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RESEARCH LETTER

Contemporary Management and Rechallenge Practices for 5-Fluorouracil–Associated Cardiotoxicity: Insights From an International Cardio-Oncology Society Survey

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Fluoropyrimidines, including 5-fluorouracil, remain central to the treatment of gastrointestinal malignancies. Cardiotoxicity is a clinically significant complication that may require treatment discontinuation and adversely affect outcomes.¹ While chest pain and ischemic electrocardiographic changes are the most recognized manifestations, 5-fluorouracil cardiotoxicity also includes atrial and ventricular arrhythmias, heart failure, and rarely sudden cardiac death.¹ Despite decades of use, evidence guiding evaluation, acute management, and rechallenge remains limited, resulting in substantial practice variation. We conducted an international survey of cardio-oncology physicians to characterize current approaches to evaluation, management, and rechallenge of suspected 5-fluorouracil-associated cardiotoxicity.

An anonymous electronic survey was distributed to 1209 members of the International Cardio-Oncology Society between October and November 2025. Items assessed demographics, practice characteristics, clinical manifestations, diagnostic and management

strategies, rechallenge practices, institutional protocols, and barriers to care. Practice type was categorized as academic or nonacademic, and years in practice as <5, 5 to 10, or >10 years. Rechallenge success was defined as clinical success in ≥50% of rechallenged patients. Descriptive statistics summarized responses, and comparisons by practice type and years in practice were performed using χ^2 tests or Fisher's exact tests when expected cell counts were <5. Requirement for institutional review board approval was waived by the institutional review board at Winship Cancer Institute of Emory University. Data are available upon request from a third party.

Of 152 respondents (12.6% response rate), 133 were included after excluding incomplete responses. Among evaluable respondents, 59.1% (78/132) practiced at academic centers and 40.9% (54/132) in nonacademic settings. Years in cardio-oncology practice were <5 years in 36.4% (48/132), 5 to 10 years in 38.6% (51/132), and >10 years in 25.0% (33/132). Most respondents (93.2% [123/132]) managed at least 1

Key Words: 5-fluorouracil ■ cardio-oncology ■ cardiotoxicity ■ fluoropyrimidine rechallenge ■ practice patterns

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Table. Respondent Characteristics, Clinical Experience, and Key Practice Patterns (N=133)

Variable	Level	n (%)
Years in cardio-oncology practice	<5	48 (36.4)
	5–10	51 (38.6)
	>10	33 (25.0)
	Missing	1
Practice type	Academic medical center	78 (59.1)
	Nonacademic (community/private/other)	54 (40.9)
	Missing	1
Clinical exposure to 5-fluorouracil cardiotoxicity	≥1 patient with chest pain	123 (93.2)
	>10 patients with chest pain	28 (21.2)
	Missing	1
Cardiotoxicity manifestations encountered*	Chest pain	121 (91.0)
	ST-segment changes	73 (54.9)
	Troponin elevation	54 (40.6)
	Atrial arrhythmia	21 (15.8)
	Ventricular arrhythmia	16 (12.0)
	Heart failure	14 (10.5)
	Sudden cardiac death	6 (4.5)
Time to symptom onset	<24 h	33 (25.2)
	1–3 d	58 (44.3)
	>3 d	7 (5.3)
	Variable/depends on regimen	33 (25.2)
	Missing	2
Initial cardiac evaluation	ECG	123 (93.2)
	Troponin	115 (87.1)
	Echocardiography	105 (79.5)
	Coronary angiography (initial)	47 (35.6)
	Missing	1
Coronary angiography use	Routinely or selectively pursued	111 (84.1)
	Missing	1
Acute management strategies	Immediate 5-fluorouracil discontinuation	101 (76.5)
	Nitrates	92 (69.7)
	Calcium channel blockers	79 (59.8)
	Telemetry admission	66 (50.0)
	Intensive care unit/cardiac care unit admission	35 (26.5)
	Missing	
Rechallenge practices	Involved in rechallenge decisions	91 (70.0)
	Missing	3
	Vasodilator prophylaxis used	92 (74.2)
	Dose reduction strategy	56 (45.2)
	Bolus-only dosing	41 (33.1)
	Switch to capecitabine	37 (29.8)
	Missing	9
Rechallenge outcomes†	≥50% clinical success	103 (91.2)
	Missing	20

(Continued)

Table. Continued

Variable	Level	n (%)
Institutional infrastructure	Formal protocol (established)	23 (18.3)
	Protocol in development	28 (22.2)
	Missing	7
	Lack of clear guidelines cited as barrier	30 (24.4)
	Missing	10
Multidisciplinary care	Routine or case-by-case comanagement	122 (93.8)
	Missing	3

*Multiple responses permitted.

†Among respondents who attempted rechallenge.

suspected case annually, and 21.2% (28/132) managed >10 cases per year (Table). Chest pain was the most common manifestation (91.0% [121/133]), followed by ST-segment changes (54.9% [73/133]) and troponin elevation (40.6% [54/133]). Less common presentations included atrial arrhythmias (15.8% [21/133]), ventricular arrhythmias (12.0% [16/133]), heart failure (10.5% [14/133]), and sudden cardiac death (4.5% [6/133]). Symptom onset occurred most often within 1 to 3 days (44.3% [58/131]) or within 24 hours (25.2% [33/131]). Death attributable to 5-fluorouracil cardiotoxicity was reported by 23.3% (31/133).

Initial evaluation most commonly included electrocardiography (93.2% [123/132]), troponin testing (87.1% [115/132]), and echocardiography (79.5% [105/132]). Coronary angiography was part of the initial workup in 35.6% (47/132), while 84.1% (111/132) pursued it later. Immediate discontinuation of 5-fluorouracil was reported by 76.5% (101/132). Nitrates (69.7% [92/132]) and calcium channel blockers (59.8% [79/132]) were commonly initiated. Telemetry admission was used by 50.0% (66/132), and intensive care unit/cardiac care unit-level care by 26.5% (35/132). Most respondents were directly involved in rechallenge decisions (70.0% [91/130]), usually alongside oncology (93.8% [122/130]). Common rechallenge strategies included vasodilator pretreatment (74.2% [92/124]), dose reduction (45.2% [56/124]), bolus-only administration (33.1% [41/124]), or switching to capecitabine (29.8% [37/124]). Among clinicians attempting rechallenge, 91.2% (103/113) reported success in at least half of patients.

Formal institutional protocols were uncommon, reported by only 18.3% (23/126), while 22.2% (28/126) reported protocols in development. Lack of clear guidelines was identified as a barrier by 24.4% (30/123). Academic clinicians more frequently communicated directly with oncology than nonacademic clinicians (97.4% [76/78] versus 86.8% [46/53]; $P=0.03$). Involvement in rechallenge decisions (<5 years, 48.9% [23/47]; 5–10 years, 85.7% [42/49]; >10 years, 78.8% [26/33]; $P<0.01$) and recognition of lack of professional guidelines as a

barrier (<5 years, 34.1% [15/44]; 5–10 years, 8.3% [4/48]; >10 years, 36.7% [11/28]; $P<0.01$) were found to significantly vary according to years in practice.

This is, to our knowledge, the first international survey of contemporary practice patterns in 5-fluorouracil-associated cardiotoxicity. Although ischemic symptoms predominated, clinicians reported substantial arrhythmias, heart failure, and rare sudden cardiac death, underscoring the broad clinical spectrum.^{2,3} While initial diagnostic approaches were largely consistent, significant variability remained in angiography use, monitoring intensity, and pharmacologic management. Rechallenge was frequently pursued and commonly successful, particularly with vasodilator prophylaxis, dose reduction, or bolus administration, consistent with prior literature.^{4,5} These findings highlight strong multidisciplinary collaboration but also the absence of standardized protocols. Future consensus guidelines and prospective registries are needed to define rechallenge safety, angiography thresholds, and optimal monitoring strategies for fluoropyrimidine-associated cardiotoxicity.

ARTICLE INFORMATION

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Supplemental Material

STROBE Statement—Checklist

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