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REVIEW

EACVI/HFA Cardiac Oncology Toxicity Registry in breast cancer patients: rationale, study design, and methodology (EACVI/HFA COT Registry)—EURObservational Research Program of the European Society of Cardiology

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The goal of adjuvant anti-cancer therapies is cure with limited or no side effects, in particular long-term side effects with negative impact on quality of life. In the palliative setting disease control, quality of life and overall survival are important end points. Partly due to improvements in treatment, the population of cancer survivors is large and growing. However, anti-cancer drug-related cardiotoxicity (ADRC) is the leading cause of treatment-associated mortality in cancer survivors. It is one of the most common post-treatment problems among 5- to 10-year survivors of adult cancer. This is particularly true for breast cancer, the most common cancer in women. The EACVI/HFA COT registry is designed for comprehensive data collection and evaluation of the current European practice in terms of diagnosis and management of ADRC in breast cancer patients. The COT registry will be carried out in two continuing phases, the pilot study phase involving 13 countries followed by the long-term registry in which all the 56 ESC countries will be invited to participate. With the COT registry, several critical information will be obtained: on predisposing factors for the development of ADRC, the rate of subclinical LV dysfunction and its transition to overt heart failure, the clinical impact and outcome of ADRC.

Keywords breast cancer • chemotherapy • cardiac toxicity • left ventricular function • biomarkers

Cardiac toxicity of anti-breast cancer treatments

In the last decade, the cancer treatment has progressed considerably, by the introduction of targeted therapies, which increase cure and remission rate and convert cancer into a chronic disease.[1] The final result is an emerging cohort of millions of patients who will have a sufficient expectance of life to experience cardiovascular (CV) adverse effects of the anti-cancer therapies. This is particularly true for breast cancer, the most common cancer in women (464 000 new cases in Europe during 2012).[2] The introduction of adjuvant therapy (anthracyclines, taxanes, and, for patients with human epidermal growth factor receptor 2 (HER2)-positive disease, trastuzumab) remarkably improved both disease-free survival and overall mortality.[3,4] Age-adjusted 5-year survival among European women diagnosed with breast cancer from 2000 to 2002 is ~79%.[5] The prolonged

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survival resulting from cancer treatment allows patients to live long enough that cardiac toxicity can be the main determinant of quality of life and in some cases of premature mortality.[6] Patients suffering from T1a-b N0 M0 breast cancer are at higher risk to die from heart disease than from the cancer itself.[7]

Although a number of therapies used in breast cancer patients are cardiotoxic,[8] most attention focuses on anthracyclines and on trastuzumab,[9] which are largely used in the adjuvant setting.[10]

Anthracyclines (such as doxorubicin), currently combined with cyclophosphamide as a first-step therapy, directly damage the myocardium through production of oxygen free radicals. This leads to necrosis and apoptosis of cardiac myocyte, subsequent left ventricular (LV) dysfunction, and, in some cases, to irreversible cardiomyopathy.[11] Anthracycline-related cardiotoxicity (*cardiotoxicity type 1*) is irreversible, cumulative, and dose dependent, with an incidence of overt heart failure (HF) of at least 2.2% of breast cancer patients receiving doxorubicin at 390 mg/m^2 median dose.[12] Anthracycline-induced cardiomyopathy has been associated with a 2-year mortality of up to 60%.[12,13] The cardiotoxic effects of anthracyclines can be potentiated by adjunctive chest irradiation.[14] Risk factors for anthracycline-related damage include prior use of these drugs, prior or current history of cardiac dysfunction, coronary artery disease, arterial hypertension, and age.[15]

Trastuzumab is a humanized monoclonal antibody against the extracellular domain of HER2 and is part of the standard treatment for breast cancer with HER2 overexpression and/or amplification. A series of large-scale studies has conclusively shown that trastuzumab can substantially reduce the risk of recurrence and early death in women with HER2-positive breast cancers. However, trastuzumab significantly alters the expression of myocardial genes for DNA repair, which is associated with ultrastructural alterations in cardiomyocytes, and also promotes oxidative stress and apoptosis of myocardium.[16,17] Type II cardiotoxicity from trastuzumab is not tied to cumulative dose but to number of treatment sessions, manifesting as a decrease of LV systolic function, which is more reversible than anthracycline damage. Trastuzumab also increases the risk of cardiac side effects in patients with pre-existing forms of heart disease in which the cardiac stress signals are presumably already activated.[18] Trastuzumab-induced HF occurs in up to 4% of patients treated with the antibody, whereas ~14% of patients have a drop in LV ejection fraction (LVEF) responsible for therapy discontinuation.[19]

In breast cancer patients, trastuzumab is often used sequentially after anthracycline therapy completion. This sequential combination is potentially dangerous since trastuzumab potentiates the anthracycline cardiotoxicity. Combining anthracyclines with trastuzumab in the metastatic setting can cause severe HF in 27% of cases, compared with 13% taking paclitaxel (taxanes) and trastuzumab, and <7% expected taking anthracyclines alone.[20]

Rationale for the Cardiac Oncology Toxicity (COT) Registry

In the abovementioned clinical context, several issues remain controversial. First of all, by selecting breast cancer patients with a few co-morbidities, some clinical trials reported fairly low rates of protocol-defined cardiotoxicity.[3,21] These data raise concerns about type 1 and 2 cardiotoxicity prevalence. On the other hand, a substantial fraction of breast cancer patients experience asymptomatic alterations in LVEF with both anthracyclines and trastuzumab.[22–24] Although these alterations are considered to be largely benign and reversible within a period of 2–4 months after trastuzumab discontinuation, irreversible LV systolic dysfunction has been documented in up to 40% of patients treated with trastuzumab after anthracycline.[25] The rate, clinical meaning, evolution and persistence of these asymptomatic changes do not appear to be fully elucidated.

Echocardiography, brain natriuretic peptide (BNP), and cardiac troponins are investigational means to detect pre-symptomatic LV damage and evaluate cardioprotective treatments.[26–30] Monitoring cardiac function before, during, and after treatment helps doctors to detect early cardiac damage, enabling regimen modifications. This strategy is, however, controversial too, and in the absence of clear guidelines, practice varies widely. Also, the definition of asymptomatic LV systolic dysfunction varies according to studies and centres.

In addition, early treatment of LV dysfunction is important, considering the correlation between the onset time of LV dysfunction treatment and recovery (the faster the treatment, the better the results). An asymptomatic decrease in LVEF is an indication for therapy with β-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the management of HF in adults according to current ESC guidelines.[31] The cardioprotective effect of these drugs in breast cancer patients undergoing chemotherapy has been recently highlighted.[32–35] However, nearly all the corresponding studies are observational/retrospective, limited in sample size and not randomized. Moreover, to date, many cancer survivors are not receiving treatment, in disagreement with HF guidelines.

Further, the limited data available on presentation and management of patients with ADRC are derived mainly from clinical trials that—because of stringent exclusion criteria—do not reflect the current daily practice. To date, information on ADRC in breast cancer patients is largely variable or incomplete.[36] Also, information on cardiac imaging practice for the detection and follow-up of ADRC as well as on how imaging and biomarkers are integrated into clinical routine in Europe is lacking. Hence, a comprehensive systematic clinical assessment of breast cancer patients with ADRC in a large European registry compiling all relevant information would help to better understand how serious this disease is and how ADRC is managed and affects the outcome and quality of life of these patients in the real world. Such a registry could represent a substantial opportunity for collaboration between oncologists and cardiologists and the basis of the development of specific ADRC studies and guidelines.

Objectives of the COT Registry

The EACVI/HFA COT registry has been designed to examine clinical, cardiac imaging and treatment practices for ADRC in breast cancer in Europe. The main scopes are as follows: (i) to define risk factors, clinical profiles and epidemiology associated with ADRC; (ii) to determine clinical outcome and predictors of ADRC; (iii) to report the proportion of asymptomatic and symptomatic ADRC; (iv) to describe the time course of ADRC according to the initiation of chemotherapy; (v) to record the current standards for diagnostic workup (cardiac imaging/biomarkers) and clinical follow-up of patients; (vi)

to assess the changes in treatment regimen (completion of planned chemotherapy)/therapy (adjunctive drugs) related to ADRC and their impacts on ADRC; (vii) to describe the types of cardioprotective drugs and other treatment approaches used for ADRC; and (viii) to evaluate treatment adherence to ESC guidelines for HF or asymptomatic LV dysfunction.

Study design

The EACVI/HFA COT registry is a prospective, multicentre [European countries, homogenously distributed across Europe (North, South, East, Central/West)], observational study of patients presenting to imaging labs according to an oncologist's request and followed by cardiology or oncology centres in European countries (*Table 1*). The registry is performed under the umbrella of the EURObservational Research Program (EORP) of the European Society of Cardiology (ESC) (https://www.eorp.org/) and will be carried out in two continuing phases, the short pilot study phase followed by the long-term registry. To note, about one-fourth of the participating centres hold EACVI laboratory accreditation/individual certification in echocardiography. Consecutive breast cancer patients treated or to be treated by chemotherapy or any other anti-cancer treatments with known potential cardiac toxicity undergoing a cardiac imaging test for routine surveillance of LV function or evaluation of HF symptoms or suspected ADRC with or without confirmed LV dysfunction will be enrolled in the registry (*Figure 1*). Exclusion criteria include all patients with a history of pre-chemotherapy LV dysfunction. Duration of the enrolment period will be 12 months.

Collected variables and follow-up

Baseline data for each enrolled patient will include demographic characteristics, risk factors for CV diseases, co-morbidities including cancer history, clinical signs and symptoms, data on LV function and method of measure, types of biomarkers (troponin, BNP) used, current use of cardiac pharmacological treatments, chemotherapy, radiotherapy and breast surgical history and reconstruction surgery. A follow-up within 30 days, 6 and 12 months will be scheduled for all patients. A longer follow-up (5-year) will be obtained in the long-term registry.

The follow-up data will be captured by phone or during a visit to the centre for each enrolled patient and consists of monitoring regimen, types of cardiac imaging applied [(Echo [2D/3D], contrast, strain imaging), nuclear cardiology with MUGA (Volumes, LVEF, Perfusion), cardiac magnetic resonance (CMR) (function, fibrosis), stress test (contractile reserve)], types of biomarkers used (troponin, pro-BNP), evolution of LVEF (improved, stable, worsening), clinical signs and symptoms of HF, cause of death, cardioprotective drugs used (e.g. iron chelatordexrazoxane, β-blockers, ACE inhibitors, angiotensin receptor blockers, statins), and reasons for non-prescription of drugs (also recommended dosage) with a Class I recommendation in HF. If possible, a comprehensive echocardiographic evaluation will be obtained at the end of the follow-up study.

Table 1 Invited countries and national co-ordinators

Invited country	Name of national co-ordinator
Belgium	Guy Jerusalem
France	Erwan Donal Gilbert Habib
Germany	Andreas Hagendorff
Greece	George Athanassopoulos
Hungary	Laszlo Gellér
Italy	Maurizio Galderisi
Norway	Thor Edvardsen
Poland	Edyta Plonska-Gosciniak
Portugal	Nuno Miguel Cardim
Romania	Bogdan A. Popescu
Russia	Simon Matskeplishvili
Spain	Pepe Zamorano
UK	Madalina Garbi

Statistical analysis

Considering the explorative and observational nature of the current study, no formal sample size will be calculated. All the patients enrolled will be included in the analyses. Normal distribution of variables will be verified using the Kolmogorov–Smirnov test. Normally distributed continuous data will be expressed as mean values ($\pm$SD). Non-normally distributed continuous data will be expressed as median (inter-quartile range). Differences between groups will be analysed for statistical significance with the one-way analysis of variance (ANOVA), χ^2 test, or Fisher exact test as appropriate. Categorical variables will be reported as percentage. Non-normal data (e.g. troponin, BNP) will be logarithmic transformed before correlative analysis. Multivariable statistical models will be used to explore the relationships between baseline covariates and post-baseline predefined end points, as appropriate. A value of $P < 0.05$ will be considered as statistically significant.

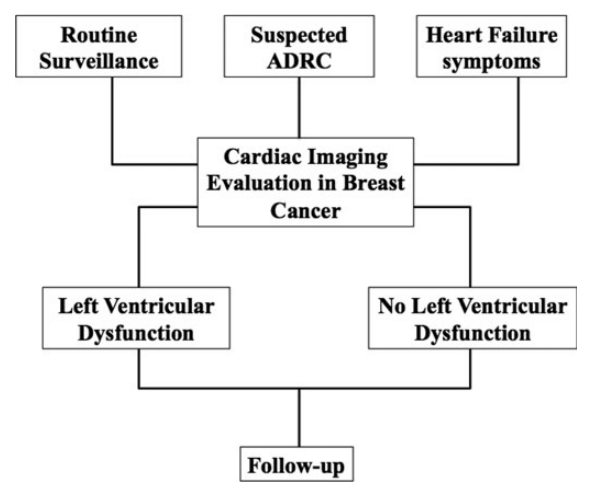

Figure 1 Study population selection and imaging entry point into the EACVI/HFA COT registry. Left ventricular dysfunction refers to a significant drop in left ventricular systolic function.

Ethical committee

The EACVI/HFA COT registry will be conducted according to the rules for research in human subjects. Protection of privacy with regards to processing of individual data will be ensured according to the National rules for observational research. The institutional ethical committee of the participating centres will approve the project. Local Institutional Review Boards will approve the study, and all patients will sign an informed consent in accordance with privacy respect and national and local guidelines.

Discussion

The EACVI/HFA COT registry is a centre-based data collection designed for comprehensive evaluation of the current European practice in terms of diagnosis and management of ADRC in breast cancer patients. The COT registry will be the first study to collect sizeable observational contemporary data on cardiac toxicity and ADRC-related subclinical LV dysfunction in relation and independent of co-morbidities on a large sample size of breast cancer patients within European countries in the real-life setting. With the COT registry, several critical information will be obtained: predisposing factors for the development of ADRC, rate of subclinical LV dysfunction and its transition to overt HF, clinical impact and outcome of ADRC.

Overall, the EACVI/HFA COT registry will serve to confirm or not in the real world the results of the clinical trials. By refining the predisposing factors, documenting the disease progression, highlighting the treatment practices, and demonstrating the gaps in adherence to HF guidelines, the COT registry has the unique ambition to assist the healthcare providers, more specifically the oncologist and cardiologist communities, to improve their knowledge about the ADRC to set up common strategies to possibly address new forms of prevention and treatment of the disease.

Also, with its unique cardiac imaging laboratories entry point in the short-term pilot phase, the COT registry will specifically address important issues regarding the imaging use in the diagnostic workup and monitoring of breast cancer patients with suspected/confirmed ADRC. The implementation of new imaging findings (myocardial fibrosis, perfusion imaging defect, contractile reserve) in the assessment and management of ADRC will also be estimated.

Future perspectives

After completion of the first short-term pilot phase (1-year inclusion and 1-year follow-up), specifically aimed at validating the structure, performance, and quality of the data set, a long-term country-based registry will be set up to have a broader representation of European countries and to obtain a larger sample of collected data over a longer duration. Beyond the longer outcome, the long-term COT registry will investigate: (i) the prevalence of symptomatic/asymptomatic and subclinical ADRC; (ii) the clinical meaning and persistence of subclinical LV dysfunction; (iii) the clinical value of cardiac imaging in comparison and in combination with biomarkers for the diagnosis and monitoring of ADRC; and (iv) the optimal timing for cardiac surveillance of breast cancer patients. In a second step, the COT registry could also serve as a framework to conduct a broader registry including other types of cancers.

Limitations

Data derived from the EACVI/HFA COT registry will be limited by their observational nature. Since the entry point into the study will be the imaging laboratories, the collected data might not be transposed to all patients with breast cancer. However, by using such an entry point, all breast cancer patients with suspected ADRC will be enrolled and evaluated. For a similar reason, the prevalence of the ADRC will not be assessable in the first phase of the study. Conversely, the long-term country-based COT registry will better characterize the importance of the ADRC.

Conclusion

The COT registry is the first EORP project carried out jointly by the EACVI and HFA under the umbrella of the ESC. Thanks to the EACVI/HFA COT registry, a comprehensive mapping of the current diagnostic and therapeutic approaches to ADRC across Europe will be for the first time available. Implementing the COT results into clinical practice will likely improve the collaboration/connexion with the oncologists in charge of breast cancer patients and promote larger scale prospective research studies in the field with the ESC.

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