Breast Cancer (2018) 25:723–728
https://doi.org/10.1007/s12282-018-0878-0

ORIGINAL ARTICLE

Patterns of on-treatment cardiac adverse events within three clinical trials of adjuvant anthracycline-based chemotherapy

Omar Abdel-Rahman[1,2]

Received: 6 March 2018 / Accepted: 5 June 2018 / Published online: 7 June 2018

Abstract

Background This study aims to assess the patterns of development of on-treatment cardiac side effects among patients with early breast cancer receiving anthracycline-based chemotherapy.

Methods This is a pooled analysis of patient-level data of patients with early-stage breast cancer who were recruited into three clinical trials to receive different adjuvant chemotherapy regimens. Univariable and multivariable analyses of factors predicting the development of on-treatment cardiac adverse events were conducted through logistic regression analysis. The following factors were evaluated in the univariable analysis: age, menopausal status, body mass index, T stage, and type of chemotherapy protocol.

Results Among the studied patients, 226 patients (6.7%) experienced 230 incidents of on-treatment cardiac toxicities. Cardiac ischemia was reported among 8 patients, cardiac dysfunction was reported among 19 patients, arrhythmias were reported in 161 patients and other non-specified forms of cardiac adverse events were reported in 42 patients. In univariable logistic regression, the following parameters were predictive of a higher probability of on-treatment cardiac adverse events ($P < 0.05$): higher age, higher body mass index and FAC chemotherapy protocol. When these factors were included in the multivariable logistic regression analysis, the following factors were predictive of a higher probability of cardiac adverse events: higher body mass index ($P = 0.050$) and FAC chemotherapy protocol ($P = 0.001$).

Conclusion On-treatment cardiac events are not uncommon during adjuvant chemotherapy for early breast cancer. Higher dose of anthracyclines and higher body mass index are associated with a higher risk of on-treatment cardiac events.

Keywords Cardiac toxicity · Breast cancer · Chemotherapy · Arrhythmia

Introduction

Adjuvant chemotherapy is an important part of the treatment paradigm of selected patients with early breast cancer following curative intent surgery [1, 2]. Such treatments might be indicated based on an assessment of potential benefits and risks in each case. The probability of early- and long-term side effects is an important consideration among those patients prior to embarking on adjuvant chemotherapy [3].

During a typical course of adjuvant anthracycline-based chemotherapy for early breast cancer, acute toxicities might include hematological and non-hematological side effects [4]. Non-hematological side effects most commonly include acute hepatic or renal toxicities. On-treatment cardiac side effects represent an uncommonly reported and evaluated category in this context (with more focus in the literature on long-term cardiac toxicities) [5].

To properly assess the patterns of on-treatment cardiac side effects, prospective controlled trials were particularly considered more suitable to achieve this target. These trials are particularly characterized by meticulous patient follow-up and adequate reporting of all events during and after treatment as well as reliable account of the treatments received by each patient [6].

The recently launched project data share (PDS) platform provides an unprecedented opportunity to tackle these research questions as it provides an opportunity to re-examine the raw data of a number of practice-changing phase III

✉ Omar Abdel-Rahman
omar.abdelrhman@med.asu.edu.eg; omar.abdelsalam@ahs.ca

[1] Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

[2] Department of Oncology, University of Calgary and Tom Baker Cancer Center, Calgary, AB, Canada

studies for early breast cancer patients receiving adjuvant chemotherapy [7].

Objective

To explore the patterns of on-treatment cardiac adverse events among early breast cancer patients treated within three trials of adjuvant anthracycline-based chemotherapy.

Methodology

Data source

The source of this pooled analysis is the raw data of the comparator arms of three clinical trials [BCIRG001 (NCT00688740); BCIRG005 (NCT00312208); BIG 02/98 (NCT00174655)]. These three trials evaluated three different regimens of adjuvant anthracycline-based treatment for early-stage breast cancer. The comparator arm of BCIRG001 study was 5-fluorouracil (500 mg/m^2) in combination with doxorubicin (50 mg/m^2) and cyclophosphamide (500 mg/m^2) on day 1 every 3 weeks for 6 cycles of treatment (746 patients); the comparator arm of BCIRG005 was adriamyicn 60 mg/m^2 as an IV bolus in combination with cyclophosphamide 600 mg/m^2 as IV infusion for four cycles followed by docetaxel 100 mg/m^2 as 1 h IV infusion on day 1 every 3 weeks for 4 cycles (1650 patients); while the comparator arm of BIG 02/98 was either of adriamycin 75 mg/m^2 i.v. day 1 every 21 days for 4 cycles, followed by cyclophosphamide 100 mg/mv orally days 1–14, (methotrexate: 40 mg/m^2 i.v. days 1 and 8 and 5-fluorouracil: 600 mg/m^2 i.v. days 1 and 8), every 28 days for 3 cycles or adriamycin 60 mg/m^2 i.v. + cyclophosphamide 600 mg/m^2 i.v., day 1, every 21 days for 4 cycles followed by cyclophosphamide/ methotrexate/ fluorouracil (as above) for 3 cycles (994 patients). The details of the methodology, as well as primary results of the three trials, were published elsewhere [8–10]. Overall, a total of 3390 patients were included in the current pooled analysis.

Data collection

The following data were extracted from each of the available datasets: age at diagnosis, Karnofsky score of performance, race, T and N stages, hormone receptor status, body mass index (calculated through weight and height), grade and histology, type of surgery, type of adjuvant chemotherapy, any cardiac adverse event (while on chemotherapy), type of cardiac adverse event (arrhythmia, cardiac dysfunction, ischemia or any other cardiac adverse event as defined in the study protocol and raw data), grade of the cardiac adverse event, relationship of the cardiac toxicity to the chemotherapy agent(s) (as judged by the investigators of each study) as well as actions taken to deal with the adverse event. According to the eligibility criteria of each of the included trials; all patients have adequate baseline cardiac function (as assessed by clinical history and examination, electrocardiogram and imaging). Additionally, cases with congestive heart failure or unstable angina pectoris, previous history of myocardial infarction within 1 year from study entry, uncontrolled hypertension or high-risk uncontrolled arrhythmias were excluded from inclusion into these studies. Moreover, all patients have normal liver, renal and bone marrow functions. Additional adjuvant therapies (including radiotherapy, hormonal therapy or trastuzumab) were administered subsequently following the end of adjuvant chemotherapy to indicated patients as per institutional guidelines. However, it has to be noted that the current study concerns only cardiac adverse events developed while on adjuvant chemotherapy treatment (and not during subsequent adjuvant therapies).

Statistical considerations

Detailed descriptive assessment regarding baseline characteristics of the patients was provided. Testing with chi-squared was used to compare characteristics of patients who suffered vs. those who did not suffer cardiac adverse events. Univariable/ multivariable analysis of cardiac adverse events' predictors was performed through logistic regression analysis. Factors with $P < 0.05$ in the univariable analysis were included in the multivariable model. The following parameters were assessed in univariable analysis: age (<40 vs. ≥ 40 years), menopausal status, body mass index (reported as a continuous variable), T stage, and type of chemotherapy protocol. P value < 0.05 (two-sided) was dealt with as significant statistically. Statistical procedures were performed using SPSS Statistics 20.0 (IBM, NY).

Results

Baseline data of patients included in the current analysis were described in Table 1. 226 patients (6.7%) developed on-treatment cardiac adverse events while 3164 patients (93.3%) did not develop any cardiac adverse events while on adjuvant chemotherapy. Compared to patients who did not develop cardiac adverse events, patients with on-treatment cardiotoxicity were more likely to be older than 40 years (90.3 vs. 84.4%), postmenopausal (42 vs. 34.9%), have higher body mass index and have undergone breast conservative surgery (57.1 vs. 41.5%). There was no difference between both groups in terms of performance status, T stage, N stage, hormone receptor status or histology.

Table 1 Baseline characteristics of included patients in the cohort (3390 patients)

Parameter	Patients with any cardiac toxicity (226 patients)	Patients without any cardiac toxicity (3164 patients)	*P* Value
Age			0.055
< 40 years	22 (9.7%)	492 (15.5%)	
≥ 40 years	204 (90.3%)	2669 (84.4%)	
Missing	0	3 (0.1%)	
Race			0.001
Caucasian	125 (55.3%)	1457 (46%)	
Others	12 (5.3%)	95 (3%)	
Missing	89 (39.4%)	1612 (50.9%)	
Karnofsky performance score			0.587
70–80	8 (3.5%)	63 (2%)	
90–100	218 (96.5%)	3099 (97.9%)	
Unknown	0	2 (0.1%)	
Body mass index			–
Mean (range)	27.1 (17.4–44.1)	26.3 (14.3–45.8)	
Missing	20	289	
Menopausal status			0.032
Postmenopausal	95 (42%)	1104 (34.9%)	
Premenopausal	96 (42.5%)	1628 (51.5%)	
Missing	35 (15.5%)	432 (13.7%)	
T Stage			0.837
T1	99 (43.8%)	1292 (40.8%)	
T2	112 (49.6%)	1637 (51.7%)	
T3	14 (6.2%)	227 (7.2%)	
T4	0	1 (< 0.01%)	
Unknown	1 (0.4%)	7 (0.2%)	
N Stage			0.954
N1	170 (75.2%)	2123 (67.1%)	
N2	35 (15.5%)	684 (21.6%)	
N3	21 (9.3%)	356 (11.3%)	
Unknown	0	1 (< 0.01)	
Grade			0.038
G1	24 (10.6%)	347 (11%)	
G2	99 (43.8%)	1400 (44.2%)	
G3	97 (42.9%)	1183 (37.4%)	
Missing	6 (2.7%)	234 (7.4%)	
Hormone receptor			0.507
ER and/or PR + ve	162 (71.7%)	2348 (74.2%)	
Both ER/PR –ve	57 (25.2%)	698 (22.1%)	
Missing	7 (3.1%)	118 (3.7%)	
Histological subtype			0.211
Invasive ductal carcinoma	188 (83.2%)	2546 (80.5%)	
Invasive lobular carcinoma	20 (8.8%)	370 (11.7%)	
Others	17 (7.5%)	193 (6.1%)	
Unknown	1 (0.5%)	55 (1.7%)	
Laterality			0.008
Right	90 (39.8%)	1255 (39.7%)	
Left	70 (31%)	1227 (38.8%)	
Unknown	66 (29.2%)	682 (21.6%)	

Table 1 (continued)

Parameter	Patients with any cardiac toxicity (226 patients)	Patients without any cardiac toxicity (3164 patients)	*P* Value
Surgery			< 0.0001
Breast conservative surgery	129 (57.1%)	1314 (41.5%)	
Mastectomy	97 (42.9%)	1847 (58.4%)	
Unknown	–	3 (0.1%)	

Patterns of on-treatment cardiac adverse events

Among the 226 patients with on-treatment cardiac adverse events, there were 230 incidents of on-treatment cardiac events (4 patients developed two different types of cardiac adverse events). Cardiac ischemia was reported among 8 patients, cardiac dysfunction (clinical and/or echocardiographic) was reported among 19 patients, arrhythmias were reported in 161 patients and other non-specified forms of cardiac adverse events were reported in 42 patients. 209 cardiac events were considered of low grade (grade 1–2); while 17 cardiac events were considered of high grade (grade 3–4). High-grade cardiac adverse events include five cases of high-grade cardiac dysfunction; eight cases of high-grade arrhythmias and four cases of other cardiac side effects.

Chemotherapy was discontinued because of the cardiac toxicity in 10 patients and three patients were hospitalized because of the cardiac toxicity. Causality relationship between different toxicities and chemotherapy agents (as judged by the investigators of each study) was as follows: possible (87 patients), probable (33 patients), remote (56 patients), no relationship (50 patients). The cardiac adverse event was categorized as serious in 14 patients.

Cardiac adverse events were encountered in the first three cycles in 114 patients; while they were encountered in the remaining cycles in 112 patients.

Predictors of the development of on-treatment cardiac adverse events

In univariable logistic regression, the following parameters were predictive of a higher probability of on-treatment cardiac adverse events development ($P < 0.05$): higher age, higher body mass index and FAC chemotherapy protocol. When these factors were included in the multivariable logistic regression analysis, the following factors were predictive of a higher probability of cardiac adverse events development: higher body mass index ($P = 0.050$) and FAC chemotherapy protocol ($P = 0.001$).

Discussion

The current analysis provides an assessment of the patterns of development of on-treatment cardiac adverse events among patients with early breast cancer treated within three clinical trials of adjuvant anthracycline-based chemotherapy. Apparently, a higher dose of anthracyclines and higher body mass index are associated with a higher risk for acute cardiac events while on treatment.

Numerous studies were published to describe the long-term cardiotoxic effect of anthracycline-based chemotherapy among early breast cancer patients [11, 12]. However, a much less attention was paid to the acute on-treatment cardiac toxicities associated with these agents.

Numerous mechanisms were proposed to explain the cardiotoxic effect of anthracyclines. In brief, anthracyclines induce cellular injury through the production of free radicals. Moreover, they change nucleic acid biology by intercalation into DNA which leads to the disruption of important homeostatic processes [13].

Multiple factors might additionally contribute to the development of on-treatment cardiac toxicities among those patients other than the direct cardiotoxic effect of chemotherapy [14]. These might include anemia, fever and/or infections (contributing to a variety of arrhythmias particularly sinus tachycardia). Additionally, some medications used in supportive care (e.g. antiemetics or steroids) might rarely predispose to acute cardiac events [15].

The current study focuses on acute cardiac events developed while receiving adjuvant chemotherapy. Other subsequent adjuvant therapies (adjuvant radiotherapy, adjuvant hormonal treatment or adjuvant trastuzumab) might also predispose to on-treatment cardiac adverse events [16, 17]. However, details about these treatments and their toxicities were not available in the raw data of the included studies; thus they were not tackled in the current analysis.

The current study has some setbacks that need to be acknowledged; these include the relatively small number of included patients which might have hindered the proper

evaluation of uncommon forms of acute cardiotoxicity (like uncommon types of arrhythmias or sub-acute cardiomyopathy). Additionally, the variability in the number of cycles as well as the agents used with each chemotherapy protocol might have confounded the proper overall assessment of cardiotoxicity. On the other hand, there are strengths in the current analysis; these include the well-controlled nature of the pooled clinical trial data as well as the detailed reporting of side effects which provided a unique opportunity for assessing acute side effects. These side effects cannot be properly assessed within institutional or registry-based retrospective studies.

Higher body mass index in the current study was associated with a higher risk of on-treatment cardiac adverse events. This adds to the ongoing body of evidence suggesting a deleterious effect of higher body mass index among early breast cancer patients both in terms of lower treatment efficacy and higher treatment early and delayed toxicity [18].

FAC chemotherapy was predictive of a higher risk of on-treatment cardiac adverse events compared to other evaluated sequential anthracycline/non-anthracycline regimens. This is expected given the impact of a higher cumulative dose of anthracyclines on cardiac outcomes.

Fortunately, in spite of the fact that 6.7% of the included patients in the current analysis were having on-treatment cardiac adverse events, only 0.5% of patients have high-grade cardiac toxicities. However, an important caveat for the interpretation of the current analysis and these numbers is the fact that those patients represent a highly selected subset of patients with minimal comorbidities and excellent performance status. Thus, it is expected that the incidence and severity of on-treatment cardiac events might be more common and/or more severe in real-life practice where patients are generally having more comorbidities and/or poorer performance status.

In conclusion, on-treatment cardiac events are not uncommon during adjuvant chemotherapy for early breast cancer. A higher dose of anthracyclines and a higher body mass index are associated with a higher risk of on-treatment cardiac events. Further studies are needed to explore the potential relationship between acute on-treatment cardiac events and long-term cardiac dysfunction that might follow anthracycline-based chemotherapy.

Acknowledgements This publication is based on research using information obtained from http://www.projectdatasphere.org, which is maintained by Project Data Sphere, LLC. Neither Project Data Sphere, LLC nor the owner(s) of any information from the website have contributed to, approved or are in any way responsible for the contents of this publication.

Compliance with ethical standards

Conflict of interest The author declared that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by the author.

Informed consent As this study is based on a publicly available dataset without identifying patient information, informed consent was not needed.

References

1. http://globocan.iarc.fr. Accessed 27 Nov 2016.
2. Abdoli G, Bottai M, Sandelin K, Moradi T. Breast cancer diagnosis and mortality by tumor stage and migration background in a nationwide cohort study in Sweden. Breast. 2017;31:57–65.
3. Abdel-Rahman O. Assessment of the prognostic and discriminating value of the novel bioscore system for breast cancer; a SEER database analysis. Breast Cancer Res Treat. 2017;164(1):231–6.
4. Adjogatse D, Thanopoulou E, Okines A, Thillai K, Tasker F, Johnston SR, et al. Febrile neutropaenia and chemotherapy discontinuation in women aged 70 years or older receiving adjuvant chemotherapy for early breast cancer. Clin Oncol (R Coll Radiol). 2014;26(11):692–6.
5. Alarid-Escudero F, Blaes AH, Kuntz KM. Trade-offs between efficacy and cardiac toxicity of adjuvant chemotherapy in early-stage breast cancer patients: do competing risks matter? Breast J. 2017;23(4):401–9.
6. Levine MN, Whelan T. Adjuvant chemotherapy for breast cancer—30 years later. N Engl J Med. 2006;355(18):1920–2.
7. https://www.projectdatasphere.org/projectdatasphere/html/home. Accessed 7 Oct 2017.
8. Fernandez-Cuesta L, Oakman C, Falagan-Lotsch P, Smoth KS, Quinaux E, Buyse M, et al. Prognostic and predictive value of TP53 mutations in node-positive breast cancer patients treated with anthracycline- or anthracycline/taxane-based adjuvant therapy: results from the BIG 02–98 phase III trial. Breast Cancer Res. 2012;14(3):R70.
9. Mackey JR, Martin M, Pienkowski T, Rolski J, Guastalla JP, Sami A, et al. Adjuvant docetaxel, doxorubicin, and cyclophosphamide in node-positive breast cancer: 10-year follow-up of the phase 3 randomised BCIRG 001 trial. Lancet Oncol. 2013;14(1):72–80.
10. Eiermann W, Pienkowski T, Crown J, Sadeghi S, Martin M, Chan A, et al. Phase III study of doxorubicin/cyclophosphamide with concomitant versus sequential docetaxel as adjuvant treatment in patients with human epidermal growth factor receptor 2-normal, node-positive breast cancer: BCIRG-005 trial. J Clin Oncol. 2011;29(29):3877–84.
11. Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. Clin Cancer Res. 2008;14(1):14–24.
12. Abdel-Rahman O. Risk of cardiac death among cancer survivors in the United States: a SEER database analysis. Expert Rev Anticancer Ther. 2017;17(9):873–8.
13. Abdel-Rahman O, Alorabi M. Use of angiotensin-converting enzyme inhibitors in the prophylaxis of anthracycline or trastuzumab-related cardiac dysfunction: preclinical and clinical considerations. Expert Rev Anticancer Ther. 2015;15(7):829 – 37.
14. Viganego F, Singh R, Fradley MG. Arrhythmias and other electrophysiology issues in cancer patients receiving chemotherapy or radiation. Curr Cardiol Rep. 2016;18(6):52.

15. Keefe DL. The cardiotoxic potential of the 5-HT3 receptor antagonist antiemetics: is there cause for concern? Oncologist. 2002;7(1):65–72.
16. Sardaro A, Petruzzelli MF, D'Errico MP, Grimaldi L, Pili G, Portaluri M. Radiation-induced cardiac damage in early left breast cancer patients: Risk factors, biological mechanisms, radiobiology, and dosimetric constraints. Radiother Oncol. 2012;103(2):133 – 42.
17. Ahmed SH, Moussa Sherif DE, Fouad Y, Kelany M, Abdel-Rahman O. Principles of a risk evaluation and mitigation strategy (REMS) for breast cancer patients receiving potentially cardiotoxic adjuvant treatments. Expert Opin Drug Saf. 2016;15(7):911 – 23.
18. Biganzoli E, Desmedt C, Fornili M, de Azambuja E, Cornez N, Ries F, et al. Recurrence dynamics of breast cancer according to baseline body mass index. Eur J Cancer. 2017;87:10–20.