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

Jun Hua Chong[1] and Arjun K Ghosh[1,2]

*1. Cardio-Oncology Service, Barts Heart Centre, St Bartholomew's Hospital, London, UK; 2. Cardio-Oncology Service, University College London Hospital, Hatter Cardiovascular Institute, London, UK*

## 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 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, 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
**Correspondence:** Arjun K Ghosh, Barts Heart Centre, St Bartholomew's Hospital, West Smithfield, London, EC1A 7BE, UK. E: arjun.ghosh@bartshealth.nhs.uk



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.[16] 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).[17–19] 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.

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.[6,20,21]

## 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.[29] 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.[26,28,30–32] Case reports of cardiotoxicity after administration of capecitabine are similar to intravenous 5-FU treatment, with the predominant symptom being chest pain.[33–35] Other less frequent adverse effects are cardiac arrhythmias, myocardial infarction, heart failure, cardiogenic shock and sudden death.[36–38]

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.[38,39] Often, angina is accompanied by ECG changes including ST depression and prolonged repolarisation abnormalities.[38] 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.[38] Significant coronary artery disease and acute plaque rupture is usually ruled out on coronary angiography, which leads to the consideration of coronary artery vasospasm.[33,40]

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.[38]

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.[41,42]

There is a higher incidence of angina with administration through continuous infusion compared to bolus infusion.[38,43] 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.[44] 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.[38,43]

While the causative relationship is unclear, endothelin-1 levels have been noted to be elevated in angina patients with 5-FU infusion.[43] 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.[16,45]

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.[46,47] In one large study, myocardial ischaemia was reported in 4% of patients receiving high-dose, continuous infusion of 5-FU.[48] 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.[24,49] Age of the patient did not seem to influence the occurrence of cardiotoxicity.[45]

## Proposed Pathophysiological Mechanisms of 5-fluorouracil-induced Cardiotoxicity

The pathophysiological mechanisms underlying 5-FU-induced cardiotoxicity remain undefined.[36,50,51] 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.[52–55] In a few cases, coronary artery vasospasm has been demonstrated during coronary angiography.[55–58]

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.[59,60] 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.[36] 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.[61] 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.[62]

### 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.[63] 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.[64–66]

### 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.[67] This observation may support the hypothesis of 5-FU-induced vasoconstriction.[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.[68,69] Endothelin-1 plays a regulatory role in coronary vascular resistance and myocardial capillary blood flow in coronary artery disease states.[69–71] Hypoxia, ischaemia or shear stress induces vascular endothelial cells to synthesise and secrete endothelin-1.[68] Endothelin-1 in turn is synthesised from the precursor peptide big endothelin.[68]

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 vasoconstriction.[59] 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.[27]

### Protein Kinase C

Staurosporine is a protein kinase C (PK-C) inhibitor and pre-treatment with it reduced 5-FU-induced vasoconstriction.[72] 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.[72]

### Acetylcholine

Acetylcholine induces vasodilation through the NO-cGMP pathway.[73] Acetylcholine is endothelium-dependant and hence intact endothelial cells are a requirement for acetylcholine-induced vasodilation.[73] In fact, in the absence of endothelial cells, acetylcholine actually leads to vasoconstriction.[73] It seems unlikely that the mechanism through which 5-FU causes functional vasoconstriction 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.[27] 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.[38]

5-FU has been found to increase the expression of thioredoxin-interacting protein (TXNIP).[74] A number of studies have shown that verapamil and diltiazem suppress TXNIP expression.[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.[76] Subsequently, the same group also demonstrated the attenuation of the pro-apoptotic effects of TXNIP by verapamil.[77] 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.[75]

This clinical effect is, in turn, inconsistent in 5-FU-induced coronary artery vasospasm. In a study by Mosseri et al., rabbit aorta rings were pre-treated *in vitro* with verapamil and diltiazem prior to 5-FU exposure.[72] Of note, there was no observed effect of the calcium channel blockers verapamil and diltiazem on vasospasm.[72] 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.[78] Nitrates and calcium channel blockers have been used to treat and prevent coronary artery spasm in high-risk patients.[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.[16] These patients might have clinical reoccurrence of coronary vasospasm with subsequent 5-FU re-exposure.[16] Although treatment with vasodilators have been proposed as prophylaxis against coronary artery vasospasm, limited effectiveness of this prophylactic therapy has been observed.[80]

Due to the potential for arrhythmias, ECG monitoring is recommended if there is any evidence for cardiac side-effects during treatment.[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.[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.[47,57,83,84]

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.[51]

Spasmogenic drugs, e.g. beta-blockers, should be avoided. This hypothesis is supported by a few reports.[85–89] 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.[47,90]

### 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.[91] 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.[92] This group noted that 5-FU caused endothelial cell senescence and dysfunction, which may contribute to its cardiovascular side-effects.[92] 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 capecitabine induced cardiotoxicity.[92]

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 improve endothelium-dependent vasodilation after exposure to 5-FU.[93] 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.[94] h-FABP is a small unbound cytoplasmic protein that is present at high levels in myocardial cells and released into the blood circulation within minutes of ischaemia.[94]

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.[94] Turan et al. studied 32 cancer patients receiving their first 5-FU-based chemotherapy were studied.[94] 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.[95] 5-FU cardiotoxicity can potentially be modulated by being selective in the treatment regimen administered in each patient with the help of genetic profiling.[95] Several studies have highlighted genetic polymorphisms in DPYD, TYMS, MTHFR and OPRT as potential risk factors for serious toxicity.[95] Determination of polymorphisms in xenobiotic metabolising enzymes through genetic profiling before 5-FU administration might suggest new and individualised strategies for optimising chemotherapy safety.[95]

Oral derivatives and pro-drugs have been developed to provide an alternative route of 5-FU administration.[95] Differences have been reported regarding the adverse effect profiles of intravenous 5-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.[95] Further investigation is required to understand the relationship between individual DPYD variants and the different 5-FU-based chemotherapy regimens.[95]

## 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 capecitabine 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: 30700139.
2. Balukumar P, Maung-U K, Jagadeesh G. Prevalence and prevention of cardiovascular disease and diabetes mellitus. *Pharmacol Res* 2016;113:600–9. https://doi.org/10.1016/j.phrs.2016.09.040; PMID: 27697647.
3. Leal YA, Fernadez-Garrote LM, Mohar-Betancourt A, Meneses-García A. The importance of registries in cancer control. *Salud Publica Mex* 2016;58:309–16. PMID: 27557391.
4. WHO. Cancer. Geneva; WHO, 2018. Available at: https://www.who.int/en/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:e11. https://doi.org/10.2196/jmir.6575; PMID: 28069561.
6. Cancer Research UK. Available at: www.cancerresearchuk.org (accessed 24 April 2019).
7. Siegel R, DeSantis C, Virgo K et al. Cancer treatment and

survivorship statistics. *CA Cancer J Clin* 2012;62:220–41. https://doi.org/10.3322/caac.21149; PMID: 22700443.
8. Barac A, Murtagh G, Carver JR, et al. Cardiovascular health of patients with cancer and cancer survivors: a roadmap to the next level. *J Am Coll Cardiol* 2015;65:2739–46. https://doi.org/10.1016/j.jacc.2015.04.059; PMID: 26112199.
9. Weaver KE, Foraker RE, Alfano CM, et al. Cardiovascular risk factors among long-term survivors of breast, prostate, colorectal, and gynecologic cancers: a gap in survivorship care? *J Cancer Surviv Res Pract* 2013;7:253–61. https://doi.org/10.1007/s11764-013-0267-9; PMID: 23417882.
10. Moser EC, Noordijk EM, van Leeuwen FE, et al. Long-term risk of cardiovascular disease after treatment for aggressive non-Hodgkin lymphoma. *Blood* 2006;107:2912–9. https://doi.org/10.1182/blood-2005-08-3392; PMID: 16339404.
11. Ghosh AK, Walker JM. Cardio-oncology – a new subspecialty with collaboration at its heart. *Indian Heart J* 2017;69:556–62. https://doi.org/10.1016/j.ihj.2017.05.006; PMID: 28822531.
12. Demers M, Krause DS, Schatzberg D, et al. Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis. *Proc Natl Acad Sci USA* 2012;109:13076–81. https://doi.org/10.1073/pnas.1200419109; PMID: 22826226.
13. Blann AD, Dunmore S. Arterial and venous thrombosis in cancer patients. *Cardiol Res Pr* 2011;2011:394740. https://doi.org/10.4061/2011/394740; PMID: 21403876.
14. Ghosh AK, Crake T, Manisty C, Westwood M. Pericardial disease in cancer patients. *Curr Treat Options Cardiovasc Med* 2018;20:60. https://doi.org/10.1007/s11936-018-0654-7 ; PMID: 29936603.
15. Chung R, Ghosh AK, Banerjee A. Cardiotoxicity: precision medicine with imprecise definitions. *Open Heart* 2018;5:e000774. https://doi.org/10.1136/openhrt-2018-000774; PMID: PMID: 30094034.
16. Giza DE, Boccalandro F, Lopez-Mattei J, et al. Ischemic heart disease: special considerations in cardio-oncology. *Curr Treat Options Cardiovasc Med* 2017;19:37. https://doi.org/10.1007/s11936-017-0535-5; PMID: 28425056.
17. Davignon J GP. Role of endothelial dysfunction in atherosclerosis. *Circulation* 2004;109(Suppl 1):11127–32. https://doi.org/10.1161/01.CIR.0000131515.03336.f8; PMID: 15198963.
18. Herrmann J, Lerman A. An update on cardio-oncology. *Trends Cardiovasc Med* 2014;24:285–95. https://doi.org/10.1016/j.tcm.2014.07.003; PMID: 25153017.
19. Wang JC, Normand SL, Mauri L, Kuntz RE. Coronary artery spatial distribution of acute myocardial infarction occlusions. *Circulation* 2004;110:278–84. https://doi.org/10.1161/01.CIR.0000135468.67850.F4; PMID: 15249505.
20. Thavendiranathan P, Nolan MT. An emerging epidemic: cancer and heart failure. *Clin Sci* 2016;131:113–21. https://doi.org/10.1042/CS20160412; PMID: 27974396.
21. Ghosh AK, Walker JM. Cardio-oncology. *Br J Hosp Med* 2017;78:C11–3. https://doi.org/10.12968/hmed.2017.78.1.C11; PMID: 28067553.
22. Iliescu CA, Grines CL, Herrmann J, et al. SCAI expert consensus statement: evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory (endorsed by the Cardiological Society of India, and Sociedad Latinoamericana de Cardiología Intervencionista). *Catheter Cardiovasc Interv* 2016;87:E202–23. https://doi.org/10.1002/ccd.26379; PMID: 26756277.
23. Naib T, Steingart RM, Chen CL. Sorafenib-associated multivessel coronary artery vasospasm. *Herz* 2011;36:348–51. https://doi.org/10.1007/s00059-011-3444-5; PMID: 21584715.
24. Stewart T, Pavlakis N, Ward M. Cardiotoxicity with 5-fluorouracil and capecitabine: more than just vasospastic angina. *Intern Med J* 2010;40:303–7. https://doi.org/10.1111/j.1445-5994.2009.02144.x; PMID: 20529041.
25. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. *Drug Saf* 2000;22:263–302. https://doi.org/10.2165/00002018-200022040-00002; PMID: 10789823.
26. Van Cutsem E, Hoff PM, Blum JL, Abt M. Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. *Ann Oncol* 2002;13:484–5. PMID: 11996484.
27. Polk A, Vistisen K, Vaage-Nilsen M, Nielsen DL. A systematic review of the pathophysiology of 5-fluorouracil-induced cardiotoxicity. *BMC Pharmacol Toxicol* 2014;15:47. https://doi.org/10.1186/2050-6511-15-47; PMID: 25186061.
28. Kosmas C, Kallistratos MS, Kopterides P, et al. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. *J Cancer Res Clin Oncol* 2008;134:75–82. https://doi.org/10.1007/s00432-007-0250-9; PMID: 17636329.
29. Malet-Martino M, Jolimaitre P, Martino R. The prodrugs of 5-fluorouracil. *Curr Med Chem Anticancer Agents* 2002;2:267–310. PMID: 12678747.
30. Jensen SA, Sorensen JB. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. *Cancer Chemother Pharmacol* 2006;58:487–93. https://doi.org/10.1007/s00280-005-0178-1; PMID: 16418875.
31. Koca D, Salman T, Unek IT et al. Clinical and electrocardiography changes in patients treated with capecitabine. *Chemotherapy* 2011;57:381–7. https://doi.org/10.1159/000331645; PMID: 21997165.
32. Ng M, Cunningham D, Norman AR. The frequency and pattern of cardiotoxicity observed with capecitabine used in conjunction with oxaliplatin in patients treated for advanced colorectal cancer (CRC). *Eur J Cancer* 2005;41:1542–6. https://doi.org/10.1016/j.ejca.2005.03.027; PMID: 15978800.
33. Cardinale D, Colombo A, Colombo N. Acute coronary syndrome induced by oral capecitabine. *Can J Cardiol* 2006;22:251–3. PMID: 16520857.
34. Coughlin S, Das S, Lee J, Cooper J. Capecitabine induced vasospastic angina. *Int J Cardiol* 2008;130:e34–6. https://doi.org/10.1016/j.ijcard.2007.06.152; PMID: 17897740.
35. Frickhofen N, Beck FJ, Jung B, et al. Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. *Ann Oncol* 2002;13:797–801. PMID: 12075751.
36. Polk A, Vaage-Nilsen M, Vistisen K, et al. Cardiotoxicity in cancer patients treated with 5-fluorouracil or capecitabine: a systematic review of incidence, manifestations and predisposing factors. *Cancer Treat Rev* 2013;39:974–84. https://doi.org/10.1016/j.ctrv.2013.03.005; PMID: 23582737.
37. Kelly C, Bhuva N, Harrison M et al. Use of raltitrexed as an alternative to 5-fluorouracil and capecitabine in cancer patients with cardiac history. *Eur J Cancer* 2013;49:2303–10. https://doi.org/10.1016/j.ejca.2013.03.004; PMID: 23583220.
38. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. *Expert Opin Drug Saf* 2009;8:191–202. https://doi.org/10.1517/14740330902733961; PMID: 19309247.
39. Wacker A, Lersch C, Scherpinski U, et al. High incidence of angina pectoris in patients treated with 5-fluorouracil. A planned surveillance study with 102 patients. *Oncology* 2003;65:108–12. https://doi.org/10.1159/000072334; PMID: 12931015.
40. Lu JI, Carhart RL, Graziano SL, Gajra A. Acute coronary syndrome secondary to fluorouracil infusion. *J Clin Oncol Off J Am Soc Clin Oncol* 2006;24:2959–60. https://doi.org/10.1200/JCO.2005.04.0766; PMID: 16782933.
41. Fajardo LF, Stewart JR. Pathogenesis of radiation-induced myocardial fibrosis. *Lab Invest* 1973;29:244–55. PMID: 4724850.
42. May D, Wandl U, Becher R, et al. Cardiac side effects of 5-fluorouracil. *Dtsch Med Wochenschr* 1990;115:618–21 [in German]. https://doi.org/10.1055/s-2008-1065055; PMID: 2328669.
43. Südhoff T, EnderleMD, Pahlke M, et al. 5-fluorouracil induces arterial vasocontractions. *Ann Oncol* 2004;15:661–4. PMID: 15033676.
44. Tsavaris N, Kosmas C, Vadiaka M, et al. Cardiotoxicity following different doses and schedules of 5-fluorouracil administration for malignancy – a survey of 427 patients. *Med Sci Monit* 2002;8:P151–7. PMID: 12070449.
45. Labianca R, Beretta G, Clerici M, et al. Cardiac toxicity of 5-fluorouracil: a study on 1083 patients. *Tumori* 1982;68:505–10. PMID: 7168016.
46. de Forni M, Malet-Martino MC, Jaillais P, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. *J Clin Oncol Am Soc Clin Oncol* 1992;10:1795–801. https://doi.org/10.1200/JCO.1992.10.11.1795; PMID: 1403060.
47. Annad AJ. Fluorouracil cardiotoxicity. *Ann Pharmacother* 1994;28:374–8. https://doi.org/10.1177/106002809402800314; PMID: 8193429.
48. Tsavaris N, Kosmas C, Vadiaka M, et al. Cardiotoxicity following different doses and schedules of 5-fluorouracil administration for malignancy – a survey of 427 patients. *Med Sci Monit Int Med J Exp Clin Res* 2002;8:P151–7. PMID: 12070449.
49. Freeman NJ, Costanza ME. 5-fluorouracil-associated cardiotoxicity. *Cancer* 1988;61:36–45. PMID: 3275485.
50. Jensen SA, Sorensen JB. 5-fluorouracil-based therapy induces endovascular injury having potential significance to development of clinically overt cardiotoxicity. *Cancer Chemother Pharmacol* 2012;69:57–64. https://doi.org/10.1007/s00280-011-1669-x; PMID: 21603868.
51. Kinhult S, Albertsson M, Eskilsson J CM. Antithrombotic treatment in protection against thrombogenic effects of 5-fluorouracil on vascular endothelium: a scanning microscopy evaluation. *Scanning* 2001;23:1–8. PMID: 11272331.
52. Ozturk MA, Ozveren O, Cinar V, et al. Takotsubo syndrome: an underdiagnosed complication of 5-fluorouracil mimicking acute myocardial infarction. *Blood Coagul Fibrinolysis* 2013;24:90–4. https://doi.org/10.1097/MBC.0b013e3283597605; PMID: 23249567.
53. Kim SM, Kwak CH, Lee B, et al. A case of severe coronary spasm associated with 5-fluorouracil chemotherapy. *Korean J Intern Med* 2012;27:342–5. https://doi.org/10.3904/kjim.2012.27.3.342; PMID: 23019400.
54. Tsiamis E, Synetos A, Stefanidis C. Capecitabine may induce coronary artery vasospasm. *Hellenic J Cardiol* 2012;53:320–3. PMID: 22796820.
55. Shah NR, Shah A, Rather A. Ventricular fibrillation as a likely consequence of capecitabine-induced coronary vasospasm. *J Oncol Pharm Pract* 2012;18:132–5. https://doi.org/10.1177/1078155211399164; PMID: 21321041.
56. Alter P, Herzum M, Soufi M, et al. Cardiotoxicity of 5-fluorouracil. *Cardiovasc Hematol Agents Med Chem* 2006;4:1–5. PMID: 16529545.
57. Shoemaker LK, Arora U, Rocha Lima CM. 5-fluorouracil-induced coronary vasospasm. *Cancer Control* 2004;11:46–9. https://doi.org/10.1177/107327480401100207; PMID: 14749623.
58. Luwaert RJ, Descamps O, Majois F, et al. Coronary artery spasm induced by 5-fluorouracil. *Eur Hear J* 1991;12:468–70. PMID: 2040332.
59. Salepci T, Seker M, Uyarel H, et al. 5-Fluorouracil induces arterial vasoconstrictions but does not increase angiotensin II levels. *Med Oncol* 2010;27:416–20. https://doi.org/10.1007/s12032-009-9226-8; PMID: 19415535.
60. Sudhoff T, Enderle MD, Pahlke M, et al. 5-fluorouracil induces arterial vasocontractions. *Ann Oncol* 2004;15:661–4. PMID: 15033676.
61. Cwikiel M, Zhang B, Eskilsson J, et al. The influence of 5-fluorouracil on the endothelium in small arteries. An electron microscopic study in rabbits. *Scanning Microsc* 1995;9:561. PMID: 8714749.
62. Cwikiel M, Eskilsson J, Wieslander JB, et al. The appearance of endothelium in small arteries after treatment with 5-fluorouracil. An electron microscopic study of late effects in rabbits. *Scanning Microsc* 1996;10:805. PMID: 9813641.
63. Senkus E, Jassem J. Cardiovascular effects of systemic cancer treatment. *Cancer Treat Rev* 2011;37:300–11. https://doi.org/10.1016/j.ctrv.2010.11.001; PMID: 21126826.
64. Fichtlscherer S, Dimmeler S, Breuer S, et al. Inhibition of cytochrome P450 2C9 improves endothelium-dependent, nitric oxide-mediated vasodilatation in patients with coronary artery disease. *Circulation* 2004;109:178. https://doi.org/10.1161/01.CIR.0000105763.51286.7F; PMID: 14662709.
65. Fleming I, Fisslthaler B, Dimmeler S, et al. Phosphorylation of Thr(495) regulates Ca(2+)/calmodulin-dependent endothelial nitric oxide synthase activity. *Circ Res* 2001;88:E68–75. PMID: 11397791.
66. Dimmeler S, Fleming I, Fisslthaler B, et al. Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation. *Nature* 1999;399:601. https://doi.org/10.1038/21224; PMID: 10376603.
67. Thyss A, Gaspard MH, Marsault R, et al. Very high endothelin plasma levels in patients with 5-FU cardiotoxicity. *Ann Oncol* 1992;3:88. PMID: 1606078.
68. Levin ER. Endothelins. *N Engl J Med* 1995;333:356–63. https://doi.org/10.1056/NEJM199508103330607; PMID: 7609754.
69. Khimji AK, Rockey DC. Endothelin – biology and disease. *Cell Signal* 2010;22:1615–25. https://doi.org/10.1016/j.cellsig.2010.05.002; PMID: 20466059.
70. MacCarthy PA, Pegge NC, Prendergast BD, et al. The physiological role of endogenous endothelin in the regulation of human coronary vasomotor tone. *J Am Coll Cardiol* 2001;37:137–43. PMID: 11153728.
71. Kinlay S, Behrendt D, Wainstein M, et al. Role of endothelin-1 in the active constriction of human atherosclerotic coronary arteries. *Circulation* 2001;104:1114–8. PMID: 11535565.
72. Mosseri M, Fingert HJ, Varticovski L, et al. In vitro evidence that myocardial ischemia resulting from 5-fluorouracil chemotherapy is due to protein kinase C-mediated vasoconstriction of vascular smooth muscle. *Cancer Res* 1993;53:3028–33. PMID: 8391384.
73. Schwartz BG, Economides C, Mayeda GS, et al. The endothelial cell in health and disease: its function, dysfunction, measurement and therapy. *Int J Impot Res* 2010;22:77–90. https://doi.org/10.1038/ijir.2009.59; PMID: 20032988.
74. Yamaguchi F, Kamitori K, Sanada K et al. Rare sugar D-allose enhances anti-tumor effect of 5-fluorouracil on the human hepatocellular carcinoma cell line HuH-7. *J Biosci Bioeng* 2008;106:248–52. https://doi.org/10.1263/jbb.106.248; PMID: 18930000.
75. Chong CR, Chan WP, Nguyen TH, et al. Thioredoxin-interacting protein: pathophysiology and emerging pharmacotherapeutics in cardiovascular disease and diabetes. *Cardiovasc Drugs Ther* 2014;28:347–60. https://doi.org/10.1007/s10557-014-6538-5; PMID: 25088927.
76. Chen J, Cha-Molstad H, Szabo A, Shalev A. Diabetes induces and calcium channel blockers prevent cardiac expression of proapoptotic thioredoxin-interacting protein. *Am J Physiol Endocrinol Metab* 2009;296:E1133–9. https://doi.org/10.1152/ajpendo.90944.2008; PMID: 19258488.
77. Xu G, Chen J, Jing G, Shalev A. Preventing beta-cell loss and diabetes with calcium channel blockers. *Diabetes* 2012;61:848–56. https://doi.org/10.2337/db11-0955; PMID: 22442301.
78. Kosmas C, Kallistratos MS, Kopterides P, et al. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. *J Cancer Res Clin Oncol* 2008;134:75–82. https://doi.org/10.1007/s00432-007-0250-9; PMID: 17636329.
79. Perrino C, Schiattarella GG, Magliulo F, et al. Cardiac side effects of chemotherapy: State of art and strategies for a correct management. *Curr Vasc Pharmacol* 2014;12:106–16. PMID: 22563720.
80. Patel B, Kloner RA, Ensley J, et al. 5-fluorouracil cardiotoxicity: left ventricular dysfunction and effect of coronary vasodilators. *Am J Med Sci* 1987;294:238–43. PMID: 3661619.
81. Rezkalla S, Kloner RA, Ensley J, et al. Continuous ambulatory ECG monitoring during fluorouracil therapy: a prospective study. *J Clin Oncol* 1989;7:509–514. https://doi.org/10.1200/JCO.1989.7.4.509; PMID: 2466960.
82. Oleksowicz L, Bruckner H. Prophylaxis of 5-fluorouracil-induced coronary vasopasm with calcuim channel blockers. *Am J Med* 1988;85:750. PMID: 3189387.
83. McGlinchey PG, Webb ST, Campbell NP. 5-fluorouracil-induced cardiotoxicity mimicking myocardial infarction: a case report. *BMC Cardiovasc Disord* 2001;1:3. PMID: 11734065.
84. Keefe D. Cardiovascular emergencies in the cancer patient. *Semin Oncol* 2000;27:244. PMID: 10864214.
85. Lestuzzi C, Viel E, Picano E, et al. Coronary vasospasm as a cause of effort-related myocardial ischemia during low-dose chronic continuous infusion of 5-fluorouracil. *Am J Med*

2001;111:316. PMID: 11566462.
86. Gorgulu S, Celik S, Tezel T. A case of coronary spasm induced by 5-fluorouracil. *Acta Cardiol* 2002;57:381. https://doi.org/10.2143/AC.57.5.2005458; PMID: 12405579.
87. Abernethy DR, Schwartz J. Calcium-antagonist drugs. *N Engl J Med* 1999;341:1447. https://doi.org/10.1056/NEJM199911043411907; PMID: 10547409.
88. Kleiman NS, Lehane DE, Geyer CE, et al. Prinzmetal's angina during 5-fluorouracil chemotherapy. *Am J Med* 1987;82:566. PMID: 3826112.
89. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combing protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 1994;331:502. https://doi.org/10.1056/NEJM199408253310803; PMID: 8041415.
90. Akpek G, Hartshorn KL. Failure of oral nitrate and calcium channel blocker therapy to prevent 5-fluorouracil-related myocardial ischemia: a case report. *Cancer Chemother Pharmacol* 1999;43:157–61. https://doi.org/10.1007/s002800050877; PMID: 9923822.
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;16:4045–9. PMID: 25987084.
92. Altieri P, Murialdo R, Barisione C, et al. 5-fluorouracil causes endothelial cell senescence: potential protective role of glucagon-like peptide 1. *Br J Pharmacol* 2017; 174:3713–26. https://doi.org/10.1111/bph.13725; PMID: 28127745.
93. Hayward R, Ruangthai R, Schneider CM, et al. Training enhances vascular relaxation after chemotherapy-induced vasoconstriction. *Med Sci Sport Exerc* 2004;36:428. PMID: 15076784.
94. Turan T, Agac MT, Aykan C, et al. Usefulness of heart-type fatty acid-binding protein and myocardial performance index for early detection of 5-fluorouracil cardiotoxicity. *Angiology* 2016;68:52–8. https://doi.org/10.1177/0003319716637516; PMID: 26980771.
95. Matsusaka S, Lenz HJ. Pharmacogenomics of fluorouracil-based chemotherapy toxicity. *Expert Opin Drug Metab Toxicol* 2015;11:811–21. https://doi.org/10.1517/17425255.2015.1027684; PMID: 25800061.