Cardiovascular toxicity in breast cancer patients – contributors and role of cardioprotective drugs

Miguel Martins Carvalho,[1,2] Ricardo Alves Pinto,[1] Tânia Proença,[1] Inês Costa,[3] Nuno Tavares,[3] Mariana Paiva,[1] Carla Sousa,[1,2] Filipe Macedo[1,2]

[1]Cardiology Department, Centro Hospitalar Universitário de São João, Porto; [2]Cardiovascular R&D Center, Faculty of Medicine, University of Porto; [3]Oncology Department, Centro Hospitalar Universitário de São João, Porto, Portugal

Abstract

Breast cancer (BC) patients treated with anthracyclines and/or anti-HER2-targeted therapies (AHT) are highly associated with cardiovascular toxicity (CVT). Our objective was to evaluate the risk of CVT secondary to cancer treatment and the role of cardioprotective-drugs (CPD) in BC patients. We collected a retrospective cohort of females with BC treated with chemotherapy and/or AHT from 2017 to 2019. CVT was defined as LVEF<50% or decline ≥10% during follow-up. As CPD, we considered renin-angiotensin-aldosterone-system inhibitors and beta-blockers. A subgroup analysis of the AHT patients was also performed. A total of 203 women were enrolled. The majority had high or very-high CVT risk score and normal cardiac function at presentation. As for CPD, 35.5% were medicated pre-chemotherapy. All patients were submitted to chemotherapy; AHT were applied to 41.7%. During a 16 months follow-up, 8.5% developed CVT. There was a significant decrease of GLS and LVEF at 12-months (decrease of 1.1% and 2.2%, p<0.001). AHT and combined therapy were significantly associated with CVT. In the AHT sub-group analysis (n=85), 15.7% developed CVT. Patients previously medicated with CPD had a significative lower incidence of CVT (2.9% *vs* 25.0%, p=0.006). Patients already on CPD presented a higher LVEF at 6-months follow-up (62.5% *vs* 59.2%, p=0.017). Patients submitted to AHT and anthracycline therapy had higher risk of developing CVT. In the AHT sub-group, pre-treatment with CPD was significantly associated with a lower prevalence of CVT. These results highlight the importance of cardio-oncology evaluation and strengthen the value of primary prevention.

Correspondence: Miguel Martins Carvalho, Serviço de Cardiologia, Centro Hospitalar Universitário de São João, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal.
Tel. +351.961076899.
E-mail: jmiguelmartinscarvalho@gmail.com

Key words: breast cancer; cardiovascular toxicity; chemotherapy; trastuzumab; anti-HER2 therapy; anthracyclines.

Contribution: NT, MP, CS, concept and design; MMC, TAP, TP, IC, experiments performing; MMC, RAP, TP, analysis and interpretation of experiments results; FM, reviewing. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no conflict of interest.

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate: the study protocol was approved by the Ethical Review Committee of our Hospital (protocol no. 128/2021 dated 2021/05/29). The committee assessed the planned project as ethically unobjectionable. Written consent to participate were obtained from all study participants.

Received: 31 December 2022.
Accepted: 30 January 2023.
Early view: 28 March 2023.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Licensee PAGEPress, Italy
Monaldi Archives for Chest Disease 2023; 93:2514
doi: 10.4081/monaldi.2023.2514

Introduction

The annual incidence of cancer is more than 20 million worldwide and 60.000 in Portugal [1]. Recent advances in cancer treatment have led to improved survival [2], albeit with cardiovascular adverse effects being some of the most frequent and feared consequences. With increased survival in these patients, cardiovascular care becomes fundamental, to prevent the development of serious cardiac impairment. Cancer and cardiovascular diseases (CVD) share some of the same risk factors: age, genetics, obesity, smoking and lifestyle. Moreover, cancer survivals have a higher risk of CVD due to the treatment toxicities (old and new anticancer drugs, chest radiotherapy), being CVD the second most frequent cause of death in these patients [2]. The need that these patients present of effective multidisciplinary care led to the development of a new discipline – cardio-oncology. The main purposes of cardio-oncology are to evaluate the patients' baseline cardiovascular risk, to ensure they receive the best possible cancer and cardiovascular treatment, to minimize treatment's cardiovascular toxicity (CVT) and to guarantee an adequate follow-up. The other purposes of cardio-oncology include monitor treatments that could be toxic, pre-operative

assessment, as well as shared decision making with the oncologist team about emerging toxicity.

Several cancer treatments are associated with CVT and it is one of the main causes of cancer treatment suspension; however, CVT can be reversible if addressed adequately. CVT can manifest in a variety of ways: from the classic form of left ventricle systolic dysfunction and heart failure to valvular and coronary disease, arrhythmic or thrombotic events.

In patients with BC, anti-HER2-targeted therapies (AHT) are highly associated with CVT, being the main reason for treatment interruption in patients receiving adjuvant trastuzumab. Trastuzumab is a monoclonal antibody that targets the HER2+ oncogene. It has been used in combination with chemotherapy in BC with significant improvements in survival outcomes and clinical benefit compared to chemotherapy alone. However, AHT are associated with an increased risk of heart failure [3], especially if combined with anthracyclines (AC) [4]. Nevertheless, since these effects do not seem to be dose-dependent, discontinuation of treatment and HF medical therapy can often reverse this process [5].

The Herceptin Adjuvant (HERA) Trial [6] included over 5000 BC patients, showing that trastuzumab associated with chemotherapy significantly improved survival, despite a significant rate of CVT (7.08% *vs* 2.21%; p<0.001).

As for AC, their cardiac toxicity is well-recognized [7]; it is dose-dependent and cumulative. It can lead to symptomatic or asymptomatic left ventricle systolic dysfunction [8].

The 2022 European Society of Cardiology [9] first edition guidelines on Cardio-Oncology recommend regular left ventricular ejection fraction (LVEF) assessments and CVT management with cardioprotective drugs (CPD). However, while secondary prevention has already entered clinical practice, either with AHT or AC, despite persistent unresolved questions, primary prevention is still giving its first steps.

The aim of our study was to evaluate the risk of CVT secondary to cancer treatment and the role of CPD in a subset of patients with BC.

Methods

We collected a retrospective cohort of females with BC treated with conventional chemotherapy (CHT) and/or AHT referred to Cardio-oncology consultation at a tertiary center from January 2017 to November 2019. All patients were evaluated before treatment initiation and at least at 3, 6 and 12-months with echocardiogram and cardiac biomarkers, namely high sensitivity troponin I (hs-cTnI) and brain natriuretic peptide (BNP). Demographic characteristics (gender, age, presence of cardiovascular risk factors, chronic kidney disease, previous vascular events and LV dysfunction) and clinical data (including cardiac and oncologic treatments and clinical outcomes) were collected. The database used in this study was completed retrospectively using the available clinical records. CVT was defined as LVEF under 50% or decline of at least 10% in LVEF during follow-up, in concordance with the HERA clinical trial [6] and several previous articles and position papers [8]. The recent European Society of Cardiology 2022 Guidelines on Cardio-Oncology [9] adopted a more complete definition, but in line with previous position papers. As CPD, we considered renin-angiotensin-aldosterone system inhibitors and beta-blockers, regardless of time of initiation. A subgroup analysis of the patients submitted to AHT was also performed, as this is assumed as higher risk patients.

Study population

The present study included a sample of female BC patients treated with CHT and/or AHT, followed in a Cardio-oncology Clinic (COC) at Centro Hospitalar Universitário de São João, a tertiary center in Porto, Portugal, from January 2017 to March 2020. The COC in our center consists of 2 dedicated cardiologists, 1 nurse and 2 sonographers. Our referrals come (mainly) from the Oncology and the Hemato-Oncology Departments. We included 203 patients. Clinical, electrocardiographic and echocardiographic data were retrospectively analyzed up to a 16-month follow-up. This study was approved by the Institutional Ethics Committee.

Definitions, data, ECG and echocardiography collection

Clinical endpoints and definitions were in accordance with previous articles and the 2022 European Society of Cardiology Guidelines on Cardio-Oncology [9].

Cardiovascular risk score was estimated using a previously described score [10] that included patient characteristics and information on planned therapies. Score values over 5 were classified as high-risk and over 6 were classified as very-high risk.

ECGs were systematically obtained at baseline (usually the day of the first COC appointment) and at least at 3, 6 and 12-months. All ECGs in our institution were electronically recorded and were assessed and reviewed by cardiologists.

Sequential transthoracic echocardiograms were performed by two sonographers; the images were acquired either on a Vivid 7 or on a Vivid E95 GE Healthcare (Chicago, IL, USA) echographer and the images were transferred to the Echo PAC workstation for offline analysis. Echocardiographic evaluation and monitoring followed the recommendations of the European and American Societies of Cardiology [11,12].

Clinical and echocardiographic data were collected from digital records.

Statistical analysis

Data are presented as mean ± SD or median IQR for continuous variables and as number and percentages for categorical variables. One-sample Kolmogorov-Smirnov test was performed to evaluate normal distribution. Categorical variables were compared using the chi-square test; odds ratios are presented when considered relevant. Continuous parametric variables were compared using t-test and non-parametric variables using Mann-Whitney U test. Differences were considered statistically significant when p<0.05. Statistical analysis was performed in IBM SPSS Statistics version 27.

Results

Baseline characteristics of the participants

A total of 203 women were enrolled with mean age 50.9±10.9-year-old (Table 1). As for the cardiovascular risk factors (CVRF), 23.5% (n=48) had hypertension, 32.3% (n=66) dyslipidemia, 9.8% (n=20) diabetes, 22,1% had obesity (n=45) and 23.0% (n=47) were smokers or previous smokers. The majority (98.5%, n=200) of patients had a high or very-high CVT risk score (score ≥5). Seven (3.4%) patients had previous cardiac disease: 3 valvular diseases, 2 ischemic heart disease, 2 pericardial disease. As for CPD, 35.5% (n=67) of patients were previously medicated before CHT: 17 were medicated with beta-blockers and 50 were medicated with renin-

angiotensin-aldosterone system inhibitors. Of note, 35 patients (17.5%) were medicated with statins. At presentation, 99.4% had normal cardiac function with mean LVEF of 62.9% and mean global longitudinal strain (GLS) of -19.4%; the mean hs-cTnI and BNP were 3.3 ng/L and 33.4 pg/mL, respectively.

Choice of treatment

All patients were submitted to CHT, whether adjuvant (n=82, 40.2%), neoadjuvant (n=116, 56.9%) or palliative (n=6, 2.9%); 81.4% (n=166) were submitted to radiotherapy. AC were applied to 83.8% (n=170); AHT were applied to 41.7% (n=85) of patients; with 27.9% (n=58) of patients taking both therapies. The average total cumulative AC dose was of 263 mg/m^2.

Table 1. Baseline characteristics of study population. Values were presented as mean ±SD or number of cases (%).

N	203
Age, yrs	50.9±10.9
Female (%)	203 (100)
Hypertension (%)	48 (23.5)
Diabetes (%)	20 (9.8)
Dyslipidemia (%)	66 (32.3)
Obesity (%)	45 (22.1)
Smokers or previous smokers (%)	47 (23.0)
CVT risk score ≥ 5 (%)	200 (98.5)
Previously medicated with CPD (%)	67 (35.5)
β-blockers (%)	17 (25.4)
Renin-angiotensin-aldosterone system inhibitors (%)	50 (75.6)
Previously medicated with statins (%)	35 (17.5)
Mean LVEF (%)	62.9±3.6%
Mean GLS (%)	-19.4±2.3%
Mean hs-cTnI (ng/L)	3.3±2.2
Mean BNP (pg/mL)	33.4±24.7

Values were presented as mean ±SD or number of cases (%). CVT, cardiovascular toxicity; CPD, cardioprotective drugs; LVEF, left ventricle ejection fraction; GLS, global longitudinal strain; hs-cTnI, high sensitivity troponin I; BNP, brain natriuretic peptide.

Cardiotoxicity

During a median follow-up of 16 months (IQR 12-19), 8.5% (n=17) of patients developed CVT, leading to initiation or titration of CPD in 76.9% (n=13) and treatment interruption in 23.5% (n=4); most of them recovered (n=15, 88.2%). No CVT related mortality was registered. During treatment there was a significantly increase of hs-cTnI (mean 19.7 ng/L at 3 months, p<0.001) and a decrease of GLS and LVEF at 12 months (decrease of 1.1% and 2.2%, respectively, both p<0.001) (Table 2). Both AHT and AHT plus AC were significantly associated with CVT (p=0.002 and p<0.001, respectively), with an extremely high prevalence in the latter group (19.6%). Nor CVRF neither RT raised the risk of CVT. Although patients on CPD did not have lower prevalence of CVT (5.6% *vs* 10.2%, p=0.268), they presented a non-significative trend to higher rate of cardiac function recovery (100% *vs* 66.7%, p=0.057). Of note, medication with statins before chemotherapy did not reduce the risk of CVT (11.8% *vs* 7.9%, p=0.467).

Anti-HER2 therapy subgroup

In the AHT group, a total of 85 patients were included with mean age of 52.4±10.2 years-old (Table 3). Concerning CVRF: 29.4% (n=25) had hypertension, 11.8% (n=10) had diabetes, 32.9% (n=28) had dyslipidemia, 22.4% (n=19) were smokers or previous smokers; all patients had a high or very-high CVT risk score. Besides AHT, 68.2% (n=58) and 80.0% (n=68) were also on AC and radiotherapy, respectively. Patients were followed for a median follow-up of 16 months (IQR 12-20). At baseline, mean hs-cTnI was 3.9 ng/L, mean LVEF was 63.1% and mean GLS was -19.7%, with all patients with normal cardiac function. During follow-up, 15.7% (n=13) of patient developed CVT with a higher rate in patients concomitantly on AC (19.6% *vs* 7.4%, p=0.151). CPD was initiated or titrated in 84.6% (n=11) of patients and 30.8% (n=4) needed to suspend AHT; overall 92.3% (n=12) of CVT patients recovered. AHT suspension was not statistically significatively associated with a higher rate of cardiac function recovery (100.0%

Table 2. Cancer treatments, incidence of CVT and recovery. Data were presented in percentage and significative p-values in bold.

Variables	Percentage	p value	Variables	Percentage	p value
Incidence of CVT			CVT recovery		0.057
AHT	7.4%	0.002	Patients on CPD	100.0%	
AHT plus AC	19.6%	<0.001	Not on CPD	66.7%	
Incidence of CVT		0.268	Risk of CVT		0.467
Patients on CPD	5.6%		With statins	11.8%	
Not on CPD	10.2%		Without statins	7.9%	
AHT therapy subgroup analysis					
Incidence of CVT		0.151	CVT recovery		0.488
AHT	7.4%		AHT suspension	100.0%	
AHT plus AC	19.6%		AHT continuation	88.9%	
Incidence of CVT		0.006	CVT recovery		**0.020**
Previously on CPD	2.9%		With CPD	100.0%	
CPD Naïve	25.0%		Without CPD	50.0%	
LVEF at 6 months		0.017			
Previously on CPD	62.5%				
CPD Naïve	59.2%				

AHT, anti-HER2-targeted therapies; AC, anthracyclines; CVT, cardiovascular toxicity; CPD, cardioprotective drugs; LVEF, left ventricle ejection fraction. CVT was defined as LVEF under 50% or decline of at least 10% in LVEF during follow-up.

vs 88.9%, p=0.488). However, CPD initiation/titration after CVT was associated with a higher rate of cardiac function recovery (100.0% *vs* 50.0%, p=0.020). When comparing patients already medicated with CPD before cancer treatment (41.7%) to those naïve of CPD, the first group present a significative decrease of CVT (2.9% *vs* 25.0%, p=0.006, OR=0.09; 95% CI 0.01-0.72). When analyzed all AHT patients (with and without CVT), patients already on CPD also presented a higher LVEF at 6 months follow-up (62.5% *vs* 59.2%, t(69)=-2.4, p=0.017), despite a non-significative lower LVEF at baseline (62.3% *vs* 63.6%, p=0.139). Medication with statins before chemotherapy didn't reduce the risk of CVT.

Discussion

Cardio-oncology is a new area in Cardiology: as it so, still much is unknown, mostly derived from the lack of understanding of the fundamental underlying mechanisms of cardiotoxicity, the late diagnosis of myocardial damage (with difficulty to prevent irreversible damage) and absence of specific and effective therapies [13]. Most of the evidence to guide clinical decisions is based on limited trials and expert opinions [9]. CVT management and allowing the patient to receive the most appropriate cancer treatment are the main concerns in Cardio-oncology. CVT diagnosis can be clinical (if symptomatic), or it can depend on cardiac biomarkers and imaging. Serial measurement of cardiac biomarkers (BNP or hs-cTnI) is recommended for baseline CVT risk stratification and follow-up of patients submitted to AC or AHT [9]. As for imaging, the most commonly used modality is echocardiogram, due to its availability and lack of radiation. Strain evaluation is of added value in this context, as it can detect early CVT (as compared with LVEF) [14].

Recent data [15-17] on patients treated with AC and AHT reported that beta-blockers and renin-angiotensin-aldosterone system blockers have a significant benefit in preventing LVEF reduction. However, to current date, they did not demonstrate a reduction on the incidence of HF or CVT mortality. It is speculated that this could be different is higher CVT risk populations.

Our study included patients treated with AC chemotherapy, AHT or a combination both. As for AC chemotherapy, the majority of patients were exposed to an average cumulative dosage that classify them as higher CVT risk [9]. We also performed a sub-group analysis on the higher risk patients, the patients submitted to concomitant AHT. AHT are essential in the current treatment of patients with HER2+ BC, both in early and metastatic context. However, AHT is associated with LVEF decline in 15% of patients and symptomatic HF can occur [3]. BC patients submitted to combined AC and AHT are the subgroup of higher CVT risk. In our population of high or very-high CVT risk patients, we observed an incidence of 8.5% of CVT - most of them detected by serum cardiac biomarkers increase and LVEF and GLS decreased; one-third of the patients were pre-treated with CPD and, although a trend to higher rate of cardiac function recovery was observed, it was non-significant.

In the sub-group of AHT patients, 15.7% of patients developed CVT. CPD initiation after CVT was associated with a higher rate of cardiac function recovery; pre-treatment with CPD was beneficial in this sub-group and showed to be preventive of CVT (2.9% *vs* 25.0%, p=0.006). Our results are in line with previous reports [18, 19] and confirm the increased incidence of CVT in the combined therapy group. Also, they suggest the value of CPD treatment (secondary prevention) and pre-treatment (primary prevention) in this population: in the AHT sub-group it reached statistical significance; in all sample it only demonstrated a trend of benefit (p=0.057). Our data supports the value of a structured Cardio-Oncology program, that can identify high CVT risk patients, initiate CPD (both in primary as in secondary prevention) and maintain regular follow-up. As hypertension is present in 1 in 4 of our patients, altering patients' medication to a CPD (in primary prevention) seems reasonable.

This is consistent with the 2022 European Society of Cardiology Guidelines on Cardio-Oncology, that recommend the use of renin-angiotensin-aldosterone system blockers and beta-blockers for primary prevention in high and very high CVT risk patients receiving AC and/or AHT [9].

The guidelines also recommend the use of statins for primary prevention in high and very high CVT risk patients [9]. In both our study groups, medication with statins before cancer-therapy didn't reduce the risk of CVT and this data is in line with previous studies [19]. Nevertheless, this negative result can be explained by the short duration and the small sample size of the studio.

The present study was a single-center retrospective observational study and that was its major limitation. Although echocardiograms were all assessed by cardiologists, there was no Core Lab responsible for revision. Our definition of CVT is not the exact same as (but is in line with) the 2022 European Society of Cardiology guidelines on Cardio-Oncology [9]. Our data was collected prior to the guidelines release.

Table 3. Baseline characteristics of the population in the AHT therapy subgroup analysis. Values were presented as mean ± SD or number of cases (%).

N	85
Age, yrs	52.4±10.2
Female (%)	85 (100)
Hypertension (%)	25 (29.4)
Diabetes (%)	10 (11.8)
Dyslipidemia (%)	28 (32.9)
Smokers or previous smokers (%)	19 (22.4)
CVT risk score ≥ 5 (%)	84 (98.8)
Mean LVEF (%)	63.1±3.9%
Mean GLS (%)	-19.7±2.4%
Mean hs-cTnI (ng/L)	3.9±2.9
Mean BNP (pg/mL)	38.8±23.8

CVT, cardiovascular toxicity; CPD, cardioprotective drugs; LVEF, left ventricle ejection fraction; GLS, global longitudinal strain; hs-cTnI, high sensitivity troponin I; BNP, brain natriuretic peptide.

Conclusions

Patients submitted to AHT had higher risk of developing CVT, especially when concomitantly on AC therapy. This and the statistically significant LVEF decline during follow-up underline the importance of long-term-monitoring of these patients in a structured Cardio-Oncology program. In the AHT sub-group, pre-treatment with CPD was significantly associated with a lower prevalence of CVT and a higher LVEF at 12-months follow-up. These results raise the question of whether CPD should be initiated in primary prevention on high-risk patients and are a call to initiate large randomized controlled studies to confirm these interventions (for both primary and secondary prevention).

References

1. World Health Organization International Agency for Research on Cancer (IARC). GLOBOCAN 2020: estimated cancer incidence, mortality and prevalence worldwide in 2020. 2020. Accessed 2022 Jul 23. Available from: https://gco.iarc.fr/today/fact-sheets-cancers
2. Naaktgeboren WR, Linschoten M, de Graeff A, et al. Long-term cardiovascular health in adult cancer survivors. Maturitas 2017;105:37-45.
3. Pondé NF, Lambertini M, de Azambuja E. Twenty years of anti-HER2 therapy-associated cardiotoxicity. ESMO Open 2016; 1:e000073.
4. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365: 1273-83.
5. Yu AF, Yadav NU, Lung BY, et al. Trastuzumab interruption and treatment-induced cardiotoxicity in early HER2-positive breast cancer. Breast Cancer Res Treat 2015;149:489-95.
6. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659-72.
7. Yamaguchi N, Fujii T, Aoi S, et al. Comparison of cardiac events associated with liposomal doxorubicin, epirubicin and doxorubicin in breast cancer: a Bayesian network meta-analysis. Eur J Cancer 2015;51:2314-20.
8. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016;37:2768-801.
9. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J 2022;43:4229-61.
10. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015;131:1981-8.
11. Barros-Gomes S, Herrmann J, Mulvagh SL, et al. Rationale for setting up a cardio-oncology unit: our experience at Mayo Clinic. Cardiooncology 2016;2:5.
12. Čelutkienė J, Pudil R, López-Fernández T, et al. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). Eur J Heart Fail 2020;22:1504-24.
13. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imag 2014;15: 1063-93.
14. Martins de Carvalho M SC. Cardio-oncology: the future is now! Rev Port Cardiol 2022;41:985-6.
15. Čelutkienė J, Plymen CM, Flachskampf FA, et al. Innovative imaging methods in heart failure: a shifting paradigm in cardiac assessment. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2018;20:1615-33.
16. Caspani F, Tralongo AC, Campiotti L, et al. Prevention of anthracycline-induced cardiotoxicity: a systematic review and meta-analysis. Intern Emerg Med 2021;16:477-86.
17. Vaduganathan M, Hirji SA, Qamar A, et al. Efficacy of neurohormonal therapies in preventing cardiotoxicity in patients with cancer undergoing chemotherapy. JACC CardioOncol 2019;1:54-65.
18. Fang K, Zhang Y, Liu W, et al. Effects of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use on cancer therapy-related cardiac dysfunction: a meta-analysis of randomized controlled trials. Heart Fail Rev 2021;26:101-9.
19. Pinho JF, Nunes JP, Paiva M, et al. Is dyslipidemia a risk factor for trastuzumab-induced cardiotoxicity in breast cancer patients? - A Systematic review and meta-analysis. Rev Port Cardiol 2023. Online Ahead of Print.