Original Study

Fluoropyrimidine Cardiotoxicity: Time for a Contemporaneous Appraisal

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Abstract

The fluoropyrimidines, 5-fluorouracil and capecitabine can cause cardiotoxicity. In a review of 16 Eastern Cooperative Group Cancer Research Group–American College of Radiology Imaging Network fluoropyrimidine-based treatment studies, exclusion of premorbid cardiovascular disease was common. Less than half of the studies (43%) specifically evaluated cardiac ischemic events. Standardized collection of cardiovascular risk factor and outcome data in oncologic trials is needed.

Introduction: Fluoropyrimidines (FPDs) are a fundamental component of many chemotherapy regimens. Cardiotoxic adverse events (AEs) such as angina, ischemia, arrhythmias, and cardiomyopathy associated with 5-fluorouracil (5-FU) and capecitabine (CAPE) have been sparingly described in studies, primarily through case reports. Data from the 1990s revealed an estimated incidence of 0.5% to 19%, with cardiovascular fatalities occurring in ≤28%. The current use of FPDs includes multiple dosing regimens, oral or intravenous delivery, and administration with additional cardiotoxic therapies. As such, it is imperative to better define the cardiotoxicity risk in the modern treatment era. We comprehensively evaluated the incidence, prevalence, and ascertainment of cardiovascular risk factors and disease within ECOG-ACRIN (Eastern Cooperative Group Cancer Research Group – American College of Radiology Imaging Network) Cancer Research Group clinical trials incorporating 5-FU and CAPE. **Materials and Methods:** Case report forms and clinical study reports from the ECOG-ACRIN Cancer Research Group database of phase II and III clinical trials incorporating 5-FU and CAPE were evaluated. A total of 16 trials from 2002 to 2017 were identified that had used bolus 5-FU (n = 1), continuous infusion 5-FU (n = 10) or CAPE (n = 5). **Results:** A history of cardiovascular disease was variably defined and was an exclusion criterion in 13 of the 16 studies (81%). The baseline risk factors and history of cardiac disease were specifically collected in only 3 studies (19%). All studies collected cardiovascular AEs using the Common Terminology Criteria for Adverse Events version available at the time of the study. Fewer than half (7 of 16; 44%) of the study case report forms had also specifically requested information on cardiac ischemia/infarction. In the 12 completed studies with clinical study reports, the following AEs were reported: dyspnea, ≤16%; arrhythmias, ≤6%; and angina, ischemia, and elevated troponin, ≤5%. Some trials only recorded cardiac AEs that were possibly associated with the novel drug being studied and not those attributed to the standard of care in the 5-FU/CAPE arm, further decreasing the numerical incidence. **Conclusion:** Inconsistent clinical trial reporting of cardiac AEs precluded accurate and precise delineation of the epidemiology of FPD-related cardiovascular AEs. Prospective knowledge of the definition and natural history will lead to the development of risk factor stratification and pre-chemotherapy interventions to reduce or prevent cardiotoxicity. We propose that the prospective collection of

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baseline cardiac data and prespecified cardiac endpoints are necessary to fully understand the incidence and cardiac risk of FDPs.

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Introduction

The fluoropyrimidine (FPD), 5-fluorouracil (5-FU), and the oral prodrug, capecitabine (CAPE), have been fundamental components of many chemotherapy regimens since 1962 with Food and Drug Administration (FDA) approval of 5-FU. The standard of care chemotherapy regimens for colorectal carcinoma have used either agent (5-FU or CAPE) as neoadjuvant treatment, as adjuvant therapy, and for disease stabilization with incurable cancer. Thus, an estimated 154,000 patients are potentially exposed to 5-FU and/or CAPE annually. FPDs will continue to be widely prescribed because currently, no pharmacologic replacements are available for colorectal carcinoma. In 2015, the combination of trifluridine and tipiracil, an oral thymidine-based nucleoside analog, was approved as third- or fourth-line therapy.[1] Serious adverse effects (AEs) associated with FPDs can alter the prescribed treatment regimen.[2,3] In particular, cardiovascular (CV) complications can obstruct the delivery of potentially curative or life-prolonging chemotherapy, with significant morbidity and increased mortality for patients predicted to have long-term oncologic survival.

The mechanisms of FPD-associated cardiotoxicity have been derived mainly from older studies using preclinical and cell models. These include coronary artery vasospasm potentially due to protein kinase C activation, vascular endothelial damage, increased myocardial oxygen consumption, and direct myocardial toxic effects.[4-8] The described CV complications encompass a broad list, including angina, arrhythmias, sudden death, hypotension/hypertension, and cardiomyopathy.[8-11] Anecdotally, these conditions have occurred with and without the presence of underlying CV disease. The reported data regarding cardiotoxicity are sparse despite multiple clinical reports and have been mainly retrospective, with a widely reported estimated incidence from systematic reviews ranging from 0.5% to 19%.[8,10]

A prospective study reported in 1992 affords the best insight into the natural history of FPDs.[11] Cancer patients (n = 367) scheduled to receive the first cycle of outpatient continuous infusion 5-FU were hospitalized and monitored in accordance with the study parameters. Of the 367 patients, 28 (7.6%) experienced cardiotoxicity such as angina and hypotension. Of these 28 patients, 8 died (28.6%) of sudden death or hypertension followed by hypotension with cardiogenic shock.[11] The CV-related mortality rate for the entire cohort was 2.2% (8 of 367). In the group of 28 patients with cardiotoxicity, 8 patients (28.6%) had an antecedent CV condition. Whether any of these 8 patients had experienced fatal cardiac toxicity was not reported. For those afflicted with 5-FU cardiotoxicity, prevention of disability and death is an unmet clinical problem.

To acquire detailed insight into the more recent incidence of cardiotoxicity with 5-FU/CAPE, we evaluated summary reports from national clinical trials performed through the Eastern Cooperative Group Cancer Research Group − American College of Radiology Imaging Network (ECOG-ACRIN).

Materials and Methods

The ECOG-ACRIN Cancer Research Group database of completed and ongoing phase II and III clinical trials was searched using the indexed Cancer Chemotherapy National Service Center (NSC) number for 5-FU (NSC 19893) and CAPE (NSC 712807) to identify all ECOG-ACRIN trials using 5-FU and/or CAPE in ≥ 1 study arm. For all trials, the study protocol and case report forms (CRFs) were reviewed, and the following information was extracted: study population, treatment regimens, CV exclusion criteria, CV disease present or CV risk factors collected at baseline, and assessment methods of CV events during the trial. For trials that had closed to accrual, the ECOG-ACRIN clinical study report (CSR) (which reports the final study results including AEs), if available, was also reviewed, and the rates of CV events were extracted.

Results

Sixteen trials using 5-FU and/or CAPE initiated from 2002 to 2016 were identified (Table 1). No ECOG-ACRIN trials of trifluridine and tipiracil were conducted during the study period. Accrual in 13 of the trials (81%) had closed. Of the 16 trials, 10 (63%) had included 5-FU, 5 (31%) had used CAPE, and 1 (6%) had included both. Of the 11 trials with 5-FU in ≥ 1 arm, 1 had used bolus dosing only, 5 had used a bolus followed by continuous infusion, and 4 had used continuous infusion only. CAPE dosing ranged from 750 mg/m^2 twice daily to 1000 mg/m^2 twice daily. Of the 16 trials, 10 (62%) were phase II and 6 (38%) were phase III trials. The malignancies studied were gastrointestinal in 13 (81%), breast in 2 (12%), and head and neck in 1 (7%).

Previous CV disease was an exclusion criterion in most of the trials (13 of 16). However, the definition of CV disease varied substantially across the trials. Potential participants with recent previous unstable angina or myocardial infarction were excluded in 11 studies, with exclusion intervals ranging from 3 to 12 months before enrollment. Other frequent exclusion criteria for conditions such as stroke, peripheral vascular disease, and heart failure were inconsistently defined. Only 3 trials specifically recorded the baseline CV history or risk factors on the CRFs. Cardiac AEs were defined according to the Common Terminology Criteria for Adverse Events (CTCAE) according to the version available during the study period (versions 2-4). In 9 trials (56%) the AE CRFs specifically asked investigators to report ≥ 1 CV AE; however, in other trials, no CV AEs were explicitly requested and thus were reported according to the CTCAE as "other" on the AE CRF. Of the 9 trials that requested CV AEs, the specific AEs included cardiac

Table 1 Description of Phase II and III ECOG-ACRIN Trials of 5-FU and/or Capecitabine, CV Exclusion Criteria, and Ascertainment of CV Events

Study	Agents	Cancer Type	Phase, and Accrual	Year Study Activated	CV Exclusion Criteria	Baseline CV Data Collected	CTCAE Version, Grade, and Attribution[a]	CV Event Definitions/ Ascertainment on AE CRF
E1103	CAPE 1000 mg/m^2 twice daily + tipifarnib	Metastatic breast cancer	Phase II; n = 71	2004	Symptomatic CV disease	None	v2, all grades; treatment related[b]	Cardiac ischemia/MI; dyspnea
E2200	5-FU 400 mg/m^2 weekly bolus + irinotecan + leucovorin + bevacizumab	Advanced colorectal cancer	Phase II; n = 92	2000	None	None	v2, all grades, treatment related[b]	HTN; dyspnea; thromboembolism
E2204	CAPE 825 mg/m^2 twice daily; arm A: + cetuximab + gemcitabine; arm B: + bevacizumab + gemcitabine	Completely resected pancreatic cancer	Phase II (randomized); n = 137	2006	Cardiac arrhythmia; TIA/stroke; arterial thromboembolic events; UA/MI within 12 mo of study entry	None	v3, all grades, treatment related[b]	Cardiac ischemia/MI; CNS cerebrovascular ischemia; HTN; dyspnea; thrombosis, thrombus, embolism; grade $\geq$3 TIA/CVA/MI/angina specifically included in primary endpoint
E2205	5-FU 180 mg/m^2 CI for 24 h on days 1-35 + oxaliplatin + cetuximab	Operable esophageal cancer	Phase II; n = 22	2008	HF; stroke/TIA; UA/MI within 6 mo of study entry	None	v3, grade 3-5, treatment related[b]	No cardiac AEs specifically ascertained
E2211	CAPE 750 mg/m^2 twice daily only or + temozolomide (arm A) or + temozolomide only, no 5-FU (arm B)	Advanced pancreatic neuroendocrine tumors	Phase II (randomized); n = 144[c]	2013	Arterial thromboembolic events; PVD; UA/MI within 12 mo of study entry	None	v4[c]	No cardiac AEs specifically ascertained
E3200	5-FU 400 mg/m^2 bolus, followed by 600 mg/m^2 CI for 22 h in arms A and B; arm A: oxaliplatin + leucovorin + bevacizumab; arm B: oxaliplatin + leucovorin; arm C: bevacizumab alone, no 5-FU	Advanced colorectal cancer	Phase III; n = 829	2001	HF; UA/MI within 3 mo	None	v2, grade 4-5 hematologic; grade 3-5 nonhematologic, treatment related[b]	No cardiac AEs specifically ascertained
E3201	5-FU bolus, followed by 2400 mg/m^2 CI for 46 h adjuvant, arms A, B, D, and E; Arms C and F: 5-FU bolus only	Stage II or III rectal cancer	Phase III; n = 179	2003	None	None	v3, grade 3-5, treatment related[b]	No cardiac AEs specifically ascertained
E3204	CAPE 825 mg/m^2 twice daily + oxaliplatin + bevacizumab + RT, then surgery, then adjuvant 5-FU 400 mg/m^2, followed by 2400 mg/m^2 CI for 46 h + leucovorin + oxaliplatin + bevacizumab	Locally advanced rectal cancer	Phase II; n = 57	2006	HF; PVD; UA/MI within 12 mo of study entry	None	v3, all grades, treatment related[b]	Chest/thorax pain, NOS; dyspnea; thrombosis, thrombus, embolism
E3205	5-FU 4000 mg/m^2 CI for 96 h + cetuximab + cisplatin; arm 1: 2 cycles; arm 2: 1 cycle	Anal carcinoma	Phase II; n = 63	2007	HF; stroke/TIA; UA/MI within 6 mo of study entry	None	v4, grade 3-5, treatment related[b]	Cardiac ischemia/MI
E4203	5-FU 400 mg/m^2 bolus, followed by 2400 mg/m^2 CI for 46 h; arms B and C: + leucovorin + oxaliplatin + bevacizumab; arm A: irinotecan + oxaliplatin + bevacizumab, no 5-FU	Metastatic colorectal cancer	Phase II; n = 211	2005	NYHA III-IV HF; UA/MI within 6 mo of study entry	None	v3, all grades, treatment related[b]	No cardiac AEs specifically ascertained
E5202	5-FU 400 mg/m^2 bolus, followed by 2.4 g/m^2 for 46 h, arm A; arm B: + bevacizumab; arm C: no chemotherapy	Stage II colon cancer	Phase III; n = 2432[c]	2005	UA/MI within previous 12 mo; symptomatic PVD; NYHA III/IV HF; symptomatic arrhythmias; TIA/stroke	Perioperative MI	v3[c]	Cardiac ischemia/MI; cardiac arrhythmia; CNS cerebrovascular ischemia; thrombosis, thrombus, embolism

Table 1 Continued

Study	Agents	Cancer Type	Phase, and Accrual	Year Study Activated	CV Exclusion Criteria	Baseline CV Data Collected	CTCAE Version, Grade, and Attribution[a]	CV Event Definitions/ Ascertainment on AE CRF
E5204	5-FU 400 mg/m2 bolus, followed by 2400 mg/m^2 CI for 46 h, arms A and B; arm B: + bevacizumab	Stage II or III rectal cancer	Phase III; n = 355	2006	UA/MI within previous 12 mo; PVD; NYHA III/IV HF; symptomatic arrhythmias; TIA/stroke	History of diabetes; HTN	v3, grades 3-5, treatment related[b]	Cardiac ischemia/MI; pain chest/thorax, NOS; CNS cerebrovascular ischemia; HTN; dyspnea; thrombosis, thrombus, embolism
E1305	5-FU 1000 mg/m^2 CI for 96 h; regimen 2: + cisplatin or carboplatin; regimen 1: docetaxel + cisplatin or carboplatin, no 5-FU	Recurrent or metastatic head and neck cancer	Phase III; n = 403[c]	2008	UA/MI or stroke within previous 6 mo; PVD; NYHA II-IV HF; serious cardiac arrhythmia requiring medication; PVD with symptoms or previous intervention; stroke within previous 6 mo	History of arterial thromboembolic events; MI; stable angina; UA; HTN; smoking	v4[c]	Acute coronary syndrome
EA1131	CAPE 1000 mg/m^2 twice daily, arm C only; arm A: observation; arm B: cisplatin versus carboplatin	Triple-negative, stage II or III breast cancer	Phase III; projected n = 750[d]	2015	None	None	v4[d]	No cardiac AEs specifically ascertained
EA2133	5-FU 4000 mg/m^2 CI for 96; arm A: + cisplatin; arm B: carboplatin + paclitaxel, no 5-FU	Advanced anal squamous cell carcinoma	Phase II; projected n = 80[d]	2016	MI within previous 6 mo; symptomatic CAD; clinically significant cardiac failure; uncontrolled cardiac arrhythmia	HTN	v4[d]	Myocardial ischemia/MI, arrhythmia; LV dysfunction
EA2142	CAPE 750 mg/m^2 twice daily; arm A: + temozolomide; arm B: platinum + etoposide, no CAPE	Advanced non—small-cell GI neuroendocrine carcinoma	Phase II (randomized); projected n = 126[d]	2015	Symptomatic HF; UA; cardiac arrhythmias	None	v4[d]	Cardiac AEs not specifically ascertained

Abbreviations: AE = adverse event; CAD = coronary artery disease; CAPE = capecitabine; CI = continuous infusion; CNS = central nervous system; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events; CV = cardiovascular; CVA = cerebrovascular accident; ECOG-ACRIN = Eastern Cooperative Group Cancer Research Group — American College of Radiology Imaging Network; 5-FU = 5-fluorouracil; GI = gastrointestinal; HF = heart failure; HTN = hypertension; LV = left ventricular; MI = myocardial infarction; NOS = not otherwise specified; NYHA = New York Heart Association (class); PVD = peripheral vascular disease; RT = radiotherapy; TIA = transient ischemic attack; UA = unstable angina; v = version.

[a]CTCAE version, grades, attribution as reported in final clinical study report.

[b]Included the following attributions: possible, probably, and definitely related to protocol treatment.

[c]Trial closed to accrual and final CSR not available at last evaluation.

[d]Accrual to trial ongoing to date.

Table 2 Phase II and III ECOG-ACRIN Trials of 5-FU and/or Capecitabine—AEs Reported in Trials With Final CRSs Available

Study	Agents	Patients Included in AE Analyses, n	Cardiac Ischemia or Chest Pain	Arrhythmias	LV Dysfunction/HF	HTN	Dyspnea	Thrombosis, Thrombus, Embolism	Other
E1103	CAPE 1000 mg/m^2 twice daily + tipifarnib	68	NR	NR	NR	NR	11 (16%)	NR	Thrombosis, embolism, 1 (2%)
E2200	5-FU 400 mg/m^2, weekly bolus irinotecan + leucovorin + bevacizumab	87	Cardiac ischemia, 2 (2%)	Dysrhythmia, 1 (1%); palpitations, 3 (3%); SVT, 1 (1%)	NR	NR	14 (16%)	11 (13%)	Cardiac, other, 1 (1%)
E2204	CAPE 825 mg/m^2 twice daily, arms A and B; arm A: cetuximab + gemcitabine; arm B: bevacizumab + gemcitabine	130	Chest pain, 2 (2%)	SVT, 2 (2%)	LV diastolic dysfunction, 1 (1%)	17 (13%)	10(8%)	8 (6%)	Cardiac arrest, nonfatal, 1 (<1%); pericardial effusion, 1 (<1%); cardiac other, 1 (<1%)
E2205	5-FU 180 mg/m^2 CI for 24 h on days 1-35 + oxaliplatin + cetuximab	Phase II; n = 22	Cardiac troponin, 1 (5%)	Heart block/asystole, 1 (5%); atrial fibrillation, 1 (5%)	NR	NR	2 (9%)	3 (14%)	Syncope, 1 (5%)
E3200	5-FU 400 mg/m^2 bolus, followed by 600 mg/m^2 CI for 22 h, arms A and B; arm A: oxaliplatin + leucovorin + bevacizumab; arm B: oxaliplatin + leucovorin; arm C: bevacizumab alone, no 5-FU	808	Cardiac ischemia, 2 (<1%); cardiac troponin, 3 (<1%); chest pain, 8 (<1%)	SVT 6 (<1%)	Cardiac LV function, 1 (<1%)	40 (5%)	NR	Thrombosis, embolism, 18 (2%)	Cardiac, other, 2 (<1%)
E3201	5-FU bolus, followed by 2400 mg/m^2 CI for 46 h, adjuvant; arms A, B, D, and E; arms C and F, 5-FU bolus only	177 (adjuvant portion)	Cardiac ischemia, 1 (<1%)	NR	NR	NR	2 (1%)	2 (1%)	NR
E3204	CAPE 825 mg/m^2 twice daily + oxaliplatin + bevacizumab + RT, then surgery, then adjuvant 5-FU 400 mg/m^2, followed by 2400 mg/m^2 CI for 46 h + leucovorin + oxaliplatin + bevacizumab	55	Chest/thoracic pain, 2 (4%)	NR	NR	2 (4%)	5 (9%)	2 (4%)	Cardiac, other, 1 (2%)
E3205	5-FU 4000 mg/m^2 CI for over 96 h + cetuximab + cisplatin; arm 1: 2 cycles; arm 2: 1 cycle	62	NR	NR	LV systolic dysfunction, 1 (2%)	NR	1 (2%)	3 (5%)	NR
E4203	5-FU 400 mg/m^2 bolus, followed by 2400 mg/m^2 CI for 46 h; arms B and C: leucovorin + oxaliplatin + bevacizumab; arm A: no 5-FU, irinotecan + oxaliplatin + bevacizumab	205	Cardiac ischemia, 1 (<1%); chest pain, 3 (1%)	Palpitations, 3 (2%); atrial fibrillation, 1 (<1%); arrhythmia, other, 2 (1%); SVT 1 (<1%)	LV diastolic dysfunction, 1 (<1%)	52 (25%)	NR	19 (9%)	Sudden death, 1 (<1%)
E5204	5-FU 400 mg/m^2 bolus, followed by 2400 mg/m^2 CI for 46 h, arms A and B; arm B: + bevacizumab	347	Cardiac ischemia, 2%; cardiac/heart pain, 1%; chest pain, 1%	NR	Cardiomyopathy, restrictive, 1%	NR	3%	4%	NR

Abbreviations: AE = adverse event; CAPE = capecitabine; CI = continuous infusion; CSR = clinical study report; CV = cardiovascular; ECOG-ACRIN = Eastern Cooperative Group Cancer Research Group — American College of Radiology Imaging Network; 5-FU = 5-fluorouracil; HF = heart failure; HTN = hypertension; LV = left ventricular; NR = not reported; RT = radiotherapy; SVT = supraventricular tachycardia.

ischemia or myocardial infarction (6 of 9), acute coronary syndrome (1 of 9), chest pain not otherwise specified (1 of 9), dyspnea (5 of 9), central nervous system cerebrovascular ischemia (4 of 9), and cardiac arrhythmias (2 of 9).

Of the 13 trials closed to accrual, final CSRs were available for 10 (77%) (Table 2). For many trials, only AEs deemed possibly, probably, or definitely related to the study drug, which was rarely 5-FU or CAPE, were included in the AE summaries. The incidence of chest pain, cardiac troponin, or cardiac ischemia ranged from 0% to 5%, the incidence of arrhythmias ranged from 0% to 6%, and the incidence of dyspnea was 16%.

Discussion

From our review of the ECOG-ACRIN Cancer Research Group database of FPD trials, we have ascertained that cardiotoxicity has been inconsistently reported, impeding enumeration of the incidence. These trials included specified objectives for the assessment of toxicity, but not explicitly for cardiotoxicity. From the present review, we have identified several considerations to incorporate into future trial designs to increase the cardiotoxicity knowledge base.

One concern in clinical trial design is the exclusion of patients with previously diagnosed CV disease. Consequently, AEs from clinical research will likely underestimate the incidence in the general population. In addition, we found that baseline cardiac disease or cardiac risk factors were infrequently documented on these CRFs, although risk factors such as obesity, hypertension, hyperlipidemia, smoking, and diabetes can affect the development of ensuing CV disease, including silent ischemia. To investigate the efficacy of new agents, later phase clinical studies avoid the effects of comorbidities and organ dysfunction on anticancer drug development. Whether to begin including patients with multiple medical conditions, such as are seen in the community setting, in clinical trials is under discussion. The current National Cancer Institute (NCI) director has prioritized revision of the NCI's National Clinical Trials Network, noting "unnecessary exclusions" and "poor accrual of underrepresented populations" in trials generate results applicable only to homogenous groups of patients.[12] Modifications of the inclusion criteria to include patients with common medical conditions will extend clinical trial eligibility for the broader cancer population with improved generalizability of the results.[13] The assessment of FPD cardiotoxicity in real-world patients could be performed by designing pragmatic trials[14] in the community setting, including conducting studies through the NCI's Community Oncology Research Program.[15] The effect of comorbid conditions or their risk factors on CV health in cancer patients is critical to understanding cardiotoxicity risk.

Additional data usually not reported are required to classify cardiotoxicity. Details such as the procedures used to diagnose the CV events, CV outcomes, and chemotherapy doses received are required to inform the natural history. Given the fluid onset of CV AEs, the requirement for toxicity grading long term during therapy, instead of recording specific points, will broaden the definitions and incidence of all drug-related toxicities. Additionally, post-therapy surveillance is essential to characterize the ensuing morbidity from chronic cardiac disease related to FPD treatment. The CTCAE are universally accepted for AE reporting in clinical studies, albeit with known limitations. The study period for these reviewed trials

Table 3 Key Elements to Consider Including in Oncology Clinical Trials

History of Diagnosed CVD	Symptoms Suggestive of CVD	Physical Examination Findings	Laboratory and Imaging Data	Cardiac Medications
CAD: MI (date), revascularization history (percutaneous coronary intervention or coronary artery bypass graft surgery), angina class; **HF/cardiomyopathy**: HF with preserved ejection fraction, HF with reduced ejection fraction, etiology of cardiomyopathy, cardiac amyloidosis, previous HF hospitalization, NYHA class; **Arrhythmias/ECG abnormalities**: atrial fibrillation, atrial flutter, other supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, previous cardiac arrest, long QT, bradycardia, sick sinus syndrome, sinus tachycardia, left bundle branch block, arrhythmia, not otherwise specified, syncope, palpitations, implantable cardioverter defibrillator, pacemaker; **Valvular disease**: aortic stenosis, aortic regurgitation, aortic valve repair or replacement, mitral stenosis, mitral regurgitation, mitral valve prolapse, mitral valve repair or replacement, pulmonic stenosis, tricuspid stenosis, tricuspid regurgitation, tricuspid valve repair or replacement, pulmonic stenosis, pulmonic regurgitation, endocarditis; **Vascular disease**: carotid disease, TIA, stroke, PVD, thoracic aortic aneurysm, abdominal aortic aneurysm, deep vein thrombosis, pulmonary embolism, pulmonary HTN, **Pericardial disease**: pericarditis, pericardial effusion; **Cardiac risk factors**: HTN, diabetes; tobacco use (previous or current), metabolic syndrome, obesity, hyperlipidemia, family history of cardiomyopathy or CAD, alcohol use (>2 drinks/d), previous chest radiation (dose, fractions, field, date), previous anthracycline chemotherapy (agent, cumulative dose, year), anti-HER2 agent (agent, duration, year)	Chest pain at rest or with exertion; shortness of breath at rest or with exertion; orthopnea; paroxysmal nocturnal dyspnea; edema; fatigue; weight gain; in patients with HF: NYHA class I, no symptoms; II, mild limitation during ordinary activity; III, marked limitations in activity due to symptoms, comfortable only at rest; IV, symptoms present at rest	Blood pressure, heart rate, height, weight, BMI, jugular venous distension, carotid bruits, S3, S4, murmur, distal pulses, rales, wheezing, hepatomegaly, ascites, edema (grade, extent)	Laboratory tests: serum creatinine, brain natriuretic peptide, N-terminal pro-brain natriuretic peptide, troponin I, troponin T, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein; echocardiography: LVEF, institutional lower limit of normal, evidence of diastolic dysfunction (grade, if present), evidence of moderate to severe valvular disease (list), left atrial dilation, right atrial dilation, right ventricular function, right ventricular dilation, regional wall motion abnormalities	Aspirin, ACE inhibitor, angiotensin receptor blocker, β-blocker, α-blocker, calcium channel blocker, diuretics, nitrates, statins, other lipid-lowering therapy, anticoagulant therapy, other

Abbreviations: ACE = angiotensin-converting enzyme; BMI = body mass index; CAD = coronary artery disease; CVD = cerebrovascular disease; ECG = electrocardiogram; HF = heart failure; HTN = hypertension; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PVD = peripheral vascular disease; TIA = transient ischemic attack.
Adapted from ECOG Baseline and Follow up Cardiovascular Form; full forms available at: http://www.ecog.org/ecogjnst/cardtoxgroup.html.

evaluated clinical research across several CTCAE versions with varying terminology.[16] Specific and consistent data element terms should be captured at baseline, throughout treatment, and during surveillance. The ECOG-ACRIN Cardiotoxicity Working Group has developed a wide-ranging list of CV data elements, including the capture of risk factors, pre-existing CV disease, and CV outcomes (Table 3).[17] Across FPD clinical trials, prospective collection of standardized cardiotoxicity endpoints will lead to clarification of the specific cardiac events associated with FPDs and will allow for formalization of definitions.

Furthermore, the current estimates of FPD cardiotoxicity incidence will likely be influenced by the evolution of dosing and delivery of 5-FU, from an intravenous bolus to 5-day continuous infusions to 48-hour infusions.[18] Our retrospective review encompassed a variety of FPD doses and schedules, some of which are no longer clinically applicable. Some data have suggested that the dose and schedule could affect the risk of FPD cardiotoxicity.[4,6,18] The contribution of concomitantly prescribed anticancer treatments, such as vascular targeted agents, to FPD cardiotoxicity risk is unknown. Future combination treatments with 5-FU and/or CAPE should be assessed for additive or synergistic cardiotoxic effects, which could heighten patients' risk of cardiotoxicity during anticancer treatment. No ECOG-ACRIN trials were found of the FDA-approved combination of trifluridine and tipiracil or other oral FPDs such as tegafur-uracil or S1, which have not yet been approved by the FDA. Thus, the reporting and cardiotoxicity of FPD agents other than 5-FU and CAPE could not be included in the present review. In the pivotal phase III trial of trifluridine and tipiracil, which included 800 participants with refractory metastatic colorectal cancer, $< 1\%$ of patients were reported to have developed cardiac ischemia in both the trifluridine/tipiracil and placebo groups.[19] Potential cardiotoxicity with trifluridine and tipiracil and other oral FPDs warrants further study.

Our overall goal of defining cardiotoxicity is to ensure the safety of colorectal carcinoma patients receiving therapy. Currently, data to inform the risk-to-benefit discussions with patients, preventive strategies, and clinical practice guidelines for patients receiving FPDs are lacking. Reporting of best clinical practices, such as the recently reported single-institution strategies to rechallenge patients who have developed FPD cardiotoxicity, will aid with informing guidelines.[20]

Conclusion

The previous variable reporting of cardiac events precluded accurate and precise delineation of the epidemiology of 5-FU/CAPE-related CV AEs. Uncertainty remains regarding the incidence and extent of FPD cardiotoxicity in the present treatment era. The influence of patient-related factors obtained from mutation analysis[21] and phenotyping and the addition of concomitant cancer treatments to 5-FU and/or CAPE are unknown. Given the mortality and unknown acute and chronic morbidity of cardiotoxicity, a critical need exists for robust collection of CV risk factors and disease from baseline to after chemotherapy, trial designs with specific cardiotoxic primary or secondary objectives, and careful consideration and evaluation regarding the study exclusion criteria in late-phase studies. The prospective knowledge acquired regarding the extent and severity of FPD cardiotoxicity will lead to the development of diagnostic criteria, risk factor stratification, and perichemotherapy interventions to reduce or prevent cardiotoxicity.

We believe that the prospective collection of baseline cardiac data and prespecified cardiac endpoints is necessary to fully understand the incidence and cardiac risk of FPDs.

Clinical Practice Points

- Cardiotoxic AEs such as angina, ischemia, arrhythmias, and cardiomyopathy have been reported with 5FU and CAPE; however, the risk factors, incidence, and outcomes of these events with current treatment regimens is not well known.
- Trial eligibility criteria and methods of collection and ascertainment of AEs can affect the reported incidence of cardiotoxicity.
- Collection of data on cardiac history and baseline cardiac risk factors could help determine which patients are at elevated risk of cancer therapy cardiotoxicity.
- Case report forms and CSRs from the ECOG-ACRIN Cancer Research Group database of 16 phase II and III clinical trials incorporating 5FU and CAPE reveal that most studies had exclusion criteria for cardiovascular history, very few studies collected information on baseline cardiac risk factors and history of cardiac disease, and fewer than half of study CRFs specifically requested information on cardiac ischemia/infarction.
- Some trials only recorded cardiac AEs possibly associated with the novel drug being studied and not those attributed to the standard of care 5FU/CAPE arm, further decreasing the numeric incidence.
- Inconsistent clinical trial reporting of cardiac events preclude accurate and precise delineation of the epidemiology of FPD-related cardiovascular AEs.
- Prospective knowledge of the definition and natural history will lead to development of risk factor stratification and prechemotherapy interventions to reduce or prevent cardiotoxicity.
- We propose that prospective collection of baseline cardiac data and prespecified cardiac end points is necessary to fully understand the incidence and cardiac risk of FPDs.

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Disclosure

The authors declare that they have no competing interests.

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