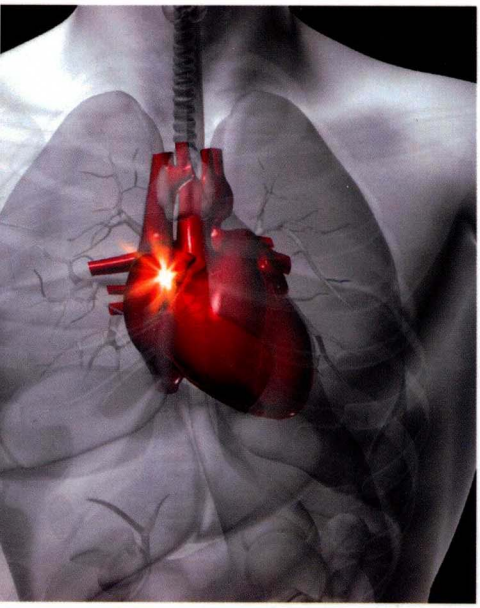
Anticancer Treatments and Cardiotoxicity

Mechanisms, Diagnostic, and Therapeutic Interventions



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Foreword

It was in early 2000 that a 60-year old woman was admitted to my service at the University Hospital in Bern because of severe heart failure. The patient was diagnosed with breast cancer 2 years earlier and treated with surgery and adjuvant chemotherapy. Unfortunately, several metastases were discovered at the end of 1999 and since the tumor was HER2-positive she was one of the first to be treated with a new, promising drug called *trastuzumab*. We quickly found out that the reason for her heart failure was a severely reduced left ventricular ejection fraction but her left ventricle was not dilated. We also knew that her cardiac function was normal prior to the start of *trastuzumab* and that she was previously treated with doxorubicin and cyclophosphamide. We had no evidence for any common reasons for acute heart failure and the dynamic of the events spoke against anthracycline cardiotoxicity. So we started to search for a more unusual cause for cardiac dysfunction and it took us a while to suspect *trastuzumab* as the key to explain what was going on. The literature about *trastuzumab* cardiotoxicity was scarce at that time and, not knowing if we would harm the patient more than helping, we opted for stopping *trastuzumab*. The patient improved quickly and her cardiac function recovered to normal within 6 weeks. It was a difficult decision to stop *trastuzumab* since the patient seemed to profit from the drug and therapeutic alternatives were limited—and our concerns became a harsh reality when the patient died a few months later because of progressive cancer.

These events prompted us to look deeper into the case of cancer drug-induced cardiotoxicity. The cardiac biopsies from the unfortunate patient gave us an opportunity to further investigate possible mechanisms and we found myocardial messenger RNA encoding for HER2 and HER4, establishing a potential link between the cancer drug and cardiac side effects. We also found that trastuzumab alone did not induce myocardial cell death in human cardiac tissue, explaining the reversibility of cardiac dysfunction in our patient. Many years later we have a substantially better understanding of trastuzumab-induced cardiac dysfunction and cancer treatment and cardiotoxicity in general. We have learned that some cancer drugs cause irreversible and progressive cardiotoxicity while others lead only to temporary, stunning-like dysfunction without long-term consequences for the patient.

But daily clinical decision-making in cancer patients experiencing cardiotoxicity remains complex. Most cancer regimens contain several drugs and it

is frequently difficult to identify those that cause side effects. And what should we do if these side effects become manifest? Should we immediately stop the potentially lifesaving cancer drugs and risk that the patient dies of cancer like our unfortunate woman? Or should we risk that the patient eventually experiences progressive cardiac disease introducing another life limiting health problem? We need to become smarter about the decision-making for our patients experiencing cardiotoxicity. We need experts who understand the complex pathophysiology of cardiotoxicity and clinicians and scientists who develop risk–benefit analysis tools to guide decision-making in clinical practice.

And this is where *Anticancer Treatments and Cardiotoxicity* comes to help. Patrizio Lancellotti and a dedicated group of experts have written a comprehensive book covering all aspects of cardio-oncology, including the important side effects of radiation therapy. This is one of few books that will help the clinician to come to the right conclusion when faced with a patient experiencing cardiotoxicity. But the authors do not stop here. They observe the tremendous progress in oncology with new drugs and treatments available at an exceedingly high pace. Several of these treatments bear the potential to cause cardiovascular harm. The book therefore also looks into the future and discusses research priorities to tackle these issues. I can only hope that every oncologist, every cardiologist, and every aspiring scientist in the area of cardio-oncology will read this book.

Thomas M. Suter

Preface

The goals of anticancer therapies are to prevent recurrence, prolong life, and provide cure. Partly due to improvements in treatment, the population of cancer survivors is large and growing. However, cancer treatment-related cardiotoxicity is the leading cause of treatment-associated mortality in cancer survivors. It is one of the most common posttreatment issues among 5–10-year survivors of adult cancer. Moreover, patients treated with cardiotoxic cancer therapies often develop multiple risk factors, further worsening cardiovascular reserve and increasing the likelihood of subsequent cardiotoxicity. The extent of cardiotoxicity is variable, depending on the type of drug used, combination with other drugs, prior mediastinal radiotherapy, and the presence of cardiovascular risk factors or history of heart disease. Early detection of the patients prone for developing cardiotoxicity is the key issue to decrease morbidity and mortality. It also facilitates more tailored therapeutic interventions. Therefore, the collaboration and interaction of cardiology and oncology may contribute to reducing the cardiovascular adverse effects and improving the results in the treatment of patients with cancer. Effective therapies to treat cancer and cancer therapy-induced cardiotoxicity must either take advantage of tissue-specific differences or affect the downstream mediators of toxicity, and there are active studies under way to develop new targeted therapies. Other effective therapies for cardioprotection include typical pharmacologic therapies used in cardiovascular disease that promote increased cardiac reserve and reverse remodeling under the stress of cancer therapy.

This book on *Anticancer Treatments and Cardiotoxicity* discusses the different aspects of cardiac effects of both radiotherapy and chemotherapy as well as diagnostic and imaging studies to evaluate/predict the development of cardiac dysfunction. New guidelines on imaging for the screening and monitoring of these patients are discussed. The book is highly illustrated. Most chapters contain a number of illustrations and tables.

Patrizio Lancellotti
Maurizio Galderisi
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Preamble

In the last decade, the therapeutic management of patients with cancer, traditionally including multiple combination of drugs, radiation therapy, and surgery, has been strongly enriched by the introduction of molecularly targeted therapies. This has led to an important reduction of morbidity and mortality of several kinds of cancer, increasing remission rate and often converting cancer into a chronic disease [1]. Nowadays, millions of cancer patients around the world are surviving long enough to develop adverse cardiovascular complications, which may become the cause of premature mortality and alter substantially the quality of life of these patients [2]. Therefore, cancer and heart are inextricably associated, including in relation to shared risk factors and diseases coexistence.

Both conventional chemotherapeutic agents, such as anthracyclines, and newer targeted agents, such as trastuzumab, can cause varying degrees of cardiac dysfunction [3]. Type I cardiac toxicity, typical of anthracyclines, may be acute or chronic, appearing even several years after therapy completion. It is dose-dependent and largely irreversible since it induces cellular necrosis. Type II cardiac toxicity, typical of newer targeted agents such as trastuzumab, is not dose-dependent and is generally reversible with cessation of the drug since it does not lead to cellular necrosis. It is noteworthy that types I and II cardiac toxicity can be associated sequentially in the same cancer patient (e.g., breast cancer) cumulating the effect of one of the drugs to the other. Accordingly, several cardiovascular adverse effects can become clinically overt years or even decades after receiving the cancer therapy: congestive heart failure, myocardial ischemia, systemic and/or pulmonary arterial hypertension, thromboembolic complications, arrhythmias, and conduction disturbances can all be clinical manifestations of these adverse effects [1,2,4]. This is particularly true for adult survivors of childhood cancers.

Also, the effect of radiation therapy shall not be underevaluated, in particular in some kinds of cancers, which are managed by irradiation of the neck and/or thorax (mainly, lymphoma and breast cancer). Radiation-induced heart disease comprises a spectrum of cardiac pathology including myocardial fibrosis and cardiomyopathy, coronary and carotid artery disease, valvular disease, pericardial disease, and arrhythmias. Tissue fibrosis is a common mediator in radiation-induced heart disease. Multiple pathways converge with

both acute and chronic cellular, molecular, and genetic changes to result in fibrosis [5]. The total cumulative dosage of radiation is a function of the number of treatments and the dose of irradiation. Although they may acutely develop, the manifestations of radiotherapy most often become clinically evident several years after irradiation.

In addition to the adverse cardiac effects produced by cancer and radiation therapies, some kinds of cancers can themselves produce detrimental effects on the cardiovascular system inducing alterations of pericardium (mainly pericardial effusion till cardiac tamponade) myocardium (myocarditis), and cardiac valves (primary or secondary localization on valve structures), with a varying degrees of hemodynamic impairment, but also producing cardiac metastasis [4].

In this panorama, the substantial importance of diagnosing the onset of clinically overt toxicity on the heart is equal to the importance of detecting subclinical cardiotoxicity in order to develop cardioprotective strategies and avoid, whenever possible, cancer therapy withdrawal. Monitoring of cardiotoxicity exclusively based on symptoms onset assessment may in fact miss the opportunity to identify early cardiac injury that is still in a reversible stage. Potential strategies to mitigate the risks of cardiac complications for cancer patients include physical examination, electrocardiogram, and use of biomarkers and/or cardiac imaging [4]. Echocardiography and biomarkers such as cardiac troponins and, to a lesser extent, brain natriuretic peptide, are current means to detect presymptomatic cardiac damage and evaluate cardioprotective treatments. The next standard echocardiography, advanced ultrasound techniques can provide an additional diagnostic power. Speckle tracking echocardiography-derived global longitudinal strain has been demonstrated in fact to be altered as the effect of cancer therapy when left ventricular ejection fraction is still normal [4]. When compared to standard 2D echo, real-time 3D echocardiography provides much more reproducible estimation of ejection fraction and can therefore be used successfully to achieve early detection of cardiotoxicity in cancer patients [4]. The more sophisticated cardiovascular magnetic resonance can be taken into account in selected cases to highlight the presence of subtle cardiac abnormalities and myocardial fibrosis (late gadolinium enhancement) or when echocardiographic images are not adequate. While the more prominent role of biomarkers or cardiac imaging remains controversial, combined use of both approaches can also be suggested since the two strategies have already shown a complimentary diagnostic power, which is superior to that of the two separate approaches [4].

The treatment of cardiac toxicity is largely influenced by the comorbities in which the damage is diagnosed. The general principles utilized in the treatment of cardiac dysfunction in all cardiac patients (i.e., adequate diet, exercise and weight control, use of cardiac drugs such as beta-blockers and renin–angiotensin system inhibitors, selective use of aldosterone antagonists) can be

considered equally important in cancer survivors experiencing cardiac toxicity. Nevertheless, conclusive data supporting the efficacy of these interventions are limited.

The reflection of strategies able to unmask subclinical cardiotoxicity on the cardiac management of patients undergoing cancer therapy has to be still definitely proven in the clinical setting. Data in selected centers highlight however that early detection of cardiotoxicity can lead to an early aggressive pharmacologic approach based on the use of ACE inhibitors and/or beta-blockers, which has been shown to be successful in anthracycline-related cardiotoxicity [6]. Data on the efficacy of cardiac drugs among childhood cancer patients are much more limited.

True prevention of overt cardiotoxicity begins before cancer therapy administration: a baseline assessment of cardiovascular health and effective treatment of cardiovascular conditions and effective treatment of cardiovascular risk factors are needed to prevent most late cardiac toxicities. Aspirin, effective control of dyslipidemia and of blood pressure in hypertensive patients, as well as cigarette smoking cessation are interventions that should be aggressively promoted when needed.

Combined together, all the above-mentioned findings, suggestions, and/or recommendations emphasize that an increased collaboration between cardiologists and oncologists is needed to determine the best treatment and the best preventive strategies that could improve the cardiac health of individual patients [7]. This means increased knowledge of the mechanisms responsible for cardiotoxicity of traditional and novel cancer therapeutics from the cardiologic side and the search for a continuous interaction with cardiologists from the oncologic side, in order to achieve the best methodology for cardiovascular prediction and risk stratification. A growing clinical demand is now producing the planning of dedicated cardio-oncology programs, which include diagnostic, interventional, and advanced heart failure services.

The present textbook has been created and developed on these grounds, to give access to both cardiologists and oncologists on the state of the art and perspectives of the interdisciplinary cardio-oncology clinical care. It includes general considerations on epidemiology and description of mechanisms underlying cardiotoxicity and radiotherapy, of detection of clinical and subclinical toxicity due to cancer therapeutics by both cardiovascular imaging and biomarkers in both adults and in childhood, presentation of traditional and innovative nonpharmacological and pharmacological management of anticancer drug-related cardiotoxicity as well as of a multidisciplinary approach to cardiac disease in cancer patients. Future research priorities, including pharmacogenomic screening, cardiac monitoring during clinical trials, and novel preventive therapies will be also presented as the new frontiers of a cardio-oncology approach to cancer patients and survivors.

Maurizio Galderisi and Patrizio Lancellotti

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How Big Is the Problem? The Oncologist's View

Fortunately, over time, the chance of cure after the diagnosis of cancer is improving. This is related to earlier diagnosis by screening or by earlier consultations and improved diagnostic procedures and more effective treatment options. Today, the oncologists are more and more concerned by the long-term side effects. Cardiac side effects are among the most frequent severe long-term side effects. Historically, it is well known that chemotherapy, radiotherapy and in particular the combination of both treatments exposes the patient to increased risk of cardiac morbidity and mortality. It has been shown more recently that some targeted therapies are also associated with increased risk of cardiac events [1,2]. Treatment decisions in the metastatic setting take mainly the short-term poor oncological prognosis into account. However, the situation is more complicated in the adjuvant setting. We frequently see now small tumors with an 80–90% probability of cure without using cardiotoxic chemotherapy or radiotherapy. The adjuvant therapies can further increase the chance of cure by 3–10% but we have to take into consideration treatment-related short- and long-term morbidity and mortality.

One of the problems is that some of these events are observed very late after the initial therapy. Consequently, it takes a very long time before these late side effects of alternative treatment options are known. Treatment modalities have changed over time in part because the awareness of cardiac side effects has increased. Chemotherapy regimens tend to include a lower cumulative dose of anthracyclines and radiotherapy fields try to avoid the cardiac region. We speculate that these modifications will have a major impact on a decrease of long-term cardiac side effects but we will really know only many years later. Unfortunately, we are facing also major problems with funding in long-term patient follow-up. Industry-sponsored clinical trials cut in general any support after 10 years of follow-up. The organization of clinical trials in the field of radiotherapy is even more challenging as there is no financial support coming from the industry either for the initiation or for the long-term follow-up. Administrative work in clinical

trials is continuously increasing, even in academic trials, making clinical research more and more expensive.

We have only limited follow-up for targeted therapies used more recently also in the adjuvant setting, such as trastuzumab in breast cancer. For the earliest studies we have a 10-year follow-up. Nevertheless, longer follow-up is needed. We have also to take into account that patients included in these studies are highly selected and in particular younger than the average patient population. Results concerning cardiac outcome in less selected patient populations including in particular a higher number of older patients are also urgently needed. This need is further illustrated by an Italian multicenter prospective evaluation of trastuzumab-induced cardiotoxicity [3]. Four hundred and ninety-nine consecutive HER2-positive patients suffering from early-stage breast cancer were treated with adjuvant trastuzumab and chemotherapy at 10 Italian institutions. Clinical heart failure occurred in 6% of the patients older than 60, compared to 2% of the younger patients. A reduction in left ventricular ejection fraction (LVEF) of >10 points was detected in 33% of the older compared to 23% of the younger patients. They have also observed that anticancer therapy was interrupted in 10% of the older patients compared to 4% of the younger patients. Another even larger population-based study using the SEER-Medicare and the Texas Cancer Registry-Medicare databases in women at least 66 years old suffering from early-stage breast cancer treated with chemotherapy reported a very high rate of congestive heart failure (CHF) [4]. Among a total of 9535 patients who were evaluated, including 23.1% receiving trastuzumab, the incidence of CHF was 29.4% if they received trastuzumab and 18.9% in those who did not received trastuzumab.

We should better identify the high-risk patients because long-term side effects become an increasing concern in oncology. Multidisciplinary treatment planning is a standard in oncology. However, currently, the experts participating in multidisciplinary discussions are mainly experts in the field of diagnosis and treatment in oncology. It is easy to have access to imaging procedures such as heart ultrasound or MUGA. It is much more challenging to have access to a consultation of a geriatrician or cardiologist with special interest in oncology at the time of treatment planning.

Most patients don't present cardiac abnormalities at the time of diagnosis but they appear during long-term follow-up. Even oncologists well aware of the cardiotoxicity of our treatments need the help of cardiologists to best interpret the available literature and to predict the cardiac risk for an individual patient. Age is not the only risk factor [5]. Data from retrospective studies also suggest an association between cardiovascular risk factors such as history of hypertension, diabetes, or known coronary artery disease and cardiotoxicity of anticancer therapy [6–7]. Sometimes, based on this advice and according to the oncological risk, we will consider either cancellation of

adjuvant therapy or, at least for systemic therapy, consideration of alternative therapy regimens which are less cardiotoxic, even if the relative risk reduction of cancer relapse may be a little lower. Time has come to create real cardio-oncology units where cardiologists and oncologists work closely together. All aspects should be considered: identification of patients at risk of developing cardiotoxicity, close monitoring of patients during treatment (such as patients receiving trastuzumab as adjuvant therapy for HER2-positive breast cancer) and long-term follow-up, including in particular optimal therapy in patients who develop toxicity.

Currently, this close collaboration mainly exists already for monitoring of cardiotoxicity during treatment. Clear guidelines for monitoring and therapy interruption exist in particular for adjuvant therapy with trastuzumab. Fortunately, these guidelines are largely followed in the clinic because cardiotoxicity is reversible in most cases if identified early. In many patients treatment can even be successfully reintroduced after interruption without observing a new event of cardiotoxicity [8]. Nevertheless, we still identify a need for earlier identification. Current guidelines are mainly based on decrease of LVEF or CHF. Serum biomarkers and more sensitive imaging techniques should be further evaluated [9]. LVEF recovery and cardiac event reduction may be more frequently achieved when cardiac dysfunction is detected early and a modern heart failure treatment is promptly initiated [10]. In addition, it is useful to point out that these guidelines are not really evidence-proofed but the reproduction of cardiac monitoring during the evaluation of a new potentially cardiotoxic drug in the registration trials. Cost-effectiveness has not been evaluated. More individualized monitoring according to risk factors should also be considered.

Among the major open questions is the role of angiotensin-converting enzyme (ACE) inhibitors in the prevention of trastuzumab-related cardiotoxicity [11]. Beta-blockers are other candidates for preventive treatments [12]. Today we consider anthracycline-free regimens and sequential use of chemotherapy and trastuzumab in patients with higher risk of cardiotoxicity but many consider this not the best treatment, in particular for high-risk patients [13]. If a preventive therapy by an angiotensin-converting enzyme inhibitor would be effective, this could be an alternative if physicians prefer the use of anthracycline-based chemotherapy followed by combined therapy with taxanes and trastuzumab in all high-risk patients. Close collaboration between oncologists and cardiologists is needed if we wish to further develop this kind of treatment strategy.

Patients with a history of cardiovascular disease are excluded from clinical trials evaluating cardiotoxic drugs. As life expectancy is increasing, many of these patients develop cancer. Sometimes, in the real world, the only remaining treatment options are based on cardiotoxic drugs. Unfortunately, no data are available to better differentiate between relative

and absolute contraindications. We need the help of cardiologists in order to decide on an individual basis the anticancer therapy and cardiovascular monitoring. There is an urgent need for a prospective register of outcome in these difficult clinical situations.

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