of risk reached during the first year of trastuzumab therapy with very few additional cases observed thereafter [17]. This is in keeping with the role of HER2 signaling in the stress-response of the heart, and the limited spanning of its consequences [18, 19].

Cardiotoxic synergism between taxanes and doxorubicin: pharmacokinetic and pharmacometabolic considerations

Whereas Trastuzumab synergizes with DOX toxicity by interrupting signaling pathways, the taxane paclitaxel (PTX) seems to act on pharmacokinetic and/or pharmacometabolic grounds. The rationale for combining DOX with PTX for an improved treatment of metastatic breast cancer was offered by an appreciation of the different mechanisms of action of the two drugs, their non-overlapping of toxicities, and the occurrence of an only limited cross-resistance. However, pivotal trials of bolus DOX followed by a 3 h infusion of PTX with a 15 min interval showed that an improved objective response was accompanied by a higher than expected incidence of CHF at cumulative doses of 420–480 mg of DOX/m^2 [20]. Pharmacokinetic studies uncovered that, compared with DOX alone, DOX–PTX schedules were characterized by a ~30% increase of the plasma area under curve (AUC) of DOX and, most notably, by an ~100% increase of the AUC of the secondary alcohol metabolite of DOX, popularly referred to as DOXOL [21]. As described by Menna et al. in a separate chapter of this special issue, there are several lines of evidence to suggest that DOXOL is a crucial determinant of the progression of cardiotoxicity from an acute/reversible phase toward a chronic/progressive phase. The effect of PTX on the plasma exposure to DOXOL was attributed to interferences of the PTX vehicle, Cremophore EL, on the biliary Pgp-mediated elimination of the anthracycline molecule, and offered a plausible framework to explain the higher cardiotoxicity of DOX–PTX as compared with DOX alone [21]. Accordingly, neither a diminished anthracycline elimination nor an aggravation of the dose-related cardiotoxicity of DOX could be observed on combining DOX with the closely related taxane docetaxel (DCT), likely because DCT was formulated in polysorbate 80 instead of Cremophore EL [22, 23].

A major caveat in the interpretation of the cardiotoxic synergism between DOX and PTX was that a polar metabolite like DOXOL would take too long to partition from plasma and damage the heart by this route [24]; likewise, the reported cardiac safety of DOX/DCT schedules could have been determined also, if not primarily, by the lower cumulative dose of DOX administered to the patients (378 mg/m^2) [23]. These concerns formed the basis to elaborate an alternate hypothesis, according to which PTX stimulated DOXOL formation inside the heart; the last few years have witnessed a growing evidence that this may be the case. Studies with translational models of human heart showed that PTX acted as an allosteric modulator of the cytoplasmic aldehyde reductases that formed DOXOL by adding two electrons to the side chain carbonyl group of DOX; this resulted in a reduced K_m value and increased V_{max} value for the reaction of DOX with such reductases, leading to an overall improvement of the catalytic efficiency (V_{max}/K_m) with which the human myocardium generated DOXOL [25]. Of note, DCT had essentially the same effect as those of DOXOL, while the structurally unrelated tubulin-active vinorelbine did not [26]. These latter observations demonstrated that stimulation of DOXOL formation within the heart was a unique characteristic of taxoid molecules.

Clinical readouts of the metabolic interactions between doxorubicin and taxanes

The observations that both PTX and DCT augmented DOXOL formation in the human myocardium changed our appraisal of the cardiotoxic synergism between DOX and taxanes, and suggested that the safety or toxicity of DOX–PTX or DOX–DCT schedules would be determined primarily by the cumulative dose of DOX associated with the taxane: in other words, also DCT might prove to aggravate the cardiac toxicity of DOX if it were combined with doses of DOX high enough to generate a threshold level of DOXOL. In keeping with these concepts, studies of DOX–PTX or DOX–DCT as primary or adjuvant treatments of operable breast cancer showed that DOX–DCT caused a trend toward more cardiotoxicity when the cumulative dose of DOX associated with DCT exceeded that associated with PTX [27–29].

Similar to what reported for Trastuzumab–anthracycline schedules, a major effort has been directed to identifying treatment modalities that retained antitumor activity while also inducing a less severe cardiotoxicity. Currently, the increase of cardiotoxicity of DOX–PTX is prevented by limiting the cumulative dose of DOX to 360 mg/m^2 or by separating DOX and PTX by longer than 4 h [30]. Another strategy may be that of substituting EPI for DOX. Trials of EPI immediately followed by PTX or DCT did not demonstrate a severe aggravation of the dose-related cardiotoxicity of EPI [31, 32], as if neither taxane stimulated DOXOL formation in the heart. Consistent with such an interpretation, studies of translational models of human

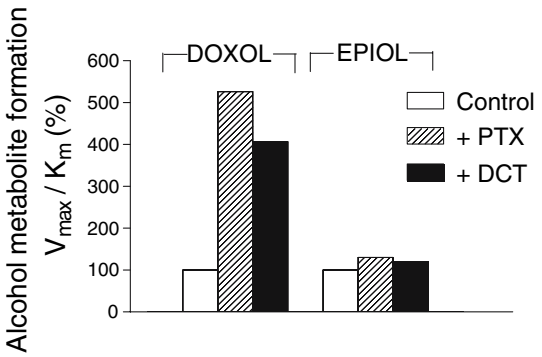

Fig. 2 Taxane stimulation of DOXOL but not EPIOL formation. Anthracycline secondary alcohol metabolite formation was measured in cytoplasmic fractions of human myocardial samples incubated with NADPH, DOX or EPI, and 1 μM PTX or DCT. The taxanes improved the catalytic efficiency (V_{max}/K_m) of DOXOL formation but not of EPIOL formation. Values are expressed as percentages to permit comparisons between different sets of experiments. Adapted from [24, 33]

heart showed that neither PTX nor DCT improved the V_{max}/K_m value with which the human myocardium converted EPI to its secondary alcohol metabolite EPIOL [33] (Fig. 2). These results successfully probed the hypothesis that taxane aggravated cardiotoxicity through a specific stimulation of alcohol metabolite formation, and identified EPI as a better partner than DOX for active but safe combinations with PTX or DCT. Another potential strategy may be that of replacing PTX or DCT with minimally modified taxanes, such as BMS-184476 (7-methylthiomethyl paclitaxel), that lack an ability to stimulate the formation of DOXOL in human myocardial samples [34].

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