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ORIGINAL ARTICLE

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Preventing 5-fluorouracil-induced ischemic events in very high-risk cardiac patients with documented ischemic heart disease: a retrospective cohort analysis

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ABSTRACT

Introduction. 5-fluorouracil (5-FU), a potent chemotherapy agent for various cancers, is linked to cardiotoxicity, particularly in patients with pre-existing ischemic heart diseases. The incidence varies, which necessitates effective preventive strategies. Among several mechanisms responsible for 5-FU-induced myocardial ischemia are coronary vasospasm and endothelial injury. Therefore, preventing vasospasm and endothelial injury may reduce the incidence of these adverse events.

We aimed to assess the effectiveness and safety of a protocol involving amlodipine and isosorbide dinitrate in preventing 5-FU-induced ischemic events in very high-risk cardiac patients with documented ischemic heart disease.

Material and methods. Nineteen patients underwent 252 cycles of 5-FU chemotherapy, with 12 patients (181 cycles) following the pre-defined protocol (5-FU protocol group) and 7 patients (71 cycles) not adhering (non-5-FU protocol group). The primary outcome measure was the prevention of 5-FU-induced ischemic events, evidenced by the absence of chest pain, elevated troponin levels, or ECG changes during 5-FU infusion.

Results. The 5-FU protocol group demonstrated significant reductions in ischemic events, and chest pain with p-values of 0.009 for both outcomes. Additionally, the frequency of ECG changes post-5-FU and an increase in troponin levels were significantly lower in the 5-FU protocol group, with p-values of 0.036 for both parameters.

Conclusions. The use of vasodilators may be effective in preventing 5-fluorouracil-induced ischemic events in very high-risk cardiac patients with documented coronary artery disease. Monitoring cardiotoxicity with maximum tolerated medical treatment and dedicated hospital protocols may be a good prophylactic approach. Further studies are needed to confirm the efficacy of this approach in a larger population.

Keywords: 5-fluorouracil, cardiotoxicity, ischemic events, nitrates, calcium channel blockers, high-risk cardiac patients, chemotherapy and vasodilators

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Introduction

5-fluorouracil (5-FU) is a chemotherapy drug commonly used in the treatment of various cancers, including breast, colon, and head and neck cancers. 5-FU cardiotoxicity can have potentially fatal side effects, which can manifest as chest pain, arrhythmias, and myocardial infarction [1]. The incidence of cardiotoxicity varies up to 10% [2]. The variability in incidence is attributed to the cohort population studied, different definitions of cardiotoxicity, and variations in the dosage and duration of 5-FU treatment.

Very high-risk patients, those with pre-existing ischemic heart disease, are more susceptible to cardiotoxicity [3]. Moreover, the incidence of recurrent cardiotoxicity with 5-FU re-challenge without any adjustment in treatment is 90% [4]. Therefore, it is essential to identify and prevent cardiotoxicity in high-risk patients.

Several preventive measures have been advocated including comprehensive baseline cardiac evaluation with electrocardiogram (ECG) and echocardiogram before 5-FU administration with close monitoring, 5-FU dose reduction or bolus infusion [5], and usage of 5-FU alternatives such as TAS-102 [6, 7].

Prevention of ischemic events in very high-risk patients by controlling modifiable cardiac risk factors and good medical treatment including vasodilators are a potential strategy in preventing 5-FU ischemic events. Among the several mechanisms responsible for 5-FU-induced myocardial ischemia are coronary vasospasm and endothelial injury. Therefore, preventing vasospasm may reduce the incidence of these adverse events. The use of vasodilators and nitrates has been studied for their role in preventing vasospasm associated with 5-FU chemotherapy. However, universal pre-treatment with vasodilators has not been adopted by international guidelines and, therefore, is not routinely recommended [8, 9].

Our study aimed to examine data on the efficacy and safety of pre-treatment with nitrates and/or calcium channel blockers (CCBS) using dedicated hospital protocol in the prevention of 5-FU-induced ischemic events in very high-risk patients who have documented ischemic heart disease.

Material and methods

We utilized a management protocol using nitrates and vasodilators to prevent 5-FU induced ischemic cardiac events in high-risk cardiac patients.

Through a retrospective analysis of medical records of patients receiving 5-FU in our healthcare facility (Sultan Qaboos Comprehensive Cancer Care and Research Centre) for 20 months, we found that a cohort of 19 individuals characterized as very high-risk cardiac patients had undergone a total of 252 cycles of a 5-FU-based chemotherapy regimen. All subjects had a medical history of cardiac ailments, including coronary artery disease (CAD) or previous myocardial infarction. The patient cohort exhibited a history of ischemic heart disease (IHD) manifesting with significant coronary artery stenosis with or without percutaneous coronary intervention (PCI) in at least one single artery or myocardial infarction that presented six weeks before initiating chemotherapy.

We categorized patients into low, intermediate, and high-risk to estimate the 10-year risk of cardiovascular disease using the European Society of Cardiology (ESC) guidelines risk assessment tools and SCORE 2/SCORE 2-OP risk assessment models [10]. Following this risk assessment, we further categorized patients into those with established atherosclerotic cardiovascular disease (ASCVD) and those with no ASCVD. Subsequently, we initiated management based on our hospital's established protocol (Fig. 1).

Patient risk categories were defined as follows. Low-risk patients were identified as individuals without established familial hypercholesterolemia, ASCVD, diabetes mellitus, chronic kidney disease (CKD), or based on criteria outlined in SCORE 2 or SCORE 2-OP. Intermediate-risk patients included those with well-controlled short-standing diabetes mellitus with no evidence of target organ damage/ASCVD, or based on SCORE 2/SCORE 2-OP criteria. High-risk patients were categorized as individuals with diabetes mellitus without ASCVD and/or severe target organ damage not meeting moderate risk criteria, or with moderate CKD, or as per SCORE 2/SCORE 2-OP criteria. Very high-risk patients were defined as those with diabetes mellitus with established ASCVD and/or severe target organ damage, those with severe CKD, or those with documented ASCVD based on clinical or imaging evidence such as [computed tomography coronary angiography (CTCA), coronary angiography (CAG), carotid ultrasound], or according to SCORE 2/SCORE 2-OP criteria. These categorizations facilitated the stratification of patients for clinical management and decision-making within the study [10].

Twelve patients who received 181 cycles of 5-FU, identified as very high-risk, were included in our protocol, and received the maximum tolerated anti-ischemic medications, along with meticulous control of other cardiac risk factors. Treatment involved a protocol comprising the maximum tolerated dose of the calcium channel blocker amlodipine, accompanied by the tolerated dose of isosorbide dinitrate administered solely during 5-FU continuous infusion. Continuous electrocardiography monitoring during the infusion took place in a high-dependency unit, and 12-lead ECG and troponin levels were measured before and after 5-FU dosing. Weekly telemedicine assessments of patient symptoms were conducted post-discharge.

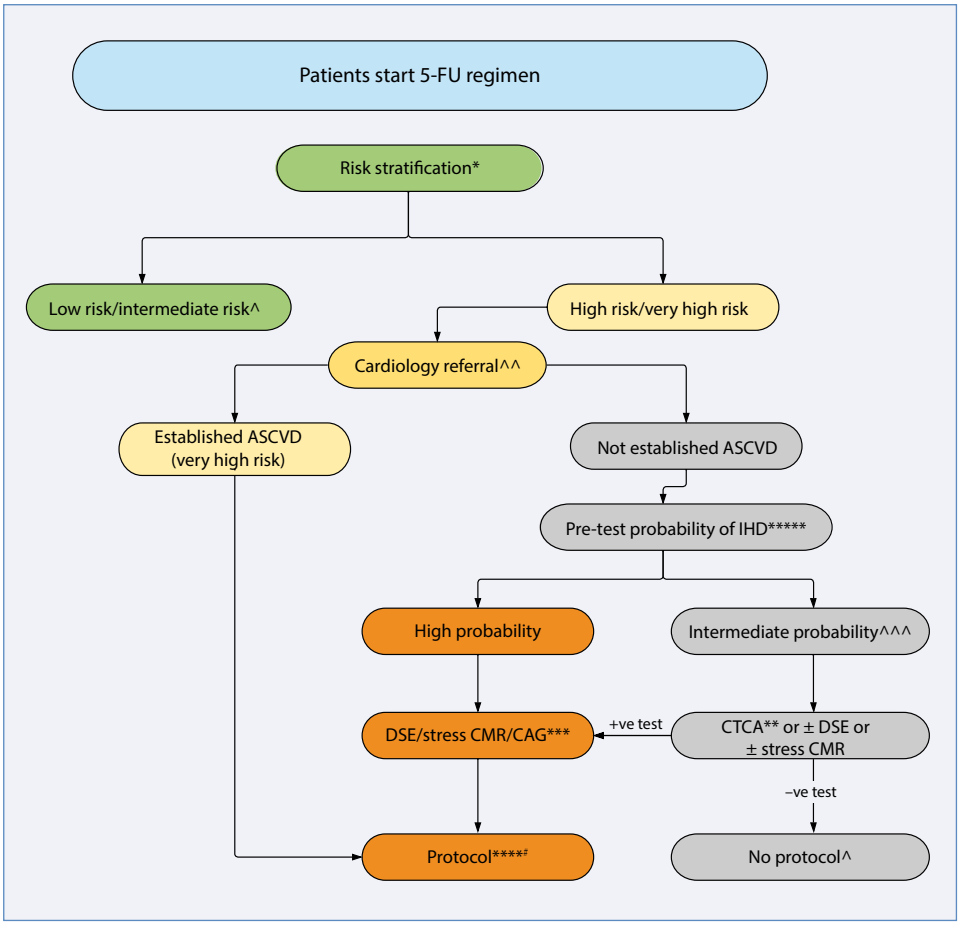

Figure 1. Sultan Qaboos Comprehensive Cancer Care and Research Centre algorthim for patients start 5-fluorouracil (5-FU) regimen; *Cardiovascular risk assessment based on 2021 European Society of Cardiology (ESC) guidleines on cardiovascular disease prevention and risk assessment models to estimate the 10-year risk of cardiovascular disease (ESC SCORE 2) and (ESC SCORE 2-OP for older people); **If computed tomography coronary angiography (CTCA) shows significant coronary stenosis, we refer patients for either dobutamine stress echocardiography (DSE) or coronary angiography (CAG); ***Patients with significant coronary artery stenosis in CAG or ≥ 3 segments in DSE or ≥ 2 segments in perfusion cardiac magnetic resonance (CMR); ****Sultan Qaboos Comprehensive Cancer Care and Research Centre protocol (maximum tolerated anti-ischemic medications including Amlodipine/Nitrates, close monitoring in High Dependant Unit (HDU) infirst sessions of 5-FU infusion, electrocardiogram (ECG) and troponin level before and after 5-FU infusion, follow-up using telemedicine, ± patients undergo coronary artery revascularization prior starting 5-FU; *****Based on 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [24]; #Coronary artery revascularization will be done according to recent revascularization guidelines in stable CAD and acute coronary syndrome; ^ Control of cardiac risk factors and lifestyle modifications; ^ ^ Baseline Echocardiography, ECG and cardiac enzymes; ^ ^ ^ Patients with low probability of IHD will undergo well control of cardiac risk factors and lifestyle modifications; ASVCD — atherosclerotic cardiovascular disease; IHD — ischemic heart disease

Seven patients who underwent 71 cycles of 5-FU were excluded from our protocol. The exclusion of seven patients from our trial can be attributed to three main reasons: inadequate identification, categorization, and patient preferences. First, inadequate identification by the involved teams, which failed to conduct risk stratification, resulted in their exclusion due to the lack of referral to our cardiology department. Second, there was an inappropriate categorization of one patient as low risk through risk stratification despite this patient being high risk, which led to their exclusion. Finally, two patients declined treatment modifications and high-dependency unit care, which also resulted in their exclusion from the trial. These factors contributed to the exclusion of these patients from our study.

The primary outcome measure was the prevention of 5-FU-induced ischemic events, evidenced by the absence of chest pain, elevated troponin levels, or ECG changes during 5-FU infusion in very high-risk cardiac patients.

To evaluate this, we specifically examined and compared the frequency of ischemic events in both the 5-FU protocol group and the non-5-FU protocol group. The comparison was conducted using Fisher's exact test. The secondary outcome focused on assessing adverse events associated with the utilization of vasodilators in this patient population.

Statistics

Descriptive analysis was performed using medians, ranges, frequencies, and proportions. A comparison between study groups was performed using Fisher's exact test for the binary variables, the Wilcoxon rank-sum test for the continuous variables (age), and the Cochran-Armitage trend test for the ordinal variables (stage). Analyses were executed using the R software version 4.3.1 [R Core Team (2023). R: A Language and Environment for Statistical Com-puting. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org].

Ethics statement

Sultan Qaboos Comprehensive Cancer Care and Research Centre Institutional Review Board and Ethics Committee approved the study based on the application, protocol, and supporting documentation. Institutional Review Board and Ethics Committee (IRB & EC) Project ID is (CCCRC-20-2024).

Results

Demographically, the patients in the 5-FU protocol group were at a median age of 73 years (range: 47–84) and were predominantly male (75%). Notably, the incidence of smoking in this group was 16.7%, diabetes prevalence was 50%, hypertension was observed in 66.7%, and 50% had a history of dyslipidemia. All patients in this group had documented ischemic heart disease, with 66.7% of patients who underwent coronary angiography (CAG) with or without percutaneous coronary intervention (PCI) (Tab. 1).

The statistically non-significant p-values for age, sex, smoking, diabetes, hypertension, dyslipidemia, ischemic heart disease, CAG ± PCI, and CABG suggested a balanced distribution of these demographic and clinical variables in both groups (Tab. 2).

The data showed a significant reduction in ischemic events and chest pain in the 5-FU protocol group compared to the non-5-FU protocol group, with p-values of 0.009 for both outcomes. Additionally, the frequency of ECG changes post-5-FU and an increase in troponin levels were significantly lower in the 5-FU protocol group, with p-values of 0.036 for both parameters (Tab. 2).

Although not statistically significant, there was a lower 5-FU-related mortality rate in the 5-FU protocol group compared to the non-5-FU protocol group (0% *vs*. 14.3%; p = 0.37). A single patient experienced an anterior wall myocardial infarction accompanied by cardiogenic shock and died.

The incidence of cancer-related mortality did not exhibit a statistically significant difference between the two groups based on TNM staging and histopathology with a p-value of 0.473 (Tab. 1).

In our study population of 19 patients, molecular analysis demonstrated a consistent pattern of proficient mismatch repair protein (MMRP) and rapidly accelerated fibrosarcoma wild type (RAFWT) status in all individuals. Specifically, all 19 patients exhibited microsatellite instability and MMRP. Additionally, the presence of RAFWT status in all patients suggested a wild-type *RAF* gene, which is associated with normal function and signaling within cellular pathways. Notably, 4 patients were found to harbor *KRAS* mutations, while 9 patients demonstrated wild-type KRAS status. Interestingly, molecular analysis for *RAS* mutations was not performed in two patients, yielding non-specific results for this genetic marker in our population.

It is noteworthy that in the 5-FU protocol group, we recorded no adverse effects related to the medications received by coronary artery disease patients.

Discussion

Previous studies suggested that patients with pre-existing cardiac diseases, such as coronary vasospasm, coronary artery disease, or cardiomyopathy, have a higher risk of cardiotoxicity [3]. Coronary vasospasm, direct myocardial injury, vascular endothelial dysfunction, and reduced oxygen delivery are some of the mechanisms for cardiotoxicity [11].

Patients receiving concurrently multi-agent chemotherapy, chest wall radiation therapy, and therapy for pre-existing cardiac disease (including CAD, structural heart disease, and cardiomyopathy) are at increased risk of cardiotoxicity [12]. Smoking, diabetes, obesity, hypertension, and hyperlipidemia (known risk factors for ischemic heart disease) do not, however, appear to be linked to the occurrence of 5-FU cardiotoxicity [13].

Protracted infusion of 5-FU is a well-recognized risk factor for cardiotoxicity. A review of 377 cases of 5-FU-related cardiotoxicity confirmed that most cases of cardiotoxicity occur in the setting of continuous infusion [5, 14]. In a retrospective study comparing different chemotherapy regimens with 5-FU used to treat colorectal and gastric cancer, patients receiving continuous infusion 5-FU had a reported incidence of cardiotoxicity as high as 10–18%. This contrasts with

Table 1. Demographic and Clinical characteristics of the study groups

	5-FU protocol n = 12 (%)	Missed 5-FU protocol n = 7 (%)	p-value
Number of patients	12	7	
Number of 5-FU cycles	181	71	
Age [years] — median (range)	73 (47–84)	69 (52–72)	0.45
Sex			1
Male	9 (75%)	5 (71.4%)	
Female	3 (25%)	2 (28.6%)	
Smoking	2 (16.7%)	3 (42.9%)	0.3
Diabetes	6 (50%)	5 (71.4%)	0.63
Hypertension	8 (66.7%)	7 (100%)	0.25
Dyslipidemia	6 (50%)	5 (71.4%)	0.63
Ischemic heart disease	12 (100%)	7 (100%)	1
CAG ± PCI	8 (66.7%)	1 (14.3%)	0.06
CABG	1 (8.3%)	1 (14.3%)	1
CT/diagnostic CAG	2 (16.7%)	5 (71.4%)	0.045
GIT cancer	11 (91.7%)	7 (100%)	1
Head and neck cancer	1 (8.3%)	0 (0%)	1
Stage			0.048
Stage II cancer	1 (8.3%)	0 (0%)	
Stage III cancer	8 (66.7%)	2 (28.6%)	
Stage IV cancer	3 (25%)	5 (71.4%)	
TNM staging			
T1N0M0	1	0	
T2N1M0	1	3	
T3N1M0	3	2	
T3N0M1	0	1	
T2N1M1	2	0	
T3N2M1	4	1	
T4N2M1	1	0	
Histopathology			0.473
Poorly differentiated ADC	5	2	
Moderately differentiated ADC	6	5	
Squamous cell carcinoma	1	0	

5-FU — 5-flurouracil; ADC — adenocarcinoma; CABG — coronary artery bypass graft; CAG — coronary angiography; CT — computed tomography; GIT — gastrointestinal; PCI — percutaneous intervention; TNM — Tumor, Node, Metastasis

a 5% rate of cardiotoxicity in patients receiving 5-FU as a bolus [15]. The likely reason for differences in cardiotoxicity between continuous and bolus infusion is that the half-life of 5-FU is 15–20 minutes, and thus the drug is rapidly cleared when given as a bolus [15].

In our study, the data showed a significant reduction in ischemic events and chest pain in the 5-FU protocol group compared to the non-5-FU protocol group, with p-values of 0.009 for both outcomes. Additionally, the frequency of ECG changes post-5-FU and an increase in troponin levels were significantly lower in the 5-FU protocol group, with p-values of 0.036 for both parameters.

Although not statistically significant, there was a lower 5-FU-related mortality rate in the 5-FU protocol group compared to the No 5-FU protocol group (0%

Table 2. Mortality and cardiovascular events in the study groups

	5-FU protocol n = 12 (%)	Missed 5-FU n = 7 (%)	p-value
Ischemic events	0 (0%)	4 (57.1%)	0.009
Chest pain	0 (0%)	4 (57.1%)	0.009
ECG changes post-5-FU	0 (0%)	3 (42.9%)	0.036
Increase troponin level	0 (0%)	3 (42.9%)	0.036
New echo findings	0 (0%)	3 (42.9%)	0.036
5-FU related mortality	0 (0%)	1 (14.3%)	0.37
Cancer related mortality	3 (25%)	1 (14.3%)	1

5-FU — 5-flurouracil; ECG — electrocardiogram; echo — echocardiography

vs. 14.3%, p = 0.37). The incidence of cancer-related mortality did not exhibit a statistically significant difference between the two groups.

These results underscore the potential benefits of implementing the protocol to reduce cardiovascular events, particularly ischemic events, and chest pain, associated with 5-FU administration in very high-risk cardiac patients. The observed trends in reduced mortality rates, while not reaching statistical significance in this study, suggest avenues for further investigation and highlight the need for larger prospective trials to validate these promising findings.

The pathophysiology of myocardial ischemia secondary to 5-FU and capecitabine therapy has repeatedly been related to epicardial coronary artery spasm and/or coronary microvascular dysfunction, both of which may result from disrupted endothelial cell homeostasis. Four proposed theories can explain cardiotoxicities including coronary vasospasm: fluoropyrimidines may lead to coronary vasospasm, reducing blood flow to the heart muscle; thrombogenic effects may induce a prothrombotic state, potentially leading to microthrombi in coronary vessels; fluoropyrimidines could impair endothelial function, contributing to cardiovascular complications and rarely direct cardiomyocyte toxicity (some evidence suggests direct toxicity to cardiomyocytes, affecting their function [16]).

However, it should be recognized that there is a lack of consensus or guidelines on prophylactic treatment with calcium-channel blockers, as some prospective studies report that patients who were pretreated before their first infusion did not show any difference in the incidence of cardiotoxicity between the treatment and control groups [17]. Calcium-channel blockers have been used to treat and rechallenge patients who developed vasospasm after their first 5-FU exposure in small case series [18]. Moreover, patients with known ischemic heart disease or known cardiovascular disease risk factors were more likely to be on potentially cardioprotective drugs such as beta-blockers, nitrates, and calcium channel blockers, which may have reduced their risk of ischemic events [19].

Using specific calcium channel blockers in primary prevention is not recommended in any guidelines. Diltiazem is used frequently in secondary prevention of 5-FU induced vasospasm, based on one case series of 5 patients, in which secondary prevention of capecitabine-associated chest pain with diltiazem was reported [20]. However, a study of primary prevention using this agent in 58 patients being treated with cisplatin and 5-FU reported a 12% incidence of cardiotoxicity, similar to the 13% incidence in their chosen historical controls [21]. Furthermore, diltiazem exhibits notable drug-drug interactions when utilized chronically alongside chemotherapy, particularly in the context of primary prevention. There are case reports of using nitrates in either primary or secondary prevention settings with mixed outcomes [22].

Our investigation highlights the potential significance of screening individuals at high risk for cardiac complications before 5-FU chemotherapy. This involves the utilization of established scores such as ESC SCORE 2 and SCORE 2-OP [23]. Our proposed approach seeks to categorize patients with underlying coronary artery diseases, prompting exploration of the advantageous outcomes associated with either intensifying medical treatment including vasodilators, or implementing coronary interventions before 5-FU chemotherapy [14, 24].

The limitations of our study should be acknowledged. First, our sample size was small, so larger patient populations are required to confirm the safety and efficacy of this method. Second, our study was retrospective, and we did not have a control group against which to compare the incidence of 5-FU-induced coronary vasospasm. Lastly, we did not evaluate the long-term outcomes for these patients, and additional research is required to determine the impact of this protocol on long-term cardiac outcomes. Addressing these limitations and conducting larger prospective multicenter studies will be essential to validate and extrapolate the observed benefits, enhancing the robustness and applicability of the proposed management approach.

Conclusions

The use of vasodilators may be effective in preventing 5-fluorouracil-induced ischemic events in very high-risk cardiac patients with documented coronary artery disease. This approach may help reduce the risk of cardiac events and improve the safety of chemotherapy in this vulnerable patient population. Monitoring cardiotoxicity with maximum tolerated medical treatment and dedicated hospital protocols may be a good prophylactic approach. Further studies are needed to confirm the safety and efficacy of this approach in a larger patient population and to assess its impact on long-term cardiac outcomes.

Article Information and Declarations

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics statement

Sultan Qaboos Comprehensive Cancer Care and Research Centre Institutional Review Board and Ethics Committee approval has been given for the above referenced study, on the basis described in the application form, protocol, and supporting documentation. IRB & EC Project ID is (CCCRC-20-2024).

Author contributions

A.B.: conceptualization, methodology, writing — original draft; R.A.O., W.D.A., A.G.: investigation, data curation; H.A.-S.: formal analysis; I.A.Q.: supervision; M.A.-M.: supervision, writing — reviewing and editing.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Supplementary material

None.

References

1. Sara JD, Kaur J, Khodadadi R, et al. 5-fluorouracil and cardiotoxicity: a review. Ther Adv Med Oncol. 2018; 10: 1758835918780140, doi: 10.1177/1758835918780140, indexed in Pubmed: 29977352.
2. Frickhofen N, Beck FJ, Jung B, et al. Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. Ann Oncol. 2002; 13(5): 797–801, doi: 10.1093/annonc/mdf035, indexed in Pubmed: 12075751.
3. Visseren FLJ, Mach F, Smulders YM, et al. ESC Scientific Document Group, ESC Scientific Document Group, ESC Scientific Document Group, ESC National Cardiac Societies, ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021; 42(34): 3227–3337, doi: 10.1093/eurheartj/ehab484, indexed in Pubmed: 34458905.
4. Shiga T, Hiraide M. Cardiotoxicities of 5-Fluorouracil and Other Fluoropyrimidines. Curr Treat Options Oncol. 2020; 21(4): 27, doi: 10.1007/s11864-020-0719-1, indexed in Pubmed: 32266582.
5. Clasen SC, Ky B, O'Quinn R, et al. Fluoropyrimidine-induced cardiac toxicity: challenging the current paradigm. J Gastrointest Oncol. 2017; 8(6): 970–979, doi: 10.21037/jgo.2017.09.07, indexed in Pubmed: 29299356.
6. Petrelli F, Barni S, Bertocchi P, et al. TAS-102, the first "cardio-gentle" fluoropyrimidine in the colorectal cancer landscape? BMC Cancer. 2016; 16: 386, doi: 10.1186/s12885-016-2409-8, indexed in Pubmed: 27377645.
7. Anaka M, Abdel-Rahman O. Managing 5FU Cardiotoxicity in Colorectal Cancer Treatment. Cancer Manag Res. 2022; 14: 273–285, doi: 10.2147/CMAR.S273544, indexed in Pubmed: 35115827.
8. Padegimas A, Carver JR. How to Diagnose and Manage Patients With Fluoropyrimidine-Induced Chest Pain: A Single Center Approach. JACC CardioOncol. 2020; 2(4): 650–654, doi: 10.1016/j.jaccao.2020.06.012, indexed in Pubmed: 34396276.
9. 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(4): 238–243, doi: 10.1097/00000441-198710000-00004, indexed in Pubmed: 3661619.
10. Visseren FLJ, Mach F, Smulders YM, et al. ESC National Cardiac Societies, ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021; 42(34): 3227–3337, doi: 10.1093/eurheartj/ehab484, indexed in Pubmed: 34458905.
11. Chong JH, Ghosh AK. Coronary Artery Vasospasm Induced by 5-fluorouracil: Proposed Mechanisms, Existing Management Options and Future Directions. Interv Cardiol. 2019; 14(2): 89–94, doi: 10.15420/icr.2019.12, indexed in Pubmed: 31178935.
12. Yuan C, Parekh H, Allegra C, et al. 5-FU induced cardiotoxicity: case series and review of the literature. Cardiooncology. 2019; 5: 13, doi: 10.1186/s40959-019-0048-3, indexed in Pubmed: 32154019.
13. Polk A, Shahmarvand N, 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(8): 974–984, doi: 10.1016/j.ctrv.2013.03.005, indexed in Pubmed: 23582737.
14. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. Expert Opin Drug Saf. 2009; 8(2): 191–202, doi: 10.1517/14740330902733961, indexed in Pubmed: 19309247.
15. Jensen SA, Baeksgaard L, Petersen LN, et al. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. Cancer Chemother Pharmacol. 2006; 58(4): 487–493, doi: 10.1007/s00280-005-0178-1, indexed in Pubmed: 16418875.
16. Layoun ME, Wickramasinghe CD, Peralta MV, et al. Fluoropyrimidine-Induced Cardiotoxicity: Manifestations, Mechanisms, and Management. Curr Oncol Rep. 2016; 18(6): 35, doi: 10.1007/s11912-016-0521-1, indexed in Pubmed: 27113369.
17. Chong JH, Ghosh AK. Coronary Artery Vasospasm Induced by 5-fluorouracil: Proposed Mechanisms, Existing Management Options and Future Directions. Interv Cardiol. 2019; 14(2): 89–94, doi: 10.15420/icr.2019.12, indexed in Pubmed: 31178935.
18. Ambrosy AP, Kunz PL, Fisher GA, et al. Capecitabine-induced chest pain relieved by diltiazem. Am J Cardiol. 2012; 110(11): 1623–1626, doi: 10.1016/j.amjcard.2012.07.026, indexed in Pubmed: 22939579.
19. Clasen SC, Ky B, O'Quinn R, et al. Fluoropyrimidine-induced cardiac toxicity: challenging the current paradigm. J Gastrointest Oncol. 2017; 8(6): 970–979, doi: 10.21037/jgo.2017.09.07, indexed in Pubmed: 29299356.
20. Ambrosy AP, Kunz PL, Fisher GA, et al. Capecitabine-induced chest pain relieved by diltiazem. Am J Cardiol. 2012; 110(11): 1623–1626, doi: 10.1016/j.amjcard.2012.07.026, indexed in Pubmed: 22939579.
21. Eskilsson J, Albertsson M. Failure of preventing 5-fluorouracil cardiotoxicity by prophylactic treatment with verapamil. Acta Oncol. 1990; 29(8): 1001–1003, doi: 10.3109/02841869009091790, indexed in Pubmed: 2278719.

22. Cianci G, Morelli MF, Cannita K, et al. Prophylactic options in patients with 5-fluorouracil-associated cardiotoxicity. Br J Cancer. 2003; 88(10): 1507–1509, doi: 10.1038/sj.bjc.6600967, indexed in Pubmed: 12771913.
23. Edvardsen T, Asch FM, Davidson B, et al. Non-invasive imaging in coronary syndromes: recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography, in collaboration with the American Society of Nuclear Cardiology, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. Eur Heart J Cardiovasc Imaging. 2022; 23(2): e6–ee33, doi: 10.1093/ehjci/jeab244, indexed in Pubmed: 34751391.
24. Knuuti J, Wijns W, Saraste A, et al. ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020; 41(3): 407–477, doi: 10.1093/eurheartj/ehz425, indexed in Pubmed: 31504439.