CURRENT THINKING IN CARDIO-ONCOLOGY

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This article will highlight preclinical and clinical studies as well as new basic science models in cardio-oncology that were presented at this year’s “Heart Failure 2017 and 4th World Congress on Acute Heart Failure,” which was held in Paris, France from April 29, 2017 to May 2, 2017 and attended by over 5000 participants from about 100 countries. Two symposium sessions during the congress were dedicated to the field of cardio-oncology. In addition, 27 posters on this topic were presented. The congress provided a good forum for cardio-oncologists to share their newest research and exchange ideas. In order to understand the underlying mechanisms in cardio-oncology better, new preclinical models were presented at the congress. Due to the growing prevalence of cardiovascular and oncology disease in the industrialized world, cardio-oncology is of great interest.

Important findings at this year’s congress included a meta-analysis associating obesity with increased cardiotoxicity and a new mechanistic understanding of the receptor tyrosine-protein kinase erbB-2 and the oncometabolite d-2-hydroxyglutarate. Chemotherapies (like anthracyclines and trastuzumab) are associated with the development of heart failure, which is currently being studied extensively. Further emphasis was placed on the development of cardio-oncology clinical services and the associated hurdles, challenges, and opportunities. When heart failure during oncology treatment occurs, adequate treatment regimens by cardiologists and oncologists are needed to treat both heart failure and tumors at the same time. The overall message of the congress was that even more collaborative approaches between cardiologists and oncologists are needed to investigate new diagnostic and research options further for these patients.

BASIC SCIENCE

Many basic researchers are currently investigating the underlying mechanisms of chemotherapy- or radiation-induced cardiotoxicity. Today, there are many different approaches. Alexander Lyon (UK) discussed data by de Korte et al1 on the receptor tyrosine-protein kinase erbB-2, which is associated with cardiac injury. After four cycles of doxorubicin chemotherapy, these receptors were upregulated in cardiomyocytes due to stress on the myocardium, demonstrating that anthracyclines (namely doxorubicin) have cardiotoxic effects.

Heinrich Taegtmeyer (US) displayed new data from his group showing that mutant leukemic cells affected cardiomyocytes. They administered the oncometabolite d-2-hydroxyglutarate, which is produced by isocitrate dehydrogenase 2 mutant leukemic cells, to rodents for 5 weeks, which induced contractile dysfunction in the heart.2 Taegtmeyer proposed that cardiac dysfunction is promoted by d-2-hydroxyglutarate by inducing histone modifications through higher ATP citrate lyase activity and disrupting the function of α-ketoglutarate dehydrogenase. In another rodent model demonstrated by Kari Alitalo (FI), VEGF-B was able to prevent cardiac atrophy after administration of doxorubicin, while preventing loss of body weight at the same time.3 The antineoplastic effects of the chemotherapy were unchanged under the administration of VEGF-B; therefore, this treatment might be of further interest in the future.

In an effort to understand the underlying mechanisms in cardio-oncology further, a talk by Catherine Vergely (FR) focused on the role of obesity. In a rodent model with obese rats, obesity was associated with increased mortality. In one arm of the study, the rats were on a normal diet, and, in the other arm, the rats were on a high-fat diet. After 43 days, the rats on the high-fat diet gained 30% more in body weight than did the rats on the normal diet, and a sublethal dose (LD10) of doxorubicin was injected in both groups. In the normal weight group, 10% of the animals died within 25 days, but, in the overweight group, 80% died. In addition, in the overweight group, cardiac biomarkers, such as troponin and creatine kinase-MB, were significantly elevated within 2 days of administering doxorubicin.4 In alignment with this data is a recent meta-analysis by Guenancia et al,5 which included 15 studies and 8745 patients with breast cancer. The meta-analysis found an increased odds ratio for cardiotoxicity related to anthracycline and trastuzumab therapy in obese and overweight patients (BMI >25 kg/m2; OR, 1.38; 95% CI, 1.06-1.80). Therefore, their group proposed potential influences of adipokines on cardiomyocytes or mitochondria.

CHEMOTHERAPY-ASSOCIATED HEART FAILURE

Many large-scale trials have shown that heart failure is associated with cardiotoxic chemotherapy. Accordingly, a study by Erin et al6 was highlighted, which included 12500 patients with breast cancer. Depending on the chemotherapy used, the 5-year incidence of heart failure significantly differed. It was elevated in patients receiving only anthracyclines (adjusted HR vs patients without che-
motherapy, 1.40; 95% CI, 1.11-1.76) or trastuzumab (adjusted HR, 4.12; 95% CI, 2.30-7.42) and highest in patients receiving both anthracyclines and trastuzumab (adjusted HR, 7.19; 95% CI, 5.00-10.35). Furthermore, Alexander Lyon talked about the Persephone trial by Earl et al., which evaluated the frequency of cardiac events with 6 months vs 12 months of adjuvant trastuzumab treatment in 2500 female patients with confirmed HER2-positive, early-stage breast cancer. Of these patients, 93% were treated with anthracyclines, and, of these, 49% additionally received taxanes. In the 6-month group, significantly fewer cardiac events (defined by the alteration or introduction of new chronic heart failure medications or symptoms and/or signs of congestive heart failure) occurred. From a cardiologist’s point of view, the 6-month arm might be preferred, but the overall survival data has to be considered once published. The trial additionally identified risk factors for cardiac events and dysfunction when patients received cardiotoxic chemotherapy, including LVEF <55%, prior use of cardiac medications, >3 cycles of anthracyclines, and patients >70 years old.

In addition, new data was discussed in one of the sessions about the association of radiotherapy with the development of heart failure. Recently, in a case-control study on 59 breast cancer patients with radiotherapy-associated HFPEF, Saiki et al showed that HFPEF could be diagnosed after a median follow-up time of 6 years after the radiation therapy was initiated. Further, higher radiation doses were associated with a more frequent occurrence of HFPEF.

Nevertheless, cardiac biomarkers have also gained more interest. In the last years, studies have shown that they are important and useful in identifying patients at a higher risk of cardiac dysfunction. A study on 452 patients with breast cancer receiving trastuzumab by Zardavas et al was highlighted, which found evidence that elevated baseline levels of troponins I and T were significantly associated with cardiac dysfunction during therapy.

### REFERENCES


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