CASE REPORT

Treatment of advanced colorectal cancer in a patient with cardiotoxic reactions to 5-fluorouracil and capecitabine using suboptimal doses

Joseph H Cioffi,¹ Derek J Estes,² Vaia Florou,³ Bach Ardalan⁴¹School of Medicine, University of Miami, Miami, Florida, USA²Internal Medicine, Jackson Memorial Hospital, Miami, Florida, USA³Department of Haematology/Oncology, Internal Medicine, Jackson Memorial Hospital, Miami, Florida, USA⁴Department of Haematology and Oncology, Internal Medicine, Sylvester Comprehensive Cancer Center, Miami, Florida, USA**Correspondence to**Joseph H Cioffi,
jhc22@med.miami.edu

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SUMMARY

A 32-year-old female with stage IV colorectal cancer and metastasis to the liver experienced cardiotoxic reactions after treatment with 5-fluorouracil and its oral prodrug capecitabine even at two-thirds the recommended dose. After careful considerations, the decision was made to attempt capecitabine retreat at a further suboptimal dose with combination chemotherapy where she no longer experienced cardiac events. As a result, the liver tumour shrank and rectal mass stabilised, tumour markers dropped and she underwent surgical resection of both masses. Later there was local recurrence of disease near the previous liver tumour, so the suboptimal capecitabine therapy was restarted without complaint. The patient became a candidate for a NanoKnife procedure, offering a potentially curative therapy. This case report summarises a novel treatment strategy for those patients with advanced colorectal cancer who experience cardiotoxic reactions to fluoropyrimidines, the active agent of gold standard treatment.

BACKGROUND

The cardiotoxic effects of 5-fluorouracil (5-FU) and its oral prodrug capecitabine are becoming well established; however, fluorouracil continues to be the mainstay of advanced colorectal cancer (CRC) therapy. The cardiotoxic effect is weighed against the survival benefit of including 5-FU in palliative and adjunctive treatment regimens for stage III and IV CRC. It has been suggested that the risk for 5-FU induced cardiotoxicity may depend on dose intensity or different treatment schedules.^{1 2} This is not well understood as there are also data indicating that it is not related to cumulative dose.³ Multiple studies offer theories as to its pathophysiology and strategies to protect patients from its effects without much success, if any.^{1 2 4} Despite the growing evidence of capecitabine toxicity as well, patients in clinical practice are still switched from 5-FU to capecitabine if cardiac toxicities occur with the former. Occasionally, physicians choose dose-reduced fluoropyrimidines along with anti-ischaemic medications rather than switching to a different chemotherapy drug class. The efficacy of this strategy remains controversial to this day and an individualised approach should be taken based on patient and disease characteristics.⁵⁻⁸ Physicians must decide between switching to less potent agents or attempt continuing treatment with capecitabine.

There is a paucity of literature regarding what to do when a patient experiences cardiac symptoms even at subtherapeutic doses. We present a 32-year-old female patient with stage IV CRC with metastasis to the liver who experienced cardiotoxicity at very low doses of capecitabine. Despite this cardiotoxicity, the decision was made to continue therapy with suboptimal dosing.

CASE PRESENTATION

The patient presented with complaints of fatigue and rectal bleeding, and a palpable rectal mass was found on physical exam. Computerised tomography (CT) scan and biopsy revealed a 4.8 cm, moderately differentiated, infiltrating rectal adenocarcinoma. The mass was partially circumferential, encircling half the lumen but was non-obstructive. At time of diagnosis, she was found to have a hypoenhancing mass in the left lobe of the liver, which was biopsy-proven adenocarcinoma, making the stage of her disease IVa (figure 1A). Pathology showed the presence of p53 mutation and the tumour marker carcinoembryonic antigen (CEA) at diagnosis was 52.1 ng/mL.

She was initially treated with FOLFIRI (5-FU 1600 mg/m², irinotecan 100 mg/m² and leukovorin 500 mg/m²). One day after the second cycle of FOLFIRI, she presented to the emergency department complaining of chest pain radiating to the right arm, rated 10/10 in severity with a pressure-like quality. She was haemodynamically stable and electrocardiogram (EKG) showed normal sinus rhythm. The patient stated she had felt similar chest pain at home after her first infusion, which resolved with acetaminophen. Her symptoms initially were treated as of musculoskeletal aetiology, and the pain resolved with infusion suspension, acetaminophen, morphine and cyclobenzaprine. On further consideration, a cardiotoxic reaction to 5-FU was considered as the more likely aetiology of the patient's chest pain in view of her age, lack of coronary artery disease (CAD) risk factors and pattern of symptomatology in relation to the 5-FU infusion. Subsequently, 5-FU was removed from the regimen and substituted with oral capecitabine at a suboptimal dose of 1 g twice daily (two-thirds of the recommended dose) with a 2-week on/1-week off protocol.

Soon after her first course of capecitabine, the patient again complained of chest pain that

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Figure 1 CT scans showing the progression of treatment on liver metastasis. (A) Initial diagnostic CT scan. (B) First CT scan after start of suboptimal chemotherapy, postcycle 3. (C) CT scan prior to resection of primary tumour and liver metastasis, postcycle 18. Note differing kidney levels due to tumour mass.

radiated to the shoulder, which was thought to be related to capecitabine. At this point in time, the team paused to consider treatment options given the patient's continued cardiotoxic reaction to gold standard treatment even at a lowered dose. After a thorough literature review and consideration of the patient's advanced disease and young age, the decision was made to attempt a rechallenge of capecitabine at a further reduced dose. The risks and benefits of treatment were discussed at length with the patient, who understood the likely risk of further cardiac events as well as the likely outcome of stopping treatment or switching to a less potent regimen. She consented to this adapted treatment and as soon as she began a dose of 1.5 g daily (half of the recommended dose), she complained of having transient chest pain again, which the patient insisted was tolerable. The CEA decreased to 2.5 ng/mL after the first cycle of capecitabine. Imaging studies, including positron emission tomography (PET) and CT, at this time showed interval decrease in size of the liver mass (figure 1B). Despite the continued cardiac complaints, the patient wished to remain on the regimen, and repeat PET/CT after cycle 3 again showed a further decrease in the liver mass along with a stable size of the rectal mass. Starting cycle 5, bevacizumab (5 mg/kg) was initiated for maximum response.

After cycle 15 with oral capecitabine, the patient presented to the emergency department complaining of palpitations and shortness of breath. She did not have chest pain. Cardiac enzymes were negative, and EKG showed multiple premature ventricular contractions without ST-T changes. Electrolytes were normal, and cardiac echocardiogram did not show any structural abnormalities. Twenty-four hour Holter monitor was placed and was negative for any arrhythmias. The multiple premature ventricular contractions were attributed to capecitabine, and the dose was further decreased to 1 g daily (one-third of the recommended dose).

The patient continued treatment without any further cardiac complaints. The mass was no longer palpable on digital rectal exam and colonoscopy confirmed this favourable response with a decrease in size of the rectal mass from 4.8 cm to 3 cm. After 18 cycles of treatment, a PET/CT scan revealed a mild interval increase in the liver mass diameter, and the patient was discussed in a multidisciplinary meeting for further treatment planning (figure 1C). The consensus was for a combined surgical resection of the liver lesion along with robotic proctectomy and diverting ileostomy after a preoperative short course of radiation therapy. She underwent these procedures after stopping the chemotherapy without complications for 1 month. Final pathology of the rectal mass was T3N2M1 with clear margins, and CEA on initial follow-up remained at 2.8 ng/mL.

The postoperative plan was for her to undergo ileostomy reversal. The patient did not receive any chemotherapy treatment for 2 months in preparation for anastomosis. Unfortunately, a

preoperative PET scan found an area of uptake adjacent to the previous liver tumour in the coeliac area. Follow-up endoscopy biopsy showed adenocarcinoma of colonic origin. Her presurgery chemotherapy dose was restarted at this point with the capecitabine now taken continuously without breaks to optimise response. She was maintained on this regimen for 10 cycles without any complaints. She then underwent a NanoKnife procedure to remove the solitary lesion for a curative intent. The plan is for future ileostomy reversal given a successful outcome. She has not been restarted on chemotherapy.

TREATMENT

- ▶ Initially FOLFIRI (5-FU 1600 mg/m², irinotecan 100 mg/m² and leukovorin 500 mg/m²)
- ▶ 5-FU switched to capecitabine 1 g twice daily (two-thirds of the recommended dose) with a 2-week on/1-week off protocol.
- ▶ Cycle 2, capecitabine lowered to 1.5 g daily (one-half of the recommended dose).
- ▶ Bevacizumab 5 mg/kg added to regimen.
- ▶ Cycle 15, capecitabine lowered to 1 g daily (one-third of the recommended dose).
- ▶ After cycle 18, patient underwent combined surgical case with resection of the liver tumour along with robotic proctectomy and diverting ileostomy after a preoperative short course of radiation therapy.
- ▶ 3 months of adapted protocol in adjunctive fashion with capecitabine 1 g daily, bevacizumab 5 mg/kg, irinotecan 100 mg/m² and leukovorin 500 mg/m².
- ▶ Treatment stopped for 2 months for anticipated ileostomy reversal.
- ▶ After recurrence, adapted combination chemotherapy regimen restarted with lowered capecitabine 1 g daily now taken continuously without break to optimise treatment.
- ▶ Patient underwent a NanoKnife procedure to remove recurrence, and ileostomy takedown is planned in the near future.

OUTCOME AND FOLLOW-UP

Discussed in case report.

DISCUSSION

This patient's case exemplifies the difficult decisions oncologists face when working on the borders of established medicine. In the absence of established guidelines, the physician must judge the risks and benefits of treatment on a patient-by-patient basis. This patient began her treatment using standard of care infusional 5-FU and was switched to capecitabine when the cardiotoxic events occurred, although the literature on doing so is controversial. There is evidence that the frequency of

capecitabine cardiotoxicity is lower when compared with continuous 5-FU infusion,⁹ while other large studies report no difference between the two.^{10 11} Pre-existing CAD or risk factors for atherosclerosis may be potential culprits predisposing to cardiac events with capecitabine, as described in a recent case report when two patients required intensive care unit admission with thrombolysis and nitroglycerin infusion after oral capecitabine.¹² Both patients had risk factors for CAD and were older than our patient.

When the lower dose of capecitabine again elicited cardiac effects, the team turned to the literature to choose our next option. Ang *et al*¹³ produced an excellent literature review of fluoropyrimidine-induced cardiac reactions, which highlights its controversial pathophysiology and treatment strategies. There are no definitive data for treatment of patients with cardiac reactions, although the prospective study by Kosmas *et al*⁹ suggests retrials of lower doses of capecitabine as a viable treatment. The addition of vasodilators along with intensive cardiological monitoring has been tried in patients where fluoropyrimidine rechallenge was deemed necessary. However, the success of cardiotoxicity prevention with such agents is not well established,^{8 14} and in a prospective study, the addition of verapamil during 5-FU therapy did not reduce the signs of ischaemia compared with patients who received no anti-angina prophylaxis with their chemotherapy treatment.⁴ In regards to alternate pharmacological choices, there are two available 5-FU derivatives: capecitabine and S1. S1 is an interesting oral drug mainly used in Japan, which combines oral fluoropyrimidine (tegafur), a dihydropyrimidine dehydrogenase inhibitor (gimeracil) and oterasil. It is not currently FDA approved in the USA and only recently was approved in Europe. Both 5-FU derivatives have different side effect profiles due to their distinct mechanisms of action. In patients with metastatic CRC treated with S1 in Japan, no cardiotoxicity was noted in the side effect profile, and this drug could offer an alternative to intravenous 5-FU in the metastatic and adjuvant settings in terms of efficacy as well.^{15 16} Given that most studies were performed in Asia, these results need to be further confirmed in non-Asian populations.

Learning points

- There is a paucity of literature in regards to protocols for patients with advanced colorectal cancer who experience cardiotoxic reactions to the gold standard treatment 5-fluorouracil (5-FU) and subsequent reactions to even suboptimal doses of its prodrug capecitabine.
- Attempting capecitabine retrial after cardiotoxic events—even at suboptimal doses—must be chosen on a patient-by-patient basis and should only move forward with patient informed consent after extensive conversations about the likely risks of administering or withholding treatment.
- Novel treatment regimens should be undertaken after a thorough literature review, and then if started under the correct circumstances, should only continue if the treatment offers the patient a significant survival benefit and quality of life.
- Finally, fluoropyrimidine dose reduction as a part of combination chemotherapy may be a feasible therapeutic option with positive outcomes in patients with advanced colorectal cancer who experience cardiotoxic reactions to both infusional 5-FU and higher doses of capecitabine.

In the case of our patient, having such a young patient with a family, we owed it to her to be aggressive. Her determination could not be ignored in our overall decision as she continued to voice a desire for treatment despite experiencing major cardiac events and constant chest pain. We would not have felt comfortable moving forward with the treatment if not for the literature review and special consideration of the patient herself. Once we found the dose that did not elicit any chest pain, the patient tolerated the treatment extremely well, and her quality of life improved to the point where she was able to continue her normal life activities. Our calculated risk using the suboptimal dose of capecitabine led to a marked reduction in the liver mass, stabilisation of the rectal primary tumour, a sustained drop in tumour markers and a successful surgical resection. After a period of remission off any treatment, her liver lesion progressed. We restarted the individualised doses of combination chemotherapy. She responded again and was able to undergo NanoKnife ablation. She has no evidence of active disease since.

This treatment strategy of reducing the fluoropyrimidine dose along with combination chemotherapy offers a feasible alternative to discontinuing the gold standard treatment even in the face of concerning side effects. However, large studies are needed to establish a therapeutic strategy for patients experiencing cardiac events on fluorouracil.

Contributors JHC: corresponding author, performed literature review and background search, worked as main writer on drafts and their revisions with aid of other authors, gave final approval of submitted version and attests to accuracy and integrity of all aspects of information. DJE: performed literature review, worked on draft and revision editing, utilised clinical experience to aid in imaging review and selection, gave final approval of submitted version and attests to accuracy and integrity of all aspects of information. VF: utilised clinical experience as haematology/oncology fellow to advise on use of novel treatment in relation to standard of care, performed literature review and further research on current state of novel treatments, worked on draft and revision editing, gave final approval of submitted version and attests to accuracy and integrity of all aspects of information. BA: responsible for implementing and recognising novelty of patient treatment, wrote first-hand experience of patient experience throughout patient treatment, obtained patient consent, utilised clinical experience for background information and current state of treatment options, worked on draft and revision editing, gave final approval of submitted version and attests to accuracy and integrity of all aspects of information.

Competing interests None declared.

Patient consent Obtained.

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