Cardiotoxicity after anticancer treatment

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FUTURE PERSPECTIVES

Advances in the treatment of breast cancer aim to increase the survival of patients suffering from this disease. Next to the conventional anticancer treatment, consisting of surgery, radiation therapy, cytostatic and hormonal therapies, the use of molecular targeted agents is a very promising new direction in the treatment of patients with breast cancer. Since more patients survive and reach an older age, long-term complications of their anticancer treatment, such as cardiac toxicity, may surface increasingly. In addition to chest wall irradiation, several cytostatic agents, of which the anthracyclines are the most important, can induce cardiotoxicity. Trastuzumab, the monoclonal antibody against HER2, increases the risk of cardiac dysfunction, especially when combined with anthracycline chemotherapy.[1] Recently, interim analyses of three large randomized trials, evaluating trastuzumab after standard adjuvant chemotherapy, showed a prolongation of disease free and overall survival in patients with HER2-positive breast cancer.[2,3] However, the interim analysis of one of these studies, which already had strict inclusion criteria concerning cardiac fitness, revealed a 3.3% incidence of severe cardiac dysfunction more than 6 months after the start of paclitaxel plus trastuzumab, compared to none in the patients who received paclitaxel alone. An additional 15% of the patients receiving paclitaxel and trastuzumab were taken off study for an asymptomatic decrease in left ventricular ejection fraction (LVEF).[4] As trastuzumab is now becoming the standard of care in the adjuvant treatment of HER2-positive breast cancer patients, the issue of trastuzumab-related cardiotoxicity becomes increasingly relevant.
Therefore, prediction and early detection of cardiotoxicity, preferentially before symptoms of cardiac dysfunction develop, are becoming increasingly important in the follow-up of cancer patients. Primary prevention and early intervention are of imminent importance.

Measurement of biochemical markers of cardiac damage, such as the plasma natriuretic peptides, is very promising in this regard, all the more considering the relative simplicity and low cost of these types of tests. Plasma B-type natriuretic peptide (BNP) measurement may become of particular interest for screening patients who are prone to develop cardiac dysfunction. Nevertheless, before plasma natriuretic peptide measurement can be taken to the clinic for monitoring (long-term) cardiotoxicity of antineoplastic treatment, proper validation of the test for this purpose needs to be performed. A well designed prospective study with long-term follow-up, measuring plasma natriuretic peptides alongside more established cardiac functional parameters, such as LVEF determination, will be required to assess the role for natriuretic peptide measurement in the screening for cardiotoxicity of anticancer treatment.
Next to plasma BNP measurement, we evaluated whether measurement of circulating apoptosis-related proteins could be used for the detection of antineoplastic treatment-related cardiotoxicity. Although we were unable to detect an association between these apoptotic proteins and the existence of cardiotoxicity,

several of the apoptotic proteins and serum HER2 were elevated in patients treated with anthracycline-containing chemotherapy for breast cancer, especially after high-dose chemotherapy. These findings suggest that antineoplastic treatment initiated an ongoing process of cellular/tissue damage, which may be associated with long-term treatment-related complications. To investigate whether the increased plasma apoptosis markers are related to long-term complications of anticancer treatment, longer follow-up regarding late sequelae of our study population would be highly interesting.

Non-invasive imaging techniques form another appealing approach regarding the early detection of cardiotoxicity due to antineoplastic treatment. ^{99m}Tc-annexin V scintigraphy for example, can be used for the detection of myocardial apoptosis.[5] Reutelingsperger et al. implemented ^{99m}Tc-annexin V scintigraphy in seven patients with acute myocardial infarction. They found that the area of ^{99m}Tc-annexin V uptake corresponded with defects in ^{99m}Tc-Sestamibi uptake in 6 of 7 patients.[6] Alternative imaging techniques aim at detection of cardiomyocyte cell damage, such as ^{111}Indium-antimyosin scintigraphy, or detection of adrenergic neuron function impairment, for instance with ^{123}Iodine-metaiodobenzylguanidine (^{123}I-MIBG) scanning. However, although positive results have been described for the early detection of anthracycline cardiotoxicity,[7,8] further development of these techniques for the early detection of anticancer treatment-related cardiotoxicity is stagnating.
The above mentioned nuclear imaging methods can detect cardiac injury and could be of use for the early detection of cardiotoxicity. However, these technique do not address agent-specific mechanisms that could underlie the cardiotoxicity. Since trastuzumab, a highly specific monoclonal antibody against HER2, is associated with an increased risk of cardiac complications, it was hypothesized that trastuzumab-related cardiotoxicity is caused by a direct effect of trastuzumab on the myocardium. We developed a method to radiolabel trastuzumab with the gamma-emitting isotope ^{111}Indium, and we showed that ^{111}In-DTPA-trastuzumab single photon emission computed tomography (SPECT) imaging can detect HER2 positive sites. Despite the fact that Behr et al. suggested in a preliminary report that pre-treatment ^{111}In-DTPA-trastuzumab scanning could predict for the development of trastuzumab-related cardiotoxicity,[9] we could not observe any predictive value for this technique regarding trastuzumab-related cardiotoxicity in HER2-positive metastatic breast cancer patients who underwent ^{111}In-DTPA-trastuzumab scintigraphy.

One hypothesis that could explain why we did not observe myocardial ^{111}In-DTPA-trastuzumab uptake in the patients who developed heart failure, is that HER2 upregulation is a transient phenomenon. The cellular growth and survival promoting signal provided for by HER2, is considered to function as a compensatory mechanism which is induced following cardiac stress, for instance

by anthracyclines. The time interval between the last dose of prior anthracycline chemotherapy and trastuzumab treatment might therefore be crucial for the detection of myocardial HER2 expression with this technique. The rationale that anthracycline-based chemotherapy induces cardiac stress, which subsequently leads to upregulation of HER2 expression in the myocardium, was the reason to design and to recently start a study in which radiolabeled trastuzumab scintigraphy is performed directly after completion of anthracycline-based anticancer treatment. The aim is to determine the value of ^{111}In-DTPA-trastuzumab SPECT imaging with regard to the early detection and/or prediction of anthracycline-induced cardiotoxicity. Remarkably, myocardial ^{111}In-DTPA-trastuzumab uptake was observed in the first patient entered in this ongoing study. Although based on only one patient, who did not undergo a scan before the onset of treatment, this finding does suggest that anthracycline chemotherapy induces myocardial HER2 upregulation. Thirteen additional patients will be enrolled in this study, before a conclusion can be drawn with regard to the value of this technique for predicting anthracycline-induced cardiotoxicity.

HER2 is indispensable for normal cardiac development in animals and is considered to play a similar role in the human heart. We observed that serum HER2 levels were higher in patients with heart failure, compared to healthy controls, which suggests that HER2 plays a role in the pathophysiology of heart failure. In a preliminary report, which was published later as a full paper, immunohistochemical analysis of 60 cardiac biopsy specimens from patients with heart failure due to cardiac disease, showed weak positive staining for cardiomyocyte HER2 membrane expression in six.[10] The authors also describe that low levels of HER2 mRNA were detectable with *in situ* hybridization in all cardiomyopathy patients. Although the expression level may be low, compared to HER2 overexpressing tumor tissue, this indicates the presence of HER2 in failing cardiomyocytes. To evaluate whether myocardial HER2 expression can be demonstrated in patients with chronic heart failure, we designed a cross-sectional study using radiolabeled trastuzumab scintigraphy in this patient category. In this ongoing study, patients are injected with a tracer dose of ^{111}In-DTPA-trastuzumab, followed by SPECT imaging at 48 and 96 hours. Six patients were recruited up to now. Myocardial uptake was not observed in any of these patients. Recent advances in our understanding of the role of HER2 in the heart may provide an explanation for this finding. It is now hypothesized that HER2 plays a role as a compensatory mechanism, counteracting cardiac stress. Loss of survival and hypertrophy promoting signaling, provided by cardiomyocyte HER2, might precede the development of heart failure. For instance, rats with a banding-induced aortic stenosis consequently develop compensatory myocardial hypertrophy. During the phase of compensatory hypertrophy, Northern blotting and immunoblotting analysis showed the presence of HER2 mRNA and protein in left ventricular myocytes. HER2 mRNA and protein levels were depressed when the animals

subsequently developed heart failure.[11] Furthermore, implantation of a left ventricular assist device in patients with severe heart failure resulted in upregulation of HER2 mRNA.[12]

Anthracyclines can induce cardiac injury through production of toxic free oxygen radicals and an increase in oxidative stress.[13] Activation of the renin-angiotensin system and oxidative stress have been linked extensively in recent literature.[14,15] It has also been reported that the angiotensin II signaling pathway plays an important role in anthracycline-induced cardiotoxicity.[16] HER1, the archetype of the HER family of receptors, is transactivated through activation of the angiotensin II type 1 receptor, which leads to myocardial hypertrophy.[17] Thus, a connection exists between (activation of) the renin-angiotensin system and the HER-related signaling in myocardial hypertrophy. In prostate cancer cells, Western blot analysis showed that angiotensin II can transactivate both HER1 and HER2.[18] It can be postulated that the renin-angiotensin system is activated due to anthracycline treatment and plays a role in compensatory HER2 signaling in the heart. Subsequent trastuzumab treatment may attenuate this compensatory signaling, leading to cardiac dysfunction. Measurement of plasma renin activity in anthracycline-treated patients prior to trastuzumab treatment, may be a logical first step to determine whether the renin-angiotensin system is involved in trastuzumab-related cardiotoxicity. If this is the case, it would be interesting to evaluate the effects of the renin-angiotensin system on HER2-mediated signaling *in vitro*. One approach to evaluate the effects of angiotensin on HER2 expression, could be to determine HER2 mRNA and protein expression, and downstream signaling, in angiotensin II-treated (rat) ventricular myocytes.

In addition to early detection, prevention or circumvention of cardiotoxicity by antineoplastic treatment are also of interest. Attempts to improve cardiac safety of potentially cardiotoxic anticancer agents include alterations of dosing schedules to modify pharmacokinetics, for instance altered dosing schedules.[19,20] Administration of liposome-encapsulated anthracyclines represent the most recent approach to the problem of anthracycline cardiotoxicity, without attenuating antitumor efficacy.[21] In Europe, only nonpegylated liposomal doxorubicin is available for clinical use. Randomized clinical trials have shown that the incidence of cardiotoxicity is substantially lower with the use of liposomal doxorubicin, compared to conventional doxorubicin, either as a single agent or in combination with other cytostatic agents.[22,23] Possible explanations for the lower cardiotoxicity incidence, compared to conventional doxorubicin, may be that nonpegylated liposomes generally extravasate in tissue and organs lined with fenestrated endothelial barriers or areas of pathology where capillaries are disrupted by inflammation or tumor growth. The myocardium is supplied by vessels with tight junctions, which prevent doxorubicin to penetrate the myocardium.[24] Application of liposomal

anthracyclines is still limited due to severe adverse effects, such as mucositis, and the fact that these agents are very expensive.

Administration of cardioprotective agents is also of interest with regard to circumvention of the cardiotoxicity problem.[25] Currently, dexrazoxane is the only cardioprotective agent that is registered for concurrent use with anthracycline chemotherapy in patients receiving doxorubicin or epirubicin for metastatic cancer, and is suggested for patients who have received a total doxorubicin dose of more than 300 mg/m^2.[26] The most important fear with the use of dexrazoxane, is that it attenuates the efficacy of antitumor treatment.[27,28] Angiotensin-converting enzyme (ACE) inhibition can ameliorate symptoms in patients with anthracycline-induced congestive heart failure.[29] Recent literature suggests beneficial effects of ACE inhibition regarding left ventricular end-systolic wall stress (echocardiography) in anthracycline-treated childhood cancer survivors, who had shown one or more cardiac abnormalities at any time during follow-up after treatment.[30] It would be interesting to evaluate whether the use of ACE inhibition is of benefit with regard to preservation of cardiac function in a randomized placebo-controlled trial in adult anthracycline-treated patients. Another interesting approach is to administer an ACE inhibitor simultaneously with anticancer treatment consisting of anthracyclines or (adjuvant) trastuzumab, in a prospective randomized trial with careful monitoring of cardiac function. In the light of the aforementioned possible interaction between HER2 and angiotensin II receptor type 1-mediated signaling, the newer angiotensin II type 1 receptor antagonists may also be of interest regarding prevention of anticancer treatment-related cardiotoxicity.

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