Capecitabine and Cardiotoxicity

1. Fluoropyrimidine-induced cardiotoxicity.

Author(s): Depetris, Ilaria; Marino, Donatella; Bonzano, Alessandro; Cagnazzo, Celeste; Filippi, Roberto; Aglietta, Massimo; Leone, Francesco

Source: Critical reviews in oncology/hematology; Apr 2018; vol. 124; p. 1-10

Publication Date: Apr 2018

Publication Type(s): Journal Article Review

PubMedID: 29548480

Abstract: Fluoropyrimidines (5-fluorouracil and capecitabine) are antimetabolite drugs, widely used for the treatment of a variety of cancers, both in adjuvant and in metastatic setting. Although the most common toxicities of these drugs have been extensively studied, robust data and comprehensive characterization still lack concerning fluoropyrimidine-induced cardiotoxicity (FIC), an infrequent but potentially life-threatening toxicity. This review summarizes the current state of knowledge of FIC with special regard to proposed pathogenetic models (coronary vasospasm, endothelium and cardiomyocytes damage, toxic metabolites, dihydropyrimidine dehydrogenase deficiency); risk and predictive factors; efficacy and usefulness in detection of laboratory markers, electrocardiographic changes and cardiac imaging; and specific treatment, including a novel agent, uridine triacetate. The role of alternative chemotherapeutic options, namely raltitrexed and TAS-102, is discussed, and, lastly, we overview the most promising future directions in the research on FIC and development of diagnostic tools, including microRNA technology.
2. Rapidly developing heart failure from capecitabine cardiotoxicity: a case study

**Author(s):** Ambesh P.; Zivari K.; Kamholz S.; Shani J.; Obiagwu C.; Shetty V.; Hollander G.

**Source:** British Journal of Clinical Pharmacology; Apr 2018; vol. 84 (no. 4); p. 800-802

**Publication Date:** Apr 2018

**Publication Type(s):** Article

Available at British Journal of Clinical Pharmacology - from Wiley Online Library Science, Technology and Medicine Collection 2017

**Database:** EMBASE

3. New-Onset Cardiovascular Morbidity in Older Adults With Stage I to III Colorectal Cancer.

**Author(s):** Kenzik, Kelly M; Balentine, Courtney; Richman, Joshua; Kilgore, Meredith; Bhatia, Smita; Williams, Grant R

**Source:** Journal of clinical oncology : official journal of the American Society of Clinical Oncology; Feb 2018; vol. 36 (no. 6); p. 609-616

**Publication Date:** Feb 2018

**Publication Type(s):** Journal Article

**PubMedID:** 29337636

**Abstract:** Purpose We sought to determine the long-term risk of cardiovascular disease (CVD)-stroke and myocardial infarction-and congestive heart failure (CHF) in older patients with colorectal cancer, as well as to understand the roles that preexisting comorbidities and cancer therapy play in increasing this risk. Patients and Methods We evaluated individuals from the SEER-Medicare database with incident stage I to III colorectal cancer at age older than 65 years between January 1, 2000, and December 31, 2011 (n = 72,408) and compared these patients with a matched cohort of Medicare patients without cancer (n = 72,408). Results Median age at diagnosis of colorectal cancer was 78 years (range, 66 years to 106 years), and median follow-up was 8 years since diagnosis. The 10-year cumulative incidence of new-onset CVD and CHF were 57.4% and 54.5% compared with 22% and 18% for control, respectively (P < .001). The interaction between hypertension and chemotherapy was significant (P < .001) for CVD, and that between diabetes and chemotherapy was significant (P < .001) for CHF. Within the first 2 years since diagnosis, exposure to capecitabine alone increased CHF hazard (hazard ratio [HR], 3.6; 95% CI, 12.76 to 4.38) compared with exposure to fluorouracil alone. Conversely, patients who were treated with fluorouracil alone had a higher CVD hazard at 2 years since diagnosis compared with patients who received capecitabine alone (2 years HR, 0.72; 95% CI, 0.62 to 0.84). Conclusion Older patients with colorectal cancer are at increased risk of developing CVD and CHF. Diabetes and hypertension interact with chemotherapy to increase the risk of cardiovascular morbidity. Future studies should assess the potential for personalized therapeutic options for those with preexisting morbidities and for structured monitoring for patients with a history of exposure to chemotherapy regimens, as well as explore the management of preexisting comorbidities to address long-term cardiovascular morbidity.

**Database:** Medline
4. Incidence of capecitabine-related cardiotoxicity in different treatment schedules of metastatic colorectal cancer: A retrospective analysis of the CAIRO studies of the Dutch Colorectal Cancer Group.

Author(s): Kwakman, Johannes J M; Simkens, Lieke H J; Mol, Linda; Kok, Wouter E M; Koopman, Miriam; Punt, Cornelis J A


Publication Date: May 2017

Publication Type(s): Journal Article

PubMedID: 28286287

Abstract: BACKGROUND The frequency of capecitabine-related cardiotoxicity has been reported to be low but includes serious adverse events. We conducted a retrospective analysis of the incidence and severity of capecitabine-related cardiotoxicity in different regimens in the treatment of metastatic colorectal cancer in three randomised phase 3 studies.

METHODS We used data of cardiac events reported in the CAIRO, CAIRO2 and CAIRO3 studies of the Dutch Colorectal Cancer Group (DCCG) and analysed the incidence and severity of cardiac events in the different treatment regimens of the trials which all included the use of capecitabine. The following events were included: chest pain, newly diagnosed cardiac ischaemia/infarction, atrial fibrillation, other arrhythmias and heart failure, all graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC).

RESULTS A total of 1973 patients were included, who received a total of 2461 capecitabine-based lines of treatment. Overall, 5.9% of patients (n = 117) experienced at least one cardiac event, and 2.3% (n = 46) experienced at least one grade ≥3 event. Three patients had two cardiac events. The most frequently observed cardiac event was ischaemia/infarction (2.9%, n = 57), followed by arrhythmias (2.0%, n = 40, including atrial fibrillation in 10 patients), chest pain (0.8%, n = 16) and heart failure (0.4%, n = 7). The highest incidence of cardiac events was observed in patients treated with capecitabine in combination with oxaliplatin and bevacizumab (12%, n = 43).

CONCLUSION We observed capecitabine-related cardiotoxicity in 5.9% of patients, and severe cardiotoxicity in 2.3% of patients. Combination treatment with capecitabine, oxaliplatin and bevacizumab was associated with the highest risk of cardiotoxicity.

Database: Medline
5. Capecitabine-Induced Takotsubo Cardiomyopathy: A Case Report and Literature Review.

**Author(s):** Qasem, Abdulraheem; Bin Abdulhak, Aref A; Aly, Abdelrahman; Moormeier, Jill

**Source:** American journal of therapeutics; 2016; vol. 23 (no. 5); p. e1188

**Publication Date:** 2016

**Publication Type(s):** Case Reports Journal Article Review

**PubMedID:** 25549075

Available at [American journal of therapeutics - from Ovid (LWW Total Access Collection 2015 - Q1 with Neurology)](https://www.americantherapeutics.com)

**Abstract:** Capecitabine is an orally administered chemotherapeutic agent that is metabolized at the tumor site to 5-fluorouracil and thought to be without significant cardiac toxicity. We report a rare case of takotsubo cardiomyopathy that is thought to be related to capecitabine where the patient presented with chest pain, and ST elevation within 48 hours of capecitabine therapy. Workup included cardiac catheterization and coronary angiogram that showed nonobstructive coronary artery disease and anteroapical left ventricular wall motion abnormality with left ventricular ejection fraction of 35%. The drug was stopped, and the patient was treated with beta-blocker and angiotensin-converting enzymes inhibitor. Six weeks later, she had a repeat echocardiogram that was normal. Capecitabine-related cardiomyopathy seems to be very rare because only 5 cases have been reported in the literature (including our case). The condition has to be anticipated and treated to prevent the serious consequence of cardiac dysfunction. All reported cases have eventually recovered after stopping capecitabine.

**Database:** Medline

6. Capecitabine-Induced Coronary Vasospasm.

**Author(s):** Henry, Danish; Rudzik, Francine; Butts, Allison; Mathew, Aju

**Source:** Case reports in oncology; 2016; vol. 9 (no. 3); p. 629-632

**Publication Date:** 2016

**Publication Type(s):** Journal Article

**PubMedID:** 27920693

Available at [Case Reports in Oncology - from Europe PubMed Central - Open Access](https://www.casesjournal.com)

Available at [Case Reports in Oncology - from Free Medical Journals . com](https://www.casesjournal.com)

Available at [Case Reports in Oncology - from PubMed Central](https://www.ncbi.nlm.nih.gov/pmc)

**Abstract:** Capecitabine, an oral prodrug of 5-fluorouracil (5-FU), is approved for early-stage and advanced colorectal cancer and metastatic breast cancer. Cardiotoxicity of 5-FU is well described in the literature. However, cardiac adverse effects of capecitabine are poorly described. We report a case of coronary vasospasm induced by capecitabine. A 41-year-old female with metastatic breast cancer presented with chest pain 3 days after starting capecitabine. The chest pain was relieved by rest and exacerbated by exertion. Her physical examination was unremarkable except for a rapid heart rate of 100 bpm. Electrocardiogram test showed no acute ischemic changes. Troponin tests were negative. CT angiography of the chest was negative for acute pulmonary embolism. An echocardiogram showed a left ventricular ejection fraction of 60% without any wall motion abnormalities. The chest pain resolved with aspirin and analgesic use. She was discharged following an inconclusive cardiac workup. Further use of capecitabine was discontinued.

**Database:** Medline

Author(s): Polk, Anne; Shahmarvand, Nahid; Vistisen, Kirsten; Vaage-Nilsen, Merete; Larsen, Finn Ole; Schou, Morten; Nielsen, Dorte Lisbeth

Source: BMJ open; Oct 2016; vol. 6 (no. 10); p. e012798

Publication Date: Oct 2016

Publication Type(s): Journal Article

PubMedID: 27798021

Available at BMJ Open - from HighWire - Free Full Text
Available at BMJ Open - from Europe PubMed Central - Open Access
Available at BMJ Open - from Free Medical Journals . com

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/m2 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.

CONCLUSION 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.

Database: Medline
8. Capecitabine induced takotsubo cardiomyopathy

**Author(s):** Sakamoto T.; Endo A.; Ito S.; Okada T.; Watanabe N.; Tanabe K.

**Source:** Journal of Cardiac Failure; Sep 2016; vol. 22 (no. 9)

**Publication Date:** Sep 2016

**Publication Type(s):** Conference Abstract

**Abstract:** Takotsubo cardiomyopathy (TCM) is caused by mental and physical stress. Drug-induced TCM has also been reported. Capecitabine is an orally administered prodrug that converts preferentially to 5-FU within tumors. Cardiomyopathy associated with capecitabine chemotherapy is very rare, but a few cases are reported. We present the case of a 60-years-old woman with advanced gastric cancer who experienced TCM with cardiogenic shock during treatment with capecitabine. Negative T waves in electrocardiography and reduced apical wall motion of the left ventricle were observed. No coronary stenosis was revealed in emergency coronary angiography. An echocardiographic examination showed a dynamic left ventricular outflow tract obstruction (maximum gradient 94 mmHg). It is important for physicians to be aware of the rare, but serious, TCM associated with capecitabine. (Figure Presented).

**Database:** EMBASE

9. Incidence of capecitabine cardiac toxicity at rest and under effort: A prospective study

**Author(s):** Lestuzzi C.; Tartuferi L.; Viel E.; Ejiofor L.; Miolo G.M.; Buonadonna A.; Banzato A.; Boz G.; De Paoli A.; Stolfo D.; Zagonel V.; Guglielmi A.

**Source:** European Heart Journal; Aug 2016; vol. 37 ; p. 782

**Publication Date:** Aug 2016

**Publication Type(s):** Conference Abstract

**Available at** European Heart Journal - from Oxford Journals - Medicine

**Available at** European Heart Journal - from HighWire - Free Full Text

**Abstract:** Background: Capecitabine (CAPE) - widely used for chemotherapy (CT) of head/neck, stomach, gut, liver and breast cancer- may cause cardiac toxicity (TOX), mostly myocardial ischemia (MI), ventricular arrhythmias (VA), left ventricular dysfunction (LVD), bradarrhythmias. According to the literature, the most commonly reported TOX is rest cardiac ischemia with vasospastic angina. Recently, cases of TOX of CAPE precipitated by effort have been reported. Since CAPE is given on ambulatory basis, for several weeks, the patients (pts) under CT might be at risk of toxicity during physical activity. Purpose: To evaluate the incidence and clinical presentation of cardiotoxicity (at rest or under effort) in a group of pts undergoing CAPE chemotherapy for various tumors. Methods: We prospectively studied 189 patients (pts), 114 males, 75 females, mean age 62, undergoing CT with CAPE alone or combined with other drugs. Cardiovascular risk factors (CVRF) were present in 133 pts (70 with >2 CVRF); 10 had ischemic heart disease (IHD). The pts had a clinical evaluation, ECG and echocardiogram (Echo) before CT. A treadmill or bicycle stress test was planned before CT in those with IHD, after >10 days of CT for all, and again during the last week of CT in those with treatments lasting >4 weeks. We considered possible signs of TOX: typical angina with ECG changes; appearance of >2 mm ST segment elevation in >2 ECG leads (both at rest or after stress); >2 mm ST depression or Lown 3 VA at rest or during stress test; appearance of negative T waves at ECG; complete atrioventricular block (CAVB). All the pts with suspected TOX underwent a stress test >10 days after withdrawing CAPE and without additional cardiologic therapy; those with LVD had also a new Echo; coronary angiography (CA) was performed in 3 pts. Only the pts with normal stress test and Echo after wash out, or with normal CA, were considered having had TOX. Results: Amongst the 189 pts, 27 (14%) had TOX: 16 silent MI, 4 angina, 4 VA, 2 ECG signs of ischemia and LV dysfunction,
1 CAVB. Seven pts had rest TOX, 20 had TOX detected under stress test only. Among the 20 pts with TOX during stress test, 3 had angina, 4 atypical symptoms, 14 no symptoms; ECG showed ST segment elevation (up to 5 mm in up to 9 leads) in 6 pts, ST segment depression in 11, both ST elevation and depression in 3, frequent VA in 9. High sensitivity Troponin T was elevated in one pt only. Conclusions: Cardiotoxicity was not infrequent during CT with CAPE. The clinical presentation ranged from myocardial ischemia to arrhythmias and/or LV dysfunction. It was triggered or worsened by physical effort in 20/27 pts, and in most cases was asymptomatic, even in presence of significant ECG changes and/or LVD. Patients treated with CAPE should be advised to avoid efforts, and should be routinely screened with ECG during CT.

Database: EMBASE

10. Fluoropyrimidine-Induced Cardiotoxicity: Manifestations, Mechanisms, and Management.

Author(s): Layoun, Michael E; Wickramasinghe, Chanaka D; Peralta, Maria V; Yang, Eric H

Source: Current oncology reports; Jun 2016; vol. 18 (no. 6); p. 35

Publication Date: Jun 2016

Publication Type(s): Journal Article Review

PubMedID: 27113369

Available at Current Oncology Reports - from SpringerLink

Available at Current Oncology Reports - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract: Fluoropyrimidines-5-fluorouracil (5-FU) and capecitabine-have been implicated as cardiotoxic chemotherapy agents. This rare, albeit potentially serious toxicity has been described in nearly four decades of case reports, case series, and in vitro modeling; however, there is a paucity in clinical trials and prospective analyses focused on cardioprotective strategies and cardiotoxic surveillance of these agents. While much attention has focused on the well-known cardiac toxicity of anthracyclines and monoclonal antibody agents such as trastuzumab, fluoropyrimidines remain one of the most common causes of chemotherapy-associated cardiotoxicity. The introduction of capecitabine, an oral prodrg of 5-FU, has made the treatment of solid tumors more convenient along with a subsequent rise in documented cardiotoxic cases. This review discusses the symptomatology, clinical manifestations, and proposed molecular mechanisms that attempt to describe the heterogeneous spectrum of fluoropyrimidine-induced cardiotoxicity. Four case examples showcasing the varied manifestations of cardiotoxicity are presented. Finally, several proposed management strategies for cardiotoxicity and post-hospital course precautions are discussed.

Database: Medline
11. Capecitabine related cardiotoxicity: A meta-analysis of randomized controlled trials

**Author(s):** Alkharji S.; Huynh T.

**Source:** Journal of the American College of Cardiology; Apr 2016; vol. 67 (no. 13); p. 1538

**Publication Date:** Apr 2016

**Publication Type(s):** Conference Abstract

Available at Journal of the American College of Cardiology - from ProQuest (Hospital Premium Collection) - NHS Version

Available at Journal of the American College of Cardiology - from Free Medical Journals . com

**Abstract:**

Background: Capecitabine (CAP) is an oral chemotherapy commonly used to treat many types of cancers. There is conflicting evidence concerning its cardiovascular safety. We aim to compare CAP-related cardiotoxicity with other chemotherapies with known cardiotoxicity such as Fluorouracil (5-FU) and anthracyclines (ANTHRA). Methods: We searched the literature (full text publications) to identify studies comparing CAP with 5FU or ANTHRA. We included adult human studies which reported major cardiovascular adverse events (MACE). MACE was defined as death, non-fatal myocardial infarction, stroke, severe hypertension, severe angina, myocarditis, sudden death or pulmonary embolism. We calculated the odds ratios by randomeffect models. Results: Of 12,140 citations, we retained 13 studies with 11 randomized controlled trials and two observational studies enrolling 3,652 patients (mean age ranged from 57-65 years). Nine randomized controlled trials and two observational studies compared CAP to 5-FU and two compared CAP to ANTHRA. Compared to 5-FU or ANTHRA Chemo, the odds ratio (OR of MACE) for CAPE was 1.08 (95% confidence intervals (CI): 0.66-1.78) (Figure 1). Excluding observational studies, the OR for MACE was 1.12 for CAPE (95% CI: 0.67-1.89). Excluding ANTHRA chemo, the OR was 1.14 (95% CI: 0.67-1.95). Conclusions: We showed similar risks of MACEs of CAPE compared to 5-FU or ANTHRA. Physicians should be aware of potential cardiotoxicity with CAPE and be vigilant with CAPE's administration. (Table Presented).

**Database:** EMBASE
12. Incidence and clinical aspects of capecitabine cardiotoxicity: A prospective study in the real world

Author(s): Lestuzzi C.; Tartuferi L.; Viel E.; De Paoli A.; Innocente R.; Virdone S.; Miolo G.M.; Spazzapan S.; Buonadonna A.; Banzato A.

Source: European Heart Journal; Aug 2015; vol. 36 ; p. 151

Publication Date: Aug 2015

Publication Type(s): Conference Abstract

Available at European Heart Journal - from Oxford Journals - Medicine
Available at European Heart Journal - from HighWire - Free Full Text

Abstract: 5-Fluorouracil (5FU) and its oral prodrug Capecitabine (CAPE) are used for chemotherapy (CT) of head/neck, stomach, gut, liver and breast cancer. Both may cause cardiotoxicity (TOX), mostly myocardial ischemia (MI), ventricular arrhythmias (VA), left ventricular dysfunction (LVD). TOX of 5FU may be precipitated by effort, but data about CAPE are lacking. Since CAPE is given on ambulatory basis for several weeks, pts under CT might be at risk of toxicity during daily physical activity. Aim of the study: To evaluate the incidence and clinical presentation of CAPE TOX during physical activity. Methods: We prospectively studied 142 patients (pts), 90 males, 52 females, mean age 62, undergoing CT with CAPE. Cardiovascular risk factors (CVRF) were present in 102 pts; 7 had ischemic heart disease (IHD). All the pts had a clinical evaluation, ECG and echocardiogram (Echo) before CT. A physical stress test was planned before CT in those with IHD, after >10 days of CT for all, and in the last week of CT if treatment lasted >4 weeks. We considered possible signs of TOX: typical angina; appearance of >2 mm ST segment elevation in >3 ECG leads (at rest or after stress); >2 mm ST depression or Lown 3 VA during stress; new negative T waves at ECG. To rule out an underlying IHD, all the pts with suspected TOX underwent a stress test >10 days after withdrawing CAPE and without additional cardiologic therapy; those with LVD had also a new Echo. Only the pts with normal ECG, stress test and Echo after wash-out were considered having had TOX. Results: Among the 142 pts, 23 (16%) had TOX: 13 silent MI, 4 angina, 4 VA, 3 ECG signs of ischemia and LVD. Six pts had rest TOX: one with acute coronary syndrome and 3 with silent ischemia at ECG did not undergo stress test; 2 with Lown 2 VA underwent stress test, and VA worsened. Among the 18 pts with TOX during stress, 3 had angina, 15 no or atypical symptoms. EGG showed ST segment elevation (up to 5 mm) in 6 pts, ST segment depression in 8, frequent VA in 9. Troponin T was elevated in one pt only. Presence of IHD or CVRF did not influence the risk of TOX. Atypical symptoms (chest discomfort, jaw pain...) during daily life before stress test were more frequent in the pts with TOX (p<0.01).

Conclusion: Cardiotoxicity was frequent during CAPE CT. It was triggered or worsened by physical effort in 78%, and in most pts was asymptomatic, even in presence of significant ECG changes and/or LVD. Pts treated with CAPE should be advised to avoid efforts, and should be routinely screened with ECG during CT.

Database: EMBASE
13. Capecitabine-induced cardiotoxicity: more evidence or clinical approaches to protect the patients’ heart?

Author(s): Fontanella, Caterina; Aita, Marianna; Cinausero, Marika; Aprile, Giuseppe; Baldin, Maria Grazia; Dusi, Veronica; Lestuzzi, Chiara; Fasola, Gianpiero; Puglisi, Fabio

Source: OncoTargets and therapy; 2014; vol. 7; p. 1783-1791

Publication Date: 2014

Publication Type(s): Journal Article

PubMedID: 25302025

Available at OncoTargets and Therapy - from Europe PubMed Central - Open Access

Abstract: Fluoropyrimidines, such as capecitabine and 5-fluorouracil, may cause cardiac toxicity. In recent years, the incidence of this side effect has increased and it is expected to further rise due to the population aging and the disproportionate incidence of breast and gastrointestinal cancers in older individuals. The spectrum of cardiac manifestations includes different signs and symptoms and the diagnosis may be difficult. Here, we report the case of a 43-year-old woman with advanced breast cancer who was rechallenged with a capecitabine-based regimen after experiencing a cardiac adverse event during the first fluoropyrimidine exposure. This real-practice case serves as a springboard for discussion about the current evidence on differential diagnosis of capecitabine-related cardiac toxicity, its risk factors, and the underpinning mechanisms of early onset. Moreover, we discussed whether a rechallenge with fluoropyrimidines could be safe in patients who had experienced a previous cardiac adverse event.

Database: Medline
13. Capecitabine induces both cardiomyopathy and multifocal cerebral leukoencephalopathy.

Author(s): Endo, Akihiro; Yoshida, Yasuyuki; Nakashima, Ryuma; Takahashi, Nobuyuki; Tanabe, Kazuaki

Source: International heart journal; 2013; vol. 54 (no. 6); p. 417-420

Publication Date: 2013

Publication Type(s): Case Reports Journal Article Review

PubMedID: 24309454

Abstract: Chemotherapy for malignant tumors has diversified, and recognizing its side effects has become more important than ever. Both cardiotoxicity and neurotoxicity are rare, but they are among the most serious side effects caused by 5-fluorouracil (5-FU). Capecitabine is an orally administered prodrug that converts preferentially to 5-FU within tumors, resulting in enhanced concentrations of 5-FU in tumor tissue. Given that it targets tumor tissue, capecitabine was expected to reduce the risk of side effects associated with fluoropyrimidine. Here, we present the case of a 62-year-old man with colorectal adenocarcinoma who simultaneously experienced cardiomyopathy with cardiogenic shock and cerebral leukoencephalopathy during treatment with capecitabine. During emergency coronary angiography, ST-segment elevation and severely reduced left ventricular wall motion were observed; however, no severe coronary stenosis or spasm was revealed. Furthermore, we present a review of the literature on capecitabine-induced cardiotoxicity. As of April 2013, 39 case reports on capecitabine-induced cardiotoxicity have been published; however, cardiomyopathy was very rare, with only 3 cases reported. It is important for physicians to be aware of the various rare, but potentially serious, adverse effects associated with capecitabine chemotherapy and to inform patients about the possibility of these side effects, including cardiotoxicity and neurotoxicity.

Database: Medline

**Author(s):** Polk, Anne; Vaage-Nilsen, Merete; Vistisen, Kirsten; Nielsen, Dorte L

**Source:** Cancer treatment reviews; Dec 2013; vol. 39 (no. 8); p. 974-984

**Publication Date:** Dec 2013

**Publication Type(s):** Meta-analysis Journal Article Review

**PubMedID:** 23582737

**Abstract:** PURPOSE To systematically review the incidence, manifestations and predisposing factors for cardiovascular toxicity in cancer patients treated with systemic 5-fluorouracil or capecitabine. DESIGN We searched PubMed, EMBASE and Web of science for studies with ≥ 20 cancer patients evaluating cardiovascular toxicity of 5-fluorouracil and capecitabine. We hand searched the reference lists of all included studies. Study selection and assessment of risk of bias were performed by two authors independently. RESULTS We identified 30 eligible studies (1 meta-analyses of 4 RCTs, 18 prospective and 11 retrospective). Symptomatic cardiotoxicity occurred in 0-20% of the patients treated with 5-fluorouracil and in 3-35% with capecitabine. The most common symptom was chest pain (0-18.6%) followed by palpitations (0-23.1%), dyspnoea (0-7.6%) and hypotension (0-6%). Severe clinical events such as myocardial infarction, cardiogenic shock and cardiac arrest occurred in 0-2%. Mortality rates ranged from 0 to 8%. Asymptomatic cardiac influence was demonstrated on ECG, in NT-proBNP measurements and with ultrasonic cyclic variation of integrated backscatter. Predisposing factors were mostly tested in univariate analyses. Preexisting cardiac disease was a risk factor in some studies, but there were divergent results. There was some evidence for increased cardiotoxicity during continuous infusion schedules and with concomitant cisplatin treatment. The effects of previous or current chest-radiotherapy were ambiguous. CONCLUSION Larger studies suggest an incidence of symptomatic cardiotoxicity of 1.2-4.3% during fluorouracil treatment, however subclinical cardiac influence are common. Possible risk factors are cardiac co-morbidity, continuous infusion schedules and concomitant cisplatin treatment, but existing evidence are of insufficient quality.

**Database:** Medline


**Author(s):** Orsucci, Daniele; Pizzanelli, Chiara; Ali, Greta; Calabrese, Rosanna; Ricci, Giulia; Lenzi, Paola; Petrozzi, Lucia; Moretti, Policarpo; Siciliano, Gabriele

**Source:** Neuromuscular disorders : NMD; Aug 2012; vol. 22 (no. 8); p. 767-770

**Publication Date:** Aug 2012

**Publication Type(s):** Case Reports Journal Article

**PubMedID:** 22652078

**Abstract:** Capecitabine plus oxaliplatin combination (XELOX) is the first-line treatment in metastatic colorectal cancer. Here we report a case of acute, severe but substantially reversible, neuromuscular and cardiac toxicity following XELOX chemotherapy. Muscle biopsy findings were consistent with a toxic myopathy with necrotizing features and vacuolar changes; COX-negative fibers were also present. The time course could support a main role for capecitabine, which may have some neurotoxic effects (more frequently central), but a detrimental interaction between the two drugs cannot be ruled out and further studies are needed.

**Database:** Medline
16. Kounis syndrome is likely culprit of coronary vasospasm induced by capecitabine.

**Author(s):** Kounis, Nicholas G; Tsigkas, Grigorios G; Almpanis, George; Mazarakis, Andreas

**Source:** Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners; Jun 2012; vol. 18 (no. 2); p. 316-318

**Publication Date:** Jun 2012

**Publication Type(s):** Journal Article Comment Review

**PubMedID:** 22020660

Available at Journal of Oncology Pharmacy Practice - from ProQuest (Hospital Premium Collection) - NHS Version

Available at Journal of Oncology Pharmacy Practice - from EBSCO (CINAHL Plus with Full Text)

**Abstract:** Capecitabine administration has been associated with various allergic reactions including acneiform skin rash, lichenoid photosensitive eruption, exudative non-healing scalp, skin reactions, pyogenic granuloma, subacute cutaneous systemic lupus erythematosus, exudative hyponychia dermatitis, and hand-foot syndrome. A patient who developed ventricular fibrillation following capecitabine-induced coronary vasospasm and necessitating cardioverter-defibrillator implantation was published recently in.

**Database:** Medline
17. Ventricular fibrillation as a likely consequence of capecitabine-induced coronary vasospasm.

Author(s): Shah, N R; Shah, A; Rather, A

Source: Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners; Mar 2012; vol. 18 (no. 1); p. 132-135

Publication Date: Mar 2012

Publication Type(s): Case Reports Journal Article

PubMedID: 21321041

Abstract: Capecitabine is a member of the fluoropyrimidine family of chemotherapeutic agents that selectively delivers 5-fluorouracil (5-FU) to tumors. It is increasingly used as part of combined modality treatment for gastrointestinal malignancies. Cardiotoxicity has been documented to occur with 5-FU, but due to an expansion in capecitabine use, reports exist of its propensity to coronary vasospasm. We report the case of a 28-year-old man, with no preceding angina, presenting with a reversible episode of ventricular fibrillation (VF) at rest in his fifth course of capecitabine chemotherapy for metastatic colorectal cancer. Emergency resuscitation successfully restored spontaneous circulation, with initial ST segment elevation in the inferolateral leads on electrocardiogram prompting emergency coronary angiography. This demonstrated normal coronary arteries. ST segments normalized post-angiography and the patient rapidly recovered with no myocardial damage sustained. An implantable cardioverter-defibrillator was placed for secondary prevention of sudden death, and capecitabine was implicated as the cause of coronary vasospasm which resulted in his presentation of VF. To our knowledge, this is the first episode of VF as a consequence of suspected capecitabine-induced coronary vasospasm occurring at rest. Our case highlights the potential for severe cardiotoxic consequences of capecitabine including sudden death from VF, and given the multi-disciplinary approach to managing oncology patients, health professionals should be aware of this.

Database: Medline


Author(s): Tunio, Mutahar Ali; Hashmi, Altaf; Shoaib, Muhammad

Source: Pakistan journal of pharmaceutical sciences; Jan 2012; vol. 25 (no. 1); p. 277-281

Publication Date: Jan 2012

Publication Type(s): Case Reports Journal Article Review

PubMedID: 22186341

Abstract: Capecitabine is an oral prodrug of 5-fluorouracil (5-FU) which is converted in tumor cells to 5-FU by the enzyme thymidine phosphorylase. Nowadays, it is being widely used into the management of colorectal, breast and head and neck cancers because of its oral route and its comparable efficacy with 5-FU. 5-FU induced cardiotoxicity (angina and myocardial infarction) has been reported the literature, but capecitabine induced cardiotoxicity is less reported event. We report a patient with diagnosis of locally advanced adenocarcinoma of rectum who developed symptomatic bradycardia and acute ischemia while receiving oral capecitabine 825mg/m(2) twice daily with preoperative radiation.

Database: Medline
19. Capecitabine-induced cardiotoxicity: Case report of severe biventricular dysfunction in a geriatric patient with aortic stenosis

Author(s): Gallucci G.; Bochicchio A.M.; Tartarone A.; Coccoro M.; Aieta M.

Source: Giornale Italiano di Cardiologia; Dec 2011; vol. 12 (no. 12)

Publication Date: Dec 2011

Publication Type(s): Conference Abstract

Abstract: Background. 5 fluorouracil (5-FU) is widely used in the treatment of gastrointestinal tumors. An alternative agent, capecitabine, is metabolized to 5-FU in tumor cells and is supposed to have less cardiotoxicity. 5-FU and capecitabine may cause myocardial ischemic syndromes. A cardiomyopathic picture has been observed, too, and may be caused by diffuse coronary microvascular spasm or direct drug toxic action on the myocite. We report the case of a patient who developed global biventricular dysfunction after oral administration of capecitabine. Case report. A 82-year-old patient with rectal adenocarcinoma underwent a Miles abdomino-perineal resection. Before surgery his ECG was normal, his echocardiogram showed severe aortic stenosis with a peak gradient of 76 mmHg, a peak velocity of 4.3 m/sec and a LVEF of 0.60. He had class II NYHA effort dyspnea, but the need of an urgent abdominal surgical procedure did not allow further evaluation for a percutaneous transcatheter aortic-valve implantation. A capecitabine schedule was started at the dose of 825 mg/m2 twice daily with the aim of radiosensitizing chemotherapy. At the end of the treatment the patient presented with severe respiratory distress. His ECG was normal, his echocardiogram showed a left ventricular ejection fraction of 0.30 with a peak transaortic underestimated gradient of 70 mmHg, moderate mitral regurgitation, severe tricuspid regurgitation and right ventricular dilatation. He was treated with diuretics and transferred in a Cardiology Department for acute treatment. Capecitabine was discontinued. The patient was then admitted to a cardio-surgical department, but the severity of left ventricular failure contraindicated any interventional procedures and he died of progressive refractory heart failure. Discussion. The incidence of 5-FU cardiotoxicity in the literature ranges from 0.55 to 8%. Capecitabine a fluoropyrimidine antimetabolite converted to 5-FU in tumor tissues via a complex pathway catalyzed by thymidine phosphorylase has a similar pattern of cardiotoxicity. Thymidine phosphorylase activity is also expressed in atherosclerotic plaques. Global endothelial dysfunction and toxicity to the myocytes (inferred by troponin release) could have caused the severe impairment of biventricular function in our patient. A concomitant epicardial coronary artery disease can be reasonably excluded because of the absence of ST-T changes and because of the diffuse impairment of ventricular function. In conclusion, oncologists and cardiologists should be aware of capecitabine cardiotoxicity and they should plan careful observations when dealing with old patients in which comorbidities are always an issue.

Database: EMBASE
20. Clinical and electrocardiography changes in patients treated with capecitabine

Author(s): Koca D.; Salman T.; Unek I.T.; Oztop I.; Yilmaz U.; Ellidokuz H.; Eren M.
Source: Chemotherapy; Jan 2011; vol. 57 (no. 5); p. 381-387
Publication Date: Jan 2011
Publication Type(s): Article
PubMedID: 21997165
Available at Chemotherapy - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract: Background: We aimed to identify the incidence of cardiac events with capecitabine treatment. Methods: The study included 52 patients (median age 59 years) with cancer treated at our Medical Oncology Clinic between 2009 and 2010. Cardiac events from capecitabine treatment were classified into 4 groups: cardiac symptoms, physical signs, electrocardiography (ECG) findings, and severe adverse cardiac effects. Results: The patients received either single-agent capecitabine or a combination chemotherapy including capecitabine. After initiation of capecitabine, 18 patients (34.6%) had new onset cardiovascular symptoms, 6 (11.5%) had new onset physical signs and 17 (32.6%) had new onset ECG findings. New onset ECG findings included prolonged corrected QT interval (n = 10, 19.2%) and prolonged PR interval (n = 3, 5.8%). Severe adverse capecitabine-induced cardiac side effects were observed in 5.8% of the patients, but none of the patients had myocardial infarction or died. Conclusion: Cardiac events are not rare during capecitabine treatment and patients should be followed closely to avoid cardiac morbidity and mortality. Copyright © 2011 S. Karger AG, Basel.

Database: EMBASE

**Author(s):** Molteni, Luisa P; Rampinelli, Irene; Cergnul, Massimiliano; Scaglletti, Ugo; Paino, Anna M; Noonan, Douglas M; Bucci, Eraldo O; Gottardi, Ornella; Albini, Adriana

**Source:** The breast journal; 2010; vol. 16

**Publication Date:** 2010

**Publication Type(s):** Research Support, Non-u.s. Gov't Case Reports Journal Article

**PubMedID:** 21050310

Available at The Breast Journal - from Wiley Online Library Science, Technology and Medicine Collection 2017

Available at The Breast Journal - from EBSCO (CINAHL Plus with Full Text)

**Abstract:** Capecitabine is an orally available fluoropyrimidine carbamate that selectively delivers fluorouracil (5-FU) to tissues expressing high levels of thymidine phosphorylase (TP) such as tumors. The drug has demonstrated efficacy in metastatic breast cancer, colorectal, and pancreatic cancer. Although these are considered safe drugs, a growing body of literature reports adverse cardiac effects. Clinical trials indicate that capecitabine has a cardiac toxicity similar to that of infused fluoropyrimidines such as 5-FU. Here, we review cardiotoxicity in the use of fluoropyrimidines, with particular attention toward capecitabine. We also describe a severe, reversible cardiac event that occurred in a 39-year-old woman, with no cardiac risk factors, treated with capecitabine for advanced breast cancer. This review and our experience confirm that fluoropyrimidine cardiotoxicity is an infrequent but documented side effect. Oncology patients under treatment should be closely observed and monitored for cardiac symptoms with particular attention in case of signs or symptoms of cardiovascular complications. The implementation of cardio-oncology interdisciplinary teams should, in the future, reduce the impact of cancer treatment-associated cardiotoxicity syndromes.

**Database:** Medline

22. Capecitabine cardiac toxicity presenting as effort angina: a case report.

**Author(s):** Lestuzzi, Chiara; Crivellari, Diana; Rigo, Fausto; Viel, Elda; Meneguzzo, Nereo

**Source:** Journal of cardiovascular medicine (Hagerstown, Md.); Sep 2010; vol. 11 (no. 9); p. 700-703

**Publication Date:** Sep 2010

**Publication Type(s):** Case Reports Journal Article

**PubMedID:** 20093950

**Abstract:** We report a case of capecitabine-induced cardiotoxicity (effort angina) in a woman with metastatic breast carcinoma. Due to cancer progression, rechallenge of therapy with capecitabine was attempted, using several strategies in order to prevent cardiotoxicity. The most (even if not fully) effective strategy was reducing capecitabine dosage together with nitrates, calcium-channel blockers and trimetazidine therapy.

**Database:** Medline
23. Cardiotoxicity with 5-fluorouracil and capecitabine: more than just vasospastic angina.

**Author(s):** Stewart, T; Pavlakis, N; Ward, M

**Source:** Internal medicine journal; Apr 2010; vol. 40 (no. 4); p. 303-307

**Publication Date:** Apr 2010

**Publication Type(s):** Case Reports Journal Article

**PubMedID:** 20529041

Available at Internal Medicine Journal - from Wiley Online Library Science, Technology and Medicine Collection 2017

**Abstract:** In this case series we present a variety of different cardiac toxicities with 5-fluorouracil and its pro-drug capecitabine, including myocardial infarction, cardiomyopathy, sinoatrial and atrioventricular node dysfunction, takotsubo cardiomyopathy and QT prolongation with torsade-de-pointes ventricular tachycardia. We stress the fact that while vasospasm is a well-recognized side-effect of this class of chemotherapeutic agent, broader cardiotoxicity is commonly seen and an increased awareness of the range of toxicity is necessary if repeat toxicity is to be avoided.

**Database:** Medline


**Author(s):** Ang, C; Kornbluth, M; Thirlwell, M P; Rajan, R D

**Source:** Current oncology (Toronto, Ont.); Feb 2010; vol. 17 (no. 1); p. 59-63

**Publication Date:** Feb 2010

**Publication Type(s):** Journal Article

**PubMedID:** 20179805

Available at Current Oncology - from Europe PubMed Central - Open Access

Available at Current Oncology - from Free Medical Journals . com

Available at Current Oncology - from PubMed Central

**Abstract:** Capecitabine, an oral prodrug of 5-fluorouracil (5FU), has been integrated into the management of multiple cancer types because of convenience of administration and efficacy comparable with 5fu. Cardiotoxicity induced by 5FU-in particular angina-has been well described in the literature, but reports of adverse cardiac events with capecitabine are also emerging. The mechanism underlying 5FU cardiotoxicity has long been thought to result from coronary vasospasm, but animal-model studies and patient echocardiographic findings both suggest a cardiomyopathic picture. Although 5FU cardiotoxicity is often reversible and can be managed supportively, presentations that are more severe-including arrhythmias, acute ischemic events, and cardiogenic shock-have been documented. In this report, we describe the case of a patient who ultimately required a pacemaker after developing symptomatic bradycardia and sinus arrest while receiving capecitabine for colon cancer.

**Database:** Medline
25. Cardiac toxicity with capecitabine, vinorelbine and trastuzumab therapy: case report and review of fluoropyrimidine-related cardiotoxicity.

**Author(s):** Le Brun-Ly, Valérie; Martin, Jean; Venat-Bouvet, Laurence; Darodes, Nicole; Labourey, Jean-Luc; Genet, Dominique; Tubiana-Mathieu, Nicole

**Source:** Oncology; 2009; vol. 76 (no. 5); p. 322-325

**Publication Date:** 2009

**Publication Type(s):** Case Reports Journal Article

**PubMedID:** 19307737

Available at Oncology - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:** A 45-year-old woman presented with a metastatic breast carcinoma and was treated with capecitabine, oral vinorelbine and trastuzumab combination therapy. The initial echocardiogram and the ECG were considered normal. She began treatment with 3-weekly cycles of the combination therapy. After the fourth dose of capecitabine, she presented with severe chest and arm pain, which was responsive to nitroglycerine spray. ECG at admission demonstrated tachycardia with ST-segment elevation suggesting ischemia. The clinical symptoms returned to baseline after a few hours and within 24 h the ECG showed inverted T in leads V3-V6. Cardiac ultrasonography revealed hypokinesia in the left ventricle without segmentary hypokinesia, with mildly reduced global systolic function, which normalized 1 week later. Two weeks later, she was rechallenged with capecitabine. After the fourth dose, the patient developed chest pain. ECG showed infero-apico-lateral injury, which normalized after administration of nitrates, nicorandil and verapamil and discontinuation of capecitabine. This case suggests that capecitabine can lead to the cardiotoxicity characteristic of other fluoropyrimidines. Therefore, it is important to inform patients about the risk of angina-like chest pain, to stop treatment immediately if symptoms occur, and to monitor the patient in hospital. Fluoropyrimidine rechallenge should be avoided because of the risk of ischemic event or sudden death.

**Database:** Medline


**Author(s):** Farina, Andrea; Malafronte, Cristina; Valsecchi, Maria Antonia; Achilli, Felice

**Source:** Journal of cardiovascular medicine (Hagerstown, Md.); Sep 2009; vol. 10 (no. 9); p. 722-726

**Publication Date:** Sep 2009

**Publication Type(s):** Case Reports Journal Article

**PubMedID:** 19584743

**Abstract:** We present a case of capecitabine-induced cardiac toxicity manifested by chest pain, ST-segment elevation and ventricular tachycardia. Symptoms and ECG alterations were completely reversible after withdrawal of the drug. Coronary angiography demonstrated the absence of epicardial coronary spasm. We suggest cardiac monitoring with ECG Holter and effort ECG during the first days of drug administration. Prompt evaluation of chest pain in this setting is of paramount importance.

**Database:** Medline
27. Cardiac toxicity with anti-HER-2 therapies: what have we learned so far?

Author(s): de Azambuja, Evandro; Bedard, Philippe L; Suter, Thomas; Piccart-Gebhart, Martine

Source: Targeted oncology; Apr 2009; vol. 4 (no. 2); p. 77-88

Publication Date: Apr 2009

Publication Type(s): Journal Article Review

PubMedID: 19418111

Available at Targeted Oncology - from SpringerLink
Available at Targeted Oncology - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract: Trastuzumab, a monoclonal antibody that blocks HER-2 receptor, improves the survival of women with HER-2-positive early and advanced breast cancer when given with chemotherapy. Lapatinib, a dual tyrosine kinase inhibitor of EGFR and HER-2, is approved for the treatment of metastatic breast cancer patients after failure of prior anthracycline, taxanes and trastuzumab therapies in combination with capecitabine. Importantly, cardiac toxicity, manifested as symptomatic congestive heart failure or asymptomatic left ventricular ejection fraction decline, has been reported in some of the patients receiving these novel anti-HER-2 therapies, particularly when these drugs are used following anthracyclines, whose cardiotoxic potential has been recognized for decades. This review will focus on the incidence, natural history, underlying mechanisms, management, and areas of uncertainty regarding trastuzumab-and lapatinib-induced cardiotoxicity.

Database: Medline

28. Capecitabine cardiotoxicity—case reports and literature review.

Author(s): Manojlovic, Nebojsa; Babic, Dragana; Stojanovic, Snezana; Filipovic, Ivana; Radoje, Doder

Source: Hepato-gastroenterology; 2008; vol. 55 (no. 85); p. 1249-1256

Publication Date: 2008

Publication Type(s): Case Reports Journal Article Review

PubMedID: 18795667

Abstract: This study presents 3 case reports of patients who experienced anginous pain during treatment with capecitabine. The interruption of capecitabine and sublingual or intravenous nitroglycerine treatment lead to recovery. Rechallenge of capecitabine with dose reduction of 30% lead to repeated anginous pain in 2 patients. Treatment with capecitabine had been replaced with weekly bolus 5FU-LV, without further cardiotoxicity. The literature contains data from about 50 patients who experienced cardiotoxicity during capecitabine treatment. The most frequent manifestations of capecitabine cardiotoxicity included: anginous pain in 38/53 (71.7%), arrhythmia in 6/53 (11.3%), myocardial infarction in 6/53 (11.3%). Cardiotoxicity of capecitabine lead to death in 6/53 (11.3%) patients. Risk factors for cardiotoxicity are associated with the grade 4 and the fatal outcome of cardiotoxicity (p = 0.035, p = 0.015), but not with the symptom recurrence upon capecitabine rechallenge (p = 0.18). The combination chemotherapy regimens are associated with the grade 4 of cardiotoxicity (p = 0.048), but not with the fatal outcome (p = 0.3). Rechallenge of capecitabine lead to symptoms recurrence in 10/16 patients. Neither the dose reduction of capecitabine (p = 0.18) nor the additional medical prophylaxis (p = 0.37) were important for the outcome of capecitabine rechallenge.

Database: Medline
29. Capecitabine induced vasospastic angina.

**Author(s):** Coughlin, Stephanie; Das, Saugata; Lee, Justin; Cooper, John

**Source:** International journal of cardiology; Oct 2008; vol. 130 (no. 1); p. e34

**Publication Date:** Oct 2008

**Publication Type(s):** Journal Article

**PubMedID:** 17897740

**Abstract:** Cardiotoxicity is a recognised side effect of intravenous 5-fluorouracils. In the two case reports described we demonstrate similar cardiotoxic side effects seen with the use of capecitabine. With the increasing use of oral adjuvant chemotherapeutic agents, capecitabine should be used with caution in those patients with existing coronary artery disease.

**Database:** Medline

30. Cardiotoxicity with fluorouracil and capecitabine revisited

**Author(s):** Tejwani A.; Yates T.; Tejwani S.

**Source:** Community Oncology; Oct 2008; vol. 5 (no. 10); p. 566-568

**Publication Date:** Oct 2008

**Publication Type(s):** Article

**Abstract:** A relatively rare but potentially fatal toxicity that has been observed in patients predominantly receiving intravenous fluorouracil (5-FU)-based chemotherapy is cardiotoxicity. Here we present two cases in which patients were treated with 5-FU-based chemotherapy and subsequently developed cardiotoxicity, in the setting of recently being exposed to continuous 5-FU. Our first patient had no history of major cardiac events but did have cardiac risk factors of tobacco use, hypercholesterolemia, and hypertension. The timing of chemotherapy and the cardiac event in this patient makes it more likely that the incident is due to 5-FU use. Interestingly, the second patient had a history of cardiac disease and had been previously treated with intravenous 5-FU and oral capecitabine with no untoward effects. However, after later exposure to continuous infusion 5-FU, he developed cardiotoxicity. Thus, the question remains as to whether or not continuous infusion 5-FU is more of a cardiotoxic risk than bolus injection 5-FU or oral capecitabine. © 2008 Elsevier Inc. All rights reserved.

**Database:** EMBASE
31. Cardiac toxicity: old and new issues in anti-cancer drugs.

**Author(s):** Sereno, M; Brunello, A; Chiappori, A; Barriuso, J; Casado, E; Belda, C; de Castro, J; Feliu, J; González-Barón, M

**Source:** Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico; Jan 2008; vol. 10 (no. 1); p. 35-46

**Publication Date:** Jan 2008

**Publication Type(s):** Journal Article Review

**PubMedID:** 18208791

**Abstract:** Although rare, cardiotoxicity is a significant complication of cancer treatment. The incidence and severity of cardiovascular side effects are dependent on the type of drugs used, dose and schedule employed, and age of patients, as well as the presence of coexisting cardiac diseases and previous mediastinal irradiation. Classically, anthracyclines are among one of the most active agents in oncology, but their use is often hampered by their cumulative dose-limiting cardiotoxicity. In the past decade, combination therapy with new drugs such as taxanes or anti-EGFR, and Her-2 therapy as a single agent have also resulted in unexpected cardiotoxicity. Cardiac damage can be secondary to an alteration of cardiac rhythm, changes in blood pressure and ischaemia, and can also alter the ability of the heart to contract and/or relax. The clinical spectrum of these toxicities can range from subclinical abnormalities to being catastrophic, life-threatening and sometimes fatal. Knowledge of this toxicity can aid clinicians to choose the optimal and least toxic regimen suitable for an individual patient. In this work we present an exhaustive review of the cardiovascular side effects associated to new anticancer drugs, from new formulations of anthracyclines to tyrosine kinase inhibitors and monoclonal antibodies.

**Database:** Medline

32. Capecitabine-related cardiotoxicity: recognition and management.

**Author(s):** Saif, Muhammad Wasif; Tomita, Megumi; Ledbetter, Leslie; Diasio, Robert B

**Source:** The journal of supportive oncology; Jan 2008; vol. 6 (no. 1); p. 41-48

**Publication Date:** Jan 2008

**Publication Type(s):** Journal Article

**PubMedID:** 18257400

**Database:** Medline
33. Heart failure induced by non-cardiac drugs.

Author(s): Slørdal, Lars; Spigset, Olav

Source: Drug safety; 2006; vol. 29 (no. 7); p. 567-586

Publication Date: 2006

Publication Type(s): Journal Article Review

PubMedID: 16808550

Abstract: Although heart failure is predominantly caused by cardiovascular conditions such as hypertension, coronary heart disease and valvular heart disease, it can also be an adverse reaction induced by drug therapy. In addition, some drugs have the propensity to adversely affect haemodynamic mechanisms in patients with an already existing heart condition. In this article, non-cardiac drugs known to be associated with the development or worsening of heart failure are reviewed. Moreover, drugs that may adversely affect the heart as a pump without causing symptoms or signs of heart failure are also included. The drugs discussed include anticancer agents such as anthracyclines, mitoxantrone, cyclophosphamide, fluorouracil, capecitabine and trastuzumab; immunomodulating drugs such as interferon-alpha-2, interleukin-2, infliximab and etanercept; antidiabetic drugs such as rosiglitazone, pioglitazone and troglitazone; antimigraine drugs such as ergotamine and methysergide; appetite suppressants such as fenfluramine, dexfenfluramine and phentermine; tricyclic antidepressants; antipsychotic drugs such as clozapine; antiparkinsonian drugs such as pergolide and cabergoline; glucocorticoids; and antifungal drugs such as itraconazole and amphotericin B. NSAIDs, including selective cyclo-oxygenase (COX)-2 inhibitors, are included as a result of their ability to cause heart disease, particularly in patients with an already existing cardiorenal dysfunction. Two drug groups are of particular concern. Anthracyclines and their derivatives may cause cardiomyopathy in a disturbingly high number of exposed individuals, who may develop symptoms of insidious onset several years after drug therapy. The risk seems to encompass all exposed individuals, but data suggest that children are particularly vulnerable. Thus, a high degree of awareness towards this particular problem is warranted in cancer survivors subjected to anthracycline-based chemotherapy. A second group of problematic drugs are the NSAIDs, including the selective COX-2 inhibitors. These drugs may cause renal dysfunction and elevated blood pressure, which in turn may precipitate heart failure in vulnerable individuals. Although NSAID-related cardiotoxicity is relatively rare and most commonly seen in elderly individuals with concomitant disease, the widespread long-term use of these drugs in risk groups is potentially hazardous. Pending comprehensive safety analyses, the use of NSAIDs in high-risk patients should be discouraged. In addition, there is an urgent need to resolve the safety issues related to the use of COX-2 inhibitors. As numerous drugs from various drug classes may precipitate or worsen heart failure, a detailed history of drug exposure in patients with signs or symptoms of heart failure is mandatory.

Database: Medline
34. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine.

**Author(s):** Jensen, Søren Astrup; Sørensen, Jens Benn

**Source:** Cancer chemotherapy and pharmacology; Oct 2006; vol. 58 (no. 4); p. 487-493

**Publication Date:** Oct 2006

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 16418875

Available at Cancer chemotherapy and pharmacology - from SpringerLink

Available at Cancer chemotherapy and pharmacology - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:** AIM5-fluorouracil (5-FU) and its prodrug capecitabine are cardiotoxic. This retrospective study aimed to identify risk factors and to give practical measures to make such chemotherapy feasible if cardiotoxicity occur. METHOD: Review of cardiotoxicity among 668 patients treated with 5-FU or capecitabine for gastrointestinal cancers. RESULT: Cardiotoxicity occurred in 29 cases (4.3%). The number of cases according to cardiotoxicity CTC grades 2-4 for patients with and without pre-existing cardiovascular disease were none, 10, and 2 cases, and 3, 14, and no cases, respectively (P=0.16). In three patients intercurrent decrease of renal clearances to <30, 48 and 71 ml min(-1) led to markedly increased cardiotoxicity. Chemotherapy dose reduction to 70 or 50%, either alone or in addition to antiangina medication prevented cardiotoxicity during subsequent chemotherapy in nine (60%) and three (20%) cases out of 15 assessable patients (P=0.001), respectively. To abolish symptoms of cardiotoxicity, sublingual nitroglycerine was efficient for 15 patients and inefficient for two (P=0.001). CONCLUSION: Cardiac and renal co-morbidity are risk factors for 5-FU induced cardiotoxicity. In this situation, rechallenge with modified 5-FU-based chemotherapy regimen supported by symptomatic medical treatment is feasible.

**Database:** Medline

35. Cardiac toxicity associated with capecitabine therapy.

**Author(s):** Saif, M Wasif; Quinn, Mary G; Thomas, Rebecca R; Ernst, Aaron; Grem, Jean L

**Source:** Acta oncologica (Stockholm, Sweden); 2003; vol. 42 (no. 4); p. 342-344

**Publication Date:** 2003

**Publication Type(s):** Case Reports Journal Article

**PubMedID:** 12899507

Available at Acta oncologica (Stockholm, Sweden) - from Free Medical Journals . com

**Database:** Medline

Author(s): Singer, Marybeth

Source: Clinical journal of oncology nursing; 2003; vol. 7 (no. 1); p. 72-75

Publication Date: 2003

Publication Type(s): Case Reports Journal Article

PubMedID: 12629938

Abstract: Oral fluoropyrimidines increasingly are being developed and studied as a novel treatment for breast, colorectal, and other cancers. Fluoropyrimidines are designed to generate 5-fluorouracil (5-FU) preferentially within tumors. Cardiotoxicity is a rare complication associated with 5-FU and oral fluoropyrimidine treatments. Chest pain is the most common presenting symptom, and, in many cases, the cardiotoxicity is partly or completely reversible. This article reviews fluoropyrimidine-induced cardiotoxicity and presents a case report of a woman who experienced this complication during capecitabine treatment.

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