International Colloquium on Cardio-Oncology

Rome (Italy), March 12-14, 2014

Organized by

DEPARTMENT OF DRUG SCIENCES
AND CLINICAL PHARMACOLOGY
UNIVERSITY CAMPUS BIO-MEDICO OF ROME

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FONDAZIONE
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ABSTRACT BOOK

Hotel Columbus
Via della Conciliazione, 33

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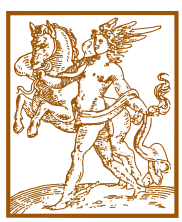

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ABSTRACT BOOK

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CONTENTS

Defining cardiotoxicity in pre-clinical models: Strengths and Weaknesses

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After having Chaired, and/or participated in, three (and now four) international meetings focused on cardiotoxicity of cancer drugs, I believe a consensus is growing that our pre-clinical models are helpful but not adequate to truly predict cardiotoxicity with the small molecule kinase inhibitors or to define mechanisms of injury. There are likely several reasons for this but one that seems to keep popping up is the lack of co-morbidities (hypertension, CAD, etc.) in the models we use. Strict management of hypertension with the VSP inhibitors has gained traction based, in part, on both clinical data and animal models.[1,2] Furthermore, Chen et. al found that the best predictor of progression to heart failure in patients taking sunitinib was the presence of CAD. These are not altogether surprising findings but highlight the critical need to bring co-morbidities into the equation. As maybe the ultimate example, we have created MI in our mouse models and have then treated them with sorafenib. There were a number of interesting findings (to be discussed) but key was profound heart failure in the MI/sorafenib-treated mice with some additional features.[3] These finding are consistent with our studies in zebrafish that readily detected cardio-toxicity with sorafenib and sunitinib.[4] Thus we are improving our models slowly but surely, but we still have a ways to go. Additional approaches will also be discussed.

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Defining cardiovascular liability of antitumor drugs in patients: What is the level of evidence?

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The incidence of adverse outcomes during the course of chemotherapy, such as congestive heart failure in doxorubicin recipients and hemorrhagic myocarditis with cyclophosphamide, have diminished in frequency through alterations in treatment strategies, but the late prevalence of cardiovascular complications remains significant. For example, late cardiovascular deaths account for 25% of the excess late mortality after childhood cancer. Progress in improving these outcomes depends on the ability to ameliorate cardiotoxicity without negatively impacting cancer cure rates. Although this issue is not limited to the anthracyclines, these agents have a large body of data concerning late outcomes. Early investigations into changes in myocardial histology manifest on myocardial biopsy demonstrated abnormalities accepted as evidence of toxicity even after 180 mg/m^2, with a dose-related increase in these histologic abnormalities, but these biopsy findings correlated poorly with clinical manifestations and outcomes. In contrast to the biopsy findings, the cumulative dose-related cardiomyopathy associated with doxorubicin demonstrates remarkable variability amongst individuals. To date, virtually all of the progress in toxicity reduction has been achieved by global reduction of cumulative drug dosage and co-administration of cardioprotectant agents. Successful individualized management based on dose modification in response to early laboratory evidence of cardiotoxicity remains elusive. For example, a fall in left ventricular ejection fraction during therapy was for some time accepted as evidence of clinically important toxicity, and cessation of drug in response to new onset ventricular dysfunction has been recommended, but there is still no evidence supporting the efficacy of this strategy in reducing all-cause mortality, an important consideration since the dose reduction may adversely impact cancer cure rates.

The poor performance of this approach may relate to the confounding effects of altered afterload and preload during the multifactorial hemodynamic variability that can be encountered in response to chemotherapy. Recent reports of newer methods purporting higher sensitivity for doxorubicin toxicity, such as altered strain rates on echocardiography and acute changes in serum biomarkers, have generally not been evaluated for their predictive capacity for clinically manifest toxicity. Abnormalities on imaging and clinical laboratory tests suggestive of cardiotoxicity could be valuable as surrogate outcomes in efforts to protect against late cardiovascular morbidity and mortality in cancer survivors, but prior to their acceptance their relationship to clinical outcomes must be verified.

Cardiotoxicity in children, adolescents, and young adults: pathophysiology, clinical course, and protection

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Advances in cancer treatment have greatly improved childhood cancer survival rates. Anthracyclines are commonly used to treat childhood leukemias and lymphomas, and other malignancies; however, their use is limited by cardiotoxicity, increasing survivors' vulnerability to treatment-related complications that can markedly affect their quality of life. Anthracyline-induced cardiotoxicity can cause persistent and progressive cardiovascular damage by mechanisms that are not yet fully understood. Survivors are more likely to suffer from heart failure, coronary artery disease, and cerebrovascular accidents compared to the general population. Identifying factors that may increase susceptibility to cardiotoxicity is of great importance. However, not all survivors are affected equally, despite receiving similar doses of anthracyclines, suggesting the possibility of genetic predisposition. Additionally, cardioprotective strategies that are currently under investigation include concomitant administration of dexrazoxane, the use of less toxic anthracycline derivatives, limiting anthracycline cumulative dose, and nutritional supplements. Evidence-based monitoring and screening that have been validated as surrogates of subsequent clinically significant cardiovascular disease before the occurrence of cardiac damage are also needed to identify early signs of cardiotoxicity, particularly in patients who may be at higher risk. Identifying the highest-risk patients may help inform the frequency of monitoring during and after treatment and identify those who would benefit most from other treatment and prevention options. The ultimate goal is to maximize the oncologic efficacy of anthracyclines and to minimize their late cardiotoxic effects in the vulnerable and less-studied population of childhood cancer survivors.

Late Cardiotoxicity in Survivors: The Role of Chronic Health Conditions

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In the general population, hypertension, diabetes, obesity, dyslipidemia, and smoking are primary contributors to the development of coronary artery disease and heart failure. While some cancer therapies increase risk for hypertension, diabetes mellitus, dyslipidemia, and obesity, many long-term survivors will develop traditional, modifiable risk factors related to aging, hereditary predisposition, or unhealthy lifestyle behaviors. It is therefore imperative to determine the extent that modifiable cardiovascular risk factors further potentiate cancer therapy-associated cardiac risk. A number of recent studies now suggest that acquisition of modifiable cardiovascular risk factors increases risk for major cardiac events, independent of cancer therapy-related risk. Moreover, among some survivors the observed risk may be greater than what would be expected under an additive assumption. The clinical implications of these studies are of importance as early diagnosis and appropriate management of hypertension, diabetes, dyslipidemia, and obesity in at-risk, aging survivors may substantially reduce the risk of premature cardiac disease in this high risk population.

Long-term risk of various cardiovascular diseases after different cancer treatments in adolescents and young adults

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Background: It is already known that Hodgkin lymphoma (HL) survivors are at increased risk to develop cardiovascular disease (CVD) after radiotherapy (RT) involving the heart and/or anthracycline-containing chemotherapy (CT). It is unclear, however, whether the increased risks of specific CVDs related to RT or anthracyclines persist after long-term follow-up and whether there are specific disease patterns in the occurrence of multiple CVDs. For most cardiac toxicities a clear quantitative radiation dose and/or volume dependence has not been shown yet, although the RT schedule, irradiated cardiac volume and irradiated structures are expected to be of great importance. There are also many questions about possible interactions between CT and RT. For instance, some studies report more than additive effects of anthracycline-containing CT and RT on CVD risk. Established risk factors for CVDs are also important to consider, especially because there are some indications that the effects of RT and smoking may be more than additive.

Methods: We performed a cohort study of 2,530 5-year HL survivors, diagnosed before age 51 and treated between 1965 and 1995. Extensive treatment data were collected from medical records and follow-up information was obtained from general practitioners and/or cardiologists until October 2013. CVD endpoints, i.e. ischemic heart disease (IHD), congestive heart failure (CHF) and cardiomyopathy (HF) and valvular disease were based on the CTCAEv4.0 grade ≥2. Cumulative incidences of CVDs were estimated accounting for death as a competing risk and risk factors for specific CVDs were evaluated using Cox regression. Standardized Incidence Ratios (SIR) were estimated to compare CVD risk with the general population. Descriptive analyses were used to study patterns of occurrence of multiple CVDs in individual patients.

Results: We identified 1209 CVDs in 747 patients, after a median follow-up of 20.4 years. After mediastinal RT, the 35-year cumulative incidence of CVDs was 45.2% (95%CI: 42.4%-48.0%), compared to 20.2% in patients not treated with mediastinal RT (15.7%-25.1%); $p<0.001$. After anthracyclines, the 30-year cumulative incidence of CHF was 16.0% (95%CI:11.8-20.8%), compared to 10.1% (95%CI: 8.6-11.8%) in patients not treated with anthrax-cyclines. The most frequently diagnosed first cardiac event was IHD, followed by valvular disease. 43% of CVD patients developed multiple CVDs. First IHD events were mostly followed by valvular disease, or a second IHD. CHF was mostly diagnosed as end stage CVD, after IHD and valvular disease (62% of CHF). Both mediastinal RT and anthracycline-containing CT increased the risk of any CVD (Hazard Ratio (HR): 3.3, 95%CI: 2.6-4.3 and HR: 1.5, 95%CI: 1.3-1.8, respectively). At 30-39 years after HL diagnosis, our patients had a 3.0–fold and 2.8-fold increased SIR of primary IHD (95%CI: 1.5-5.5) and CHF (95%CI: 0.8-7.2), respectively, compared to the general population, corresponding to 146 and 51 excess cases per 10,000 person years.

We used a a case-control design to investigate in detail treatment-related risk for factors for IHD (MI and angina pectoris) and valvular disorders after HL. Patients were included as a case when they had at least grade 3 CVD as a first event according to the CTCAEv4.0. Each case was matched to 2 controls on age at HL diagnosis, gender and year of diagnosis. Detailed data were collected from medical records and RT-charts. Furthermore, simulation films of radiation treatments were collected to perform radiation dosimetry (collaboration with Sarah Darby, Oxford).

For the valvular heart disease study we so far included 89 cases and 200 controls. Detailed radiation dosimetry has been performed by reconstructing RT on surrogate Computed Tomography (CT) data sets using a CT-based treatment planning system, including estimation of dose to the individual heart valves. The mean dose to the affected valve in cases and to the same valve in controls in equivalent dose of 2 Gray fractions (EQD2) was higher for cases than controls (37 vs. 30 Gray, $p=0.001$) and risk increased with higher radiation doses.

A linear model gave an excess odds ratio (OR) of 0.12 (95% confidence interval 0.02- 0.76) per Gray. However, this linear model did not fit the data well as there was evidence for an upward curvature at higher doses (p=0.011).
In the case-control study of ischemic heart disease (IHD) we included 180 cases with IHD and 499 matched controls. Mediastinal RT (usually performed using parallel opposed fields) was associated with an increased risk of IHD (OR: 2.6, 95%CI: 1.5-4.6). Higher prescribed radiation dose to the lower mediastinum was associated with increased IHD risk. As compared to patients who did not receive mediastinal irradiation, we observed increased risks of IHD for patients who received 20-34 Gy (OR: 1.8, 95%CI: 1.02-3.2), 35-39 Gy (OR: 1.8, 95%CI: 1.4-2.4) or ≥40 Gy on the mediastinum (OR: 3.2, 95%CI: 2.2-4.6) ($p<0.001$). No associations or interactions were found with (anthracycline-containing) CT.

Conclusion: Cardiovascular toxicity is an important side-effect of RT and combined modality treatments for HL. The persistence of increased risk over prolonged follow-up time is of concern. General risk factors for CVDs should be recognized and treated on indication. Modern RT techniques enable more accurate sparing of the heart. Further development of these techniques is of great importance because of the improved survival following many malignancies and the increased use of systemic treatment causing cardiovascular toxicity. Screening of HL survivors treated with cardiotoxic treatments is indicated.

Oncologic efficacy vs cardiotoxicity: Risk: benefit and cardiac prevention issues

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The use of chemotherapy to control cancer has resulted in dramatic improvements in the overall outcomes of patients with cancer. There has been tremendous advancement in the development of newer therapeutics each with more potency and newer molecular targets for cancer control. The cardiovascular system, one of the most metabolically active areas of the human body, is likely to be affected by anti- cancer therapies intended to impair cellular turnover or uncontrolled metabolism.
With this intrinsic struggle in mind, it is important to consider the balance of potential cardiac damage with ultimately cancer control. Most importantly, how can we ready our patients for battle and keep them in the fight if there are effective treatments for their cancer?

Some general steps to assist in the treatment planning are:

1. A critical piece necessary to prepare for aggressive treatment is adequate cardiac risk stratification. Asymptomatic heart disease is very common in a typical population being treated for cancer and early identification and management of common CV conditions is of paramount importance.

2. Ongoing optimal management of these identified CV conditions also has a major impact over the course of active treatment and in the survivorship phase of a patient's clinical course.

3. Sophisticated cardiac testing is an adjunct but cannot replace sound clinical judgement and active collaborative input.

4. Cardiac biomarkers, generally considered simple inexpensive and widely available tests, have provided enhanced risk identification strategies that can guide cardioprotective therapeutic choices.

5. Collaboration, with significant discussion among providers from different disciplines, is the future template for the best practice.

Older patients

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The population is aging- a virtual "tsunami" of cancer in the elderly. Besides its prevalence, cancer in the elderly presents special challenges because of pre-existing co morbidities, age-related changes in drug pharmacokinetics, altered physical and cognitive function, lack of social support and poorer response rates. In addition, the lack of enrollment of older patients with existing co morbidities, such as cardiac disease, onto clinical trials has limited the accumulation of evidence-based clinical knowledge.

Anthracycline-based chemotherapy improves survival in multiple solid and hematologic malignancies. Doxorubicin is the anthracycline used most frequently and its use is associated with, and often limited by, a risk of cardiotoxicity manifested by left ventricular dysfunction (LVD).

The following observations may provide management guidelines: First, toxicity is more likely to occur in the elderly and because of this, they are often undertreated. Second, asymptomatic toxicity is common and may progress over time to symptomatic LVD; diastolic dysfunction maybe the first clinical manifestation. Third, symptomatic LVD can occur with any exposure to anthracycline regardless of formulation and total dosing. Fourth, the risk of LVD tends to be highest in the first year. Subsequently, there is a latent period with prevalence increasing as the time after treatment completion increases. Fifth, there may be a cardioprotective effect from blocking the renin-angiotensin system. Sixth, LVD, when it occurs, is not clinically different from that caused by nonanthracyclines. Seventh, current evidence-based guidelines for the management of LVD can be applied to these patients. Eighth, cardiovascular management can be approached from the following three perspectives: first, primary prevention to give the oncologist every opportunity to optimally treat the underlying cancer; second, a proactive approach to early detection

to attenuate the potential of LVD; and third, apply modern treatment when there is any LVD, with or without symptoms.

The constant increase in cancer incidence and the projected explosive growth of the older population over the next 25 years are compelling forces driving us to answer critical questions of cancer care delivery for the future. These include, but are not limited to, the following: Can we accurately predict who will develop chemotherapy related cardiotoxicity? Can patients with underlying heart disease receive doxorubicin or other potentially cardiac toxic chemotherapy? How should we look for and manage patients with cardiotoxicity? Current assessment tools "ignore" underlying cardiac disease- Is there an assessment tool that can be specifically applied and be validated to this population for cardiotoxicity?

Cancer therapy in patients with pre-existing cardiovascular disease

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Increasing numbers of patients with cardiovascular disease (CVD) such as myocardial infarction and heart failure are surviving to develop malignancies, and these patients pose a special challenge to their cardiology and oncology providers. Pre-existing CVD in a patient newly diagnosed with cancer is likely to change the treatment options offered by some medical and surgical oncologists. A careful cardiological assessment should be done at that time and considerable discussion between cardiology and oncology provider is ideal to develop a collaborative plan that takes into account both the CVD and malignancy history, prognosis, ongoing therapies. Many commonly used medications for CVD may alter metabolism and transport of cancer therapies, including anthracyclines, and may therefore alter both their anti-tumor and cardiovascular effects. Other cancer treatments challenges for the health care team to consider are managing fluid status, neurohormonal blockade, and thromboembolic risk during cycles of cancer therapy that may promote fluid retention, change hemodynamics, and increase thrombosis or bleeding risk. Some familiarity with the medications used in oncology may improve the likelihood that a patient with CVD can be managed effectively during cancer treatment without an exacerbation. Specific examples of challenges for the Cardio-Oncology team will be discussed.

Patients with prior chemotherapy

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There are several potential cardiovascular problems in patients with cancer. Cardiotoxicity induced by chemotherapy (CT), however, represents an unresolved problem which strongly impacts on the quality of life and the overall survival of cancer patients. Cardiotoxicity is becoming increasingly important in the modern medical practice, in parallel with the increasing number of patients treated with CT, the development of new drugs with possible cardiotoxic effect, the increased survival time after CT, and the higher number of patients recovering from cancer. The most typical form of cardiotoxicity, a dilated cardiomyopathy (CMP), usually becomes manifest late in the course of the disease, and it is classically considered to be refractory to therapy. However, the response to modern heart failure (HF) therapy of CT-induced CMP has never been evaluated in clinical trials, and no definite guidelines are currently adopted. Although it is likely that medications used for other forms of CMP, in particular angiotensin-converting-enzyme inhibitors (ACEI) and beta-blockers, may be highly effective, there is still some unjustified concern to use them in cancer patients.

We have recently demonstrated that the time elapsed from the end of CT to the start of HF therapy (time-to treatment) with a combination of ACEI and, when tolerated, with beta-blockers is a crucial variable for recovery of cardiac dysfunction. Indeed, the likelihood of obtaining a complete left ventricular ejection fraction (LVEF) recovery is higher in patients in whom the treatment is initiated within 2 months of the end of CT. After this time limit, however, this percentage progressively decreases, and no complete LVEF recovery is observed after 6 months. We can therefore speculate that in most previously published studies, the poor response to heart failure therapy was possibly due to the under-use of modern drugs, and to the long (>12 months) time-to-treatment, i.e. when cardiac damage was not reversible.

This emphasizes the critical relevance of early detection of cardiotoxicity, and suggests that an aggressive approach based on the association of ACEI and beta-blockers should be considered in all cases of CT-induced CMP.

Moreover, the present definition of cardiotoxicity, based on the occurrence of heart failure symptoms and/or LVEF reduction, born in the oncologic setting decades ago, is obsolete by now. Indeed, it refers to identification of cardiac damage only after the onset of cardiac dysfunction, thus, not allowing for any early preventive strategy.

The cardiologist has always demonstrated to have low interest in the management of cardiovascular problems of oncologic patients, thinking that a small number of patients, with a short life expectancy, were involved. The survival rate of cancer patients, however, has greatly increased over the past twenty years, and those recovered from cancer represent today a growing population at higher risk for cardiovascular events.

In our view, cardiotoxicity is a cardiologists' business, and he/she has to be involved from the beginning of a CT treatment, sharing patients' management in close collaboration with oncologists. Guidelines regarding cardiotoxicity should be reviewed by oncologists and cardiologists together, in order to optimize management of cancer patients, and improve both oncologic and cardiologic outcomes.

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

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Background
Radiotherapy for breast cancer often involves some incidental exposure of the heart to ionizing radiation. The effect of this exposure on the subsequent risk of ischemic heart disease is uncertain.

Methods
We conducted a population-based case–control study of major coronary events (i.e., myocardial infarction, coronary revascularization, or death from ischemic heart disease) in 2168 women who underwent radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark; the study included 963 women with major coronary events and 1205 controls. Individual patient information was obtained from hospital records. For each woman, the mean radiation doses to the whole heart and to the left anterior descending coronary artery were estimated from her radiotherapy chart.

Results
The overall average of the mean doses to the whole heart was 4.9 Gy (range, 0.03 to 27.72). Rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray (95% confidence interval, 2.9 to 14.5; $P<0.001$), with no apparent threshold. The increase started within the first 5 years after radiotherapy and continued into the third decade after radiotherapy. The proportional increase in the rate of major coronary events per gray was similar in women with and women without cardiac risk factors at the time of radiotherapy.

Conclusions
Exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease.

The increase is proportional to the mean dose to the heart, begins within a few years after exposure, and continues for at least 20 years. Women with pre-existing cardiac risk factors have greater absolute increases in risk from radiotherapy than other women.

ONCO-cardiology: Horse before Cart.
Lessons from Long-term Follow-up of Survivors of Childhood Cancer

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Childhood cancer, collectively a group of rare malignancies, is curable in approximately 75% of patients, with even higher cure rates for relatively common diseases such as acute lymphoblastic leukemia (ALL), Hodgkin and non-Hodgkin lymphoma, and Wilms tumor. Amongst children cured, approximately 50% will have been treated with cardiotoxic anthracyclines. Rarely is anthracycline-related cardiotoxicity an acute clinical event; thus the role of the pediatric cardiologist is relatively minor during cancer treatment. Yet, pathophysiologically, sub-clinical cardiac toxicity, as measured by biomarkers, occurs with each dose of anthracycline. Long-term follow-up of adult survivors of childhood cancers has demonstrated progressive changes in echocardiographically-measured cardiac function, with evidence of an increased risk of developing very late-occurring congestive heart failure. The leading cause of death in adult survivors of childhood cancer is heart disease. And the leading cause of that heart disease is prior treatment with anthracycline. Long-term outcomes of anthracycline-treated children will be discussed, including a discussion on prevention of cardiotoxicity.

Genotyping for anthracycline induced cardiotoxicity and the level evidence

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Anthracycline induced cardiotoxicity after treatment for childhood cancer is a serious problem. Hundreds of studies have been performed to identify risk factors for this severe adverse effect. The cumulative dose of anthracyclines seems to be the most important risk factor. However, some children can even tolerate a high dose of anthracyclines of 500 mg/m^2 and some children will develop severe cardiotoxicity after a low dose of 100 mg/m^2. The observed individual variation in anthracycline cardiotoxicity can be explained by genetic susceptibility. Genetic variations in drug metabolizing enzymes and drug transport systems may lead to large differences in drug exposure between individuals resulting in toxicity.

One of the goals of research in the field of pharmocogenetics is to identify genetic variants that predict the occurrence of adverse effects. Pharmacogenetics can help to identify patients who are at risk to develop a severe adverse effect of a drug. Genetic variations in drug to metabolizing enzymes and in drug transport systems can lead to differences in drug exposure between individuals resulting in severe toxicity in some of these patients.

Many enzymes are involved in the metabolism and transportation of anthracyclines. Variation in enzyme efficiency due to genetic factors can increase the concentration of anthracyclines and the risk of cardiotoxicity. Several studies identified associations with specific polymorphisms and chemotherapeutic induced cardiotoxicity. However most studies were performed in small study groups and included a few candidate genes and have not been replicated. In one of our studies with a Canadian group we investigated 220 key genes involved in absorption, distribution, metabolism and elimination of anthracyclines.

We investigated these genes in a discovery cohort, a replication cohort and an independent cohort. We identified multiple genetic variants associated with anthracycline cardiotoxicity defined as a shortening fraction below 30% and symptomatic heart failure.

For future pharmacogenetic studies focussing on cardiotoxicity of anthracycline therapy it will be essential to achieve sufficient statistical power. A large number of childhood cancer survivors is needed to identify a higher number of genetic risk factors, especially when there is not a very large effect of each genetic factor. Furthermore it will be essential to use clinical relevant and valid outcome definitions and to take other factors that can increase the risk of cardiotoxicity into account.

For clinical practice it is too early to incorporate a genetic variant into a diagnostic test that will predict the cardiotoxic effect of anthracyclines in a child. Perhaps in the future prediction rules that take the genetic susceptibility and the other known risk factors into account can inform the individual patient and professional about the risk of anthracycline cardiotoxicity. For children with a high risk of anthracycline cardiotoxicity safer treatments can be provided.

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Identifying at-risk patients during therapy: biomarkers and many doubts

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The diagnosis of cardiotoxicity by the evidence of symptomatic heart failure (HF) or asymptomatic decrease in left ventricular ejection fraction (LVEF) precludes any chance of preventing its development. We recently demonstrated that the time elapsed from the end of chemotherapy (CT) and the beginning of HF therapy is of crucial importance in determining complete, partial or non recovery from anthracyclines (AC)-induced cardiomyopathy. This highlights the need for an early diagnosis of cardiac injury.[1] Today, by using troponin we have the opportunity to detect CT-induced cardiotoxicity at a very early phase, long before any reduction in LVEF has occurred. Troponin is the gold standard biomarker for myocardial injury from any cause. Its evaluation during high-dose CT permits the early identification of patients at risk of developing cardiac dysfunction (CD),[2] the stratification of cardiac risk after CT,[3] thus allowing for preventive therapy in selected high-risk patients.[4] More recently, we have also observed an increase in this marker in patients treated with standard doses of AC, and with new antitumoral agents. In particular, in trastuzumab-treated patients, troponin identifies patients at risk for cardiotoxicity who are unlikely to recover from CD, despite HF therapy, allowing us to distinguish between reversible and irreversible cardiac damage.[5] The possibility of identifying high-risk patients by means of troponin provides a rationale for targeted preventive strategies against cardiotoxicity. Indeed, a prophylactic treatment with enalapril, in patients with early troponin increase after CT seems to prevent CD and associated cardiac events not only in high-dose AC-treated patients,[4] but also in patients treated with standard dose AC and trastuzumab-containing regimens.

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Menarini Foundation Symposia: 244