Coronary Artery Vasospasm Induced by 5-fluorouracil: Proposed Mechanisms, Existing Management Options and Future Directions

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Abstract

Cardiovascular disease and cancer are leading contributors to the global disease burden. As a result of cancer therapy-related cardiotoxicities, cardiovascular disease results in significant morbidity and mortality in cancer survivors and patients with active cancer. There is an unmet need for management of cardio-oncology conditions, which is predicted to reach epidemic proportions, and better understanding of their pathophysiology and treatment is urgently required. The proposed mechanisms underlying cardiotoxicity induced by 5-fluorouracil (5-FU) are vascular endothelial damage followed by thrombus formation, ischaemia secondary to coronary artery vasospasm, direct toxicity on myocardium and thrombogenicity. In patients with angina and electrocardiographic evidence of myocardial ischaemia due to chemotherapy-related coronary artery vasospasm, termination of chemotherapy and administration of calcium channel blockers or nitrates can improve ischaemic symptoms. However, coronary artery vasospasm can recur with 5-FU re-administration with limited effectiveness of vasodilator prophylaxis observed. While pre-existing coronary artery disease may increase the ischaemic potential of 5-FU, cardiovascular risk factors do not appear to completely predict the development of cardiac complications. Pharmacogenomic studies and genetic profiling may help predict the occurrence and streamline the treatment of 5-FU-induced coronary artery vasospasm. Echocardiographic measures such as the Tei index may help detect subclinical 5-FU cardiotoxicity. Further research is required to explore the cardioprotective effect of agents such as coenzyme complex, GLP-1 analogues and degradation inhibitors on 5-FU-induced coronary artery vasospasm.

Keywords

5-fluorouracil, capecitabine, coronary artery vasospasm, calcium channel blockers, verapamil, diltiazem

Disclosure: The authors have no conflicts of interest to declare.

Received: 25 February 2019 Accepted: 17 April 2019 Citation: Interventional Cardiology Review 2019;14(2):89–94. DOI: https://doi.org/10.15420/icr.2019.12

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Cardiovascular disease is the leading cause of morbidity and mortality worldwide.1 The WHO estimates that 17 million people die each year of cardiovascular disease, about 30% of all deaths.2 Cancer is the second leading cause of death globally and is associated with 9 million deaths each year.3 According to the WHO, the incidence of cancer is expected to rise by about 70% over the next 20 years.4 Half of those diagnosed with cancer will survive for at least a decade, but this survival rate is expected to increase significantly in future and worsen the burden of cancer-related complications experienced by the global population.5,6

Significant progress in cancer therapy has greatly improved the mortality of cancer patients, with non-malignant comorbid conditions becoming important determinants of their quality of life and overall survival.7 Among this heterogeneous group of comorbid conditions, cardiovascular diseases are a major contributor to overall morbidity and mortality in cancer survivors and patients with active cancer.8

Factors Contributing to the Clinical Entity of Cardio-oncology

Heart disease and cancer share common risk factors in an ageing population and are further linked through cardiotoxic effects of contemporary cancer treatment.9–11 Many cancer patients have subclinical cardiovascular disease, which can be worsened by the pro-inflammatory and hypercoagulable states associated with cancer, although precisely defining cardiotoxicity can be a challenge.12–15

Pathophysiology of Accelerated Atherosclerosis and Plaque Rupture in Cardio-oncology

Many cancer therapies cause acute endothelial damage, vasospasm, platelet-platelet activation and aggregation, and attraction of elevated low-density lipoprotein cholesterol particles.16 This can lead to formation of potentially unstable lipid-rich coronary plaques and to the initiation and acceleration of the atherosclerosis process.17 When these lipid-rich plaques result in haemodynamically significant flow-limiting stenosis, symptoms of cardiovascular ischaemia such as angina can ensue.18 Vulnerable plaques, composed of a thin fibrous cap and large lipid cores (also known as thin-cap fibroatheromas), are also more susceptible to rupture with acute thrombus formation, resulting in acute coronary syndromes (ACS).19–21 Optimum management of ischaemic heart disease is necessary for this complex group of cardio-oncology patients to improve their overall outcome and quality of life.
Coronary Artery Vasospasm Induced by 5-fluorouracil

The relatively new, unmet medical need for management of chemotherapy- and radiotherapy-induced cardiovascular disease is predicted to reach epidemic proportions in the near future.4,5,21

Cardiotoxicity Secondary to 5-fluorouracil and Capecitabine

Cardiac ischaemia associated with chemotherapy has been linked to several antineoplastic agents and is multifactorial in aetiology.22 Coronary artery vasospasm is one of the most commonly reported effects of cancer therapy that can lead to myocardial ischaemia or infarction.23,24 The chemotherapy agent 5-fluorouracil (5-FU) or its oral pro-drug capecitabine can result in coronary vascular endothelial dysfunction causing coronary artery spasm, and possibly coronary thrombosis, with a wide range of reported incidence between 1% and 68%.25,26 These agents are used to treat solid cancers, including gastrointestinal, breast, head, neck and pancreatic cancers.27 These drugs have also been shown to be associated with myocardial infarction or malignant ventricular arrhythmias.28

Capecitabine is converted to 5-FU in a three-step process involving several enzymes.29 The last stage is catalysed by thymidine phosphorylase.30 Many body tissues express thymidine phosphorylase, but this enzyme is expressed in higher concentrations in some carcinomas than in the surrounding normal tissues.29 Based on this theory, the concentration of 5-FU at the tumour site should be increased compared to the concentration of 5-FU in healthy tissues, resulting in fewer side-effects involving healthy tissue.29

The incidence of capecitabine-associated cardiac side-effects is 3–35%, gathered from the few studies of capecitabine cardiotoxicity.24,26,30–32 Case reports of cardiotoxicity after administration of capecitabine are similar to intravenous 5-FU treatment, with the predominant symptom being chest pain.23–25 Other less frequent adverse effects are cardiac arrhythmias, myocardial infarction, heart failure, cardiogenic shock and sudden death.26–29

Chest pain onset is often abrupt during infusion of 5-FU, but can also be delayed, presenting within the first 72 hours after 5-FU administration.28,30 Often, angina is accompanied by ECG changes including ST depression and prolonged repolarisation abnormalities.28 Cardiac enzymes are infrequently elevated in angina (12% of cases), and echocardiography can show regional or global hypokinesis that usually return to baseline within 48 hours of 5-FU cessation.30 Significant coronary artery disease and acute plaque rupture is usually ruled out on coronary angiography, which leads to the consideration of coronary artery vasospasm.23,30

In a review of 377 patients with 5-FU-induced cardiotoxicity, cardiovascular risk factors such as smoking, diabetes, hypercholesterolaemia and family history of heart disease were found in 37% of the patients. Smoking was the most common risk factor among these groups of patients.31

Previous or concomitant radiation therapy may play a role in 5-FU-induced cardiac toxicity as radiation can cause small-vessel thrombosis. 5-FU is a radiosensitiser and may enhance radiation-induced thrombosis.1,12

There is a higher incidence of angina with administration through continuous infusion compared to bolus infusion.38,39 It is unclear if this effect is dose-dependent, and although cessation of 5-FU results in resolution of angina, symptoms have been reported to last up to 12 hours.40 Re-initiation of 5-FU has been associated with increased incidence of angina with serious complications including acute coronary syndrome, hypotension, cardiac failure, and even death.38,41

While the causative relationship is unclear, endothelin-1 levels have been noted to be elevated in angina patients with 5-FU infusion.36 Patients with known pre-existing history of coronary artery disease also have a higher incidence of angina, and are considered to have an increased risk of developing cardiac ischaemia.34,42

In addition to high doses of 5-FU, prior mantle radiation, or simultaneous administration of another cardiotoxic chemotherapeutic agent are factors that can contribute to development of cardiac ischaemia in patients treated with antimetabolite drugs.44,45 In one large study, myocardial ischaemia was reported in 4% of patients receiving high-dose, continuous infusion of 5-FU.46 However, the failure of ergonovine and 5-FU to produce direct vasospasm during cardiac catheterisation has questioned the hypothesis of abnormal vasoreactivity being the predominant mechanism causing 5-FU associated myocardial ischaemia.24,47 Age of the patient did not seem to influence the occurrence of cardiotoxicity.46

Proposed Pathophysiological Mechanisms of 5-fluorouracil-induced Cardiotoxicity

The pathophysiological mechanisms underlying 5-FU-induced cardiotoxicity remain undefined.46,50–52 Several mechanisms have been proposed, including vascular endothelial damage followed by coagulation, ischaemia secondary to coronary artery spasm, direct toxicity on the myocardium and thrombogenicity.27

The theory of 5-FU-induced vasospasm resulting in myocardial ischaemia has been proposed in the context of failure of coronary angiography in general to show fixed stenoses in patients with acute 5-FU-induced cardiotoxicity.43–45 In a few cases, coronary artery vasospasm has been demonstrated during coronary angiography.45–54

In the study of the effect of 5-FU on the peripheral vasculature, vasoconstriction of the brachial artery was noted to appear immediately after 5-FU injection.39,40 While vasoconstriction has been observed immediately after 5-FU injection, clinical cardiotoxicity often presents at the end of the infusion, or even hours to days later.46 Moreover, cardiotoxicity may occur only after several cycles of 5-FU or its oral pro-drug capecitabine.

Cwikiel et al. examined the endothelium of small arteries from rabbits after incubation with 5-FU.41 Vessel wall and endothelial cell contraction, cell oedema, cytolysis, occurrence of denuded areas, platelet adhesion/aggregation and fibrin formation were evaluated. The findings support the hypothesis that direct cytotoxic mechanisms on endothelial cells predominate, whereas thrombogenic features play a minor role.22

Endothelial Nitric Oxide Synthase

One proposed mechanism for the pathophysiology of 5-FU-induced coronary spasm is that it exerts toxic effects on the vascular endothelium through endothelial nitric oxide synthase (eNOS), leading to coronary spasm and endothelium-independent vasoconstriction via protein kinase C.46 Nitric oxide (NO) produced by eNOS and its
interaction with serine/threonine protein kinase Akt/PKB, with caveolin and calmodulin is a key determinant of cardiovascular tone.\textsuperscript{66,69}

**Endothelin-1**

Raised plasma levels of endothelin-1 were observed by Thyss et al. in patients receiving 5-FU, especially in those experiencing 5-FU-induced cardiotoxicity.\textsuperscript{67} This observation may support the hypothesis of 5-FU-induced vasoconstriction.\textsuperscript{27} Endothelin-1 is a potent vasoconstrictor, which is produced by endothelial cells, cardiomyocytes and cardiac fibroblasts, as well as several noncardiac tissues such as the lungs.\textsuperscript{68,69} Endothelin-1 plays a regulatory role in coronary vascular resistance and myocardial capillary blood flow in coronary artery disease states.\textsuperscript{69–71} Hypoxia, ischaemia or shear stress induces vascular endothelial cells to synthesise and secrete endothelin-1.\textsuperscript{14} Endothelin-1 in turn is synthesised from the precursor peptide big endothelin.\textsuperscript{44}

Salepci et al. found a trend towards increased big endothelin levels in the plasma of 5-FU treated patients, but this trend was not restricted to patients who experienced vasosonstriction.\textsuperscript{25} To further understand the role of endothelins in 5-FU-induced cardiotoxicity, the cellular source of endothelin-1 and the effect of endothelin-1 on vasomotor tone during the infusion of 5-FU should be further studied.\textsuperscript{27}

**Protein Kinase C**

Staurosporine is a protein kinase C (PK-C) inhibitor and pre-treatment with it reduced 5-FU-induced vasoconstriction.\textsuperscript{70} Phorbol 12,13-dibutyrate is an activator of PK-C and pre-treatment with it increased the magnitude of 5-FU-induced vasoconstriction by 23 times.\textsuperscript{72}

**Acetylcholine**

Acetylcholine induces vasodilation through the NO-cGMP pathway.\textsuperscript{73} Acetylcholine is endothelium-dependant and hence intact endothelial cells are a requirement for acetylcholine-induced vasodilatation.\textsuperscript{73} In fact, in the absence of endothelial cells, acetylcholine actually leads to vasoconstriction.\textsuperscript{73} It seems unlikely that the mechanism through which 5-FU causes functional vasosonstriction is through impaired vasodilatory response, as it has been observed that both acetylcholine-induced vascular relaxation and vascular relaxation by glyceryl nitrate were intact during 5-FU infusion.\textsuperscript{72} More research is required in this area to further delineate pathophysiological mechanisms behind proposed 5-FU-induced coronary artery vasospasm.

**Proposed Management of 5-fluorouracil-induced Cardiotoxicity**

**Controversy Over the Use of Calcium Channel Blockers**

Prophylactic nitrates and calcium channel blockers do not appear to reduce chest pain incidence, and vasospasm has not been clearly seen on coronary angiography.\textsuperscript{26}

5-FU has been found to increase the expression of thioredoxin-interacting protein (TXNIP).\textsuperscript{74} A number of studies have shown that verapamil and diltiazem suppress TXNIP expression.\textsuperscript{75} Chen et al. reported that verapamil and diltiazem reduced TXNIP transcription and protein levels in cultured cardiomyocytes in the presence of raised glucose concentrations.\textsuperscript{75} Subsequently, the same group also demonstrated the attenuation of the pro-apoptotic effects of TXNIP by verapamil.\textsuperscript{75} It may be appropriate therefore to determine whether TXNIP suppression might contribute to the clinical effectiveness of calcium channel blockers in inhibiting coronary artery spasm.\textsuperscript{75}

This clinical effect is, in turn, inconsistent in 5-FU-induced coronary artery vasospasm. In a study by Moss et al., rabbit aorta rings were pre-treated in vitro with verapamil and diltiazem prior to 5-FU exposure.\textsuperscript{75} Of note, there was no observed effect of the calcium channel blockers verapamil and diltiazem on vasospasm.\textsuperscript{75} The clinical translation of this study remains to be determined.

**Treatment Options for 5-fluorouracil-induced Coronary Artery Spasm**

While pre-existing coronary artery disease may increase the ischaemic potential of 5-FU, the presence of cardiac risk factors does not appear to completely predict the development of adverse cardiac side-effects.\textsuperscript{69} Nitrates and calcium channel blockers have been used to treat and prevent coronary artery spasm in high-risk patients.\textsuperscript{79}

In patients with angina and electrocardiographic evidence of myocardial ischaemia due to coronary artery vasospasm while receiving chemotherapy, termination of therapy and administration of calcium channel blockers or oral nitrates can improve the ischaemic symptoms.\textsuperscript{78} These patients might have clinical reoccurrence of coronary vasospasm with subsequent 5-FU re-exposure.\textsuperscript{67} Although treatment with vasodilators have been proposed as prophylaxis against coronary artery vasospasm, limited effectiveness of this prophylactic therapy has been observed.\textsuperscript{80}

Due to the potential for arrhythmias, ECG monitoring is recommended if there is any evidence for cardiac side-effects during treatment.\textsuperscript{81} Subsequent to non-invasive testing and risk stratification for the presence of coronary artery disease, coronary angiography should be considered in patients who develop coronary artery vasospasm. Prophylactic treatment with verapamil and nitrates could be considered for patients with coronary artery disease and patients who had already been symptomatic following 5-FU administration.\textsuperscript{82} Due to the severity of cardiac side-effects, including sudden cardiac death, early discontinuation of 5-FU and modification of the therapeutic regimen should be taken into account.\textsuperscript{83,84}

Kinhult et al. showed that antithrombotic treatment with dalteparin can protect against thrombogenic effects of 5-FU, secondary to its direct toxic effect on the vascular endothelium.\textsuperscript{31}

Spasmodic drugs, e.g. beta-blockers, should be avoided. This hypothesis is supported by a few reports.\textsuperscript{85,86} Taking haematological disorders into account, inhibition of platelet aggregation potentially could be helpful as well.

Patients developing ischaemic events usually have recurrences if the drug is subsequently administered, so consideration must be given to withholding future 5-FU therapy if a patient develops ischaemic events while on the drug.\textsuperscript{87,88}

**Developing and Experimental Treatment Options**

In a 54-patient study by Zhang et al., coenzyme complex was found to decrease cardiotoxicity when combined with chemotherapy in treating elderly patients with gastrointestinal cancer.\textsuperscript{81} Coenzyme complex was postulated to confer cardioprotection through cell membrane stabilisation, enhanced mitochondrial energy production, antioxidant action and favourable effects on metabolism of long-chain fatty acids. Further research is required in this area to explore the cardioprotective effect of coenzyme complex on 5-FU-induced coronary artery vasospasm.
In a cell-based study by Altieri et al., GLP-1 counteracted 5-FU-initiated endothelial cell senescence and reduced eNOS and SIRT-1 expression, with this protection being mediated by GLP-1 receptor, ERK1/2 and, possibly, PKA and PI3K. This group noted that 5-FU caused endothelial cell senescence and dysfunction, which may contribute to its cardiovascular side-effects. 5-FU-induced endothelial cell senescence was found to be prevented by GLP-1, raising the possibility of using GLP-1 analogues and GLP-1 degradation inhibitors to treat 5-FU and capetabine induced cardiotoxicity.

Since it is known that the complex system of eNOS regulation is crucial for the vascular tone, Hayward et al. addressed the hypothesis that regular physical activity may help induce endothelium-dependent vasodilation after exposure to 5-FU. Rats were stratified into one group with regular exercise training and one sedentary group. After 8 weeks of physical training, aortic rings were obtained and used to assess contractile and relaxation characteristics. Exercise training resulted in increased maximal endothelium-dependent vasorelaxation to acetylcholine after norepinephrine-induced vasoconstriction. Rings obtained from exercise-trained animals demonstrated enhanced vasorelaxation in response to acetylcholine after 5-FU-induced vasoconstriction when compared with rings obtained from sedentary animals. In addition, exercise training enhanced eNOS protein content and eNOS enzyme activity. Thus, exercise training enhanced endothelium-dependent vasorelaxation after 5-FU-induced vasoconstriction. This could have clinical implications if translated into human studies.

**Future Directions**

Heart-type fatty acid-binding protein (h-FABP) and the myocardial performance index have been suggested to have the potential to be useful in the early detection of ischaemic coronary vasospasm induced by 5-FU. h-FABP is a small cytoplasmic protein that is present at high levels in myocardial cells and released into the blood circulation within minutes of ischaemia.

Myocardial performance index, also known as the Tei index, is a Doppler index that can evaluate left ventricular systolic and diastolic functions concurrently and can assist in detecting subtle changes in cardiac function. Turan et al. studied 32 cancer patients receiving their first 5-FU-based chemotherapy were studied. Prior to chemotherapy and 24 hours after the initiation of chemotherapy, all patients underwent echocardiography. The authors measured h-FABP and troponin I (TnI) levels at different time points during the first 24 hours of 5-FU administration. Post-infusion echocardiography revealed worsening in the Tei index. Clinically overt cardiotoxicity was evident in four members (12.5%) of the study group. h-FABP and TnI levels were within normal ranges throughout. These results suggest that the Tei index can be proposed as a sensitive indicator of occult 5-FU cardiotoxicity.

Pharmacogenomics studies have shed insight into the correlations of drug efficacy and toxicity with patient genome variations. 5-FU cardiotoxicity can potentially be modulated by being selective in the treatment regimen administered in each patient with the help of genetic profiling. Several studies have highlighted genetic polymorphisms in DPYD, TYMS, MTHFR and OPRT as potential risk factors for serious toxicity. Determination of polymorphisms in xenobiotic metabolising enzymes through genetic profiling before 5-FU administration might suggest new and individualised strategies for optimising chemotherapy safety.

Oral derivatives and pro-drugs have been developed to provide an alternative route of 5-FU administration. Differences have been reported regarding the adverse effect profiles of intravenous S-FU and its oral pro-drug. The impact of genetic variations on the risk of severe toxicity may potentially differ between the two administration forms. Further investigation is required to understand the relationship between individual DPYD variants and the different 5-FU-based chemotherapy regimens.

**Conclusion**

Cardiovascular disease and cancer are the two leading causes of disease burden in the world. As a result of cardiotoxicities of cancer therapies and the prevalence of cardiovascular comorbidity, cardiovascular diseases are a major contributor to overall morbidity and mortality in cancer survivors and patients with active cancer. There is an unmet medical need for management of cancer therapy-induced cardiovascular disease which is predicted to reach epidemic proportions in the near future and better understanding of the pathophysiology and treatment of cardio-oncology conditions are urgently required. High-dose 5-FU or its oral pro-drug capetabine is thought to cause coronary vascular endothelial dysfunction resulting in coronary artery spasm, and possibly coronary thrombosis.

The pathophysiological mechanisms underlying 5-FU-induced cardiotoxicity remain undefined with several proposed mechanisms being vascular endothelial damage followed by coagulation, ischaemia secondary to coronary artery spasm, direct toxicity on the myocardium and thrombogenicity.

In patients with angina and electrocardiographic evidence of myocardial ischaemia due to coronary artery vasospasm while receiving chemotherapy, termination of therapy and administration of calcium channel blockers or oral nitrates can improve the ischaemic symptoms.

Coronary artery spasm can, however, reoccur with 5-FU re-administration with limited effectiveness of vasodilator prophylaxis observed. While pre-existing coronary artery disease may increase the ischaemic potential of 5-FU, the presence of cardiac risk factors does not appear to completely predict the development of adverse cardiac side-effects. Pharmacogenomic studies and genetic profiling may help predict the development of 5-FU-induced coronary artery vasospasm. Further research is required to explore the cardioprotective effect of agents such as coenzyme complex, GLP-1 analogues and degradation inhibitors on 5-FU-induced coronary artery vasospasm.

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 2019;139:e56-e528. https://doi.org/10.1161/CIR.0000000000000659; PMID: 30703139.
2. Balakumar P, Maung-U K, Jagadesh G. Prevalence and 5-FU and capecitabine induced cardiotoxicity. 92 senescence was found to be prevented by GLP-1, raising the possibility of using GLP-1 analogues and GLP-1 degradation inhibitors to treat S-FU and capetabine induced cardiotoxicity.
3. Leal YA, Fernadez-Garrote LM, Mohar-Betancourt A, Meneses-Garcia A. The importance of registries in cancer control. Salud Publica Mex 2016;58:309–16. PMID: 27537931.
4. WHO. Cancer. Ezzat; WHO. 2018. Available at: https://www.who.int/immunization/news-room/fact-sheets/detail/cancer (accessed 1 May 2019).
5. Lucas G, Marcu A, Piano M, et al. Cancer survivors’ experience with telehealth: a systematic review and thematic synthesis. J Med Internet Res 2017;19(9):e11. https://doi.org/10.2196/jmir.6746; PMID: 28009561.
6. Cancer Research UK. Available at: www.cancerresearchuk.org (accessed 24 April 2019).
7. Siesig R, Dentiants C, Virgo K et al. Cancer treatment and...
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Coronary vasospasm is typically defined as a coronary artery narrowing of >90% in diameter, lasting for >6 min, and as a result of an episodic increased spontaneous tone without a known precipitating factor. This condition usually occurs in patients with stable coronary artery disease (CAD) or in the presence of risk factors for CAD. Coronary vasospasm can lead to acute coronary syndromes, particularly myocardial ischemia and heart attacks. The exact mechanisms underlying coronary vasospasm are still not fully understood, but they involve a complex interplay between endothelial dysfunction, inflammatory processes, and genetic predispositions.

Several studies have investigated the role of 5-fluorouracil (5-FU) and capecitabine, fluoropyrimidines commonly used in the treatment of various cancers, in inducing coronary vasospasm. These drugs are known to cause a variety of side effects, including cardiotoxicity, but the relationship between these drugs and coronary vasospasm is not well established.

In a retrospective study, Koca et al. (2013) evaluated 1106 patients who received either 5-FU or capecitabine and found a higher incidence of congestive heart failure (CHF) in patients receiving 5-FU compared to those receiving capecitabine. However, the study did not provide evidence for a direct causal relationship between 5-FU or capecitabine and coronary vasospasm.

Blann and Dunmore (2009) reviewed the literature on arterial and venous thrombosis in cancer patients and summarized the evidence for a causal relationship between cancer treatments and vascular events. They concluded that there is a significant risk of thrombotic events in cancer patients, especially those receiving chemotherapy.

In a subsequent study, Ng et al. (2010) evaluated the frequency and predictors of vascular events in cancer patients receiving chemotherapy. They found that the risk of vascular events was highest in the first 6 months after chemotherapy initiation and that patients with a history of vascular events were at increased risk of future events.

Herrmann and Lerman (2009) provided an update on cardio-oncology, a subspecialty that focuses on the cardiotoxic effects of cancer treatments. They emphasized the importance of early detection and management of cardiovascular complications in cancer patients.

Wang et al. (2009) conducted a systematic review of the cardiotoxic effects of 5-FU and capecitabine. They identified several studies reporting cardiac symptoms and cardiovascular events in patients receiving these drugs, but the evidence was not conclusive due to the heterogeneous nature of the studies and the lack of randomized controlled trials.

In conclusion, while 5-FU and capecitabine are widely used in cancer treatment, their cardiotoxic effects, including coronary vasospasm, remain a concern. Further research is needed to establish a causal relationship and to develop strategies for early detection and management of these complications.
86. Gorgulu S, Celik S, Tessel T. A case of coronary spasm induced by 5-fluorouracil. *Acta Cardiol* 2002;57:381. https://doi.org/10.2143/AC.57.3.1055579.

87. Abernethy DR, Schwartz J. Calcium-antagonist drugs. *N Engl J Med* 1999;341:1447. https://doi.org/10.1056/NEJM199910043411507; PMID: 10567408.

88. Kleinman ML, Leier AE, Sleyter CE, et al. Prinzmetal’s angina during 5-fluorouracil chemotherapy. *Am J Med* 1987;82:566. PMID: 3824112.

89. O’Connell MJ, Martenson JA, Winstead HJ, et al. Improving adjunct therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *Ann R Coll* 1994;331:502. https://doi.org/10.1056/NEJM199408033310803; PMID: 8041415.

90. Akpek G, Hartshorn KS. Failure of oral nitrate and calcium channel blocker therapy to prevent 5-fluorouracil-related myocardial ischemia: a case report. *Cancer Chemother Pharmacol* 1994;43:157–161. https://doi.org/10.1007/s002800050877; PMID: 9928823.

91. Zhang HY, Lu X. Coenzyme complex decreased cardiotoxicity when combined with chemotherapy in treating elderly patients with gastrointestinal cancer. *Asian Pac J Cancer Prev* 2015;16:4045–49. PMID: 2598784.

92. O’Connell MJ, Martenson JA, Winstead HJ, et al. Improving adjunct therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *Ann R Coll* 1994;331:502. https://doi.org/10.1056/NEJM199408033310803; PMID: 8041415.

93. Hayward R, Ruangthai R, Schneider CM, et al. Training enhances vascular relaxation after chemotherapy-induced vasoconstriction. *Med Sci Sport Exerc* 2004;36:408. PMID: 15076784.

94. Turan T, Agar MF, Akyük C, et al. Usefulness of heart-type fatty acid-binding protein and myocardial performance index for early detection of 5-fluorouracil cardiotoxicity. *Angiology* 2016;67:35–43. https://doi.org/10.1177/0003319716639516; PMID: 26980771.

95. Matsuda S, Lenz HJ. Pharmacogenomics of fluorouracil-based chemotherapy toxicity. *Expert Opin Drug Metab Toxicol* 2015;11:811–21. https://doi.org/10.1517/17425251.2015.1027684; PMID: 25800061.