REVIEW

Managing 5FU Cardiotoxicity in Colorectal Cancer Treatment

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Abstract: Fluorouracil (5FU) is the backbone chemotherapy agent in the treatment of colorectal cancer (CRC). Cardiotoxicity represents an uncommon but serious side effect of treatment with 5FU. Here, we review the current literature on 5FU-cardiotoxicity in the setting of CRC specifically, with a focus on data from the modern era of combination chemotherapy. Despite decades of study, there is little consensus on risk factors and biomarkers for 5FU-cardiotoxicity, nor how patients with CRC should be managed following a cardiotoxicity event. Given the elevated risk of recurrent cardiotoxicity on rechallenge, the use of alternative regimens that do not contain 5FU is a critical aspect of management. Data on the cardiotoxicity risk and efficacy of non-5FU regimens in CRC are therefore reviewed in detail.

Keywords: fluoropyrimidine, chemotherapy, adverse events, capecitabine, fluorouracil

Introduction

Fluoropyrimidines (FPD), most commonly Fluorouracil (5FU) and its derivative capecitabine, have been the backbone of chemotherapy regimens used to treat colorectal cancer (CRC) for decades.[1,2] FPD-based combinations are the standard of care for palliative treatment of metastatic disease and adjuvant therapy for Stage III disease, while FPD monotherapy is employed for adjuvant treatment of high-risk stage II disease and for metastatic disease in some cases. Cardiotoxicity represents an uncommon but serious side effect of treatment with 5FU. This review will discuss the epidemiology and management of 5FU cardiotoxicity in CRC specifically, with a focus on data from the modern era of combination chemotherapy. Given the elevated risk of recurrent cardiotoxicity on rechallenge, data on the cardiotoxicity risk and efficacy of non-5FU regimens for the treatment of CRC are discussed. Areas of incomplete understanding are highlighted, with suggestions for how they might be addressed in future research.

Manifestations and Pathogenesis

Cardiotoxicity occurs most commonly during the first cycle of treatment,[3,4] but can occur during later cycles as well.[5] The most common cardiac manifestation of 5FU-cardiotoxicity is anginal chest pains; however, other cardiac presentations also occur. A systematic review of 30 studies found chest pain, palpitations, and dyspnea to be the most common symptoms.[6] A large case series of 377 patients also identified angina (45%), and arrhythmias (23%) as the most common presentations, with rare presentations including acute pulmonary edema (5%), cardiac arrest (1.4%), and pericarditis (1.4%).[4] With regard to changes in cardiac investigations, 69% had evidence of ischemic electrocardiogram (ECG) changes, and 12% had abnormal cardiac enzymes.[4] In patients who undergo prolonged ECG monitoring, asymptomatic ST-T changes are common, while other asymptomatic changes such as bradycardia, increased atrial and ventricular premature complexes, and QT-interval prolongation have also been reported.[7–12]

The pathogenesis of 5FU-induced cardiotoxicity is incompletely understood. Multiple mechanisms have been proposed, and it is likely that the impact of 5FU on the cardiovascular system is multifactorial. A systematic review has been published of 26 studies concerning the pathophysiology of 5FU-induced cardiotoxicity.[13] They grouped available evidence into several

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mechanisms, including coronary artery vasospasm, endothelial injury resulting in thrombosis, oxidative stress causing myocardial damage, and impaired oxygen transfer from red blood cells causing ischemia. The evidence for coronary vasospasm is perhaps the most well developed, with data that ranges from in vitro experiments showing vascular smooth muscle cell contraction in response to 5FU,[14] case reports with supportive angiographic findings,[15] and a study which used high-resolution ultrasound to identify brachial artery contractions after 5FU administration, which were blocked by pre-treatment with nitrates.[16] Endothelial damage resulting in thrombosis is likewise supported both by experimental animal data,[17] as well as study using plasma samples from CRC patients being treated with FOLFOX that demonstrated reversible endothelial dysfunction causing a procoagulant state.[18]

Evidence of oxidative stress causing myocardial damage as a mechanism comes from pre-clinical studies, such as increased levels of superoxide anion following 5FU treatment of a rat heart tissue cell line,[19] and decreased levels of antioxidant systems such as sodium oxide dismutase in guinea pigs treated with 5FU.[20] Evidence for 5FU-induced impaired oxygen transfer from red blood cells as a potential cause of ischemia comes from the finding of decreased pO2 and increased deoxyhemoglobin in ex vivo treated erythrocytes, and increased deoxyhemoglobin in blood samples from patients treated with 5FU based on NMR spectroscopy analysis.[21]

Finally, there is evidence from rat studies that 5FU is metabolized by the liver into the known cardiac toxin fluoroacetate via an intermediate metabolite alpha-fluoro-beta-hydroxypropionic acid.[22] A related metabolite, alpha-fluoro-beta-alanine (FBAL), has also been observed to be elevated in a patient who had cardiotoxicity after receiving 5FU as a treatment for metastatic colon cancer.[23] However, another study detected fluoroacetate in the urine of 5FU treated patients whether or not they had cardiotoxicity.[24]

There is little published information concerning the mechanism underlying 5FU-induced arrhythmias. Arrhythmias may be secondary to 5FU-induced ischemia, although ECG changes independently associated with arrhythmias such as QT prolongation, increased QT dispersions, and more frequent premature complexes have also been reported in the absence of evidence of ischemia.[7,12]

Epidemiology

The current data describing the epidemiology of 5FU cardiotoxicity contains significant heterogeneity in terms of study setting, quality, design, and the types of malignancies and 5FU-containing regimens included. A 2013 meta-analysis of studies published from 1978 to 2012 identified rates of symptomatic 5FU cardiotoxicity ranging from 0% to 35%, although the largest studies (>400 patients) reported an incidence between 1.2% and 4.3%.[6] Most studies were observational with a high risk of bias. It is worth noting that even randomized controlled trials suffer from potential bias in reporting 5FU cardiotoxicity, given that patients with prior cardiovascular disease are often excluded from trials, and many did not specifically report on adverse cardiac events.[25] In prospective monitoring studies, the incidence of ECG changes ranged between 6.0% and 44.0%.[6] One study identified pathologically elevated troponin levels in 57% of patients;[26] however, two others reported no change.[7,27]

There are fewer studies which focus on CRC specifically, although these more recent analyses appear to identify a higher rate of cardiotoxicity than the studies reviewed in Polk et al.[6] Three papers described pooled analyses from randomized clinic trials (RCTs). One included 3223 patients with metastatic CRC from 5 RCTs involving 1st line FPD combination chemotherapy identified cardiotoxicity in 255 patients (7.9%).[28] Another pooled 3 RCTs of capecitabine and capecitabine combinations included 1973 patients and had an incidence rate of 5.9%.[29] A pooled analysis of two trials of CAPOX for CRC included 153 patients, identifying an incidence of 6.5%.[3] Several prospective observational studies limited to CRC patients have also been completed. One study of 25 patients identified no echocardiographic changes after a course of adjuvant 5FU and reported a symptomatic cardiotoxicity incidence of 8%.[30] A study of 106 patients with CRC being treated adjuvant FOLFOX4 found that while most patients had a rise in NT-proBNP after administration of chemotherapy (48% of which exceeded the assay reference range), only nine (8.5%) had corresponding cardiac symptoms and ECG changes.[5]

Outcomes

Data on outcomes following 5FU-cardiotoxicity are sparse. Beyond mentions in individual case studies, there is no clear picture of how often cardiotoxicity-related concerns result in presentation to emergency departments, admission to hospital, or admission to a specialized cardiac or intensive care units.

Studies on heart function as an outcome are mixed. A prospective echocardiographic study of 25 patients who received 5FU as adjuvant therapy for colon cancer found no changes at the end of treatment or 6 months after treatment.[30] Another prospective study of 106 patients with colorectal cancer treated with adjuvant FOLFOX4 showed no changes on left ventricular ejection fraction (LVEF).[5] A small prospective study found no changes in systolic or diastolic function in 12 patients treated with 5FU.[7] However, these studies did not specifically address changes in cardiac function in patients who had experienced symptoms of cardiotoxicity. A prospective study of 102 patients treated with 5FU identified 19 patients who developed cardiac toxicity, 2 of whom developed reduced LVEF, which did not recover with time.[11] Another study identified hypokinesia in 9 of 16 patients tested with echocardiography following the onset of cardiac symptoms, which was reversible in some but not all cases.[24]

Death is the outcome with the most available data. In a compilation of data from 377 patients in case reports and case series, the incidence of death in patients experiencing cardiotoxicity was 8%, and 13% of patient re-exposed to 5FU after experiencing cardiotoxicity died.[4] Another retrospective series of 5FU alone or in combination included 301 patients, 60 of which developed symptomatic cardiotoxicity, 9 of which died, for a 15% mortality rate.[31] Results from prospective studies including multiple cancer types are variable, and range from a mortality rate in symptomatic patients from 0% to 28.6%.[24,32–35] Two studies reported cardiotoxicity-related mortality in clinical trials of colon cancer patients. The first was a pooled analysis of two Phase III trials comparing capecitabine vs 5FU.[36] Of 1189 patients, 39 experienced cardiotoxicity, of which 2 died (mortality rate 5.1%). In the second pooled analysis including 153 patients from two trials investigating CAPOX for the treatment of metastatic colorectal cancer, 10 patients experienced cardiotoxicity, of which 2 died (mortality rate 20%).[3]

Risk Factors

Attempts to identify patient-level risk factors predictive of 5FU-cardiotoxicity have not resulted in any reliable measures. Pre-existing cardiac risk factors or a history of cardiovascular disease is not consistently associated with higher rates of 5FU-cardiotoxicity. There are retrospective series which identified association between cardiac risk factors, cardiac disease and 5FU cardiotoxicity,[34,37] although other retrospective and prospective studies report no significant associations.[4,35,38] Increasing age is not clearly associated with increased risk.[28,34,37,39] In fact, one large single centre retrospective series of 4019 patients treated with 5FU actually identified significantly increased incidence in younger patients, who were also significantly less likely to have cardiac risk factors, and less likely to be on cardioprotective medications.[40] In colorectal cancer specifically no association was seen between cardiac disease or risk factors and the level of NT-proBNP rise after 5FU,[5] or with cardiac risk factors or cardiac disease in two separate pooled clinical trial analyses.[3,28]

In regard to the risks associated with specific regimens, longer infusions of 5FU appear to be associated with a higher incidence of cardiotoxicity than shorter infusions (6.3 vs 2.2% in one study[33]). Older studies of bolus 5FU regimens reported rates between 1.6% and 3%.[37,41] Dose does not seem to be related to cardiotoxicity.[34] Capecitabine appears to be associated with a similar incidence of cardiotoxicity to 5FU, with reported incidence ranging from 3% to 5.5%.[29,33,36]

Combination of 5FU with other chemotherapy agents represents another potential risk factor. Individual studies involving multiple cancer types have identified an increased risk of cardiotoxicity for 5FU in combination with etoposide[34] and cisplatin.[31] In CRC specifically, FPD combination regimens appear to be associated with increased cardiotoxicity. An incidence of 6.5% was identified in patients treated with CAPOX across two trials.[3] A pooled analysis of 5 CRC trials included patients treated with FOLFOX or FOLFIRI in combination with either bevacizumab and panitumumab.[28] On multivariate regression analysis, only bevacizumab and panitumumab regimens were predictive of cardiotoxicity. Bevacizumab-containing regimens were significantly more likely to be associated with any cardiac toxicity (9.8% vs 6.1%), specifically ischemic events (2.9% vs 1%). Panitumumab-containing regimens were significantly more likely to be associated with any cardiac toxicity (11.5% vs 6.6%), and specifically arrhythmias (7.5% vs 3.7%).[28] Another pooled analysis of 3 clinical trials of capecitabine and capecitabine combination regimens in CRC found that CAPOX + bevacizumab was associated with the highest rate of cardiotoxicity (12% vs 4% for capecitabine monotherapy), with the caveat the CAPOX + bevacizumab + cetuximab had a cardiotoxicity incidence of 7%.[29] It is not clear whether the increased incidence of cardiotoxicity with the addition of biologics is synergistic or additive, given that

these agents are associated independently with cardiac adverse events. Cetuximab and panitumumab have previously been associated with increased risk of new-onset heart failure.[42] Panitumumab is also known to induce electrolyte disturbances, in particular hypomagnesemia, which may contribute to the increased incidence of arrhythmias.[43] Bevacizumab, along with other anti-VEGF agents, has likewise been independently associated with heart failure, myocardial ischemia, and other arterial thromboembolic events in large metanalyses.[44,45]

Data on any potential relationship between dihydropyrimidine dehydrogenase (DPD) polymorphisms and 5FU cardiotoxicity are sparse. A retrospective study of 59 patients with unanticipated toxicity from 5FU found that 19 had DPD deficiency, only 1 of which had cardiotoxicity.[46]

Primary Prevention

Efforts towards primary prevention of 5FU-cardiotoxicity are hampered by the lack of consistent data on risk factors for its development. Nevertheless, this issue must be considered by treating clinicians both in routine practice and by those developing clinic trial protocols. A review of clinical trials that involved 5FU or capecitabine from ECOG-ACRIN Cancer Research Group found that pre-existing cardiovascular disease was an exclusion criterion in 13/16 trials.[25] Participants with recent acute coronary syndrome (ACS; unstable angina or myocardial infarction) were excluded in 11 studies, with the definition of "recent" ranging from 3 to 12 months prior to enrollment. Guidelines, such as those from the Canadian Cardiovascular Society (CCS) on the evaluation and management of cardiovascular complications of cancer therapy, make no specific recommendations about deferring treatment with 5FU after ACS.[47]

There are little data on the ability of pre-treatment investigation to predict patients who may develop cardiotoxicity. A small prospective study which enrolled 52 patients treated with capecitabine found that an abnormal echocardiogram at baseline was associated with the development of cardiotoxicity.[48] The significantly higher increase in NT-proBNP following 5FU treatment in patients who went on to develop cardiac toxicity suggests a potential for this test to become a predictive biomarker,[5] although it has not yet been evaluated for this use. Data on the prophylactic use of cardio-protective medications are all in the setting of secondary prevention and are described below. In the absence of robust data, attempts at primary prevention remain empiric, and largely consist of a clinical judgement as to which patients may have a relative contraindication to receiving 5FU.

Secondary Prevention

Rechallenge in patients with 5FU-induced cardiotoxicity appears to carry a significant risk of recurrent cardiac events, with one case series reporting the incidence of recurrence to be 90%.[49] Severe outcomes may also be more common. A review of 377 cases found that 13% of patients who were rechallenged following initial 5FU-related cardiac events died from recurrent toxicity, vs an 8% mortality rate for initial events.[4] Rechallenge must therefore be carefully considered, and a variety of efforts have been made to reduce the incidence of recurrent cardiotoxicity upon rechallenge. One case series of 5 patients reports of secondary prevention of capecitabine-associated chest pain with diltiazem,[50] but a study of primary prevention using this agent in 58 patients being treated with cisplatin and 5FU reported a 12% incidence of cardiotoxicity, similar to the 13% incidence in their chosen historical controls.[51] There are case reports of using nitrates in the secondary prevention setting with mixed outcomes.[52,53] CCS guidelines do not explicitly recommend the use of prophylactic vasodilators.[47]

Dose reduction does not appear to be effective in preventing recurrent toxicity,[4] and in keeping with data that suggests there is no dose-relationship between 5FU and cardiotoxicity.[34] Infusional 5FU is associated with more cardiotoxicity than bolus 5FU, and there is limited evidence that switching from infusional 5FU to a bolus 5FU regimen can prevent recurrent toxicity. This includes a single centre case series that demonstrated no recurrent cardiotoxicity in six patients who were switched from FOLFOX to FLOX, where 5FU is given as a weekly bolus.[54] Given the paucity of data available on rechallenge, decisions on who to rechallenge are empiric. Factors to consider include the severity of the initial event, the intent of treatment (curative vs palliative), and the availability and efficacy of alternative agents with a lower risk of cardiotoxicity.

Cardiotoxicity of Alternative Agents

Given the paucity of reliable data on risk factors, biomarkers, and prophylaxis during rechallenge, the primary means of primary and secondary prevention of 5FU-cardiotoxicity for patients with CRC involves the use of chemotherapy regimens that do not include 5FU. This is especially challenging in the management of patients with CRC, given that 5FU is the backbone of the chemotherapy regimens used in all disease stages. Understanding the risk-benefit profile of any decision to deviate from well established standard regimens requires an understanding of the associated cardiotoxicity risk of the involved chemotherapy agents, and the efficacy of alternative agents relative to 5FU in the treatment of CRC.

There are case reports of successful treatment with capecitabine following 5FU-related cardiotoxicity,[55,56] but more robust evidence is lacking. Given what appears to be an equivalent risk of cardiotoxicity with capecitabine as an initial therapy described above, in the absence of more robust data supporting safety switching from 5FU to capecitabine, it cannot be recommended if there are any viable alternatives. Switching to either an alternative FPD with a lower risk of cardiotoxicity, or a non-fluoropyrimidine containing regimen, represent safer options from a cardiotoxicity perspective.

UFT is a combination of fluorouracil prodrug ftorafur and uracil, which serves to inhibit fluorouracil degradation. Reported cardiotoxicity across multiple studies is less than 1%.[57–60] However there are no prospective or large retrospective series supporting its use following 5FU cardiotoxicity, and a death secondary to congestive heart failure has been observed following this approach.[38] Availability can also be an issue; UFT is not approved for use in North America.

S1 is another oral fluoropyrimidine that contains ftorafur, in combination gimeracil and oteracil. Gimeracil is a DPD inhibitor, which prevents the breakdown of fluorouracil into FBAL,[61] which as described above is implicated in 5FU-induced cardiotoxicity. Remarkably, there are no reports of cardiotoxicity following treatment with S1.[62–64] There are case reports of successful use of S1 after 5FU-induced cardiotoxicity,[23] but no larger case series. Availability is also limited to some Asian and European countries.

Trifluridine/tipiracil (TAS-102) contains an oral fluoropyrimidine (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil). Among the 534 patients treated with trifluridine/tipiracil in the phase III trial supporting its use in metastatic colorectal cancer, only 2 patients developed cardiac ischemia (0.37%), vs 1 of 266 patients treated with placebo (0.38%).[65] An abstract describing a systematic review and meta-analysis of 1877 patients treated in 4 trials has been published, and found no increase in cardiac events relative to placebo.[66] There are no available reports of treatment with Trifluridine/tipiracil after 5FU-induced cardiotoxicity.

Raltitrexed is an antimetabolite chemotherapy agent that functions through inhibition of thymidylate synthase. A systematic review of cardiotoxicity in patients treated with raltitrexed included four pivotal trials in CRC and pancreatic cancer, with no reported cardiotoxicity.[67] In the same study, a retrospective review of raltitrexed included 111 patients where raltitrexed was used first line due to elevated cardiovascular risk, or second line after FPD-related cardiotoxicity. It found a cardiovascular event rate of 4.5% (5/111 patients) in a presumably high-risk population.[67] Four of those patients died, apparently of events related to disease progression, although more details were lacking. In contrast, another retrospective review of raltitrexed use following FPD-cardiotoxicity included 42 patients and reported no cardiac events.[68] Regardless of the potential reduction in cardiotoxicity, caution is warranted with raltitrexed given that treatment-related mortality was as high as 6% in some clinical trials.[69]

Efficacy of Alternative Regimens in CRC

While switching to a non-FPD containing regimen or an alternative FPD with a lower risk of cardiotoxicity likely represent safer options from a cardiotoxicity perspective, a full picture of the risk/benefit profile of this strategy requires an understanding of their relative efficacy in the treatment of CRC patients.

Given the curative intent of treatment, cardiotoxicity and resulting modifications to adjuvant regimens for resected CRC are of particular concern. Results of Phase III studies of alternative agents are shown in Table 1. Two large, randomized studies have shown equivalent results with UFT and leucovorin (LV) in comparison to bolus 5FU/LV in the adjuvant treatment of CRC.[70,71] Data on adjuvant S1 in CRC are mixed. Adjuvant S1 was found to be non-inferior to UFT in the treatment of Stage III CRC patients in a randomized phase III study.[72] However, S1 was not found to be non-inferior to capecitabine in a randomised Phase 3 trial of adjuvant therapy for stage III CRC, with capecitabine showing

Table 1 Summary of Phase III Studies of FPD Alternatives for Adjuvant Treatment of CRC

Regimen	Comparator	Primary Outcome	OS at 5 Years	DFS at 5 Years	DFS at 3 Years	Reference
UFT	5FU/LV bolus	OS. HR 1.014; P = 0.90.	78.5	67.0	–	[70]
UFT	5FU/LV bolus	DFS. HR 1.016; non-inferiority P = 0.0236.	82.4	73.6	–	[71]
S1	UFT	DFS at 3 years. HR 0.85; non-inferiority P < 0.001.	–	–	72.5	[72]
S1	Capecitabine	DFS at 3 years. HR 1.23, non-inferiority P = 0.46.	–	–	77.9	[73]
Raltitrexed	Bolus 5FU/LV	Relapse-free survival. HR 1.16.	61.9%	–	–	[83]

superior disease-free survival at an interim analysis.[73] There are no Phase III studies incorporating oxaliplatin in combination with an alternative agent to replace 5FU. As rates of cardiotoxicity are apparently higher with infusional 5FU, switching to a bolus 5FU bolus with evidence in the adjuvant setting is another option. For stage III patients for whom an oxaliplatin-containing adjuvant regimen is indicated, the use of FLOX represents a bolus-5FU alternative. Adjuvant FLOX appears to have similar efficacy to FOLFOX, albeit with a different toxicity profile.[74] There are reports of the use of FLOX following cardiotoxicity with adjuvant infusion 5FU, with no recurrent cardiac events.[75] For patient with Stage II CRC, the Roswell Park regimen is an established bolus 5FU-monotherapy alternative.[76]

There are more options available in the metastatic setting, with relevant Phase III studies summarized in Table 2 (first-line studies) and Table 3 (second line and later studies). UFT appeared comparable to bolus 5FU in the metastatic setting.[77] UFT combinations with oxaliplatin and irinotecan likewise appear comparable to FOLFOX and FOLFIRI in the treatment of mCRC, although data is limited to Phase II studies.[78]

Data supporting single agent S1 in the treatment of metastatic CRC come from two single-arm studies showing evidence of objective responses.[79,80] S1 and oxaliplatin were found to be non-inferior to capecitabine/oxaliplatin in a phase III study of patients with advanced CRC.[81] S1 and irinotecan was likewise found to be non-inferior to FOLFIRI in a randomized phase II/III study of mCRC in the second line.[82]

A phase III trial comparing raltitrexed to bolus 5FU in the adjuvant treatment of stage III CRC failed to show non-inferiority after early termination, with raltitrexed associated with a lower relapse free survival and high toxicity in the setting significant protocol deviations related to adjustment for creatinine clearance.[83] Two phase III studies comparing raltitrexed to 5FU in advanced CRC patients showed similar response rates, although with one showing a significantly shorter PFS for raltitrexed.[84,85] Another phase III study in the metastatic setting found raltitrexed to have a similar overall survival to the de Gramont regimen, but significantly worse quality of life and an increase in treatment-related deaths.[86] Raltitrexed has been studied in combination with both oxaliplatin and irinotecan. In a Phase II study described in an abstract only, TOMOX was compared to FOLFOX in the first-line treatment of metastatic CRC. There were no significant differences in response rate, time to progression, or overall survival.[87] Two single arm trials of second-line treatment with TOMOX after progression on 5–FU likewise showed evidence of activity.[88,89] In addition, a single centre retrospective case series describing use of TOMOX after discontinuation of 5FU-based treatment due to severe toxicity in 44 patients found a three year relapse free of 70.8% and overall survival of 83.6%.[90] The combination of raltitrexed and irinotecan has also been investigated in the metastatic setting. In a Phase II trial comparing raltitrexed and irinotecan with TOMOX, there were no significant differences in efficacy measures between the regimens, with response rates of 46% and 34%, respectively.[91] Further data on raltitrexed + irinotecan comes from two single arm Phase II studies in the first-line setting, with comparable results.[92,93] Raltitrexed + irinotecan was also shown to be active after progression on 5FU, with a response rate of 15.4% in a single arm study.[94]

Table 2 Summary of Phase III Studies of FPD Alternatives for First-Line Treatment of Metastatic CRC

Regimen	Comparator	Primary Outcome	ORR (%)	PFS (Months)	Overall Survival (Months)	Reference
UFT	Bolus 5FU/LV	OS. HR 0.964; P=0.630.	11.7	3.5	12.4	[77]
UFT	Bolus 5FU/LV	PFS. Logrank P=0.591.	10.5	3.4	12.2	[114]
Raltitrexed	Bolus 5FU/LV	PFS. HR 1.15; P=0.197.	19	3.9	10.9	[84]
Raltitrexed	Bolus 5FU/LV	PFS. HR 1.08; P=0.44.	19.3	4.7	10.3	[85]
Raltitrexed	Infusional 5FU/LV	OS. HR 0.99; P=0.94.	18	4.8	8.7	[86]
Irinotecan	5FU/LV and 5FU/LV/ irinotecan	PFS. Statistics not shown for irinotecan vs 5FU/LV.	18	4.3	12	[99]
Irinotecan + oxaliplatin (IROX)	Irinotecan + 5FU/LV	PFS. HR 1.14; P=0.178.	41	7.2	19	[104]
S1 and oxaliplatin	Capecitabine + oxaliplatin	PFS. HR 0.809, non-inferiority P = 0.087.	48.9	7.1	20.9	[81]

Table 3 Summary of Phase III Studies of FPD Alternatives in Second Line or Later Treatment of Metastatic CRC

Regimen	Comparator	Primary Outcome	ORR (%)	PFS (Months)	Overall Survival (Months)	Reference
Irinotecan (after 5FU)	BSC	OS. Logrank P=0.0001.	–	–	9.2	[100,104]
Irinotecan (after 5FU)	Infusional 5FU	OS. Logrank P=0.035.	–	4.2	10.8	[101]
Irinotecan + cetuximab (after irinotecan-based regimen)	Cetuximab	ORR. P=0.007.	22.9	4.1	8.6	[102]
Irinotecan + cetixumab (after FOLFOX)	Irinotecan	OS. HR 0.975; P=0.71.	16.4	4.0	10.7	[103]
IROX (after 5FU)	Irinotecan	OS. HR 0.78; P=0.0072.	22	5.3	13.4	[105]
S1 + irinotecan (after 5FU ± oxaliplatin)	FOLFIRI	PFS. HR 1.077, non-inferiority P = 0.039.	18.8	5.8	19.5	[82]
TAS-102 (3rd line, after 5FU, oxaliplatin, irinotecan)	Placebo	OS. HR 0.68 P<0.001.	1.6	2.0	7.1	[65]

Trifluridine/tipiracil was initially evaluated in patients with metastatic CRC who had progressed on standard chemotherapy regimens include, making it difficult to compare the efficacy of trifluridine/tipiracil and traditional FPDs. Trifluridine/tipiracil has a demonstrated overall survival benefit vs placebo in patients who have progression on 5FU, oxaliplatin, and irinotecan.[65] A randomized Phase II trial in metastatic CRC patient not eligible for standard first-

line 5FU-doublet chemotherapy compared trifluridine/tipiracil plus bevacizumab and capecitabine plus bevacizumab, and found comparable efficacy.[95,96] Randomized Phase III studies in the first and second line are ongoing.[97,98]

Irinotecan is active as a single agent in metastatic CRC. In the first-line setting, outcomes are similar to 5FU/LV, although inferior to a 5FU/LV + irinotecan regimen.[99] In two second-line Phase III studies, irinotecan has activity after progression on 5FU.[100,101] Two Phase III studies also demonstrated evidence of activity for second-line irinotecan + cetuximab after progression on either FOLFOX or an irinotecan-5FU regimen,[102,103] although overall survival results are comparable to irinotecan as a single agent. Irinotecan + oxaliplatin (IROX) is another option with Phase III data. First-line IROX had comparable results to a first-line regimen of infusional 5FU, leucovorin, and irinotecan.[104] In the second line after progression on 5FU, IROX showed significant improvement of OS relative to single agent irinotecan.[105]

Treatment of Cardiotoxicity

There are little data on which to guide the acute management or work-up of 5FU-related cardiotoxicity, and suggested strategies are therefore extrapolated from other settings, and primarily reflect expert opinion. Unfortunately, many cardio-oncology guidelines from major organizations contain little to no information on 5FU-related cardiotoxicity.[106–108] CCS guidelines present the most comprehensive approach.[47] If symptoms of ischemia occur during a 5FU-infusion, the infusion should be stopped immediately. Symptoms should be treated with nitroglycerin, as well as opioids if needed. The initial work-up should include an ECG and troponin levels, and patient should be placed on cardiac monitors. If the troponin is elevated, patients should be managed using established algorithms for ACS. If there is no evidence for ACS, elective work-up for underlying coronary artery disease can be considered. Given the lack of specific biomarkers, the diagnosis of 5-FU cardiotoxicity requires a plausible temporal relationship between drug and symptoms. If a diagnosis of 5FU-cardiotoxicity is apparent, rechallenge should only be considered if no alternative treatments are available. Rechallenge should be performed in a monitored setting, include dose reduction or transition to a bolus regimen, consideration made of prophylaxis with nitrates or calcium channel blockers despite the mixed evidence.[47]

Other individual researchers have proposed algorithms for work-up. One suggests work-up stratified by the patient's underlying risk for coronary artery disease (CAD).[109] Lower risk patients would undergo non-invasive testing such as CT coronary angiogram, while high-risk patient would undergo coronary angiogram to attempt to identify a contributing coronary lesion. No finding of significant CAD supports a diagnosis of 5FU-cardiotoxicity, and alternative treatment strategies would be pursued. For patients with significant CAD that might contribute to symptoms, revascularization may be followed by cautious rechallenge with close monitoring and prophylaxis with vasodilators.[109]

Uridine triacetate was developed as an antidote for fluoropyrimidine overdose. Uridine triacetate is a prodrug, which is metabolized into uridine and competes with incorporation of 5FU into RNA, attenuating toxicity.[110] A summary of two single arm, open label trials using uridine triacetate to treat 5FU overdose in 135 patients, primarily due to dose miscalculations and pump errors, has been published.[111] They found that the survival rate in patients treated with uridine triacetate was 96%, vs 16% for a set of historical controls. This included two patients who presented with symptoms of cardiac toxicity and experienced rapid reversal of symptoms. There is further evidence for efficacy in the setting of cardiotoxicity from case reports.[112] It was approved by the FDA for treatment of severe FPD toxicity in 2015.[113] Further studies will be needed to determine whether uridine triacetate can be incorporated routinely into the management of patients' 5FU-cardiotoxicity.

Summary

Cardiotoxicity is a well-known toxicity of 5FU. However, despite many years of study of this long-recognized problem, we still do not have a clear picture of risk factors for its development, predictive biomarkers, or a clear approach to primary or secondary prevention. This situation is especially problematic in the setting of CRC, where 5FU and capecitabine are key components of first-line treatment options. The lack of large prospective studies comparing alternative regimens to modern 5FU-combination chemotherapy is therefore another major obstacle in the management of 5FU-cardiotoxicity in CRC. Unfortunately, the risk of cardiotoxicity appears higher with the combination regimens used in CRC, in particular those that incorporate bevacizumab and panitumumab. 5FU-cardiotoxicity therefore remains

an issue that should be prioritized for further study. We believe that rigorous collection of information on cardiotoxicity and patient-level cardiac risk factors should be a part of every CRC clinical trial that incorporates FPDs, even when they are not the experimental agent. Prospective studies to evaluate predictive biomarkers, including modern cardiac imaging tests, are needed. Strategies such as prophylaxis with cardioprotective medications during rechallenge also require more extensive validation. Data on alternative adjuvant regimens for Stage III CRC are lacking. In the metastatic setting combinations of S1 and oxaliplatin or irinotecan appear comparable to their 5FU counterparts based on data from RCTs, and the IROX regimen represents a means to expose patients to two highly active agents. However, availability of S1, and a lack of data on combining any of these regiments with biologics, gives an incomplete picture of their ability to replace treatments including 5FU. Management of 5FU-cardiotoxicity in CRC therefore remains an open problem.

Abbreviations

5FU, fluorouracil; ACS, acute coronary syndrome; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CRC, colorectal cancer; DPD, dihydropyrimidine dehydrogenase; ECG, electrocardiogram; FBAL, alpha-fluoro-beta-alanine; FPD, fluoropyrimidine; LV, leucovorin; LVEF, left ventricular ejection fraction; RCT, randomized control trial.

Disclosure

MA reports no conflicts of interest related to the topic of this work.

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