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# Efficacy of glyceryl trinitrate in reducing cardiac events when given concomitantly with capecitabine for at least 3 months in various tumors

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**Abstract**: Capecitabine is an oral pro-drug of 5-flourouracil used in treatment of different cancers. It has cardiotoxicity incidence of 3-35%, which can be significant enough to cause myocardial infarction. To evaluate the efficacy of glyceryl trinitrate in reducing cardiac events when given concomitantly with capecitabine for at least 3 months in various tumors. A quasi-experimental study was conducted in Hameed Latif Hospital from January 2019 to December 2023. A total of 65 patients with various malignancies and ECOG 0-2 were included. Glyceryl trinitrate was given before capecitabine for at least 3 cycles with 2.6 mg dosage twice a day. Cardiotoxicity was assessed after each 21-days cycle by taking history and ECG. Echocardiogram was done at 3-month follow up Patients aged from 49 to 86 years. Adverse events were noted in 3 (4.6%) patients. Two patients (3.1%) suffered from angina (grade 2 cardiotoxicity) while 1 (1.5%) suffered from a myocardial infarction (grade 3 cardiotoxicity). On stratification, only treatment in adjuvant setting ($p<0.001$) was found to be a possible risk factor. Glyceryl trinitrate may have potential to be used concomitantly with capecitabine to reduce the frequency of serious cardiac events in cancer patients. However, further studies are needed.

**Keywords**: Capecitabine, cardiotoxicity, cancer, efficacy, glyceryl trinitrate.

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## INTRODUCTION

Fluoropyrimidine is uracil derivative where fluorine replaces hydrogen at fifth position of carbon, preferential uptake of uracil by tumor is reason of its marked cytotoxic activity. It belongs to anti-metabolite class of anti-cancer drugs. Capecitabine, an oral pro-drug of fluorouracil, an anti-metabolite which exerts its anti-tumor effect by inhibiting pyrimidine synthesis (Siddiqui *et al*., 2019). It is widely used in different clinical settings and in various solid malignancies including breast and colon cancer (Lluch *et al*., 2020, Murthy *et al*., 2020). Major toxicities of capecitabine include diarrhea, stomatitis, neutropenia, alopecia, hand foot syndrome and cardiotoxicity (Brazelton *et al*., 2022, Sherry *et al*., 2020). Cardiotoxicity, though uncommon, is serious side effect which affects approximately 3-35% of patients receiving capecitabine (Dyhl-Polk *et al*., 2020). Larger studies have shown incidence of cardiotoxicity 1.2-4.3% during fluorouracil treatment, however subclinical cardiac effects are also common (Osterlund *et al*., 2022). However, among these, 0.7-0.8% of patients are at risk of developing grade 3 or 4 cardiotoxicity (Raber *et al*., 2020).

Presence of co-morbids, structural and functional heart diseases, combination chemotherapy, previous history of chest wall irradiation are some known risk factors for capecitabine-induced cardiotoxicity. But their relationship with cardiotoxicity is not well established. Clinical presentation can vary from asymptomatic ECG changes to severe chest pain, shortness of breath, dilated cardiomyopathy, ventricular arrhythmias and even sudden cardiac arrest (Yuan *et al*., 2019). Although precise pathophysiology of capecitabine-induced cardiotoxicity is yet unknown, fluoropyrimidine-induced coronary vasospasm leading to ischemia, MI/angina is most often accepted explanation. Furthermore, cardiac myocytes may sustain direct damage, which would further exacerbate development of cardiotoxicity. Other possible reasons include hypercoagulability raising the likelihood of thrombotic events and endothelial dysfunction, which compromises the integrity of blood vessels (Deac *et al*., 2020). It is thought that mitochondrial dysfunction is caused by oxidative stress, which mediates cytotoxic effects on cardiomyocytes. Disruption of mitochondrial function triggers the activation of caspase-3, that facilitates apoptosis and ultimately leads to cell death. Therefore, it seems that ischemia, direct cellular injury, and oxidative damage work together to cause cardiotoxicity (Deac *et al*., 2020).

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Efforts to prevent 5FU-induced cardiotoxicity are hindered by inconsistent data on risk factors contributing to its development. There are case reports on the use of nitrates for secondary prevention, showing mixed results (Anaka and Abdel-Rahman 2023). Nitrates offer symptomatic relief for in acute situations, but routine pre-treatment with vasodilators has not been proven to reduce the risk of coronary vasospasm and is thus not generally recommended (Padegimas and Carver 2020).

Effective strategies to prevent this life-threatening complication of fluoropyrimidine are need of the hour which makes this an area of active ongoing research. Several drugs have shown their activity in prevention of cardiotoxicity which include calcium channel blocker, long- acting nitrate and beta blockers. Uridine trinitrate has been found to be safe and effective in preventing over-dose related acute toxicities.

Organic nitrates are traditionally used in the management of cardiac ischemia. Their main action is on vascular smooth muscles. These agents cause both arterial and venous dilatation, thus reduce after load and improve venous refilling of heart. This leads to decrease oxygen demand and increase oxygen supply to cardiac myocytes (Liu *et al*., 2020). Having known the efficacy of commonly used nitrates (e.g., Glyceryl Trinitrate) in management of symptomatic cardiac events and still gap in previous studies regarding its efficacy for capecitabine-induced cardiotoxicity; we have designed this phase 2 study to evaluate the effect of concomitant administration of glyceryl trinitrate on incidence and severity of capecitabine-induced cardiotoxicity.

## MATERIALS AND METHODS

### *Study Design*

This quasi-experimental study was designed because it is appropriate for evaluating treatment effects in real-world context without the need for randomization, which might be ethically challenging in cancer treatment. This method allows for collection of pertinent data on patient outcomes, leading to deeper understanding of the cardiotoxic effects linked to capecitabine therapy. Additionally, it enables control over confounding factors through careful inclusion and exclusion criteria. Therefore, this design successfully aligns with study's objectives by addressing the complexities of treatment responses within diverse patient population. To be eligible for the study, patients who were meeting the selection criteria were included.

### *Inclusion criteria*

Patients receiving capecitabine alone or in combination therapy regardless of dose, between ages of 18 and 70 years and above, have adenocarcinoma confirmed on histology and had adequate hematologic, hepatic and renal functions, and Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (Azam *et al* 2020).

### *Exclusion criteria*

Those who had received vasodilators such as calcium channel blockers, or had history of ischemic heart disease (as confirmed on previous history (chest pain, shortness of breath) and medical records i.e. ECG changes, and echocardiography findings) and ECOG >2 (Azam *et al* 2020) were excluded.

### *Sample size collection*

Sample of 65 patients was estimated using 95% confidence level, 10% margin of error and expected percentage of capecitabine induced cardiotoxicity was taken as 21.8% (Wang *et al.,* 2020). Sampling was done using non-probability convenient sampling technique, this technique was chosen due to ease of implementation. This technique allows for the selection of participants based on their availability and willingness to participate, which is often essential when dealing with specific patient populations. Given the time constraints, resource limitations and potential difficulties in accessing wider pool of patients, convenience sampling suitable to ensure feasible sample size can be gathered efficiently.

### *Data collection procedure*

This quasi-experimental study was conducted from January 2019 to December 2023 on 65 patients meeting the selection criteria, at Oncology Department of Hameed Latif Hospital. Written informed consent was taken all patients. The study was approved by the ethical board of hospital. Data was assembled on predesigned Performas. Demographic details, co-morbids and ECOG performance status of all patients were noted. Underlying diagnosis and details of chemotherapy and Multitherapy types was also documented.

### *Glyceryl trinitrate dose*

Starting from cycle 1, glyceryl trinitrate (2.6 mg morning and evening dose before capecitabine) was given concomitantly with capecitabine for 14 days at beginning of each cycle for at least 3 cycles.

### *Cardiotoxcity assessment*

Cardiotoxicity was assessed at end of each 21-days cycle by taking history of symptoms (left sided chest pain, shortness of breath and palpations) and ECG changes (ST-T changes) in terms of angina and MI. Echocardiogram was done at 3 monthly intervals. And grades of cardiotoxicity were noted; Grade 1: Asymptomatic/mild symptoms (e.g., mild ECG changes), and no impact on daily activities. Grade 2: Symptomatic, chest pain that may affect daily activities. Grade 3: Severe symptoms, significant chest pain e.g., Myocardial infarction. Grade 4: Life-threatening consequences, e.g., arrhythmias.

**Table 1**: Frequency of Qualitative variables

| Demographics | | Frequency | Percentage (%) |
|---|---|---|---|
| Age (years) | | Median (IQR): 60.00(11) | |
| Gender | Male | 26 | 40 |
| | Female | 39 | 60 |
| ECOG performance status | 0 | 19 | 29.2 |
| | 1 | 37 | 56.9 |
| | 2 | 9 | 13.8 |
| Co-morbid illness | Diabetes mellitus | 16 | 24.6 |
| | Hypertension | 12 | 18.5 |
| | IHD | 1 | 1.5 |
| | Multiple | 17 | 26.2 |
| | No illness | 19 | 29.2 |
| Cancer Diagnosis | Colorectal Cancer | 29 | 44.6 |
| | Breast cancer | 24 | 36.9 |
| | Pancreatic cancer | 4 | 6.2 |
| | Gastric cancer | 5 | 7.7 |
| | Neuroendocrine tumor | 3 | 4.6 |
| Chemotherapy setting | Neo-Adjuvant | 2 | 3.1 |
| | Adjuvant | 14 | 21.5 |
| | Metastatic | 49 | 75.4 |
| Chemotherapy regimen | Single agent Capecitabine | 22 | 33.8 |
| | Multiple agents | 43 | 66.2 |
| Multi-therapy types | Capecitabine+ Oxaliplatin | 33 | 50.8 |
| | Capecitabine + anti Her2 | 3 | 4.6 |
| | Capecitabine+Gemcitabine | 1 | 1.5 |
| | Capecitabine + Irinotecan | 1 | 1.5 |
| | Capecitabine + Others | 5 | 7.69 |

**Table 2**: Frequency of Cardiac events and their grades

| | | Frequency | Percentage (%) |
|---|---|---|---|
| Cardiac Event | Angina | 2 | 3.1 |
| | Myocardial Infarction | 1 | 1.5 |
| Grade of Cardiotoxicity | Grade 1/2 | 2 | 3.1 |
| | Grade 3/4 | 1 | 1.5 |

## ETHICAL APPROVAL

Ethical approval of study was taken from IRB Department of Hameed Latif Hospital vide No.HLH/1020/2021.

## STATISTICAL ANALYSIS

Quantitative variables (like age, income number of treatments cycle, number of treatment duration in months) were presented as mean and standard deviations if data was normally distributed or median and interquartile range if data was not normally distributed. For qualitative variables (like gender, ECOG performance status, Co-morbid illness, Cancer Diagnosis, Chemotherapy setting, Chemotherapy regimen, Multitherapy types, Cardiac Event, Grade of Cardio-toxicity), frequency and percentages were calculated. Association of various variables with cardiac events was assessed using Chi-square test with $p<0.05$ taken as significant.

## RESULTS

Total 65 patients with age range 49-86 years and Median (IQR): 60.00(11) were enrolled. On average patients received Median (IQR): 6.00(6) cycles. Median duration of treatment was Median (IQR): 6.00(4) months (table 1). Cardiac events were noted in 3 (4.6%) patients which included angina (grade 2 cardiotoxicity) in 2 (3.1%) and myocardial infarction (grade 3 cardiotoxicity) in 1 (1.5%) patient (table 2). On stratification, only chemotherapy setting ($p<0.001$) was found to be possible risk factors (table 3).

## DISCUSSION

Current study was designed to see clinical benefit of added glyceryl trinitrate in reducing the incidence of cardiotoxicity in patients of various malignancies. According to findings, only 4.6% patients experienced cardiac event and among them 1 patient experienced MI (grade 3 cardiotoxicity). Incidence of these events in our study is similar to some previous studies. (Pouya *et al*., 2021). However, some reviews have given broad range of cardiac event 1%-18% and 1-19%, respectively (Deac *et al*., 2020 and Kanduri *et al*., 2019). Although there are a few studies which report higher incidence (Pietrantonio *et al*., 2020). Variations from previous studies occurred, because these studies have reported incidence of cardiac

**Table 3**: Association of various variables with cardiac event

| Variables | Cardiac Event | | P Value |
|---|---|---|---|
| | Yes | No | |
| ECOG Performance Status: | | | |
| 0 | 0 (0%) | 19 (29.2%) | 0.304 |
| 1 | 3 (4.6%) | 34 (52.3%) | |
| 2 | 0 (0%) | 9 (13.8%) | |
| Co-morbid illness | | | |
| Diabetes | 1 (1.5%) | 15 (23.1%) | |
| Hypertension | 1 (1.5%) | 11 (16.9%) | 0.826 |
| Ischemic Heart Disease | 0 (0%) | 1 (1.5%) | |
| Multiple diseases | 1 (1.5%) | 16 (24.6%) | |
| No illness | 0 (0%) | 19 (29.2%) | |
| Cancer Diagnosis | | | |
| Colorectal cancer | 1 (1.5%) | 28 (43.1%) | |
| Breast cancer | 2 (3.1%) | 22 (33.8%) | 0.840 |
| Pancreatic cancer | 0 (0%) | 4 (6.2%) | |
| Gastric cancer | 0 (0%) | 5 (7.7%) | |
| Neuroendocrine tumor | 0 (0%) | 3 (4.6%) | |
| Chemotherapy setting | | | |
| Neo-adjuvant | 1 (1.5%) | 1 (1.5%) | 0.007 |
| Adjuvant | 0 (0%) | 14 (21.5%) | |
| Metastatic | 2 (3.1%) | 47 (72.3%) | |
| Chemotherapy regimen | | | |
| Single | 0 (0%) | 22 (33.8%) | 0.205 |
| Multiple | 3 (4.6%) | 40 (61.5%) | |

events where no preventive measures were used. However, in current study most patients had co-morbids which made them highly susceptible to cardiotoxic effects of capecitabine. So, we can hypothetically postulate that probably real incidence would have been much lower in patients without any pre-disposing condition.

In one recent meta-review, 78 received CCBs and/or nitrates before further 5-FU treatment, while 3 continued without any pre-treatment. Those who continued 5-FU with pre-treatment had lower risk of death (HR 0.42, P = 0.005) and none of the pre-treated patients experienced MI, though chest pain recurred in 19.2% of pre-treated patients versus 66.7% without pre-treatment (P = 0.048). There was no significant variance in recurrence of vasospasm or efficacy between those treated with single drug and those on combination therapy CCB + nitrates, P 0.26 (Zafar *et al*., 2022).

The incidence of above-mentioned cardiac events was found to be correlated with treatment setting with higher incidence in adjuvant setting and lower in metastatic setting. This can be explained well as most of patients receive full dose in adjuvant setting which makes them at high risk compared with those having metastatic setting where dosage can be adjusted based on their tolerability so not to compromise their quality of life. Other studies have reported similar findings in their study where cardiotoxicity was associated with prolonged administration schedule of 5-FU along with dose strength (Alqahtani *et al*., 2022, Alzahrani *et al*., 2023, Adams *et al*., 2021). However, current study has included subjects regardless of dose.

In current study, patient on multiple therapy found to have all burden of cardiotoxcity i.e. 4.6%, and this is in concordance with previous studies (Cura *et al*., 2023, Auber *et al*., 2021, Mettu *et al*., 2022, Dyhl-Polk *et al*., 2020). One pooled analysis of trials showed that combination therapies can increased the risk of cardiotoxicity. Among them Bevacizumab regimens had higher rate vs capecitabine alone, 2.9% vs 1%, while panitumumab regimens were linked to higher cardiac toxicity 11.5% vs 6.6% (Abdel-Rahman 2019). Another analysis of three trials found that CAPOX when combined with bevacizumab had highest cardiotoxicity rate (12% vs 4% for capecitabine alone), though combination of bevacizumab + cetuximab + CAPOX had 7% frequency (Kwakman *et al*., 2017).

Pre-existing cardiac co-morbidities were also found to be significantly associated with the incidence of capecitabine-induced cardiotoxicity. These findings resonate with the precious studies where increased cardiac toxicity was observed in patients with multiple co-morbid conditions (Anaka and Abdel-Rahman, 2023, Keramida *et al*., 2019). Contrary to it, Wang *et al* have reported no association of pre-existing disease with cardiotoxicity (Wang *et al*., 2023).

There are few limitations of the study. One of which is small sample size. Due to small sample size and even smaller number of cardiotoxic events, the statistical power is low. Another limitation is that most of our patients had co-morbid illnesses which made them highly susceptible to cardiotoxic events, thus masking true potential efficacy

of glyceryl trinitrate. Furthermore, dosage needs to be studied too. Moreover, specific dosages of capecitabine were not studied, which limits our ability to draw conclusions regarding the dose-response relationship. So, further research will be needed on larger cohort with no or controlled comorbid, to cover these deficiencies. This would improve results' statistical robustness and enable more accurate evaluation of study drug efficacy. These recommendations can help future research produce more dependable and broadly applicable findings.

## CONCLUSION

The results suggest that glyceryl trinitrate could provide protective effects against the cardiotoxicity linked to capecitabine treatment. The notable correlation between chemotherapy settings and highest incidence of cardiac events with metastasis highlights the importance of closely monitoring of these patients. In summary, these findings enhance our understanding of how to manage cardiotoxicity in individuals undergoing capecitabine therapy.

## REFERENCES


Adams RA, Fisher DJ, Graham J, Seligmann JF, Seymour M, Kaplan R, Yates E, Parmar M, Richman SD, Quirke P and Butler R (2021). Capecitabine versus active monitoring in stable or responding metastatic colorectal cancer after 16 weeks of first-line therapy: Results of the randomized FOCUS4-N trial. *J Clin Oncol*., **39**(33): 3693-704.

Abdel-Rahman O (2019). 5-Fluorouracil-related cardiotoxicity; Findings from five randomized studies of 5-fluorouracil-based regimens in metastatic colorectal cancer. *Clin colorectal Cancer*, **18**(1): 58-63.

Alqahtani S, Alzaidi R, Alsultan A, Asiri A, Asiri Y and Alsaleh K (2022). Clinical pharmacokinetics of capecitabine and its metabolites in colorectal cancer patients. *SPJ*., **30**(5): 527-531.

Alzahrani SM, Al Doghaither HA, Al-Ghafari AB and Pushparaj PN (2023). 5-Fluorouracil and capecitabine therapies for the treatment of colorectal cancer. *Oncol Rep*., **50**(4): 175.

Anaka M and Abdel-Rahman O (2023). Managing 5FU cardiotoxicity in colorectal cancer treatment. *Cancer Manage Res*., **14**: 273-285.

Auber ML, Wen S, Hobbs G and Higa GM (2021). Capecitabine as maintenance therapy for high-risk, resected colorectal cancer. *Gastrointest Tumors*. **8**(2): 81-6.

Azam F, Latif MF, Farooq A, Tirmazy SH, AlShahrani S, Bashir S and Bukhari N (2019). Performance Status Assessment by using ECOG (Eastern Cooperative Oncology Group) score for cancer patients by oncology healthcare professionals. *Case Rep. Oncol.*, **12**(3): 728-736.

Brazelton A, Yande S, Pope R, Johnson ML, Musher B and Trivedi MV (2022). Racial and ethnic differences in capecitabine toxicity in patients with gastrointestinal tract cancers. *Ann. gastroenterol.*, **35**(2): 182.

Cura Y, Perez-Ramírez C, Sánchez-Martin A, Membrive-Jimenez C, Valverde-Merino MI, González-Flores E and Morales AJ (2023). Influence of single-nucleotide polymorphisms on clinical outcomes of capecitabine-based chemotherapy in colorectal cancer patients: A systematic review. *Cancers*, **15**(6): 1821.

Deac AL, Burz CC, Bocsan IC and Buzoianu AD (2020). Fluoropyrimidine-induced cardiotoxicity. *World J Clin Oncol.*, **11**(12): 1008.

Dyhl-Polk A, Vaage-Nilsen M, Schou M, Vistisen KK, Lund CM, Kümler T, Appel JM and Nielsen DL (2020). Incidence and risk markers of 5-fluorouracil and capecitabine cardiotoxicity in patients with colorectal cancer. *Acta. Oncol.* **59**(4): 475-83.

Kanduri J, More LA, Godishala A and Asnani A (2019). Fluoropyrimidine-associated cardiotoxicity. *Cardiol. Clin*., **37**(4): 399-405.

Keramida K, Charalampopoulos G, Filippiadis D, Tsougos E and Farmakis D (2019). Cardiovascular complications of metastatic colorectal cancer treatment. *J. Gastrointest. Oncol.*, **10**(4): 797.

Kwakman JJ, Simkens LH, Mol L, Kok WE, Koopman M and Punt CJ (2017). Incidence of capecitabine-related cardiotoxicity in different treatment schedules of metastatic colorectal cancer: A retrospective analysis of the CAIRO studies of the Dutch Colorectal Cancer Group. *EJC*, **76**: 93-99.

Liu Y, Croft KD, Hodgson JM, Mori T and Ward NC (2020). Mechanisms of the protective effects of nitrate and nitrite in cardiovascular and metabolic diseases. *Nitric Oxide*, **96**: 35-43.

Lluch A, Barrios CH, Torrecillas L, Ruiz-Borrego M, Bines J, Segalla J, Guerrero-Zotano Á, García-Sáenz JA, Torres R, de la Haba J and García-Martínez E (2020). Phase III trial of adjuvant capecitabine after standard neo-/adjuvant chemotherapy in patients with early triple-negative breast cancer (GEICAM/2003-11_CIBOMA/2004-01). *J. Clin. Oncol.*, **38**(3): 203-213.

Mettu NB, Ou FS, Zemla TJ, Halfdanarson TR, Lenz HJ, Breakstone RA, Boland PM, Crysler OV, Wu C, Nixon AB and Bolch E (2022). Assessment of capecitabine and bevacizumab with or without atezolizumab for the treatment of refractory metastatic colorectal cancer: A randomized clinical trial. *JAMA Net Open*, **5**(2): e2149040-e2149040.

Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, Lin NU, Borges V, Abramson V, Anders C and Bedard PL (2020). Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *NEJM*, **382**(7): 597-609.

Osterlund P, Kinos S, Pfeiffer P, Salminen T, Kwakman JJM, Frodin JE, Shah CH, Sorbye H, Ristamäki R,

Halonen P and Soveri LM (2022). Continuation of fluoropyrimidine treatment with S-1 after cardiotoxicity on capecitabine-or 5-fluorouracil-based therapy in patients with solid tumours: A multicentre retrospective observational cohort study. *ESMO Open*, **7**(3): 100427.

Padegimas A and Carver JR (2020). How to diagnose and manage patients with fluoropyrimidine-induced chest pain: A single center approach. *Cardio. Oncology*, **2**(4): 650-654.

Pietrantonio F, Lobefaro R, Antista M, Lonardi S, Raimondi A, Morano F, Mosconi S, Rimassa L, Murgioni S, Sartore-Bianchi A and Tomasello G (2020). Capecitabine and temozolomide versus FOLFIRI in RAS-mutated, MGMT-methylated metastatic colorectal cancer. *Clin. Cancer Res.*, **26**(5): 1017-1024.

Pouya FD, Rasmi Y, Camci IY, Tutar Y and Nemati M (2021). Performance of capecitabine in novel combination therapies in colorectal cancer. *J. Chemother.*, **33**(6): 375-389.

Raber I, Warack S, Kanduri J, Pribish A, Godishala A, Abovich A, Orbite A, Dommaraju S, Frazer M, Peters ML and Asnani A (2020). Fluoropyrimidine associated cardiotoxicity: A retrospective case control study. *The Oncol.*, **25**(3): e606-e609.

Sherry AD, Mayer IA, Ayala-Peacock DN, Abramson VG, Rexer BN and Chakravarthy AB (2020). Combining adjuvant radiotherapy with capecitabine in chemotherapy-resistant breast cancer: Feasibility, safety, and toxicity. *Clin. Breast Cancer*, **20**(4): 344-352.

Siddiqui NS, Godara A, Byrne MM and Saif MW (2019). Capecitabine for the treatment of pancreatic cancer. *Expert Opin Pharmacother.*, **20**(4): 399-409.

Wang Y, Wang W, Dong H, Wang G, Chen W, Chen J and Chen W (2023). Risk factors for fluoropyrimidine-induced cardiotoxicity in colorectal cancer: A retrospective cohort study and establishment of a prediction nomogram for 5-FU induced cardiotoxicity. *Front. Oncol*., **13**: 1017237.

Yuan C, Parekh H, Allegra C, George TJ and Starr JS (2019). 5-FU induced cardiotoxicity: Case series and review of the literature. *Cardio-oncology*, **5**: 1-7.

Zafar A, Drobni ZD, Lei M, Gongora CA, Quinaglia T, Lou UY, Mosarla R, Murphy SP, Jones-O'Connor M, Mahmood A and Hartmann S (2022). The efficacy and safety of cardio-protective therapy in patients with 5-FU (Fluorouracil)-associated coronary vasospasm. *PLoS One*, **17**(4): e0265767.