BMJ Open

Incidence and risk factors for capecitabine-induced symptomatic cardiotoxicity: a retrospective study of 452 consecutive patients with metastatic breast cancer

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To cite: Polk A, Shahmarvand N, Vistisen K, *et al*. Incidence and risk factors for capecitabine-induced symptomatic cardiotoxicity: a retrospective study of 452 consecutive patients with metastatic breast cancer. *BMJ Open* 2016;**6**:e012798. doi:10.1136/bmjopen-2016-012798

▸ Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-012798).

Received 24 May 2016
Revised 1 August 2016
Accepted 12 September 2016

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ABSTRACT

Objectives: Case reports of capecitabine cardiotoxicity resemble those seen with intravenous 5-fluorouracil (5-FU) with chest pain as the predominant manifestation, but few studies of capecitabine cardiotoxicity are available. We aimed to determine the incidence of symptomatic cardiotoxicity from capecitabine in patients with breast cancer and to identify risk factors.

Methods: We reviewed medical records of consecutive women with breast cancer treated with capecitabine (1000 mg/m^2 two times per day) from 2002 to 2012 at one institution.

Results: 22 of 452 patients (4.9%) (95% CI 2.9% to 6.9%) had symptoms of cardiotoxicity (chest pain: n=13, dyspnoea: n=9, palpitations: n=2). 11 patients had changes on ECG (atrial fibrillation: n=5, ST deviations: n=3, T-wave abnormalities: n=2 and QTc prolongation: n=1). 2 patients (0.4%) sustained acute myocardial infarction. 1 patient (0.2%) developed cardiac arrest with lethal outcome. 4 of 6 patients (66%) retreated with capecitabine had recurrent symptoms at retreatment. Cardiac comorbidity (p=0.001), hypercholesterolaemia (p=0.005) and current smoking (p=0.023) were risk factors for cardiotoxicity in univariate analyses and remained significant when adjusted for age. Patients with cardiac comorbidity were 5.5 times (95% CI 2.0 to 14.8) more likely to develop cardiotoxicity. In the subgroup of patients with apparently no cardiac comorbidity, the incidence of cardiotoxicity was lower (3.7%) and hypercholesterolaemia (p=0.035) and current smoking (p=0.020) were risk factors of cardiotoxicity.

Conclusions: The incidence of cardiotoxicity from capecitabine resembles that of intravenous 5-FU (≈5%). Cardiac comorbidity, hypercholesterolaemia and current smoking were associated with development of cardiotoxicity.

Strengths and limitations of this study

- Our study is a large single-centre study, including all patients with breast cancer treated with capecitabine over a 10-year period.
- The primary end point, cardiotoxicity, is mainly diagnosed on the basis of subjective symptoms (chest pain, dyspnoea, palpitations) which may cause information bias.
- In spite of a relatively large sample size, the number of events is low which limit the power of the logistic regression analyses used to analyse for risk factors.
- Our study is a retrospective clinical study. The patients' history records are incomplete with respect to information on risk factors for cardiovascular disease (hypertension, hypercholesterolaemia, diabetes and smoking) and baseline ECG.

INTRODUCTION

Capecitabine is an oral prodrug of 5-fluorouracil (5-FU) that is converted to 5-FU in a three-stage process involving several enzymes.[1] The last step is catalysed by thymidine phosphorylase.[1] Many tissues throughout the body express thymidine phosphorylase, but some human carcinomas express this enzyme in higher concentrations than surrounding normal tissues.[1] This in theory should increase the concentration of 5-FU at the tumour site and decrease the concentration of 5-FU in healthy tissues resulting in less side effects.[1]

Capecitabine is licensed for adjuvant treatment in patients with colon cancer stage III and for the treatment of metastatic colorectal cancer, metastatic breast cancer and advanced gastric cancer (combination therapy). The main side effects from capecitabine are hand-and-foot syndrome, diarrhoea, stomatitis, fatigue, anorexia, nausea and vomiting, abdominal pain, myelosuppression, hyperbilirubinemia and cardiotoxicity.[2–5]

Case reports of cardiotoxicity after administration of capecitabine are similar to those

seen with intravenous 5-FU treatment with chest pain as the predominant manifestation.[6–14] Other less frequent clinical manifestations are arrhythmias, myocardial infarction, heart failure, cardiogenic shock and sudden death.[15–19] Cardiotoxicity from 5-FU occurs with an incidence of 0.55–19.9%.[15] There are few studies of capecitabine cardiotoxicity with incidences ranging from 3% to 35%.[20–24]

We aimed to study the pattern and incidence of symptomatic cardiotoxicity in women with metastatic breast cancer treated with capecitabine and to identify potential risk factors for capecitabine-induced cardiotoxicity.

MATERIALS AND METHODS

Selection of patients

We included patients with metastatic breast cancer consecutively treated with capecitabine from 1 January 2002 to 31 December 2012. Inclusion criteria were woman, metastatic breast cancer and capecitabine treatment (±trastuzumab). The chemotherapy regimen was capecitabine 2000 mg/m² divided in two daily doses for 14 days followed by 1 week off.

Data collection

Approval from the Danish Data Protection Agency was obtained. We collected data from medical records on age, height, weight, body surface area, capecitabine dose, cardiotoxicity, cardiac comorbidity (a history of previous acute myocardial infarction, ischaemic heart disease, arrhythmias, heart failure or reduced ejection fraction), risk factors for ischaemic heart disease (a history of hypertension or intake of antihypertensive drugs, smoking status, a history of hypercholesterolaemia or intake of lipid lowering drugs, a history of diabetes or intake of antidiabetics), ECG (before treatment start and if symptoms), haemoglobin levels, creatinine levels and previous treatment with anthracyclines, trastuzumab, breast and thoracic radiotherapy. Renal function (estimated glomerular filtration rate, eGFR) was estimated by the Chronic Kidney Disease Epidemiology Collaboration equation for Caucasian women incorporating age and plasma creatinine concentrations. All the collected data were prospectively selected.

Registration of symptoms and identification of cases with cardiotoxicity

Before start of chemotherapy and before each cycle adverse events were scored according to NCI/CTCAE V.3.0. ECGs were performed before the first cycle of capecitabine and at clinical suspicion of cardiotoxicity. Medical records were reviewed by one of the authors. Cardiotoxicity was defined as significant symptoms of likely cardiac origin (chest pain or acute myocardial infarction (confirmed with elevation in troponins over the cut-off point), palpitations, dyspnoea of likely cardiac origin and incompensation) and/or changes on ECG that started during treatment with capecitabine and was not present before treatment start. Cases with suspected cardiotoxicity were further reviewed by one cardiologist (MV-N) who made the final decision to classify the case as cardiotoxicity or not. All patients were followed to cessation of capecitabine. End points were evaluated non-blinded, and the investigators had access to patients' medical record.

Statistics

Mann–Whitney U test was used to compare differences in age between patients with cardiotoxicity and patients without cardiotoxicity. Fisher's exact test and χ^2 test were used to analyse differences in numeric variables between the two groups. χ^2 test for trend were used to analyse differences for ordinal variables. Possible risk factors for cardiotoxicity were tested using univariate binomial logistic regression and adjusted for age with multivariate binomial logistic regression. In order to test the robustness of the data and due to missing data, sensitivity analyses were performed for variables that tended to be significant or were significant in univariate analyses. Sensitivity analyses were performed both with multiple imputation and as worst-case and best-case scenarios for one variable at a time. Owing to the low number of events (=22), the potential risk of over fitting of the statistical models and the risk of collinearity among the covariates, we only adjusted for age in the multivariate logistic regression analyses. C statistics were performed for variables that were significant in univariate logistic regression analyses. p Values below 0.05 were regarded significant. IBM SPSS software V.21 was used for all analysis.

RESULTS

Study population

A total of 452 consecutive women with metastatic breast cancer were eligible for analysis (figure 1). Patient characteristics are listed in table 1. The median age was 63 years, 333 patients initially (74%) received 100% dose, while 84 patients (19%) were treated with 75% dose and 26 patients (6%) were treated with 50% dose, respectively. Totally, 242 patients (54%) had previously received treatment with anthracyclines, 54 patients (12%) were treated previously or concurrent with trastuzumab, while 132 patients (29%) had a history of left-sided breast irradiation. Radiotherapy was given ~3 months after the primary diagnosis of breast cancer and the mean time from diagnosis to start of capecitabine was 4 years (0.9–58 years). Forty-two patients (9.3%) had cardiac comorbidities prior to initiation of treatment. Of these, 6 (1%) had a history of ischaemic heart disease while 37 (8%) had other types of cardiac disease, including atrial fibrillation (n=13), supraventricular tachyarrhythmia (n=3), pericardial exudatives (n=3), epirubicin-induced cardiomyopathy (n=3), atrioventricular blocks (n=1), aortic valve disease (n=1) and

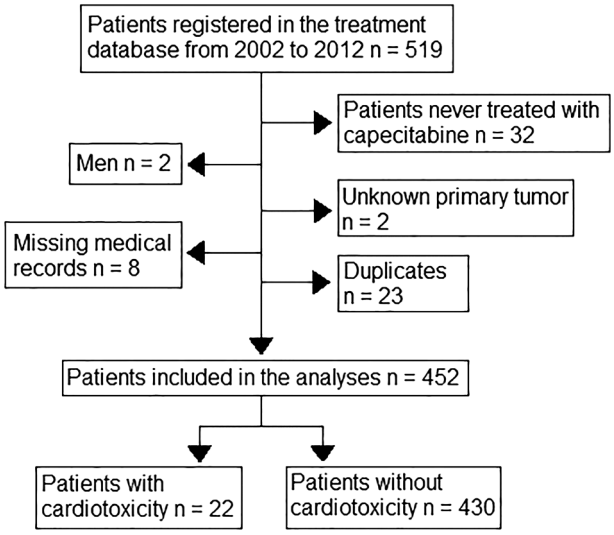

Figure 1 Flow diagram.

reduced left ventricular ejection fraction of unknown cause (n=4).

Cardiotoxicity

Twenty-two cases of symptomatic cardiotoxicity (4.9%) (95% CI 2.91% to 6.89%) were identified from medical records (see online supplementary table). The most common symptoms were chest pain (13 patients) followed by dyspnoea (9 patients) and palpitations (2 patients) (figure 2). Of these 22 patients, 11 (50%) had changes on ECG. Five patients had atrial fibrillation (one paroxysmal and four new onset), while three patients had ST deviations and two patients developed negative or fluctuating T-waves. Of the 13 patients with chest pain, 2 (0.4%) had elevated troponins and were classified as acute myocardial infarctions. One patient (0.2%) with dyspnoea and progressing chest pain developed cardiac arrest with lethal outcome.

First occurrence of cardiotoxicity was in the first cycle for 11 patients (50%), the second cycle for four patients (18%), the third cycle for 3 patients (14%) and the fourth cycle for 1 patient (4.5%), while three patients (14%) had late occurrence of cardiotoxicity (8th, 9th and 12th cycle).

Cardiac therapy was initiated in 10 of the 22 patients with cardiotoxicity (see online supplementary table), while 6 were retreated with capecitabine. Three patients were retreated at the same dose intensity without initiation of cardiac therapy, two were retreated at the same dose intensity, but received cardiac therapy with verapamil, and one patient were treated at reduced dose. The three patients treated with full dose and no initiation of cardiac therapy all had recurrent symptoms at retreatment, while one patient treated with verapamil had recurrent symptoms. The other two patients, one treated with verapamil and one treated at reduced dose intensity, did not have symptoms at retreatment.

Seven events of cardiotoxicity occurred in the subgroup of patients with cardiac comorbidity (n=42) (16.7%), while 15 patients in the subgroup of patients with apparently no cardiac comorbidity (n=410) developed cardiotoxicity (3.7%).

Risk factors for symptomatic cardiotoxicity

In univariate logistic regression analyses, cardiac comorbidity (p=0.001), hypercholesterolaemia (p=0.005) and current smoking (p=0.023) were risk factors for cardiotoxicity (table 2), and they remained significant after adjustment for age with multivariate logistic regression. Patients with cardiac comorbidity were 5.5 times (95% CI 2.0 to 14.8) more likely to develop cardiotoxicity than patients without cardiac comorbidity. In the subgroup of patients with apparently no cardiac comorbidity, hypercholesterolaemia (p=0.035) and current smoking (p=0.020) were significant risk factors in univariate analyses and remained significant after adjustment for age (table 2).

Sensitivity analyses were performed for variables significant in the univariate analyses. In the entire study group, hypercholesterolaemia, cardiac comorbidity and current smoking remained significant risk factors after multiple imputation of missing values (p=0.008, p=0.001 and p=0.023, respectively) and after imputation with worst-case and best-case scenarios (hypercholesterolaemia p=0.005 (best-case), p=0.032 (worst-case); cardiac comorbidity p=0.007 (worst-case), p=0.001 (best-case); current smoking p=0.045 (worst-case), p=0.032 (best-case)). In the subgroup of patients with apparently no cardiac comorbidity, current smoking remained significant after both multiple imputation analyses (p=0.021) and worst-case and best-case analyses (p=0.025 and p=0.042, respectively), while hypercholesterolaemia was unaffected by multiple imputation (p=0.043) but susceptible to worst-case and best-case analyses. The p value for the univariate regression analysis was significant (p=0.035) when cases with missing data were imputed with best-case scenario (none having hypercholesterolaemia) but became insignificant (p=0.132) in worst-case scenario (all having hypercholesterolaemia).

C statistics: predictors of symptomatic cardiotoxicity

The ability of the variables, cardiac comorbidity, hypercholesterolaemia and current smoking, to discriminate between patients that will develop symptomatic cardiotoxicity and those who will not was tested with c-statistics. In unselected patients, the presence of cardiac comorbidity was a poor predictor of symptomatic cardiotoxicity (c=0.617 (95% CI 0.483 to 0.754), p=0.061), as was the presence of hypercholesterolaemia (c=0.662 (95% CI 0.478 to 0.766), p=0.072) and smoking status (c=0.651 (95% CI 0.523 to 0.779), p=0.031). In the subgroup of patients with apparently no cardiac comorbidity, the presence of hypercholesterolaemia (c=0.601

Table 1 Patient characteristics

Characteristics	All patients (n=452) No. (%)	Patients with cardiotoxicity (n=22) No. (%)	Patients without cardiotoxicity (n=430) No. (%)	p Value*
Age (n=452)				
Median	63	63	63	0.742
Range	28–88	36–82	28–88	
Capecitabine dose (n=443)				
50%	26 (6)	1 (5)	25 (6)	0.636
75%	84 (19)	6 (27)	78 (18)	
100%	333 (74)	15 (68)	318 (74)	
IHD (incl. previous ACS) (n=436)	6 (1)	0	6 (1)	1.000
Other cardiac diseases (n=436)	37 (8)	7 (32)	30 (7)	0.000
ECG at treatment start† (n=161)				
Normal	132 (29)	9 (41)	123 (29)	0.454
Abnormal	29 (6)	3 (14)	26 (6)	
Hypertension (n=442)	126 (28)	9 (41)	117 (27)	0.186
Hypercholesterolaemia (n=390)	53 (12)	7 (32)	46 (11)	0.002
Diabetes mellitus (n=435)	21 (5)	1 (5)	20 (5)	1.000
Smoking status (n=371)				
Current smoker	105 (23)	9 (41)	96 (22)	0.264
Former smoker	66 (15)	4 (18)	62 (14)	
Never smoked	200 (44)	5 (23)	195 (45)	
BMI (n=382)				
Underweight (BMI <18.5)	21 (5)	3 (14)	18 (4)	0.337
Normal (BMI 18.5–24.9)	208 (46)	8 (36)	200 (47)	
Overweight (BMI 25.0–29.9)	109 (24)	9 (41)	100 (23)	
Obese (BMI > 29.9)	44 (10)	0	44 (10)	
Number of risk factors for IHD‡ (n=452)				
0	131 (29)	3 (14)	128 (30)	0.005
1	182 (40)	8 (36)	174 (41)	
2	90 (20)	5 (23)	85 (20)	
3	32 (7)	3 (14)	29 (7)	
4	17 (4)	3 (14)	14 (3)	
5	0	0	0	
Previous treatment with anthracyclines (n=444)	242 (54)	9 (41)	233 (54)	0.189
Previous or concurrent treatment with trastuzumab (n=403)	54 (12)	3 (14)	51 (12)	0.752
Previous breast irradiation (n=431)	275 (61)	8 (36)	267 (62)	0.052
Left side	132 (29)	5 (23)	127 (30)	0.218
Right side	115 (25)	1 (5)	114 (27)	
Bilateral	25 (6)	2 (9)	23 (5)	
Side unknown	3 (1)	0	3 (1)	
Previous thoracic irradiation (n=407)	96 (21)	4 (18)	92 (21)	1.000
Anemia§ (n=437)	126 (28)	3 (14)	123 (29)	0.164
eGFR (n=429)				
Low (<60 mL/min/1.73 m^2)	71 (17)	6 (27)	65 (15)	0.105
Normal (≥60 mL/min/1.73 m^2)	358 (79)	13 (59)	345 (80)	

*p Value for the statistical tests of differences between patients with cardiotoxicity and patients without cardiotoxicity.
†All patients do routinely have ECG taken before treatment start and all ECGs are routinely seen by doctors, but not all ECGs were available in the medical records.
‡Risk factors for IHD include hypertension, hypercholesterolaemia, diabetes mellitus, smoking and BMI.
§Defined according to the WHO: Hgb<7.4 mmol/L for non-pregnant women.
ACS, acute coronary syndrome; BMI, body mass index; eGFR, estimated glomerular filtration rate; IHD, ischaemic heart disease.

(95% CI 0.427 to 0.775), p=0.216) and smoking status (c=0.691 (95% CI 0.526 to 0.857), p=0.031) were poor factors to discriminate between patients who will develop cardiotoxicity and those who will not.

DISCUSSION

Incidence of symptomatic cardiotoxicity

We observed an incidence of symptomatic cardiotoxicity from capecitabine at ≈5% in women with metastatic

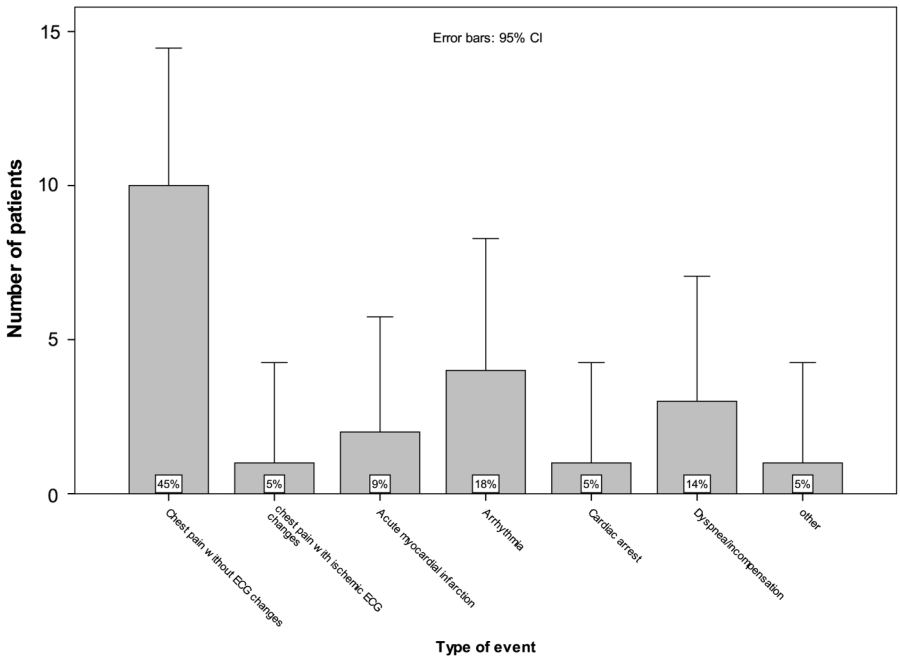

Figure 2 The distribution of the different manifestations of cardiotoxicity. The percentages showed on each bar reflect the distribution of symptoms among the 22 patients with cardiotoxicity. Proportion of patients with chest pain without ECG changes (n=10), chest pain with ECG changes but not acute myocardial infarction (n=1), acute myocardial infarction (n=2), arrhythmia (n=4), cardiac arrest (n=1), dyspnoea/incompensation (n=3) and other (n=1, with QT prolongation and right bundle branch block). Patients with more than one of the manifestations (n=2) are classified according to their primary symptom.

breast cancer which is similar to incidences reported in previous studies of men and women treated with capecitabine,[22–24] although some studies have reported lower[20] or higher incidences.[21] The difference in incidences in-between studies may be due to different risk profiles in the study populations. Moreover, prospective studies with regular cardiac assessments may detect more cardiotoxicity since they may identify asymptomatic patients and patients with mild symptoms.

The incidence of symptomatic cardiotoxicity in our study and other studies of capecitabine cardiotoxicity is within the range of incidences of symptomatic cardiotoxicity in studies with 5-FU[15 21 24–26] and a large study found similar incidences for the two treatments.[24] However, a prospective study with 644 patients reported similar incidences of cardiotoxicity for capecitabine and continuous 5-FU infusion schedules, but a lower incidence for short (bolus) 5-FU infusion schedules.[22]

Pattern of symptomatic cardiotoxicity

The most common event of symptomatic cardiotoxicity was chest pain, which was the main symptom in 59% of the 22 cases. Most of the patients with chest pain had normal ECG and normal coronary enzymes, and severe events, such as acute myocardial infarction and cardiac arrest with lethal outcome, were rare. This pattern is in concordance with other studies,[15] and the sudden onset of chest pain and the rare occurrence of life-threatening complications correspond well to the theory of fluoropyrimidine-induced vasospastic angina. Furthermore, the angiographically normal arteries reported in several case reports[6–8 11] and the presence of silent ischaemic episodes on Holter recordings[27] support this theory.

Retreatment of patients with symptomatic cardiotoxicity

Retreatment with capecitabine after occurrence of cardiotoxicity was attempted in 6 of 22 patients with little success. Four patients had recurrent cardiac symptoms, suggesting that retreatment should be carried out with great precaution. However, a retrospective study of 668 patients[20] and a prospective study of 644 patients[22] treated with 5-FU or capecitabine reported a benefit from dose reduction and initiation of antiangina therapy that prevented symptoms at retreatment in 9 of 12 patients and 12 of 15 patients, respectively. Their findings suggest that retreatment at reduced dose and with appropriate antiangina therapy are feasible, however close cardiac monitoring is crucial. Furthermore, nitroglycerine was effective to abolish symptoms of cardiotoxicity.[20] In contrast, a small and non-randomised study could not demonstrate an prophylactic effect of calcium channel blockers on occurrence of cardiotoxicity.[28] Larger studies with systematic, predefined strategies for dose reduction and initiation of antiangina therapy are needed.

Risk factors for symptomatic cardiotoxicity

Patients with cardiac comorbidity were at increased risk of symptomatic cardiotoxicity, which is in accordance with four previous studies of 5-FU or capecitabine cardiotoxicity,[21 25 27 29] while other studies found no increased risk for patients with pre-existing heart disease.[23 30–33] While heart disease may be a risk marker for cardiotoxicity, it is not a prerequisite for cardiotoxicity to occur. The patient who sustained cardiac arrest and died in our study had no cardiac comorbidities and no risk factors for ischaemic heart disease. Likewise, severe cardiotoxicity has been reported for several patients without cardiac comorbidity.[11 34–37] Also, we

Table 2 Univariate and bivariate logistic regression models of risk factors for symptomatic cardiotoxicity

Variable	β coefficient (95% CI) Univariate	OR (95% CI)	p Value	β coefficient (95% CI) Bivariate: adjusted for age	OR (95% CI)	p Value
All patients (N=452) (events=22)						
Age*	0.01 (−0.03 to 0.04)	1.01 (0.97 to 1.05)	0.789	–	–	–
Hypercholesterolaemia†	1.42 (0.43 to 2.40)	4.12 (1.54 to 11.00)	**0.005**	1.42 (0.38 to 2.46)	4.14 (1.46 to 11.75)	**0.008**
Hypertension†	0.58 (−0.29 to 1.46)	1.79 (0.75 to 4.31)	0.192	0.60 (−0.33 to 1.52)	1.82 (0.72 to 4.57)	0.206
Diabetes†	−0.07 (−2.12 to 1.99)	0.94 (0.12 to 7.32)	0.949	−0.11 (−2.17 to 1.96)	0.90 (0.11 to 7.13)	0.921
Smoking†						
Current smoker	1.30 (0.17 to 2.42)	3.66 (1.19 to 11.21)	**0.023**	1.30 (0.18 to 2.42)	3.66 (1.19 to 11.22)	**0.023**
Former smoker	0.92 (−0.42 to 2.27)	2.52 (0.66 to 9.66)	0.179	0.92 (−0.43 to 2.27)	2.51 (0.65 to 9.67)	0.181
BMI*	−0.05 (−0.16 to 0.06)	0.95 (0.85 to 1.06)	0.380	−0.05 (−0.16 to 0.07)	0.96 (0.85 to 1.07)	0.413
Previous irradiation of left breast†	−0.14 (−1.05 to 0.78)	0.87 (0.35 to 2.18)	0.763	−0.13 (−1.05 to 0.80)	0.88 (0.35 to 2.22)	0.785
"Cardiac comorbidity"†	1.63 (0.67 to 2.59)	5.12 (1.96 to 13.39)	**0.001**	1.70 (0.70 to 2.69)	5.47 (2.02 to 14.80)	**0.001**
Anemia†	−0.86 (−2.12 to 0.39)	0.42 (0.12 to 1.47)	0.176	−0.86 (−2.12 to 0.39)	0.42 (0.12 to 1.47)	0.176
eGFR*	−0.01 (−0.03 to 0.02)	0.99 (0.97 to 1.02)	0.487	−0.01 (−0.03 to 0.02)	0.99 (0.97 to 1.02)	0.638
Previous anthracyclines†	−0.58 (−1.43 to 0.29)	0.56 (0.24 to 1.34)	0.194	−0.73 (−1.77 to 0.31)	0.48 (0.17 to 1.36)	0.171
Previous or concurrent trastuzumab†	0.08 (−1.17 to 1.34)	1.08 (0.31 to 3.80)	0.903	0.11 (−1.17 to 1.41)	1.12 (0.31 to 4.09)	0.864
Dose of capecitabine*	−0.01 (−0.03 to 0.02)	1.00 (0.97 to 1.02)	0.666	−0.01 (−0.03 to 0.02)	1.00 (0.97 to 1.02)	0.682
Previous thoracic irradiation†	0.08 (−1.08 to 1.24)	1.08 (0.34 to 3.44)	0.892	0.12 (−1.05 to 1.28)	1.12 (0.35 to 3.60)	0.847
Patients with no history of heart disease (n=399) (events=15)						
Age*	0.001 (−0.04 to 0.05)	1.00 (0.96 to 1.05)	0.949	–	–	–
Hypercholesterolaemia†	1.32 (0.01 to 2.55)	3.75 (1.10 to 12.81)	**0.035**	1.34 (0.04 to 2.63)	3.81 (1.04 to 13.94)	**0.043**
Hypertension†	0.05 (−1.11 to 1.22)	1.05 (0.33 to 3.38)	0.929	0.04 (−1.17 to 1.25)	1.04 (0.31 to 3.51)	0.947
Diabetes†	0.48 (−1.61 to 2.57)	1.62 (0.20 to 13.10)	0.651	0.48 (−1.63 to 2.58)	1.61 (0.20 to 13.26)	0.658
Smoking†						
Current smoker	1.64 (0.26 to 3.01)	5.13 (1.30 to 20.33)	**0.020**	1.63 (0.25 to 3.00)	5.09 (1.28 to 20.18)	**0.021**
Former smoker	0.18 (−2.10 to 2.46)	1.20 (0.12 to 11.76)	0.876	0.19 (−2.10 to 2.47)	1.21 (0.12 to 11.85)	0.872
BMI*	−0.04 (−0.18 to 0.09)	0.96 (0.84 to 1.09)	0.530	−0.04 (−0.17 to 0.10)	0.96 (0.84 to 1.10)	0.578
Previous irradiation of left breast†	−0.41 (−1.56 to 0.76)	0.67 (0.21 to 2.13)	0.495	−0.41 (−1.56 to 0.77)	0.67 (0.21 to 2.15)	0.497
Anemia†	−1.62 (−3.51 to 0.43)	0.20 (0.03 to 1.54)	0.121	−1.62 (−3.51 to 0.43)	0.20 (0.03 to 1.54)	0.121
eGFR*	0.00 (−0.03 to 0.03)	1.00 (0.97 to 1.03)	0.876	0.01 (−0.03 to 0.05)	1.01 (0.97 to 1.05)	0.668
Previous anthracyclines†	0.67 (−0.39 to 1.72)	1.96 (0.68 to 5.60)	0.212	0.92 (−0.33 to 2.18)	2.52 (0.72 to 8.86)	0.150
Previous or concurrent trastuzumab†	0.42 (−0.87 to 1.72)	1.53 (0.42 to 5.60)	0.525	0.48 (−0.87 to 1.83)	1.62 (0.42 to 6.26)	0.484
Dose of capecitabine*	−0.01 (−0.04 to 0.02)	0.99 (0.96 to 1.02)	0.573	−0.01 (−0.04 to 0.02)	0.99 (0.96 to 1.02)	0.579
Previous thoracic irradiation†	0.35 (−1.02 to 1.72)	1.42 (0.36 to 5.59)	0.621	0.40 (−0.99 to 1.79)	1.48 (0.37 to 5.96)	0.577

Bold p values indicate a significant difference (p<0.05).
*Scale variable.
†Categorical variable.
'Cardiac comorbidity', all types of heart disease; BMI, body mass index; eGFR, estimated glomerular filtration rate.

found that a history of heart disease was a poor predictor of cardiotoxicity.

In the present study, hypercholesterolaemia and current smoking were risk factors for symptomatic cardiotoxicity in the entire study group and in the subgroup of patients with no apparent cardiac comorbidity. Similarly, a larger prospective study of 644 patients without cardiac comorbidities reported that smoking was associated with ECG changes in bivariate analyses.[22] However, they found no association between ECG changes and hyperlipidaemia.[22] While Kosmas *et al*[22] prospectively measured cholesterol and triglyceride levels in blood; our study is based on medical recordings. Thus, incomplete data with risk of information bias is a limitation of the present study. Both studies have a low number of events limiting the statistical power, and multiple testing increases the risk of false-positive results.

Previous treatment with potentially cardiotoxic therapy with anthracyclines or previous or current treatment with trastuzumab did not increase the risk of symptomatic cardiotoxicity. However, two of three patients with epirubicin-induced cardiomyopathy developed symptomatic cardiotoxicity during treatment with capecitabine, suggesting that the degree of pre-existing heart damage may be relevant. Patients with previous left-sided breast irradiation were not at increased risk of cardiotoxicity in our study. Similarly, a large prospective study of 5-FU cardiotoxicity found that previous breast irradiation was not a risk factor.[25] The lack of association between other cardiotoxic therapies and capecitabine-induced cardiotoxicity suggests that the mechanisms behind these cardiotoxicities are different. Moreover, radiation-induced cardiovascular disease may be a late event.[38] In our study, the mean time from chest irradiation to capecitabine start was 4 years.

Methodological considerations

The predominant manifestation of symptomatic cardiotoxicity from fluoropyrimidines is chest pain followed by other subjective symptoms and ECG changes or other objective signs of cardiotoxicity are not always present. In our study, only ~50% of the patients had objective signs (mostly ECG changes) of cardiotoxicity. Thus, the event (cardiotoxicity) was based mainly on subjective symptoms and is therefore affected by the patient's own perception and reaction to the symptoms and the physician's assessment of the patient's symptoms. Patients and physicians may pay more attention to cardiac symptoms if the patient has heart disease before treatment start. These factors may explain some of the difference in incidence in-between studies. Research in new and sensitive cardiac biomarkers like, for example, copeptin to detect myocardial ischaemia is needed.[39]

In spite of a relatively large sample size, the number of events is low (22 events) leading to wide CIs, low statistical power and increased risk of type II statistical errors. With respect to the logistic regression analyses, the low number of events limits the number of covariates allowed in the model. The low number of events and multiple testing (increasing the risk of false-positive results) are weaknesses of most studies analysing risk factors, and it makes the conclusions that can be drawn from these studies less valid.

Like most other large studies on this subject, our study is retrospective which may results in underestimation of the incidence of cardiotoxicity due to incomplete data and overlooking patients with mild symptoms and asymptomatic patients. Missing data affect power and if not missing at random, they may cause bias. We dealt with the missing data by sensitivity analyses with worst-case and best-case scenarios and with multiple imputation. The sensitivity analyses showed that missing data had little influence on our study results.

A major limitation is that baseline ECGs were only preserved for 36% of the patients. Among the 11 patients with ECG changes during capecitabine treatment, 2 had missing baseline ECGs.

CONCLUSIONS

The incidence of symptomatic cardiotoxicity from capecitabine of ≈5% is close to that of 5-FU with incidences of 1–5% in larger studies. Our study results suggest that cardiac comorbidity and current smoking are risk factors for symptomatic cardiotoxicity. Whether smoking cessation can prevent some cases of symptomatic cardiotoxicity deserves further investigations. All the identified risk factors were poor predictors of symptomatic cardiotoxicity and initial optimal cardiac treatment, information about the risk and follow-up if symptoms present are the options today.

Acknowledgements The authors thank Professor Stig Egil Bojesen and the Department of Clinical Biochemistry at Herlev and Gentofte University Hospitals for providing data on creatinine levels and haemoglobin levels. They also thank Hanne Michelsen and Sofie Seit Jespersen for data entry and Anne Birgitte Christiansen for help with review of medical records.

Contributors AP contributed to data collection, data processing, statistics, writing of the paper and incorporation of input from the other authors. NS and KV contributed to conception and design of the study, data collection and review of the manuscript. MV-N involved in review of cases with suspected cardiotoxicity and review of the manuscript. FOL involved in conception and design of the study and review of the manuscript. MS involved in interpretation of study results and statistics and review of the manuscript. DLN contributed to conception and design of the study, data collection, data interpretation, input to the manuscript and review of the manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or non-profit sectors.

Competing interests None declared.

Ethics approval Approval from the Danish Data Protection Agency was obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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