Incidences of cardiotoxicity with 5-fluorouracil analogues in gastrointestinal cancers- a large single centre experience.

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BACKGROUND

- Fluoropyrimidines (5-FU, capecitabine, S-1) are widely used in gastrointestinal (GI) cancers.
- Despite efficacy, cardiotoxicity is a serious complication — presenting as angina, arrhythmias, myocardial infarction, or sudden death.
- Incidence of FP-related cardiovascular toxicity ranges from 1 to 19% and mortality has been reported to be 2.2–13.3%
- Mechanisms proposed: coronary vasospasm, endothelial injury, toxic metabolites.
- Risk factors (variably reported): ischemic heart disease, age >65, continuous infusion
- Real-world data lacking from low- and middle-income countries, particularly on newer analogues like S-1.
- This study evaluates incidence and patterns of cardiotoxicity with various fluoropyrimidines in GI cancers at a large tertiary Indian center.

RATIONALE

- Most pivotal clinical trials involving fluoropyrimidines **exclude** patients with significant cardiovascular disease, thereby underestimating the true incidence in real-world settings.
- Determine the real-world incidence of both minor and major cardiotoxic events associated with fluoropyrimidine analogues in GI cancers.
- Evaluate drug-specific risks among different fluoropyrimidines.
- Identify clinical risk factors associated with increased cardiotoxicity.
- Generate practice-changing evidence to inform screening, monitoring, and management guidelines, especially in resource-constrained, high-burden oncology settings.

METHODS

Patients with GI cancers treated with infusional 5 FU, Cape and S1 between January 2023 and December 2023 were retrieved from a prospectively maintained database at Tata memorial Hospital (Mumbai). Baseline demographic and clinical variables were evaluated.

OBJECTIVES

Primary endpoint - Comparison of the incidence of major cardiac toxicities after administration of 5FU, Cape or S1 by odds ratio (OR).

Secondary endpoints - To evaluate the time to onset of cardiotoxicity from the initiation of fluoropyrimidine therapy and To identify clinical and demographic variables associated with increased risk of cardiotoxicity

RESULTS

TABLE 1 - BASELINE CHARACTERISTICS

Variable	5-FU (n = 1342)	Cape (n = 1073)	S-1 (n = 55)
AGE			
< 60	924 (70%)	877 (82%)	35 (64%)
>= 60	418 (30%)	196 (18%)	20 (36%)
GENDER			
Male	896 (67%)	721 (67%)	31 (56%)
Female	446 (33%)	352 (33%)	24 (44%)
Smokers	199 (15%)	180 (17%)	6 (11%)
COMORBIDITIES			
Diabetes	310 (23%)	194 (18%)	13 (24%)
Hypertension	322 (24%)	191 (18%)	17 (31%)
Hypercholesterolemia	148 (11%)	107 (10%)	8 (15%)
HEMOGLOBIN LEVELS			
>12	401 (30%)	382 (35%)	25 (45%)
10–12	635 (47%)	395 (37%)	24 (44%)
8–10	266 (20%)	235 (22%)	5 (9%)
<8	40 (3 %)	61 (6%)	1 (2%)
RENAL INSUFFICIENCY			
Yes	47 (3%)	25 (2%)	2 (4%)
No	1295 (97%)	1048 (98%)	53 (96%)
HISTORY OF CARDIAC DYSFUNCTION			
CAD	36 (3%)	29 (3%)	3 (6%)
Arrhythmia	6 (0.5%)	4 (0.5%)	3 (6%)
CHF	0 (0.0%)	1 (0.1%)	0 (0.0%)
RHD	0 (0.0%)	0 (0.0%)	0 (0.0%)
Others	7 (0.5%)	6 (0.6%)	1 (2%)
DISEASE STAGE			
Metastatic	672 (50%)	561 (52%)	29 (53%)
Non-metastatic	670 (50%)	512 (48%)	26 (47%)

CONCLUSION

1. The incidence of cardiotoxicity appears to be similar between infusional 5-FU and Capecitabine. Firm conclusions cannot be drawn with regard to S1 due to very few patients receiving the same.
2. The most common cardiac abnormalities with 5-FU and its analogues appear to be asymptomatic bradycardia.
3. The presence of Hypertension and probably diabetes mellitus is associated with an increased incidence of cardiac events

TABLE 2 – CARDIAC CHARACTERISTICS

Variable	5-FU (n = 1342)	Cape (n = 1073)	S-1 (n = 55)
CARDIAC EVENT			
Yes No	29 (2%) 1313 (98%)	9 (1%) 1064 (99%)	2 (4%) 53 (96%)
MAJOR CARDIAC EVENT (All except asymptomatic bradycardia)	16 (1.1%)	7 (0.7%)	2 (4%)
Timing of Cardiac Event -			
5-FU ongoing	20 (69%)	–	–
Cape or S1 ongoing	–	8 (89%)	2 (100%)
Upto 72 hrs post 5-FU	6 (20%)	–	–
Upto 120 hrs post 5-FU	3 (10 %)	–	–
Upto 120 hrs post Cape/S1		1 (11%)	
Drug Temporarily Stopped			
Yes	17 (59%)	7 (78%)	2 (100%)
No	12 (41%)	2 (22%)	0
Recovery from Event			
Yes	28 (97%)	7 (78%)	2 (100%)
Fatal event	1 (3%)	2 (22%)	0
Rechallenge			
Yes	20 (69%)	5 (56%)	2 (100%)
No	9 (31%)	4 (44%)	0
Repeat Cardiac Event	0	0	0

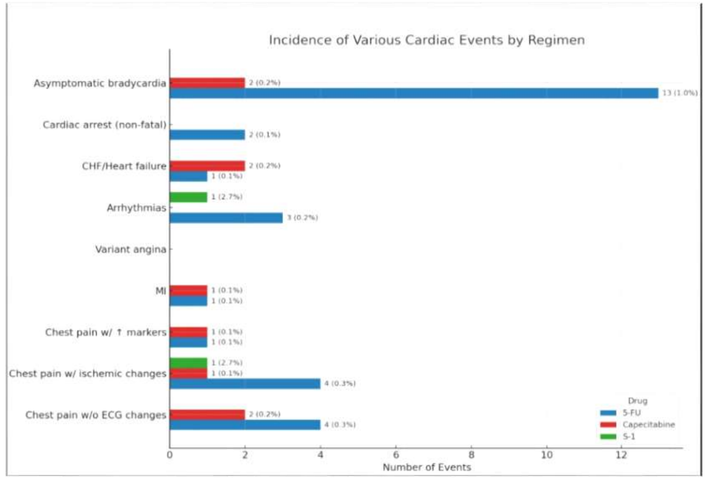
TABLE 3 - CORRELATION OF PRETREATMENT VARIABLES WITH MAJOR CARDIAC EVENTS

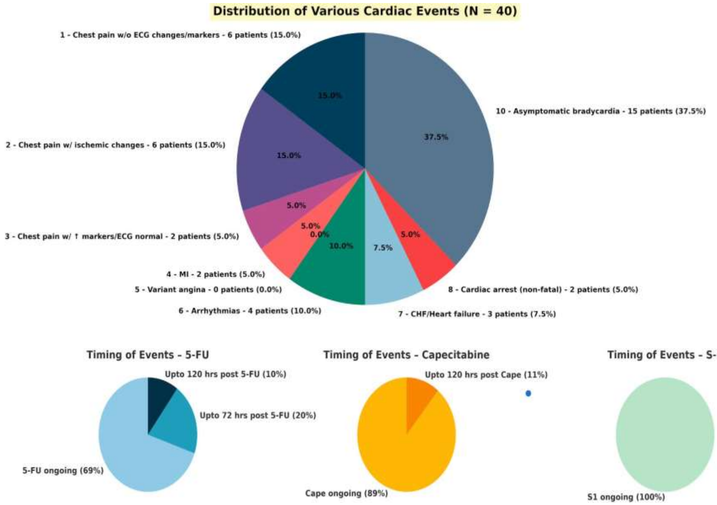
Variables	P	OR	CI
Age <60 >= 60	0.16	1.59	0.814 – 3.001
Gender	0.70	0.87	0.434 – 1.679
Former Smokers	0.63	0.77	0.209 – 2.050
Current Smokers	0.36	1.73	0.465 – 4.634
Diabetes	0.07	0.53	0.281 – 1.065
Hypertension	0.03	0.49	0.261 – 0.964
Hypercholesterolemia	0.15	0.46	0.150 – 1.390
Anemia (Hb < 8)	0.54	0.45	0.003 – 3.720

TABLE 4 - CORRELATION OF 5 FU ANALOGUES WITH MAJOR CARDIAC EVENTS

REGIMEN BASED	p value	OR	CI
CAPECITABINE	-	1	-
5 FU	0.21	0.56	0.196- 1.362
S 1	0.03	6.63	1.216 – 25.569

-Major cardiac events defined as cardiac events excluding asymptomatic bradycardia





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