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EVALUATION OF 5-FLUOROURACIL-INDUCED CARDIOTOXICITY: ROLE OF CARDIAC BIOMARKERS

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***Background*: Side effects of chemotherapy in cancer patients need to be investigated in more detail. *Aim*: To determine the incidence of cardiotoxicity in patients treated with different chemotherapy regimens containing 5-fluorouracil (5-FU) in Zanjan, Iran. *Patients and Methods*: In a prospective cohort study, patients with different types of solid gastrointestinal tumors who were candidates for 5-FU based chemotherapy regimens were enrolled. The study population consisted of 100 patients (48 females and 52 males) with a mean age of 63.99 ± 12.40 years. We measured serum cardiac troponin I (cTnI) levels before and during each chemotherapy cycle and determined the occurrence of cardiotoxicity in patients based on the levels of cTnI, clinical signs and symptoms as well as electrocardiogram findings. In addition, we assessed a history of diabetes, hypertension, smoking, dyslipidemia and previous chest radiation as potential risk factors for cardiotoxicity. *Results*: The incidence of cardiotoxicity was 8%, of which 5 patients were diagnosed with acute coronary syndrome, 2 patients with arrhythmias and one with hypotension. In addition, there was no significant association between studied risk factors and 5-FU induced cardiotoxicity. *Conclusion*: The incidence of cardiotoxicity in patients receiving 5-FU infusion regimens was notable. Thus, paying more attention to the 5-FU-induced cardiotoxicity is necessary in order to improve the prognosis of patients with cancer.**

***Key Words*: cardiac troponin I, 5-fluorouracil, cardiotoxicity, chemotherapy, gastrointestinal tumors.**

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While the incidence of cancer is increasing worldwide, the cancer mortality rate has dropped dramatically in recent years due to advances in its treatment [1–3]. Chemotherapy-induced cardiotoxicity is an issue that affects the quality of life and overall survival of cancer patients and can hinder further treatment in these patients [4–8]. The main strategy for these patients is timely diagnosis and treatment of high-risk individuals [9]. Fluoropyrimidines are a group of chemotherapy drugs that include two important anti-metabolite drugs called 5-fluorouracil (5-FU) and capecitabine [10–12]. Either drugs can cause cardiotoxicity [13, 14]. The incidence of 5-FU and capecitabine induced cardiotoxicity has been reported to be 1–18% [15] and 3–35%, respectively [16]. Fluoropyrimidines are the second most widely used chemotherapy drug after anthracyclines to cause cardiovascular complications, with 5-FU being the third most common chemotherapy drug worldwide for treatment of solid malignancies such as cervical and gastrointestinal malignancies, and are commonly used in conjunction with radiotherapy [12]. This aforementioned widespread utilization puts a greater emphasis on the importance of early diagnosis and treatment of cardiovascular complications of chemotherapy. 5-FU-induced cardiotoxicity can lead to asymptomatic changes in the electrocardiogram (ECG) to serious and symptomatic cardiovascular complications, including acute coronary syndrome (ACS), arrhythmias, heart failure, hypotension, cardiogenic shock and even death [17]. There is ample evidence that cardiac troponins might be acceptable biomarkers for early detection of myocardial injury and cardiotoxicity [18, 19]. Since 2000, troponins have been recognized as the standard marker for the diagnosis of heart muscle injury, and because they are cheaper and less invasive than

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Abbreviations used: 5-FU – 5-fluorouracil; ACS – acute coronary syndrome; BMI – body mass index; cTnI – cardiac troponin I; ECG – electrocardiogram; STEMI – *ST*-elevation myocardial infarction.
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other diagnostic methods such as echocardiography, they can be a valid diagnostic tool for early detection of cardiotoxicity [7]. Due to the increase in patients with cancer undergoing chemotherapy regimens and associated cardiotoxicity, there is a need for a reliable method for timely detection of cardiotoxicity caused by chemotherapy agents. Therefore, the present study aimed to evaluate the cardiotoxicity related risk factors and the incidence of 5-FU-induced cardiotoxicity in patients with gastrointestinal solid tumors with a focus on cardiac troponin I (cTnI)application for the diagnosis.

PATIENTS AND METHODS

Study design and subjects. In a prospective cohort study, 174 patients with solid tumors who were candidates for 5-FU regimens were enrolled between January 2018 and December 2019. Patients over 18 years with definite diagnosis of gastrointestinal solid tumors who were candidates for 5-FU-containing regimens were included. We excluded patients with a history of heart disease (e.g. angina, valvular disease, and arrhythmias) or left ventricular output less than 55%, patients with renal and liver diseases, undergoing regimens with cardiac toxicity (anthracyclines, trastuzumab, cyclophosphamide, bevacizumab and panitumumab) [20] or concomitant use of any medications with an effect on the heart. We determined bilirubin >2 mg/dl and aspartate aminotransferase >2 × the upper limit of normal as hepatic dysfunction and serum creatinine >1.5 mg/dl as renal insufficiency. In addition, patients who needed to change or stop chemotherapy were excluded. After complete explanation of the study design and aims, written informed consent was obtained from all patients or their legal representatives. Study protocol was evaluated and approved by the ethics committee of Zanjan University of Medical Sciences [ZUMS.REC.1396.107].

Chemotherapy regimens. Four chemotherapy regimens were used: FOLFOX4 (oxaliplatin, 180 mg/m^2 on day 1, leucovorin 400 mg/m^2 over 2 h on days 1 and 2, 5-FU, 400 mg/m^2 bolus, then 600 mg/m^2 over 22 h on days 1 and 2, repeated every two weeks), FOLFIRI (Irinotecan, 180 mg/m^2 on day 1, leucovorin 400 mg/m^2 over 2 h on day 1, 5-FU, 400 mg/m^2 bolus on day 1, followed by 2400 mg/m^2 continuous infusion over 46 h, repeated every two weeks), 5-FU+cisplatin (cisplatin 100 mg/m^2 on day1, 5-FU750 mg/m^2 continuous infusion over 24 h for 3 days, repeated every 3 weeks), 5-FU+leucovorin (5-FU 425 mg/m^2 infusion over 22 h daily for 5 days, leucovorin 20 mg/m^2 bolus daily for 5 days, repeated every 4 weeks). In each regimen, we followed up patients for 3 cycles.

Cardiotoxicity evaluation. Two cardiologists appraised cardiotoxicity based on new clinical signs and symptoms related to heart disease, as well as ECG findings and cTnI test results. At the beginning of the study, history taking, clinical examination and echocardiography were performed. Echocardiography was carried out only once to assess the condition of heart in terms of defining the inclusion criteria. However, a complete history of cardiovascular symptoms (chest discomfort, shortness of breath, palpitations, etc.) and clinical examination before chemotherapy cycles and a 12-lead ECG before and after the completion of each cycle using the same device was recorded from the patients. Besides, in case of any cardiac symptoms during the study, all relevant diagnostic procedures and tests were performed.

Furthermore, cTnI was measured before initiation of each cycle and 24 h (T0), 48 h (T2) and 72 h (T3) after initiation of the chemotherapy cycles for FOLFOX and FOLFIRI regimens. For 5-FU+cisplatin regimen in addition to the previous ones, it was measured at 96 h (T4) and for 5-FU+leucovorin regimen in addition to the previous, it was also measured just after termination (T5) and 24 h later (T6). The serum level of cTnI was assessed using Elecsys Troponin I STAT immunoassay (Roche Diagnostics, Canada) according to the manufacturer's instructions with cut-off point = 0.3 ng/ml and a limit of detection = 0.16 ng/mL.

In case of cardiotoxicity, cardiac monitoring was started, then the dose of 5-FU reduced or switched to another chemotherapy regimen, and sublingual nitrates or calcium channel blockers was administered depending on the patient's condition.

Potential risk factors of cardiotoxicity such as a history of diabetes, hypertension, smoking, dyslipidemia and previous chest radiation were also studied. A history of dyslipidemia was considered based on the patient's previous lab tests (low density lipoprotein ⩾ 180 mg/dl or triglyceride ⩾ 200 mg/dl), a history of hypertension was defined as systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg or being treated with antihypertensive drug. Diabetes was defined based on the patient's previous lab tests as a fasting plasma glucose > 126 mg/dL in multiple measure-

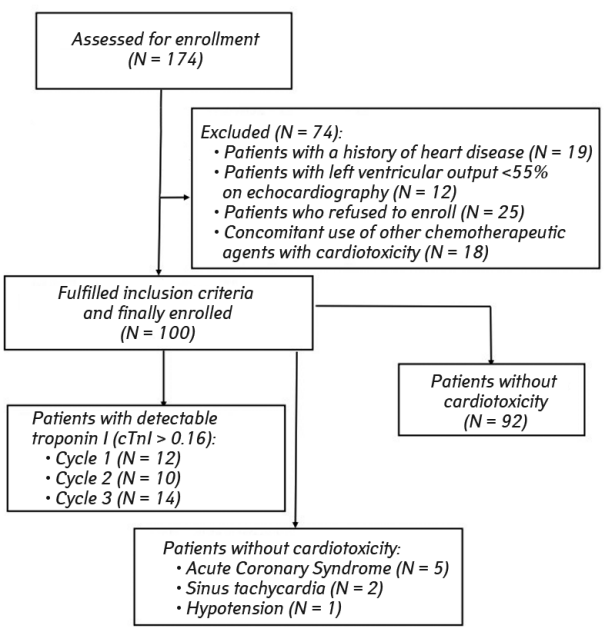

Figure. Study flow diagram

Table1. Patient basic and clinical characteristics

Variable	Patients n (%)
Gender, male	52 (52)
Type of cancer	
Esophageal	15 (15)
Gastric	9 (9)
Colon	52 (52)
Rectal	20 (20)
Anal	4 (4)
Chemotherapy regimens	
FOLFOX4	25 (25)
FOLFIRI	5 (5)
5-FU+cisplatin	28 (28)
5-FU+leucovorin	42 (42)
Previous chest radiation	24 (24)
Concurrent radiotherapy	19 (19)
Diabetes	9 (9)
Hypertension	23 (23)
Dyslipidemia	17 (17)
Smoking	
Current smoker	6 (6)
Former smoker	4 (4)
Never smoked	90 (90)
BMI	
Normal	41 (41)
Underweight	26 (26)
Overweight	27 (27)
Obese	6 (6)

ments or current use of antidiabetic medications. Body mass index (BMI) was calculated based on formula: weight (kg)/[height (m)]^2 and patients were categorized as underweight (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (> 29.9 kg/m^2).

Interpretation of ECG findings. ACS was defined as *ST*-elevation myocardial infarction (STEMI), non-STEMI or unstable angina. STEMI was considered ⩾ 1 mm elevation in *ST*-segment on 2 adjacent leads in all leads except for V2 and V3 in which cut-point was ⩾ 2 mm in men ⩾ 40 years, ⩾ 2.5 mm in men < 40 years and ⩾ 1.5 mm in women regardless of age. Non-STEMI or unstable angina were determined as a depression on *ST*-segment ⩾ 0.5 mm in two adjacent leads and/or an inversion on *T* wave > 1 mm in two adjacent leads with prominent *R* wave or *R/S* ratio > 1.

Statistical analysis. Descriptive statistics were reported using mean ± standard deviation or percentage (frequency), as applicable. The normality of data distribution was determined using Kolmogorov — Smirnov test. Chi-squared and Fisher's exact tests was performed to compare differences between categorical variables. McNemar test was used to compare the number of patients with elevated troponin before and during chemotherapy. Data were analyzed using IBM SPSS Statistics for Windows version 23.0. The significance level for all analyzes was considered $p < 0.05$.

Table 3. Temporal changes in proportion of patients with detectable cTnI

Variable	cTnI > 0.16 ng/ml N (%)	cTnI ⩽ 0.16 ng/ml N (%)	P-value
Cycle 1			
Before	8 (8)	92 (92)	0.28
During	12 (12)	88 (88)	
Cycle 2			
Before	6 (6)	94 (94)	0.12
During	10 (10)	90 (90)	
Cycle 3			
Before	9 (9)	91 (91)	0.063
During	14 (14)	86 (86)	

RESULTS

Of 174 patients assessed for eligibility, 100 patients with solid gastrointestinal tumors undergoing 5-FU containing chemotherapy regimens were included (Figure). The study population consisted of 48 females (48%) and 52 males (52%) with mean age of 63/99 ± 12/40 years. Most patients had colorectal (72%) cancer (Table 1).

Eight cardiotoxic events (8%) consisted of 6 ACS (6%), 2 arrhythmias (2%) and one hypotension (1%) occurred during the study. The majority of events were seen in the first cycle (4 patients) followed by the second (3 patients) and third cycles (1 patient). Elevated cTnI above the cut-off point 0.3 ng/ml (cTnI = 4.15) was seen only in one patient with STEMI. Four patients were diagnosed with unstable angina, two with sinus tachycardia and one with hypotension. Additionally, the main clinical symptom was chest pain and FOLFOX was the most common regimen among patients with cardiotoxicity (4 patients) (Table 2).

We found only one patient with increased cTnI levels above the cut-off (0.3 ng/ml). Besides, detectable cTnI levels (> 0.16 ng/ml) were observed during the first, second, and third cycles in 12 (12%), 10 (10%), and 14 patients (14%), respectively. Nonetheless, we failed to demonstrate a statistically significant difference in the proportion of patients

Table 2. Cardiotoxic events among patients

Patient	Age	Gender	Risk factor	Type of cancer	Cardiac symptoms	Regimen	Cycle (day)	Cardiotoxic event	Elevated cTnI	ECG changes
1	49	Male	No	Colon	Chest pain	FOLFOX4	1 (1)	Unstable angina	Yes (0.16–0.3 ng/ml)	*ST* depression
2	51	Male	Hypertension	Esophageal	Chest pain and severe nausea	5-FU+cisplatin	1 (3)	STEMI	Yes (> 0.3 ng/ml)	*ST* elevation
3	67	Female	No	Colon	Palpitation, chest pain	FOLFOX4	1 (2)	Sinus tachycardia	NO	Narrow *QRS* complex
4	65	Male	Hypertension and smoking	Colon	Chest pain, dyspnea	FOLFOX4	2 (2)	Unstable angina	NO	NO
5	58	Male	No	Colon	Palpitation	5-FU+leucovorin	2 (3)	Sinus tachycardia	NO	Narrow *QRS* complex
6	62	Female	No	Rectal	Chest pain	5-FU+leucovorin	1 (2)	Unstable angina	Yes (0.16–0.3 ng/ml)	*ST* depression and *T* wave inversion
7	72	Male	No	Colon	Dizziness	FOLFOX4	3 (1)	Hypotension	NO	NO
8	66	Female	Hypertension	Colon	Chest pain	5-FU+leucovorin	2 (3)	Unstable angina	NO	NO

Note: STEMI, *ST*-elevation myocardial infarction.

Table 4. Cardiotoxic events by gender, age and risk factors

Variable	Cardiotoxicity		P-value
	Yes	No	
Age, years			
< 65	4 (7.1)	52 (92.9)	0.72
⩾ 65	4 (9.1)	40 (90.9)	
Gender			
Male	5 (9.6)	47 (90.4)	0.71
Female	3 (6.3)	45 (93.8)	
Chemotherapy regimens			
FOLFOX4	4 (14.3)	24 (85.7)	0.51
FOLFIRI	0 (0)	5 (100)	
5-FU+cisplatin	2 (8.3)	22 (91.7)	
5-FU+leucovorin	2 (4.7)	41 (95.3)	
Previous chest radiation			
Yes	0 (0)	24 (100)	0.19
No	8 (10.5)	68 (89.5)	
Concurrent radiotherapy			
Yes	17 (89.5)	6 (75)	0.64
No	6 (7.4)	75 (92.6)	
Diabetes			
Yes	0 (0)	9 (100)	1.00
No	8 (8.8)	83 (91.2)	
Hypertension			
Yes	4 (17.4)	19 (82.6)	0.079
No	4 (5.2)	73 (94.8)	
Dyslipidemia			
Yes	0 (0)	17 (100)	0.34
No	8 (9.6)	75 (90.4)	
Smoking			
Current smoker	1 (16.7)	5 (83.3)	0.58
Former smoker	0 (0)	4 (100)	
Never smoked	7 (7.8)	83 (92.2)	
BMI			
Normal	3 (7.3)	38 (92.7)	0.88
Underweight	3 (11.5)	23 (88.5)	
Overweight	2 (7.4)	25 (92.6)	
Obese	0 (0)	6 (100)	

with detectable cTnI before and during each cycle (cycle 1, $p = 0.28$, cycle 2, $p = 0.12$, cycle 3, $p = 0.063$) (Table 3).

Considering potential risk factors for cardiotoxicity, there was no significant association between having a history of diabetes, hypertension, smoking, dyslipidemia and previous chest radiation and developing a cardiotoxic event (Table 4).

DISCUSSION

The evidence suggests that cardiac troponins are powerful markers for detecting myocardial injury so that the most common cause of elevated cardiac troponin is myocardial infarction (MI) [21]. The current study was aimed at determining the incidence of cardiotoxicity among patients undergoing 5-FU infusion regimens with an emphasis on the efficacy of cTnI for diagnosis. It is worth mentioning, we only included patients with continuous infusion regimens due to the fact that in various studies, 5-FU infusion regimens have been shown to be associated with an increased incidence of cardiotoxicity compared with the bolus route of administration. In fact, the bolus 5-FU can be considered as an alternative choice among patients with infusion 5-FU-induced cardiotoxicity [22, 23].

We found the incidence of 5-FU induced cardiotoxicity to be 8%. Furthermore, there was no significant difference in the proportion of patients with detectable cTnI before and during chemotherapy cycles. We observed no statistically significant difference in the prevalence of potential risk markers between patients with and without 5-FU-induced cardiotoxicity.

It is imperative to develop prompt and accurate diagnostic measures, given the potential for 5-FU-induced cardiotoxicity to be associated with life-threatening complications i.e. ischemia, arrhythmia and even death. However, no specific clinical guideline has yet been issued for the diagnosis and management of this condition mainly due to the scarcity of relevant clinical trials [24].

Jensen *et al*. [25] reported an 8.5% incidence of 5-FU-induced cardiotoxicity in 106 patients with colorectal cancer. In addition, they did not find any significant association between developing cardiotoxicity and potential risk factors (cardiovascular disease, hypercholesterolemia, hypertension, diabetes mellitus, BMI and smoking), which is completely in line with results of the present study.

It has been shown that several risk factors might increase the risk of cardiotoxicity, including age (elderly and very young), previous chest radiotherapy, BMI and particularly a history of cardiovascular disease [17, 25, 26]. However, in general, there is no strong evidence to prove these factors to be associated with an increased risk of 5-FU-induced cardiotoxicity in healthy patients, genetically prone patients, underlying heart diseases and renal insufficiency should be considered as paramount risk factors [27, 28].

In another study, Dyhl-Polk *et al*. [29] showed that 8 patients developed cardiotoxic-related clinical events, of which 6 patients (5.6%) had ACS. They also demonstrated that the proportion of patients with detectable cTnI before and during the chemotherapy cycles was not statistically significantly different, which is completely in line with our findings.

Evidence suggests that long 5-FU infusion schedules as well as regimens containing cisplatin or leucovorin are more likely to cause cardiotoxicity [13]. However, in the present study there were no significant differences between 5-FU regimens in terms of 5-FU-induced cardiotoxicity incidence.

In the present study, 5 patients reported chest pain (5%) which has been shown to be the most common manifestation of 5-FU-induced cardiotoxicity among patients with cancer [13]. In a multicenter study of 527 patients with solid tumors, 49 patients (25%) diagnosed with 5-FU-associated cardiotoxicity of whom 21 patients (4%) reported chest pain and palpitation and only 2 patients developed myocardial infarction. In addition, among risk markers for cardiotoxicity only a history of heart diseases and HTN were significantly associated with increased risk of experiencing cardiotoxicity [17]. Even so, as an exclusion criteria, patients with pre-existing heart diseases were not enrolled in the present study.

In a study by Holubec *et al*. [30], considering the cut-off of 0.04 μg/l for cTnI, 57% of patients had elevated cTnI levels and with cut-off of 0.3 μg/l, an in-

crease in cTnI was observed in 14% of patients. They have recommended measurement of cardiac troponins as a beneficial marker for monitoring patients during chemotherapy. Even so, we failed to show such findings and therefore could not recommend cTnI as a significantly suitable biomarker for prognosis or diagnosis purposes. In the present study, the cut-off was 0.3 ng/ml and the level above 0.16 ng/ml was considered a detectable level according to the kit instructions.

In a study of 32 cancer patients treated with 5-FU, Turan *et al*.[31]. found no significant increase in plasma cTnI levels following 5-FU administration, It should be noted that in their study, the cut-off point for cTnI was 0.1 ng/ml. Oztop *et al.* [32] also conducted a study on 22 patients with gastrointestinal cancer to examine the cardiotoxicity of 5-FU containing regimens, in the results of this study, serum troponin I was at normal level in all measurements and all patients.

It implies that one of the reasons for the lack of significant increase in cTnI levels during chemotherapy may be the utilization of conventional methods for its detection. The increased levels of troponin in chemotherapy-induced cardiotoxicity are small and may not be detectable by conventional methods. Thus, new high-sensitivity assays appear to be able to detect very small amounts of plasma troponin [9] and are more reliable markers for detecting subtle changes in cTnI levels. Indeed, even a small increase in cTnI levels can be associated with a poor prognosis and an increased risk of death [30]. In several studies, in which cTnI has been applied as a marker for diagnosing chemotherapy-related myocardial injury, various cut-offs have been reported and only in some studies high-sensitivity assays have been used to detect cTnI [30–33]. The use of troponin as a marker of myocardial injury has made significant progress in recent years, and its use is not limited to the diagnosis of acute myocardial infarction but also for diagnosis in outpatients and the risk stratification of myocardial injury. Measurement of cardiac troponins using high-sensitivity assays has increased the chance of early cardiotoxicity detection among patients undergoing chemotherapy [34]. Sawaya *et al.* [35] showed that plasma cTnI concentrations in patients with anthracyclines and trastuzumab-treated breast cancer could predict the progression of cardiotoxicity, as in the third month of chemotherapy, 28% of patients had increased cTnI.

Another reason might be due to the mechanisms by which 5-FU induces cardiotoxicity. One of the proposed mechanisms is through the impact of 5-FU on the coronary arteries, leading to vascular endothelial damage, platelet aggregation and fibrin formation. Other mechanisms could be prostacyclin release from endothelial cells, coronary vasospasm, or even an immunoallergic reaction [22]. For instance, a study showed that 14.1% of patients on Holter recording developed ischemia whereas, the increase in the proportion of patients with elevated troponin were not statistically significant during the chemotherapy [29]. Perhaps, with regard to the said mechanisms, 5-FU-induced cardiotoxicity is less likely to cause myocardial injury and therefore an increased troponin level.

In 2012, the European Society of Medical Oncology recommended to monitor patients undergoing chemotherapy using serial measurements of cardiac biomarkers. Nevertheless, there is still insufficient evidence to endorse the application of cardiac biomarkers for prognosis or diagnosis of chemotherapy-induced cardiotoxicity [36]. Taking into account the fact that cardiac biomarkers such as N-terminal pro-brain natriuretic peptide, creatine phosphokinase, and cardiac troponins have been shown to have a low negative predictive value, indicating an inability to rule out cardiotoxicity even in presence of normal levels of such biomarkers. On the other hand, with silent ischemia as a relatively common manifestation of cardiotoxicity, which has been demonstrated to be well recognized during Holter monitoring, patients close monitoring throughout the chemotherapy should be considered an integral part of diagnosing cardiotoxicity [28].

The main limitation of this study is the use of conventional cTnI assay which has less sensitivity in comparison to high-sensitivity methods to detect very small amounts of cTnI elevations. In addition, we followed patients only for three cycles, which may lead to the missing of a number of cardiotoxic events that might manifest in the fourth and subsequent cycles. However, we measured cTnI levels at regular intervals before, during, and after chemotherapy cycles to provide reliable measurements in order to determine the proportion of patients with elevated cTnI.

In summary, the incidence of 5-FU-induced cardiotoxicity in our study was 8%. There was no significant association between known risk markers of cardiotoxicity and experiencing a cardiotoxic event. Furthermore, the elevation of cTnI during the chemotherapy was not statistically significant. Together, the use of cTnI alone as a diagnostic marker might not be sufficient, especially for diagnosing silent ischemia. As far as the authors are concerned, diagnosis and management of chemotherapy-induced cardiotoxicity needs a multi-disciplinary approach from a perfect history taking and physical examination to a close cardiac monitoring along with the use of potential cardiac biomarkers. In fact, further clinical trials are needed to address this controversial topic, making it possible to establish clinical guidelines and assist both cardiologists and oncologists effectively.

AUTHOR CONTRIBUTIONS

ZKM, MR, AZ, HF, AK, and HA designed the study. ZKM and AZ supervised the study. MR and AK conducted the statistical analysis. ZKM provided the data

and performed data analyses and quality control. MR and ZKM drafted the manuscript and all authors contributed substantially to its revision. AZ takes responsibility for the paper as a whole.

AVAILABILITY OF DATA AND MATERIAL

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in compliance with the Declaration of Helsinki, guidelines on Good Clinical Practice and with the approval of the Ethics Committee of Zanjan University of Medical Sciences [ZUMS.REC. 1396. 107]. A written informed consent was obtained from all participants.

COMPETING INTERESTS

Authors declare no conflicts of interest.

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ОЦІНЮВАННЯ КАРДІОТОКСИЧНОСТІ, СПРИЧИНЕНОЇ 5-ФЛОРОУРАЦИЛОМ: ЗНАЧЕННЯ КАРДІОБІОМАРКЕРІВ

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Стан питання*:** Побічні ефекти хіміотерапії у онкологічних хворих потребують більш детального дослідження. ***Мета: Визначити частоту кардіотоксичності у хворих в клінічному центрі Занджан в Ірані, які отримували хіміотерапію за різними схемами, що включала 5-флуороурацил (5-ФУ). ***Хворі та методи***: У проспективне когортне дослідження було включено хворих із різними типами солідних пухлин шлунково-кишкового тракту, які були кандидатами на проведення хіміотерапії з 5-ФУ. Досліджувана група включала 100 хворих (48 жінок та 52 чоловіки), середній вік становив 63,99 ± 12,40 року. Визначали вміст у сироватці крові кардіотропоніну I до та в процесі кожного циклу хіміотерапії, а також оцінювали розвиток кардіотоксичності, виходячи з рівнів кардіотропоніну I, клінічних ознак та симптомів, результатів ЕКГ. Оцінювали наявність в анамнезі цукрового діабету, артеріальної гіпертензії, тютюнопаління, дисліпідемії та попереднього опромінення грудної клітки як потенційних факторів ризику розвитку кардіотоксичності. ***Результати***: Прояву кардіотоксичності було визначено у 8% досліджуваних хворих. З них у 5 хворих було діагностовано гострий коронарний синдром, у 2 — аритмію та ще у одного — артеріальну гіпотензію. Не було виявлено вірогідної асоціації між досліджуваними факторами ризику та розвитком кардіотоксичності внаслідок застосування 5-ФУ. ***Висновок***: У досліджуваній групі хворих виявлено досить помітну кількість проявів кардіотоксичності при терапії 5-ФУ, що потребує більшої уваги з метою поліпшення прогнозу при хіміотерапії у онкологічних хворих.

***Ключові слова*:** кардіотропонін I, 5-флуороурацил, кардіотоксичність, хіміотерапія, пухлини шлунково-кишкового тракту.