ORIGINAL RESEARCH

The Incidence, Risk Factors, and Outcomes With 5-Fluorouracil–Associated Coronary Vasospasm

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ABSTRACT

BACKGROUND Coronary vasospasm is a recognized side effect of 5-fluorouracil (5-FU). There are limited and conflicting data on the incidence, risk factors, and prognostic effect of 5-FU–associated vasospasm.

OBJECTIVES This study sought to assess the incidence, risk factors, and prognostic implications of 5-FU coronary vasospasm among patients receiving 5-FU regimens at a single tertiary care center.

METHODS The study conducted a retrospective analysis of all patients who received 5-FU at a single academic center from January 2009 to July 2019. Vasospasm was defined as the occurrence of a typical chest pain syndrome in the presence of 5-FU. The presence of associated electrocardiogram changes or elevated biomarkers was used to further confirm the diagnosis. Patients with vasospasm were compared with patients treated with 5-FU without vasospasm in a 1:2 ratio. Data regarding demographics, medical history, and follow-up were collected by manual chart review.

RESULTS From approximately 4,019 individual patients who received 5-FU from 2009 to 2019 at a single center, 87 (2.16%) developed vasospasm. Patients who developed vasospasm were younger (age 58 ± 13 years vs. 64 ± 13 years; p = 0.001) and were less likely to have any cardiovascular risk factors (70.1% vs. 84.5%; p = 0.007). Patients with vasospasm and patients without vasospasm were otherwise similar in terms of types of cancer, stage of cancer, sex, and race. There was no significant difference in progression-free survival, overall mortality or cancer specific mortality between patients who developed vasospasm versus those who did not.

CONCLUSIONS In a large, single-center report of 5-FU–associated vasospasm, patients who developed vasospasm were younger, had lower rates of traditional cardiovascular risk factors, and had no significant difference in progression-free or overall survival compared with those who did not develop vasospasm. (J Am Coll Cardiol CardioOnc 2021;3:101–9) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ABBREVIATIONS AND ACRONYMS

5-FU = 5-fluorouracil

CI = confidence interval

ECG = electrocardiogram

IQR = interquartile range

Fluorouracil (5-FU) is an antimetabolite that has remained the standard of care for the treatment of solid organ tumors over the last 4 decades, including adenocarcinomas of the breast and adenocarcinomas and squamous cell carcinomas of the bladder, gastrointestinal tract, and head and neck (1). Upshaw et al. (2) reported that an estimated 154,000 patients are treated with 5-FU or capecitabine annually in the United States. 5-FU is pyrimidine analog that inhibits thymidine synthesis and DNA replication by inhibiting the enzyme thymidylate synthase, thereby attacking rapidly dividing solid tumors (1). While 5-FU is the third most common drug used for the treatment of solid malignancies, it is the second most common drug associated with cardiotoxicity after anthracyclines, in terms of the total number of patients who develop cardiotoxicity (3). There are several reported presentations of 5-FU-associated cardiotoxicity, with the commonest manifestation as chest pain (3,4). Chest pain presentation varies from atypical chest pain to typical angina, acute coronary syndrome, and myocardial infarction (3). Other less common presentations include arrhythmias, pericarditis, myocarditis, heart failure, and even death (3-5).

The most common mechanism for chest pain in the setting of 5-FU is thought to be coronary vasospasm. This is likely due to the effect of 5-FU on smooth muscle cells as demonstrated by in vitro studies (6,7) and vasospasm noted during coronary angiography in clinical studies (8). Despite multiple case reports and combined series of 5-FU-associated coronary vasospasm, there is no clear consensus on the incidence, risk factors, and prognosis of 5-FU-associated coronary vasospasm. The reported incidence in the literature varies from 1% to 35%, likely owing to the sample population being studied, the broad cardiac definitions and inclusion of multiple different cardiotoxicities from 5-FU, and the varied formulations or administration protocols for the drug (3,9). For example, some studies included bradycardia as a definition of 5-FU cardiotoxicity (5), while others included myocarditis and sudden death (10).

Therefore, our objective was to specifically assess the incidence of coronary vasospasm presenting as a chest pain syndrome, among a heterogeneous group of patients receiving bolus or infusional formulations of 5-FU at a single academic medical center. We further hoped to define any risk factors that predispose patients to developing coronary vasospasm and assess the prognostic implications of developing vasospasm on overall survival and cancer progression.
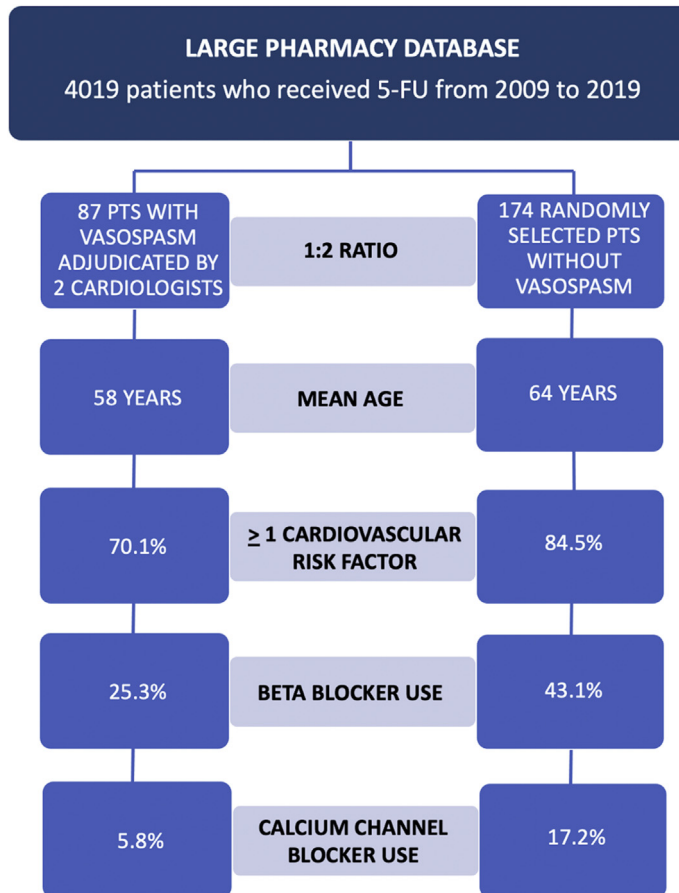
METHODS

STUDY DESIGN. We conducted a retrospective analysis of all patients who received 5-FU at a single academic center (Massachusetts General Hospital, Boston, Massachusetts) from January 2009 to July 2019. Individuals were flagged based on keyword search for *5-fluorouracil* in their charts. The results were then narrowed based on keyword search for *5-fluorouracil* and *vasospasm* among these individuals. Vasospasm was defined as the new occurrence of a typical chest pain syndrome at rest in the presence of recent 5-FU with or without electrocardiogram (ECG) or biomarker changes. However, the presence of associated ECG changes (new ST-segment or T-wave changes) or elevated biomarkers was used to further confirm the diagnosis. We further searched the list of all patients for the diagnosis of myocardial infarction based on International Classification of Diseases codes, entered within a year of receiving 5-FU, to ensure completeness of our vasospasm dataset. The diagnosis of 5-FU-associated coronary vasospasm was independently adjudicated by 2 cardiologists. This approach is fully detailed in the Supplemental Appendix. Patients who had received 5-FU but did not develop vasospasm were then randomly selected using a 2:1 ratio and compared with those who did develop vasospasm. The institutional review board at Massachusetts General Hospital approved the study, and the requirement for written informed consent was waived.

COVARIATES OF INTEREST. Data regarding demographics, baseline medical history, and last known follow-up or date of death were collected by manual chart review from electronic medical records. Cardiovascular disease risk factor was defined as a composite of hypertension, hyperlipidemia, diabetes mellitus, and current or prior smoking. Ischemic heart disease was defined as prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting. Baseline parameters were identified from the oncology consult note prior to 5-FU initiation. Coronary vasospasm admission specific parameters included clinical presentation, diagnostic testing on admission (ECG, echocardiography, coronary angiogram), and relevant labs (cardiac biomarkers, complete blood count, basic metabolic panel). The stage of cancer at the time of diagnosis was obtained from the initial oncology consult note.

CENTRAL ILLUSTRATION Study Design and Key Differences Between Patients With and Without Vasospasm

LARGE PHARMACY DATABASE
4019 patients who received 5-FU from 2009 to 2019

87 PTS WITH VASOSPASM ADJUDICATED BY 2 CARDIOLOGISTS	**1:2 RATIO**	174 RANDOMLY SELECTED PTS WITHOUT VASOSPASM
58 YEARS	**MEAN AGE**	64 YEARS
70.1%	**≥ 1 CARDIOVASCULAR RISK FACTOR**	84.5%
25.3%	**BETA BLOCKER USE**	43.1%
5.8%	**CALCIUM CHANNEL BLOCKER USE**	17.2%

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Flow chart outlining study design and key differences between patients who developed 5-fluorouracil (5-FU)–associated vasospasm and those who did not. A total of 4,019 patients received 5-FU at a single tertiary care center, and 87 developed vasospasm after receiving 5-FU. Patients with vasospasm were compared with those who did not develop vasospasm in a 1:2 fashion. Patients who developed vasospasm were younger, had fewer cardiovascular risk factors, and were less likely to be on cardioprotective medications.

Of note, stage 3 encompassed a large group of people depending on number of positive lymph nodes; however, for the purposes of this study, they were grouped together. Data regarding 5-FU dosing and chemotherapy regimen were obtained from pharmacy dispense records.

STATISTICAL ANALYSES. Baseline characteristics of all patients are presented as continuous variables and summarized as mean ± SD or median (interquartile range [IQR]) for continuous variables and as count and percentage for categorical variables. Differences between continuous variables were assessed using the *t* test or Wilcoxon rank sum test, dependent on normality, while differences between categorical variables were assessed using the chi-square test.

Normality was assessed using visual estimation of the Q-Q plot for each continuous parameter. Overall survival and progression-free survival between the 2 groups was analyzed by comparing the median overall survival and median progression-free survival between patients with vasospasm and patients without vasospasm, using Kaplan-Meier methods and the log-rank test. We also performed Cox proportional hazards regression analysis to calculate hazard ratios for progression of underlying cancer, cancer-related death, and overall mortality for patients who developed vasospasm. The hazard ratios were adjusted for the appropriate covariates including age, underlying stage of cancer, baseline cardiovascular risk factors (smoking, hypertension, diabetes), known ischemic

TABLE 1 Comparison of Baseline Characteristics of Patients With Vasospasm and Patients Without Vasospasm

	Patients With Vasospasm (n = 87)	Patients Without Vasospasm (n = 174)	p Value
Age, yrs	58 ± 13	64 ± 13	0.001
Female	42.5 (37)	41.4 (72)	0.859
White	87.4 (76)	89.1 (155)	0.681
Median stage of cancer	3	3	0.896
I	8.1 (7)	7.5 (13)	0.869
II	11.5 (10)	18.4 (32)	0.153
III	41.4 (36)	30.0 (52)	0.064
IV	39.1 (34)	44.3 (77)	0.426
Upper GI cancer	18.4 (16)	16.7 (29)	0.728
Colorectal cancer	56.3 (49)	47.7 (83)	0.189
Pancreatic cancer	13.8 (12)	20.1 (35)	0.210
Other cancer	11.5 (10)	15.5 (27)	0.380
≥1 cardiovascular risk factor	70.1 (61)	84.5 (147)	0.007
Hypertension	46.0 (40)	57.5 (100)	0.079
Hyperlipidemia	43.7 (38)	54.6 (95)	0.096
Diabetes mellitus	16.9 (14)	25.0 (42)	0.136
Smoking	42.5 (37)	46.6 (81)	0.538
Ischemic heart disease	18.4 (16)	27.0 (47)	0.125
CKD	6.9 (6)	8.6 (15)	0.629
ASA	31.0 (27)	42.0 (73)	0.087
Beta-blockers	25.3 (22)	43.1 (75)	0.005
ACE inhibitor/ARB	29.1 (25)	33.9 (59)	0.433
Diuretics	6.9 (6)	9.8 (17)	0.440
Aldosterone antagonist	2.3 (2)	1.2 (2)	0.476
Nitrate	8.0 (7)	5.7 (10)	0.478
Calcium-channel blocker	5.8 (5)	17.2 (30)	0.010
Dihydropyridine	2.3 (2)	13.2 (23)	0.005
Nondihydropyridine	3.5 (3)	4.0 (7)	0.813

Values are mean ± SD or % (n). The p values were calculated using Student's *t*-test or Wilcoxon rank sum test for continuous variables, and chi-square test for categorical variables.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ASA = acetylsalicylic acid; CKD = chronic kidney disease; GI = gastrointestinal.

heart disease, and heart failure, where appropriate. The proportional hazards assumption was tested on the basis of Schoenfeld residuals. We also performed sensitivity analyses using survival using Fine and Gray's method, to account for the competing risk of death when evaluating progression-free survival. Last, we also performed sensitivity analyses in which coronary vasospasm was treated as a time-dependent covariate, in addition to the previous analysis. All statistical tests were 2-sided, and 5% was set as the level of significance. Statistical analysis was performed using STATA version 15.1 (StataCorp, College Station, Texas).

RESULTS

PATIENT CHARACTERISTICS. From January 2009 to July 2019, 4,019 individual patients received 5-FU at Massachusetts General Hospital. Among these 4,019

individuals, 87 (2.16%) developed 5-FU-associated coronary vasospasm, who are identified as patients with vasospasm from hereon. From the 3,932 patients who did not develop vasospasm, 174 patients were randomly selected for comparison with those who did develop vasospasm (**Central Illustration**). Patients who developed vasospasm were younger at the time of their first dose of 5-FU (age 58 ± 13 years vs. 64 ± 13 years; p = 0.001). There was no difference in the proportion of female patients between the 2 groups (42.5% [n = 37 of 87] for patients with vasospasm vs. 41.4% [n = 72 of 174] for patients without vasospasm; p = 0.859). There was also no difference between the proportion of White individuals between the 2 groups (87.4% [n = 76 of 87] for patients with vasospasm vs. 89.1% [n = 155 of 174] for patients without vasospasm; p = 0.681). The 2 groups were similar in terms of the type and stage of cancer (**Table 1**). The median stage of cancer for both was stage 3 (p = 0.896).

Patients with vasospasm were significantly less likely to have any cardiovascular risk factors (70.1% [n = 61 of 87] for patients with vasospasm vs. 84.5% [n = 147 of 174] for patients without vasospasm; p = 0.007) (**Central Illustration**). The respective prevalence of each of the individual cardiovascular risk factors is presented in **Table 1**. There was a lower prevalence of ischemic heart disease among patients with vasospasm (18.4% [n = 16 of 87]) versus patients without vasospasm (27.0% [n = 47 of 174]); however, this difference was not statistically significant (p = 0.125). Similarly, the prevalence of hypertension among patients with vasospasm was 46.0% (n = 40 of 87) versus 57.5% (n = 100 of 174) for patients without vasospasm (p = 0.079), and hyperlipidemia among patients with vasospasm was 43.7% (n = 38 of 87) versus 54.6% (n = 95 of 174) for patients without vasospasm (p = 0.096).

Patients with vasospasm were less likely to be on cardiac medications. Aspirin use among patients with vasospasm was 31.0% (n = 27 of 87) versus 42.0% (n = 73 of 174) for patients without vasospasm (p = 0.087). Beta-blocker use was 25.3% (n = 22 of 87) among patients with vasospasm versus 43.1% (n = 75 of 174) among patients without vasospasm (p = 0.005). Patients with vasospasm were similarly less likely to be on calcium-channel blockers, 5.8% (n = 5 of 87) for patients with vasospasm versus 17.2% (n = 30 of 174) for patients without vasospasm (p = 0.010). This difference was especially significant for dihydropyridine calcium-channel blockers, 2.3% (n = 2 of 87) for patients with vasospasm versus 13.2% (n = 23 of 174) for patients without vasospasm (p = 0.005). There was no statistically significant difference in the use of angiotensin-converting

enzyme inhibitors or angiotensin II receptor blockers, diuretics, or aldosterone antagonists between patients with vasospasm and patients without vasospasm. Last, there was no statistically significant difference in baseline long-acting nitrate use (8.0% [n = 7 of 87] for patients with vasospasm vs. 5.7% [n = 10 of 174] for patients without vasospasm; p = 0.478).

5-FU REGIMENS. Patients received combination (bolus and infusion), bolus only, and infusion only regimens. The different types of 5-FU regimens used among the 2 groups (with and without vasospasm) are presented in **Table 2**. The majority of patients in both groups received combination regimens, 75.9% (n = 66 of 87) for patients with vasospasm and 69.5% (n = 121 of 174) for patients without vasospasm. The sample size for each individual regimen was too small to make any meaningful inferences.

VASOSPASM PRESENTATION. Among 87 patients who had coronary vasospasm, 63 (72.4%) patients had vasospasm during their first cycle of 5-FU, 8 (9.2%) had it during cycle 2, and 7 (8.1%) had it during cycle 3. The remaining 9 (10.3%) patients had vasospasm after their third cycle. Chest pain as their primary symptom during the index presentation in 84 (96.6%) patients. Clinical evidence of heart failure on presentation was noted in 4.6% of the vasospasm patients. Of the 79 patients with vasospasm who had their vasospasm presentation ECG available for review, 58 (73.4%) had ST/T-wave changes.

Baseline sodium, white blood count, hemoglobin, natriuretic peptide, and troponin levels of patients with vasospasm at time of presentation are presented in **Table 3**. Of note, 34 of 53 (64.2%) patients with vasospasm had an elevated conventional troponin measurement, and 16 of 19 (84.2%) patients with vasospasm had an elevated high-sensitivity troponin measurement during their vasospasm admission. A total of 50 of 72 (69.4%) patients with vasospasm who had troponins (conventional or high sensitivity) measured during their vasospasm admission had a value that was above the upper limit of normal. The median conventional troponin was 0.06 (IQR: 0.01 to 0.18) ng/ml, while the median high-sensitivity troponin was 26 (IQR: 14 to 34) ng/l (**Table 3**).

SURVIVAL AND CANCER PROGRESSION ANALYSIS. The total median dose of 5-FU received by patients with vasospasm was significantly lower than patients without vasospasm (11,725 [IQR: 5,913 to 29,392] mg vs. 26,253 [IQR: 13,650 to 47,925] mg; p < 0.001). Similarly, the total median 5-FU dose adjusted for body surface area received by patients with vasospasm was significantly lower than that for patients without

vasospasm (5,388 [IQR: 2,800 to 10,310] mg/m^2 vs. 11,241 [IQR: 7,170 to 24,288] mg/m^2; p < 0.001). The median progression-free survival for patients with vasospasm was 553 (95% confidence interval [CI]: 427 to 924) days for patients with vasospasm versus 608 (95% CI: 456 to 833) days for patients without vasospasm (p = 0.771). The median overall survival for patients with vasospasm was 1,277 (95% CI: 780 to 2,039) days versus 1,150 (95% CI: 822 to 1,637) days for patients without vasospasm (p = 0.573) (**Figure 1**).

A detailed analysis of cancer-specific mortality in patients who developed vasospasm versus those who did not was also performed. Among patients who developed coronary vasospasm, 43 of 87 were reported dead at the time of this analysis, and 40 of them were cancer-related deaths. Among patients who did not develop coronary vasospasm, 113 of 174 were reported dead, and 91 of them were cancer-related. Adjusting for age and stage of cancer, the hazard ratio for progression of underlying cancer for patients with vasospasm was 1.130 (95% CI: 0.797 to 1.595; p = 0.498). When adjusting for age,

TABLE 2 5-FU Chemotherapy Formulations Received by Patients With and Without Vasospasm

	Patients With Vasospasm (n = 87)	Patients Without Vasospasm (n = 174)
Combination (bolus and infusion) regimens		
FOLFIRINOX	12	21
FOLFIRI	4	7
FOLFIRI/cetuximab	1	1
FOLFOX	42	83
FOLFOX + bevacizumab or cetuximab	4	3
5-FU/leucovorin (deGramont)	0	3
Docetaxel/cisplatin/fluorouracil	3	3
Total	66	121
Bolus-only regimens		
FLOX	1	0
5-FU IV bolus only	0	4
Bolus 5-FU/leucovorin/carboplatin	0	1
Cyclophosphamide/methotrexate/fluorouracil	1	0
Total	2	5
Infusion-only regimens		
5-FU IV infusion/radiation	2	11
5-FU IV infusion	6	23
FOLFOXIRI	2	0
5-FU/mitomycin	4	8
5-FU/cisplatin/radiation	0	5
5-FU continuous intravenous infusion/carboplatin/cetuximab	0	1
Total	14	48
Other		
Capecitabine	5	0

5-FU = 5-fluorouracil; IV = intravenous.

TABLE 3 Vasospasm Presentation for Patients (N = 87)

Presenting symptom	
Chest pain	96.6 (84)
Shortness of breath	21.8 (19)
Syncope	3.4 (3)
Palpitations	4.6 (4)
Physical exam	
Jugular venous distension	4.6 (4)
Crackles	3.4 (3)
Lower extremity edema	4.6 (4)
Heart rate, beats/min	80 ± 16
Systolic blood pressure, mm Hg	124 ± 16
Diastolic blood pressure, mm Hg	73 ± 11
Temperature, °F	97.8 (97.1–98.2)
Respiratory rate, breaths/min	18 (16–18)
Electrocardiogram findings	
Sinus rhythm	92.4 (73/79)
Heart rate, beats/min	75 (67–92)
PR, ms	150 (134–163)
QRS, ms	88 (80–108)
QTc, ms	435 (418–460)
ST/T-wave changes	73.4 (58/79)
Labs	
Sodium, mmol/l	138 (136–140)
Hemoglobin, g/dl	11.5 (10.2–12.7)
White blood count, K/μl	6.24 (4.78–8.92)
N-terminal pro-B-type natriuretic peptide, pg/ml	325 (123–1,058)
Troponin	
Conventional troponin peak, ng/ml	0.06 (0.01–0.18)
% of cases with troponin > ULN	64.2 (34/53)
High-sensitivity troponin peak, ng/l	26 (14–34)
% of cases with troponin > ULN	84.2 (16/19)

Values are % (n), mean ± SD, median (interquartile range), or % (n/N).
ULN = upper limit of normal.

cardiovascular risk factors (smoking, hypertension, diabetes), known ischemic heart disease, heart failure, and stage of cancer, the hazard ratio for cancer-related mortality among those with vasospasm was 1.230 (95% CI: 0.827 to 1.84; p = 0.303). Using these same confounders, the adjusted hazard ratio for overall mortality among those with vasospasm was 1.090 (95% CI: 0.746 to 1.580; p = 0.664).
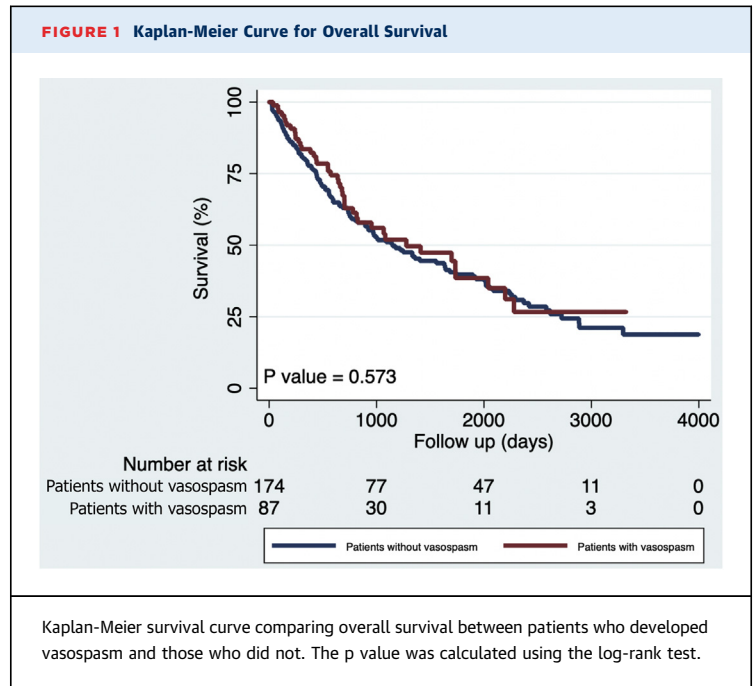
DISCUSSION

In this retrospective study of patients receiving 5-FU at a single tertiary medical center, we found an incidence of coronary vasospasm of 2.16%. To our knowledge, this is the largest cohort study of coronary vasospasm patients, which allowed us to identify baseline differences between patients who developed vasospasm and those who did not. On average, coronary vasospasm patients were younger than were patients without vasospasm. In addition,

vasospasm patients were less likely to have ischemic heart disease or risk factors for developing coronary artery disease, such as hypertension, and hyperlipidemia. Vasospasm developed early, in which almost 90% of the patients with vasospasm developed coronary vasospasm at some point during their first 3 doses of 5-FU (>70% during their first cycle). More than 95% presented with chest pain, and >70% had ST/T-wave changes on their admission ECG. We further found that the development of vasospasm has a negative effect on the cumulative dose of 5-FU administered.

There are conflicting data on the association between cardiovascular risk factors and the occurrence of 5-FU-associated vasospasm (4,11). Polk et al. (10) reported 5-FU cardiotoxicity, diagnosed on the basis of clinical symptoms (chest pain, dyspnea, palpitations), in 22 of 452 (4.9%) women who received capecitabine for breast cancer. They identified cardiac comorbidity (defined as previous history of coronary artery disease, arrhythmias, or heart failure), current smoking, and hyperlipidemia as significant risk factors for the development of 5-FU cardiotoxicity (10). Of note, their patient cohort only included women treated exclusively with capecitabine, and the total number of patients with vasospasm was 22. The difference in the composite category of cardiac comorbidity was principally driven by an increased prevalence of heart failure and arrhythmias among patients with vasospasm and was not due to any difference in the history of ischemic heart disease between patients with vasospasm and patients without vasospasm. Similarly, Raber et al. (12) identified 8 patients with 5-FU-associated coronary vasospasm of 177 patients who received 5-FU or capecitabine at a single institution in 2018. Only 4 of the vasospasm patients had chest pain along with ECG changes or biomarker elevation. They noted a higher prevalence of coronary artery disease among patients with vasospasm than among patients without vasospasm; however, this conclusion was based on the comparison of 3 of 8 (37.5%) patients with vasospasm versus 12 of 169 (7%) patients without vasospasm. Given the variability in the definition of cardiotoxicity, Rezkall et al. (13) conducted a prospective study in which they performed continuous ambulatory ECG monitoring on 25 patients undergoing 5-FU infusion. Although only 1 patient developed anginal chest pain, 17 patients had asymptomatic ECG changes during 5-FU infusion. Thus, it is possible that studies that define 5-FU cardiotoxicity solely on the basis of chest pain symptoms could miss patients with silent ischemic changes and thus underestimate the incidence of 5-FU cardiotoxicity.

Our findings of a lower age and reduced rates of cardiovascular risk factors are consistent with the findings of Ambrosy et al. (14), who showed that in a case series of 5 patients who had capecitabine-induced coronary vasospasm, the mean age was 58.6 years, and none of the patients had a history of coronary artery disease. Similarly, Chakrabarti et al. (15) published a retrospective review of patients who received infusional 5-FU (FOLFOX and CAPOX regimens) at the Mayo Clinic from January 2011 to January 2018 and identified 10 patients who developed coronary vasospasm. The median age of these patients was 56.6 years, and only 1 patient had a history of coronary artery disease (15). This is also consistent with the conclusions of a review by Robben et al. (16) published in 1993, in which 134 vasospasm patients were compiled from multiple small case reports and case series from the literature. They estimated that the prevalence of coronary artery disease was 18% among patients who developed coronary vasospasm versus 71% among patients without vasospasm. Wacker et al. (17) evaluated 102 patients before 5-FU infusion therapy and then after 3 months with ECG, echocardiograms, and radionuclide ventriculography. A total of 19% of the patients developed symptoms of cardiotoxicity, but none had a history of coronary artery disease (17).

This study was not designed to understand the mechanisms involved in the development of 5-FU vasospasm, but we hypothesize that the presence of coronary artery disease induces ischemic preconditioning in patients and allows them to better tolerate episodes of transient coronary vasospasm during 5-FU therapy. Chong et al. (18) further elaborated on this idea in a review in which they questioned the role of remote ischemic conditioning in preventing 5-FU coronary vasospasm. They hypothesized that because one of the proposed mechanisms of 5-FU toxicity is vascular endothelial damage followed by thrombus formation, the proven protective effects of ischemic conditioning on endothelial function and the microvasculature may represent a plausible target for a preventive strategy for coronary vasospasm. Last, patients with known ischemic heart disease or known cardiovascular disease risk factors are more likely to be on potentially cardioprotective drugs such as beta-blockers and calcium-channel blockers, which may reduce their risk of coronary vasospasm (19). In our study, patients without vasospasm who had a higher incidence of ischemic heart disease were more likely to be on beta-blockers (p = 0.005) and calcium-channel blockers (p = 0.010) when compared with patients who developed vasospasm. In further support of this

FIGURE 1 Kaplan-Meier Curve for Overall Survival

Number at risk				
Patients without vasospasm	174	77	47	11	0
Patients with vasospasm	87	30	11	3	0

P value = 0.573

Kaplan-Meier survival curve comparing overall survival between patients who developed vasospasm and those who did not. The p value was calculated using the log-rank test.

hypothesis, calcium-channel blockers such as diltiazem have been used to treat and rechallenge patients who developed vasospasm after their first 5-FU exposure in small case series (14,19,20). However, it should also 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 prior to their first infusion did not show any difference in the incidence of cardiotoxicity between the treatment and control groups (21).

One of our goals for this study was to assess progression-free survival and cancer-related and overall mortality in patients who developed vasospasm compared with those who did not. Of note, our patients with vasospasm and patients without vasospasm were well matched in terms of types and stages of cancer. It is also important to note that coronary vasospasm patients were an average of 10 years younger and were less likely to have underlying ischemic heart disease or other cardiovascular risk factors at baseline. However, the adjusted hazard ratio for progression of underlying cancer for patients with vasospasm was 1.130 (95% CI: 0.797 to 1.595; p = 0.498). Similarly, the adjusted hazard ratio for cancer-related death among patients with vasospasm was 1.230 (95% CI: 0.827 to 1.840; p = 0.303). There are limited prior comparative data. In 1999, Becker et al. (9) reported in a review that the overall mortality among patients with vasospasm was estimated at between 2.2% and 13.3%. It is possible that the

previous results were not significant due to a smaller sample size. We hypothesize that a lower progression-free survival in patients with vasospasm could be observed due to the decreased availability of a key cancer medication. This hypothesis is supported by the finding that the dose of 5-FU received by the vasospasm patients in our series was significantly lower than patients without vasospasm (5,388 [IQR: 2,800 to 10,310] mg/m^2 vs. 11,241 [IQR: 7,170 to 24,288] mg/m^2; p < 0.001), as the occurrence of vasospasm most often leads to cessation of 5-FU therapy, and patients may or may not be rechallenged [20]. There are very limited data on the successful rechallenge of vasospasm patients with or without pretreatment with antianginal therapies. Tsavaris et al. [22] observed that "intensive cardiologic monitoring and prophylactic nitrate administration may result in fairly good subsequent tolerance" among the 20 patients who developed coronary vasospasm in their study. However, they cautioned against extrapolating that result to all-comers given the small number of patients in their study. Kwakman et al. [23] successfully rechallenged 7 patients, who had previously developed coronary vasospasm with capecitabine, with oral fluoropyrimidine S-1, which has a lower concentration of cardiotoxic metabolites than 5-FU or capecitabine. Furthermore, there are minimal long-term oncologic outcome data on these patients that were treated with either lower doses of 5-FU or different formulations. Our group is currently in the process of collecting this information for our patient cohort, and we hope to further analyze the efficacy and safety of different antianginal regimens prior to rechallenge.

STUDY LIMITATIONS. The study should be interpreted within the context of the study design. This was a retrospective study design; however, given the low incidence of coronary vasospasm among all-comers receiving 5-FU therapy, a retrospective design is necessary. In addition, given the definition of vasospasm in this study as the presence of a chest pain syndrome, we were not able to include patients who might have had asymptomatic events. Thus, the true incidence may be underestimated, and the characteristics of those asymptomatic patients cannot be defined from this study. We were still able to identify important baseline distinctions between patients who developed coronary vasospasm after 5-FU therapy and those who did not. Despite the retrospective nature of our study, the relatively large scale allowed us to show a statistically significant difference in the absence of cardiovascular risk factors among patients who developed vasospasm. Differences in baseline characteristics are important to identify patients who might be at high risk for developing vasospasm, and thus could require closer monitoring, including continuous ECG monitoring and biomarker testing during 5-FU therapy [1,24]. Furthermore, because our patient selection spanned a time period of almost 10 years, there were limited follow-up data available for patients that predated the implementation of electronic medical records at our institution. Every attempt was made to review scanned records and obtain complete information in these cases. Last, we identified the stage of cancer at the time of diagnosis from the initial oncology consult note. We recognize that stage 3 encompasses a large heterogeneous group of people depending on the number of positive lymph nodes, and that could inadvertently bias our results. However, the Cox proportional hazards regression analysis for progression-free survival and cancer-related deaths was adjusted for the baseline stage of cancer, which could address this issue to some extent.

CONCLUSIONS

To our knowledge, this is the largest published report of 5-FU-associated vasospasm. In our study, patients who developed vasospasm were younger and had lower rates of traditional cardiovascular risk factors. In the future, we hope to further examine treatment strategies that may allow patients who develop coronary vasospasm to be successfully rechallenged with 5-FU therapy, and to examine the cardiac safety and the cancer efficacy of rechallenge.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our study demonstrates that patients who developed 5-FU–associated coronary vasospasm were younger and without any defined cardiovascular risk factors or a history of ischemic heart disease compared with those who did not develop vasospasm. Most patients develop symptoms during their first cycle, commonly manifesting as chest pain.

TRANSLATIONAL OUTLOOK: We hypothesize that the lower prevalence of coronary vasospasm among patients with known cardiovascular disease risk factors is due to the concurrent use of cardioprotective medications such as aspirin, beta-blockers, and calcium-channel blockers. Further research is needed to study the prophylactic use of these medications prior to 5-FU therapy, and possible use prior to rechallenging patients with known 5-FU–associated vasospasm, in terms of cardiac safety and cancer efficacy.

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KEY WORDS 5-FU, cardiotoxicity, coronary vasospasm, fluorouracil

APPENDIX For an expanded Methods section, please see the online version of this paper.