E12. Cardiology for the oncologist – Cardiovascular side effects of medical breast cancer treatment

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The concept

The cardiovascular side effects of breast cancer therapy have been known for quite some time. Anthracycline cardiotoxicity, for example, was first described over 30 years ago and remains an important consideration even today.[1,2] Despite enormous progress in recent years, cardiotoxicity is still a limiting factor in the treatment of breast cancer for several reasons:

1. Due to the success of therapy, many cancer patients now survive long-term. Since serious cardiovascular side effects frequently manifest only months to years after the initial cancer therapy, cancer survivors and patients with metastatic disease may experience cardiovascular side effects.
2. Due to changes in demographics, many breast cancer patients are elderly and therefore have other medical conditions. This increases the risk of cancer treatment-associated cardiovascular side effects.
3. The introduction of new signalling inhibitors, for example, the anti-HER2 therapeutics, have increased efficacy for some breast cancer types. However, since these therapeutics are not targeted to the cancer cells but rather act systemically, cardiovascular side effects are not unexpected.[3] Furthermore, it now appears that quite a few of these signalling inhibitors also modulate important survival pathways in the heart. This explains why the use of some of the "targeted therapeutics" is particularly dangerous in combination with (oxidative) stress-inducing cytotoxic therapeutics, such as anthracyclines, or in patients with pre-existing cardiovascular conditions.
4. Some of the newer cancer drugs that will potentially be used in the treatment of breast cancer, for example, angiogenesis inhibitors, affect signalling pathways that are important for the homeostasis of the cardiovascular system. Induction of arterial hypertension and thrombosis is a direct effect of these drugs and the long-term consequences are not yet foreseeable.
5. The strategy to increase therapeutic efficacy by inhibiting several signalling cascades in cancer cells will inevitably lead to more cardiovascular side effects as long as these therapeutics are not specifically targeted to cancer cells. The heart is a postmitotic organ with almost no capacity to replace lost myocardium. Despite missing mitosis in myocardial muscle cells, the plasticity of the heart to adapt to changing needs is enormous. This plasticity depends on intact signalling pathways, many of which are now investigated as therapeutic targets in cancer treatment.[4,5]

Based on this, it should be expected that therapeutic trends in medical oncology will be associated with an increasing, rather than decreasing, incidence of cardiovascular side effects. Although our prime goal should still be to avoid these unwanted consequences of cancer treatment entirely, it is likely a more realistic goal to prevent serious, progressive cardiovascular side effects, while accepting reversible effects of cancer drugs on the cardiovascular system.[6]

The manifestation

The *clinical manifestations* of anti-cancer drug-associated cardiovascular side effects include the induction of

1. *Arrhythmias and QT prolongation* can be a problem with some of the newer cancer drugs. ECG monitoring is important, particularly in combination with other QT prolonging therapeutics.
2. *Pericarditis and Myocarditis*; Pericarditis is mainly associated with acute effects of anthracyclines (and radiation therapy) but seems to have no long-term consequences for the patient. In contrast, myocarditis can lead to severe progressive cardiac disease in patients treated with cyclophosphamide, but luckily this is rare.
3. *Vasoconstriction* and *Thromoboembolism*, potentially leading to ischaemia and arterial hypertension. Vasoconstriction of the coronary arteries is typically associated with 5-fluorouracil and its oral analogue capecitabine. Changing the infusion rate and supportive therapeutics, such as nitrates or calcium channel blockers, can frequently ameliorate or completely avoid these side effects. More concerning is early data from angiogenesis inhibitors which can induce arterial and venous thrombosis, potentially leading to ischaemia in vital organs. Furthermore, these compounds lead to arterial hypertension in a significant proportion of treated patients. Preventive and therapeutic strategies are currently being studied but many questions remain unsolved. If these drugs are

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ever to be used in the treatment of breast cancer outside of clinical trials, more data is needed to assess the risk. [7]

4. *Cardiac contractile dysfunction* and *heart failure*. Currently, the most serious cardiovascular side effects are cancer drug-induced cardiac dysfunction and heart failure. Recent data suggest, however, that not all drugs inducing cardiac dysfunction have the same long-term consequences for the patients. The anthracyclines are the classical example of cancer drugs leading to dose-dependent myocardial cell death. This initial damage can be compensated by activation of neurohormonal mechanisms and survival factors and frequently patients remain asymptomatic or minimally symptomatic early on. However, additional stresses such as age, hypertension, diabetes, cardiac conditions and late effects of radiation therapy can eventually lead to progressive cardiac disease and heart failure, typically years after the initial cancer therapy. All members of the anthracycline class exhibit this type of cardiotoxicity, although quantitatively the effect might be different among the members of the group. [1] In contrast to the anthracyclines, the cardiac adverse effects of anti-HER2 therapeutics mainly manifest during treatment, are dose-independent and characterised by a relatively high rate of reversibility. [3,6] Currently, the best data on the incidence of anti-HER2 induced cardiac side effects come from the adjuvant trastuzumab breast cancer trials where 0 to 4% of the patients experienced severe (NYHA class 3 and 4) heart failure and 3 to 18% cardiac dysfunction. [3] Although it is difficult to compare the cardiotoxicity of trastuzumab in the different adjuvant trials, it appears that 1. the type of pre-trastuzumab chemotherapy, 2. the time between chemotherapy and initiation of trastuzumab, 3. the left ventricular ejection fraction prior to trastuzumab and 4. pre-existing arterial hypertension influence the event rate. Data with a median follow-up time of approximately 4 years suggest that 80% of patients with trastuzumab-induced cardiac dysfunction improve their myocardial function over time. [8] However, preclinical experiments also indicate that anti-HER2 treatment can worsen anthracycline cardiotoxicity. [9] Since anthracycline toxicity frequently manifests only years after the initial treatment, long-term surveillance of the patients treated with anthracyclines followed by anti-HER2 therapeutics is warranted.

The patient

There is considerable variation of patients' susceptibility to cancer drug-associated cardiotoxicity and many factors responsible for cardiovascular side effects are still not known. The identification of individual patients who carry an increased risk therefore remains difficult and serial assessment of clinical parameters and cardiovascular function tests are necessary to detect early signals. Furthermore, the cardiotoxicity data for some of the newer drugs, namely the anti-HER2 and antiangiogenics, are still incomplete and the population tested was restricted to relatively young patients with no significant pre-existing cardiac conditions or other co-morbidities. Further research is needed to better understand the risk of patients who were excluded in these early trials.

The future

There is considerable activity in the field to increase the efficacy of breast cancer treatment by introducing new cytotoxic drugs and signalling inhibitors. The tendency to combine these compounds conceptionally will increase efficacy but is also likely to worsen cardiovascular toxicity, at least as long as these treatments are not targeted to the cancer cells. In addition, most of the currently used signalling inhibitors block the system high up in the signalling cascade. Since signalling in biological systems is redundant, alternative pathways can compensate for the inhibited signalling cascade, limiting the cardiovascular toxicity. The tendency to block multiple signalling pathways or to inhibit signalling low in the cascade will inevitably increase cardiovascular side effects. Furthermore, many of the new therapeutic targets in oncology are critically important for the plasticity and survival of the heart. Only a close collaboration between cancer and cardiovascular biologists, oncologists and cardiologists will allow increased efficacy of cancer treatments while ensuring the cardiovascular safety of our patients.

Conflict of interest statement

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References

[1] Gianni L, Norton L, Wolmark N, Suter TM, Bonadonna G, Hortobagyi GN. Role of anthracyclines in the treatment of early breast cancer. *J Clin Oncol* 2009;27:4798–808.

[2] Von Hoff DD, Rozencweig M, Layard M, Slavik M, Muggia FM. Daunomycin-induced cardiotoxicity in children and adults. A review of 110 cases. *Am J Med* 1977;62:200–8.

[3] de Azambuja E, Bedard PL, Suter T, Piccart-Gebhart M. Cardiac toxicity with anti-her-2 therapies: What have we learned so far? *Target Oncol* 2009;4:77–88.

[4] Bergh J. Quo vadis with targeted drugs in the 21st century? *J Clin Oncol* 2009;27:2–5.

[5] Hill JA, Olson EN. Cardiac plasticity. *N Engl J Med* 2008;358:1370–80.

[6] Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: Time to recognize a new entity. *J Clin Oncol* 2005; 23:2900–2.

[7] Elice F, Jacoub J, Rickles FR, Falanga A, Rodeghiero F. Hemostatic complications of angiogenesis inhibitors in cancer patients. *Am J Hematol* 2008;83:862–70.

[8] Procter MJ, Suter T, de Azamuja E, Muehlbauer S, Dafni U, van Veldhuisen DJ, Muscholl M, Piccart-Gebhart M. Assessment of trastuzumab-related cardiac dysfunction in the herceptin adjuvant (HERA) trial with 3.6 years median follow-up. *J Clin Oncol* (Meeting Abstracts) 2009;27:540.

[9] Timolati F, Ott D, Pentassuglia L, Giraud MN, Perriard JC, Suter TM, Zuppinger C. Neuregulin-1 beta attenuates doxorubicin-induced alterations of excitation-contraction coupling and reduces oxidative stress in adult rat cardiomyocytes. *J Mol Cell Cardiol* 2006;41:845–54.