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Cardiovascular Risk Factors and Timing of Anthracyclines and Trastuzumab Cardiac Toxicity

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Abstract. *Background/Aim: Cardiovascular risk factors (CVRFs) predict cardiotoxicity in cancer patients but their role in late cardiac toxicity is less clear. Patients and Methods: This was a retrospective analysis of patients treated with anthracyclines (A) and/or trastuzumab (T) and a correlation with early (≤5 years) or late (>5 years) cardiac toxicity, and baseline CVRFs and CVRFs at toxicity time. Results: A total of 610 patients were included, 422 with (Group A) and 188 without (Group B) baseline CVRFs. In group A toxicity incidence was 4.7% with all events during treatment or immediately after [mean onset time 0.7 years (range=0.2-1.6)]. Events rate was 3.2% in group B with all events after five years [mean time onset 6.9 years (range=5.2-7.5)]. All group B patients who developed late cardiac toxicity presented with CVRFs at the time of toxicity not reported before. Conclusion: CVRFs could predict late cardiac toxicity and their control should be part of the survivorship program.*

Improvements in anti-cancer global strategy resulted into better outcomes for a large part of cancer patients, with many of them experiencing definitive cure or long-term survival, mainly in the case of breast cancer. On the other hand, antitumor treatments display relevant cardiac side-effects so that the risk of death from cardiac disease, in very early breast cancer survivors, paradoxically exceeds that of cancer recurrence (1). Cardiac toxicity of anthracyclines has been documented since decades (2) with early reports dating back to the sixties (3). Trastuzumab dramatically reduces the recurrence rate of early breast cancer when administered after adjuvant chemotherapy (4) but its use, despite the improvements in patient selection and management, is still associated with a relatively high incidence of cardiac toxicity (5). A pre-existing cardiovascular disease or the presence of traditional cardiovascular risk factors (CVRFs) results in a higher incidence of cardiac side-effects (6). Therefore, the control of comorbid conditions and baseline CVRFs in patients who are planned to receive potentially cardiotoxic anticancer treatment has received growing attention. The importance of CVRFs control in preventing cardiac toxicity of anticancer agents is in fact highlighted in major international guidelines of the European and the American medical Societies (7, 8). Given that myocardial toxicity associated with anthracycline use can occur both early during treatment or late after exposure (9) traditional CVRFs assessment should also constitute part of the survivorship program (10). For instance, in women with breast cancer both anti-cancer treatments and the disease itself can contribute to weight gain and reduced physical activity (11, 12) and, thus to increased cardiovascular risk. As mentioned, the importance of CVRFs is well defined before and during a potentially cardiotoxic treatment. However, whether later (years after treatment completion) CVRFs development affects cardiac toxicity in breast cancer survivors is less

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known. On these grounds, we conducted a retrospective study to assess the association between later (during follow up) development of CVRFs and cardiac toxicity in patients treated with anthracyclines with or without trastuzumab.

Patients and Methods

We performed a database search for medical oncology files obtained from 2008 to 2016. We selected records of patients (age >18 yrs) with early breast cancer receiving adjuvant treatment with anthracyclines and trastuzumab in HER2-positive cases who underwent appropriate cardiac monitoring. We then extended the search to other solid cancers with possible use of anthracyclines in advanced disease (*i.e.* Gastric cancer, sarcoma *etc.*). Patients were considered to have "appropriate" cardiac monitoring when periodic evaluation (every 3 months during treatment and every year after treatment) including echocardiogram (or cardiac magnetic resonance imaging) was available.

The investigation conforms with the principles outlined in the Declaration of Helsinki. The selection did not require formal approval by local Ethical Committee given the retrospective and observational design of the study. Patients' names were coded and not revealed. All available clinical and pathological characteristics were recorded. Medical records of patients fulfilling selection criteria were then analyzed for the presence of traditional CVRF at baseline and during follow-up visits. Traditional CVRF considered were: Age (>50 years for trastuzumab and >65 years for anthracyclines), family history of early CV disease (<50 years), arterial hypertension, diabetes mellitus, hypercholesterolaemia, smoking, and obesity (BMI >30 kg/m^2).

Cardiac toxicity was defined as the occurrence of one or more of the following: signs or symptoms of congestive heart failure, cardiac death, drop >10% of left ventricular ejection fraction (LVEF) from baseline even within the normal range or drop of LVEF below the upper limit of normality (55%). We accounted for only one event in case of heart failure with depressed LVEF and we assigned it to the congestive heart failure group. A timeline cut-off of 5 years was chosen to distinguish between "early" and "late" events in relation to the median duration of hormone therapy used in the majority of adjuvant breast cancer treatments. Survival data were collected from medical records or Registry Office. Given the observational design of this retrospective analysis no formal statistical design was set-up. Descriptive data are presented as percentages of the whole patient number while time data are presented as median with range.

Results

A total of 610 patients fulfilled inclusion criteria and were included for analysis. The vast majority of the study population (561 out of 610 pts, 92%) had been diagnosed with early breast cancer. The remaining 49 patients had been diagnosed with other solid tumors.

Among the included patients, 422 (69.2% of the whole study population) presented with at least one CVRF at treatment initiation time (Group A). The remaining 188 patients did not have any CVRF at baseline (Group B). Mean age of Group A was 56 (range=28-74) years and the vast majority were females. There was a clear predominance of breast disease as primary cancer site followed by gastric cancer and sarcoma. Mean baseline CVRF was 1.2/patient. Age (32%) together with hypertension (26%) and smoking (24.4%) were the most prevalent CVRFs, followed by hypercholesterolemia (22.3%), obesity (8.5%), family history (8.1%) and diabetes (5.9%). Not unexpectedly, Group B patients were younger (mean age 47 years, range=28-57 years) and 97.5% were females. Breast cancer as primary site was reported with the higher frequency (95.2%) as compared to the whole study population, followed by gastric cancer and sarcoma.

As per protocol, all patients received treatment with a potentially cardiotoxic agent, with anthracyclines being the most widely used drug (96%). A small patient subset in Group A (3.8%) received trastuzumab without anthracyclines, and this was in relation to a contraindication for anthracyclines use due to high cardiovascular risk. A similar percentage of patients in both groups presented with left sided breast cancer and received adjuvant radiotherapy. Moreover, the frequency of adjuvant hormone therapy did not differ between the two groups. Detailed baseline study population characteristics are shown in Table I. Global incidence of cardiac toxicity was 4.2% (26 out of 610). We observed a total of 20 events of cardiac toxicity (4.2%) in group A patients. All toxicities occurred within five years following initial treatment with a mean onset time of 0.7 (range=0.2-1.6) years. The majority of events (90%, 18 out of 20) occurred during treatment or within the first year after initiation of treatment. Event details are shown in Table II (upper panel). Patients experiencing a cardiac side effect had a mean number of 1.7 (range=1-3) CVRFs at baseline. Conversely, patients without baseline CVRFs showed no early cardiac toxicity, with all 6 recorded events (3.2%) observed after five years from initiation of cancer treatment, with a mean onset time of 6.9 (range=5.2-7.5) years. Details of this late cardiac toxicity are shown in Table II (bottom panel). Although the time to the first cardiac event was clearly different (0.7 *vs.* 6.9 years), the overall percentage of cardiac toxicity in patients with and without baseline CVRFs grossly overlapped (Figure 1). Interestingly, all patients without baseline CVRFs experiencing late toxicity presented at the time of cardiac toxicity with CVRFs not reported before [mean number of CVRFs 2 (range=1-3)]. Conversely, Group B patients who did not experience any cardiotoxicity presented with fewer CVRFs at follow up [mean number of CVRFs 0.8 (range=0-2)].

Discussion

Therapeutic approaches must be based on a careful assessment of the risk profile for each single patient with the aim of tailoring the treatment. This assumption becomes even more relevant in the adjuvant setting when facing potentially cured patients. Anthracyclines and trastuzumab (in HER2 positive cases only) dramatically reduce recurrence rate in early breast cancer patients and, as such, are considered cornerstones of adjuvant treatment. Nevertheless, clinicians should also consider the cardiac side effects of these drugs and balance

Table I. *Study population characteristics*.

Group A (n=422)	
Age (yrs) median (range)	56 (28-74)
Gender (F/M)	397/25
Cancer site (n/%)	
Breast	382/422 (90.6%)
Gastric	27/422 (6.7%)
Sarcoma	10/422 (2.6%)
Miscellanea	3/422 (0.1% rounded)
CVRFs (n/%)	
Age*	135/422 (32%)
Hypertension	110/422 (26%)
Family History	34/422 (8.1%)
Diabetes	25/422 (5.9%)
Hypercholesterolemia	94/422 (22.3%)
Smoking	103/422 (24.4%)
Obesity	36/422 (8.5%)
Treatment (n/%)	
Anthracyclines	405/422 (96.0%)
Anthracyclines plus Trastuzumab	107/422 (25.3%)
Non-Anthracyclines plus Trastuzumab	16/422 (3.8%)
Group B (n=188)	
Age (yrs) median (range)	47 (28-57)
Gender (F/M)	177/11
Cancer site (n/%)	
Breast	179/188 (95.2%)
Gastric	6/188 (4.3%)
Sarcoma	2/188 (0.3% rounded)
Miscellanea	1/188 (0.2% rounded)
Treatment (n/%)	
Anthracyclines	188/188 (100%)
Anthracyclines plus Trastuzumab	55/188 (29.3%)

*>50 years for trastuzumab and >65 years for anthracyclines; Miscellanea: adrenal, hepatocellular carcinoma, prostate; CVRFs: cardiovascular risk factors. Non anthracyclines treatment consisted of docetaxel plus cyclophosphamide.

Table II. *Details of cardiac toxicity events in patients with (Group A; upper panel) and without (Group B; bottom panel) baseline CVRFs*.

Group A (n=422)	
Overall number of events (n/%)	20/422 (4.7%)
Onset time (median [range])	0.7 (range=0.2-1.6) years
Type of event (n/%)	
Congestive heart failure	8/20 (40%)
Cardiac death	0/20 (0%)
Drop of LVEF*	12/20 (60%)
Group B (n=188)	
Overall number of events (n/%)	6/188 (3.2%)
Onset time (median [range])	6.9 (range=5.2-7.5) years
Type of event (n/%)	
Congestive heart failure	1/6 (16.7%)
Cardiac death	0/6 (0%)
Drop of LVEF*	5/6 (83.3%)

CVRFs: Cardiovascular risk factors; LVEF: left ventricular ejection fraction. *Drop >10% of LVEF from baseline even within the normal range or drop of LVEF below the upper limit of normality (55%). We accounted for only one event in case of heart failure with depressed LVEF and we assigned it to the congestive heart failure group.

potential benefits of treatment against harmful effects. The evaluation of the risk of cardiac toxicity must always be performed when a potentially cardiotoxic treatment is planned. Besides treatment-related risk factors (type of drug, cumulative dose, combination treatments, *etc*.), a pre-existent cardiovascular disease or the presence of traditional CVRFs are essential to define global patient risk for developing cardiotoxicity (13, 14). According to these baseline estimates alternatives to standard adjuvant anthracyclines regimens should be considered in very high-risk patients (7).

In line with prior studies (15), the overall incidence of cardiac toxicity in our study population was 4.2%. As expected for an unselected, real world population, the majority of patients presented with at least one baseline CVRF and this was reflected in a higher incidence of cardiac side effects in Group A. Patients in Group B experienced some events as well, but these appeared at later time points. Indeed, while in group A all events occurred early during treatment or in the first year after treatment stop, in group B the mean onset time was dramatically longer. Interestingly, all late cardiac toxicities in group B occurred in subjects that presented with subsequent CVRFs. This may be due to the modified cardiovascular risk profile of patients after cancer diagnosis and subsequent potentially cardiotoxic treatments. Armenian and Colleagues have reported a higher cardiovascular risk in patients who survived to various adult-onset solid cancers including breast cancer (16). This higher risk reached a peak when associated with the presence of at least two CVRFs, leading to a poorer survival as compared to cancer survivals without a cardiovascular disease. The incidence of diabetes and dyslipidemia but not hypertension have been reported to be higher after hematopoietic cell transplantation (HCT) and independently associated with ischemic heart disease. Conversely, healthier lifestyle characteristics among survivors attenuated cardiovascular conditions. The relevance in terms of prediction of cardiovascular events of a persistent exposure to CVRFs before and after HCT has been highlighted by Chow et al. (17). Hypertension and dyslipidemia at one year after HCT with the persistence of these conditions for at least two years was associated with higher risk of multiple cardiovascular events. Long term observation of pediatric, adolescent and young adult populations who survived from Hodgkin's lymphoma has shown an appreciably higher frequency of cardiovascular disease at the age of 50 years with respect to control population

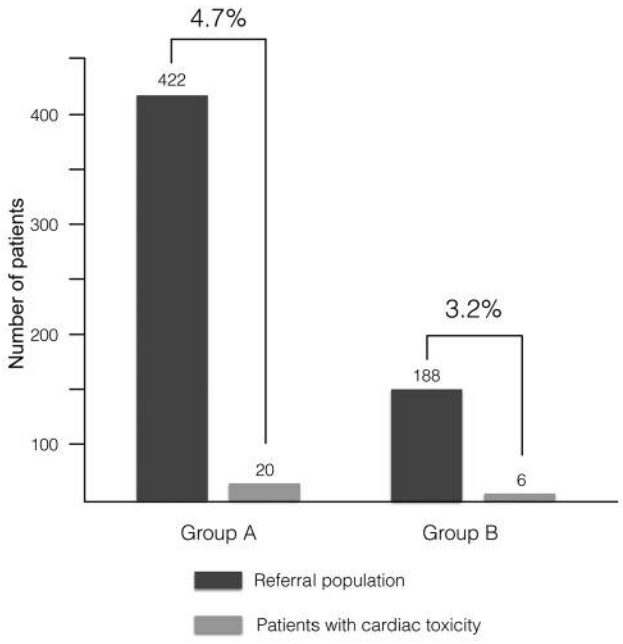

Figure 1. *Incidence of cardiac toxicity in group A (4.7%, 20 out of 422 patients) and group B (3.2%, 6 out of 188 patients).*

(18). The role of CVRFs in predicting cardiovascular complications in cancer patients exposed to cardiotoxic drugs peaks in elderly people. Retrospective analysis in elderly ladies receiving trastuzumb showed that patients with cardiotoxicity presented more often with CVRFs at baseline (19). A prospective study has confirmed the relevance of CVRFs in predicting cardiovascular toxicity in elderly patients treated with trastuzumab (20). The reasons for increased cardiovascular risk in cancer survivors are multiple. Basically, cardiovascular disease and cancer share a number of risk factors and due to both general population aging and improved cancer therapies millions of future cancer survivors will be at risk for cardiovascular disease (21). Various effective cancer therapies have potentially cardiac side effects, so patients who received such drugs will develop an additional cardiovascular risk factor that will be added to classical ones. Moreover, we have to take into consideration social, familial and phycological aspects; after cancer diagnosis harmful lifestyle habits could replace previous more healthy behaviors. A reduction in physical activity together with weight gain are frequent in breast cancer patients leading to a worsening in cardiovascular risk profile (11, 12, 22). From a clinical and practical point of view, patients presenting without baseline CVRFs frequently undergo a non-intensive follow-up strategy due to their predicted low risk of developing cardiac toxicity. Thus, we probably miss the onset of new CVRFs after treatment completion or mild cardiovascular events and we do not properly highlight the importance of weight control and physical activity in such group of patients. Our data showed that even in low-risk patients at baseline, cardiac disease can occur although later. Patient education and empowerment should not be reserved to patients with baseline CVRFs and/or at high risk for cardiac toxicity but must be proposed to all cancer patients irrespective of baseline risk within a complete survivorship program tailored on long-term potential patients' needs (23). Managing with a proper follow-up strategy a larger population could be challenging so a tight cooperation with general practitioners or out-of-hospital care centers is crucial. Given the retrospective nature of this single center study definite conclusions about the role of CVRFs that develop later during follow up cannot be drawn. However, presented data should be considered as hypothesis generating and should stimulate the control of CVRF also in low risk patients during systematic follow up.

Classical CVRFs are predictive of future cardiovascular events for patients who are planned to start with cardiotoxic anticancer treatment, but they appear to predict cardiac toxicity also when they develop later during subsequent follow up. Therefore, their identification and control should be considered in all patients, irrespective of baseline cardiovascular risk profile. Lifestyle modification, including physical activity programs together with a high weight control, should be widely proposed to adjuvant patients even after treatment completion. General practitioners should be informed of possible late consequences of cardiotoxic anticancer drugs even in low risk patients and cooperate to a proper follow-up strategy.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

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Authors' Contributions

Conception: MLC, AC, DA, GC, IB, IP, CL, AS; Design: MLC, AC, AH, AL, JDM, SD, AS, LT; Literature review and processing: MLC, IP, IB, CL, GC, DA, LT, AS, SD, AL, JDM; Writing: MLC, AC, AH, IP, CL, AS, LT; Critical review: MLC, IB, CL, IP, DA, GC, AS, JDM, SD; Final approval: All Authors.

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