Original Study

Efficacy and Cardiotoxic Safety Profile of Raltitrexed in Fluoropyrimidines-Pretreated or High-Risk Cardiac Patients With GI Malignancies: Large Single-Center Experience

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Abstract

In this large cohort of gastrointestinal cancer patients with high cardiac risk factors or those with previous fluorouracil-based cardiac toxicities, we demonstrated the safety and efficacy of raltitrexed-based chemotherapy in patients. This study will offer reassurance to physicians who may encounter a clinically challenging situation.

Background: Gastrointestinal (GI) cancer patients may not be considered for therapy with fluoropyrimidines (FPs) because of previous cardiovascular (CV) toxicity or preexisting risk factors; such patients may benefit from raltitrexed-based therapy. **Patients and Methods:** Patient, tumor, and treatment characteristics, as well as clinical outcomes of all consecutively treated patients with raltitrexed at the Royal Marsden Hospital between October 1998 and July 2011 were examined. GI cancer patients who developed CV toxicity as a result of FPs and those with significant CV risk factors receiving raltitrexed were included in this analysis. **Results:** A total of 247 patients (155 and 92 with CV FP-related CV toxicities and significant CV risk factors, respectively) treated with raltitrexed alone or in combination were examined after a median follow-up of 47.1 months. CV toxicity profiles of patients receiving capecitabine (n = 110) and 5-fluorouracil (n = 45) were largely similar. Of raltitrexed-treated patients, 13 (5%) experienced CV toxicities and 1 (< 0.1%) died as a result of myocardial infarction. The median progression-free survival (PFS) and overall survival (OS) were 36.0 months (95% confidence interval [CI], 26.5-48.6) and 44.3 months (95% CI, 33.1-56.8), respectively. The 5-year survival for early stage GI malignancies (n = 140) was 62.0% (95% CI, 50.1-71.9). Median PFS and OS were not reached in this group (interquartile range = 38.4 months to NR); median PFS and OS for advanced GI malignancies (n = 107) were 18.8 (95% CI, 11.9-25.7) and 23.7 months (95% CI, 17.0-26.9), respectively. **Conclusion:** A raltitrexed-based regimen is well-tolerated therapy with comparable efficacy to FPs in patients with GI malignancies with significant CV toxicities or risk factors.

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Introduction

Fluoropyrimidines (FPs), including 5-fluorouracil (5-FU) and capecitabine, are the backbone of chemotherapy regimens for many cancers, including gastrointestinal (GI), breast, and head and neck malignancies.[1] FPs principally act by inhibiting thymidylate synthase enzyme causing depletion of thymidine, which is necessary for DNA synthesis.[2] These agents are the mainstay of cytotoxic chemotherapy, either alone or in combination, both in early stage and metastatic GI cancers.[3-6]

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The common toxicities associated with FPs such as oral mucositis, diarrhea, and hand–foot syndrome are reasonably well managed in most patients; however, up to 1.6% to 12.5% of patients may experience overt cardiac toxicity.[7] One study measured a marker of left ventricular ejection fraction—N-terminal probrain natriuretic peptide—in patients treated with 5-FU and demonstrated elevated brain natriuretic peptide levels in 29% of patients, suggesting subclinical cardiac toxicity of FPs with unknown late consequences.[8] The likely mechanisms for cardiotoxicity are dose- and schedule-dependent coronary vasospasm and damage at the cellular level in red blood cells, myocardial cells, and endothelial cells mainly driven by reactive oxygen species.[9-11] Coronary artery spasm causing angina-like symptoms is the most widely reported symptomatic cardiac toxicity of FPs.[12,13] More serious cardiac toxicities such as myocardial infarction, major arrhythmias, heart failure, and pericarditis have also been reported.[12,13]

Preexisting heart and renal disease are established factors for developing cardiac toxicity while receiving FP treatment.[7] Managing the adverse events (AEs) by discontinuing the treatment is possible, but premature chemotherapy discontinuation may compromise the desired oncologic outcomes. Rechallenging with the same therapy is not always possible because cardiac toxicity may recur in 20% to 100% of cases,[14] with fatal outcome in as many as 13% of patients.[13] Therefore, patients with cardiac toxicity who are receiving a FP-based regimen have few treatment options.

Substitution of FPs with raltitrexed, a folate analog with inhibitory thymidylate synthase enzyme activity, is an alternative treatment strategy for patients who experienced FP-related cardiac AEs. Raltitrexed demonstrated equal efficacy compared to 5-FU in studies involving patients with metastatic colorectal cancer[15-17]; however, the use of this drug in the clinic is often limited because of increased mortality reported in a large clinical trial.[18] It is noteworthy that frequent protocol violations were reported in this trial because of a lack of appropriate dose adjustments when creatinine clearance dropped, which may have resulted in high mortality.[18]

Patients with known cardiovascular (CV) disease are more likely to be prone to FP-related cardiac AEs.[7] We hypothesized that patients with a significant cardiac history might be spared from cardiac symptoms and potentially severe complications by up-front treatment with single-agent raltitrexed or with another appropriate combinations. At the Royal Marsden Hospital, patients with significant CV disorders and those who experienced 5-FU/capecitabine-induced cardiac AEs receive a raltitrexed-containing chemotherapy regimen instead of rechallenging with FPs. The data on safety and efficacy of such a substitution strategy are few, and apart from some recent retrospective studies with small patient numbers,[12,19] the available clinical information is largely based on physicians' anecdotal experiences.

The current study examined the presentation of 5-FU/capecitabine-induced cardiac AEs as well as the safety and efficacy of a raltitrexed substitution strategy in patients who developed symptoms while receiving therapy with FPs and in patients with significant underlying CV conditions who receive up-front raltitrexed-containing regimens.

Patients and Methods

Study Design. This retrospective study included all patients consecutively treated with raltitrexed at the Royal Marsden Hospital from October 1998 to July 2011. Only patients who had confirmed histologic diagnosis of any GI malignancies and those who were treated with raltitrexed as a single agent or in combination because of high cardiac risks or because of CV complications from FPs were included. Patients were divided into 2 groups: those who were switched to raltitrexed as a result of CV toxicity from FPs, and those who received raltitrexed up front as a result of previous CV risk factors. Electronic patient records were reviewed. The clinicopathologic parameters prospectively collected for this study included age, gender, site of origin of primary tumor, histologic subtype, details of chemotherapy regimens, therapeutic responses, reasons for raltitrexed use, cardiac toxicity during and 4 weeks after treatment, and timings of toxicities associated with raltitrexed. The study was approved by the institute's research ethics committee.

Patient Follow-up and Response Evaluation

Surveillance strategy for colorectal cancer patients with no metastatic disease at our institute included follow-up assessments once every 3 months in year 1, once every 6 months in years 2 and 3, and annual follow-up for years 4 and 5, with a carcinoembryonic antigen (CEA) test performed at each visit. In addition, annual computed tomographic (CT) scans were performed for the first 3 years, and routine colonoscopies were performed every 2 to 3 years. Positron emission tomography scan was not routinely performed in these patients. For patients who underwent localized therapeutic options with curative intent after being diagnosed with oligometastatic disease, the surveillance strategy included follow-up with CEA once every 3 months during year 1, once every 6 months during years 2 to 5, and annually during years 6 and 7, with CEA performed at each visit. CT scans were performed every 6 months for years 1 and 2, followed by annual CT scans during years 3 to 5. Colonoscopies were performed as per the routine follow-up scheme described above. Patients with other GI tumors were monitored once every 3 months in year 1, once every 6 months in years 2 and 3, and annually in years 4 and 5; CEA and CA19-9 were checked at each,visit but CT scan was only performed when clinically indicated.[20]

Baseline tumor measurements in advanced metastatic disease patients were performed within 4 weeks before cycle 1, day 1. Tumor measurements were repeated every 12 weeks while receiving treatment using the Response Evaluation Criteria in Solid Tumors version 1.0. Tumor responses were confirmed prospectively by a radiologist. Toxicity data were collected as originally recorded in the electronic medical records. In all patients included in the present analysis, toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 2.0 or 3.0. Survival data were obtained from the hospital electronic medical record, and when necessary by contacting the general practitioner or referring institution.

Statistical Analysis

Overall survival (OS) was defined as the interval between diagnosis date and either the date of death or censored at the date of last

follow-up (if death was not observed during the follow-up period). For patients with evaluable data, progression-free survival (PFS) was defined by the time elapsed between diagnosis date until radiologic progression or disease-related death (which ever occurred first); if no evidence of progression was documented at the last follow-up, PFS was censored at the date of last follow-up.

Categorization of numeric variables was undertaken on the basis of considerations of the standard reference values (normal range vs. low/elevated) or according to median values. Estimates of median PFS, OS, and 95% confidence interval (CI) were determined by the Kaplan-Meier method, and Cox regression was used to compare the survival rates and to produce hazard ratios (HR) along with 95% CIs.

Results

Patient Characteristics

Two hundred forty-seven patients (72.5% women; mean age, 65.5 years; range, 31-88 years) were treated with raltitrexed during the study time period at the GI unit of the Royal Marsden Hospital. Colon (46.1%), rectum (21%), adenocarcinoma esophagus (14.6%), squamous-cell carcinoma of the esophagus (8%), and gastric cancers (7.7%) were the most common cancers in the examined group (Table 1 and Supplemental Table 1). Of the 247 patients who fulfilled the study's inclusion criteria, 155 had developed cardiac toxicities while receiving 5-FU or capecitabine therapy, and 92 patients had a high cardiac risk, as assessed according to their physician, and thus were treated with a raltitrexed-containing regimen to avoid 5-FU/capecitabine-associated cardiac toxicity (Supplemental Table 2).

Presentation of Cardiac Toxicity While Receiving 5-FU/Capecitabine-Containing Chemotherapy

A total of 155 patients received raltitrexed after they had developed cardiac 5-FU/capecitabine-induced cardiac AEs. Cardiac complications started during the first treatment cycle in 70% of these patients (Table 2). The median time from starting 5-FU or capecitabine therapy to the onset of cardiac symptoms was 6 days (range, 1-63 days) (Figure 1). The most common AE was angina (86% of patients). Seven patients experienced myocardial infarction. There was no difference in the type or timing between AEs that occurred while receiving 5-FU or capecitabine. Nine patients underwent coronary angiography, and 1 patient underwent a thallium scan shortly after experiencing angina episodes. One patient was found to have a tight left anterior descending artery and a critically tight circumflex artery on angiography, which required stenting. The remaining 8 patients had no detectable coronary abnormalities. These results are consistent with previous reports that cardiac toxicities with thymidylate synthase inhibitors frequently occur despite normal coronary blood vessels.[7]

Raltitrexed Treatment Dosage

The standard raltitrexed dose of 3 mg/m^2 was administered as a 15-minute infusion in 80 patients (32%). Fifty-five patients (22%) received reduced dose (range, 1.3-2.8 mg/m^2) for one of the following reasons: thrombocytopenia (n = 2), renal impairment (n = 13), pyrexia (n = 1), neutropenic sepsis (n = 2), diarrhea (n = 2), tiredness (n = 1), and reason not specified (n = 34). The remaining patients (n = 108, 44%) received higher doses within a range of 3.10 to 6.60 mg/m^2. The records of 4 patients did not specify the dose.

Table 1 Baseline Patient Characteristics

Characteristic	Value
All	247 (100)
5-Fluorouracil	45 (18.2)
Capecitabine	110 (44.5)
Cardiovascular risk factors	92 (37.3)
Age at study entry (years), median (range)	67 (31-88)
Gender	
Female	179 (72.5%)
Male	68 (27.5%)
Tumor Type	
Upper GI	75 (30.4)
Gastric	19 (7.7)
Gastro-esophageal	4 (1.6)
Esophageal	52 (21.1)
Lower GI	162 (65.6)
Anal	3 (1.2)
Colorectal	159 (64.4)
Miscellaneous	10 (4.0)
Cecal	7 (2.8)
Cholangiocarcinoma	1 (< 0.1)
Neuroendocrine	1 (< 0.1)
Unknown origin	1 (< 0.1)
Intent of Chemotherapy	
Neoadjuvant	22 (8.9)
Neoadjuvant + radiochemotherapy	29 (11.7)
Radiochemotherapy	5 (2)
Adjuvant	84 (34)
Palliative chemotherapy	107 (43.3)
Staging	
All early stage	140 (56.7)
Upper GI	37 (15.0)
Lower GI	101 (40.9)
Miscellaneous	2 (0.8)
All advanced metastatic	107 (43.3)
Upper GI	38 (15.4)
Lower GI	61 (24.7)
Miscellaneous	8 (3.2)

Data are presented as n (%) unless otherwise indicated.
Abbreviation: GI = gastrointestinal.

Safety of Substituting 5-FU or Capecitabine With Raltitrexed in Patients With Cardiac Toxicities

Of the 247 patients, 31% and 68% received single-agent raltitrexed therapy and raltitrexed combination chemotherapy, respectively. (Data were not available for 2 patients.) The 155 patients whose treatment regimen was switched to raltitrexed because of cardiac toxicity while receiving 5-FU/capecitabine subsequently received a median number of 5 cycles of raltitrexed treatment (range, 1-8 cycles). The remaining 92 patients with preexisting CV conditions received a median of 6 cycles (range, 1-11 cycles). A total of 80.5%

Table 2 Presentation and Timing of Cardiac Toxicity Associated With 5-Fluorouracil and Capecitabine Treatment

Characteristic	Total (N = 155)	5-Fluorouracil (N = 45)	Capecitabine (N = 110)
Cardiac Toxicity			
Angina	133 (85.8)	37 (82.2)	96 (87.3)
Angina + palpitations	3 (1.9)	0	3 (2.7)
Angina + arrhythmia	1 (< 0.1)	0	1 (< 0.1)
Left ventricular hypertrophy	1 (< 0.1)	0	1 (< 0.1)
Palpitations	3 (1.9)	1 (2.2)	2 (1.8)
Arrhythmia	3 (1.9)	1 (2.2)	2 (1.8)
Atrial flutter	2 (1.3)	2 (4.4)	0
Myocardial infarction	7 (4.5)	4 (8.9)	3 (2.7)
Ventricular flutter	2 (1.3)	0	2 (1.8)
Treatment Cycle			
After first cycle	93 (60.0)	18 (40.0)	75 (68.2)
After second cycle	32 (20.6)	15 (33.3)	17 (15.4)
After third and subsequent cycles/ other	30 (19.4)	12 (26.7)	18 (16.4)
Days After Starting Drug Administration			
Median (range)	6 (1-63)	5 (1-60)	6 (1-63)
No. of patients with missing data	49 (31.6)	15 (33.3)	34 (30.9)

Data are presented as n (%) unless otherwise indicated.

and 73% of patients with FP-related cardiotoxicities and preexisting CV conditions, respectively, received at least one standard dose of raltitrexed (3 mg/m^2), while the remaining patients received lower raltitrexed doses because of renal impairment or general frailty, or at their physician's discretion.

A total of 13 patients (5%) developed cardiac toxicities while receiving raltitrexed-based chemotherapy (Table 3); of these, 4 received single-agent treatment and 9 received combination chemotherapy. Three patients had arrhythmias and palpitations, and one patient had angina-like symptoms. All of these toxicities were graded as mild to moderate, and these patients continued chemotherapy without delay or dose reduction. Two patients in the high-risk CV risk group developed a myocardial infarction, one of which was fatal. The total CV mortality was 0.004% (1/247) in the whole group. This patient was a 59-year-old man with a history of ischemic heart disease and heart failure who experienced myocardial infarction after 2 cycles of raltitrexed (2.6 mg/m^2) and carboplatin combination.

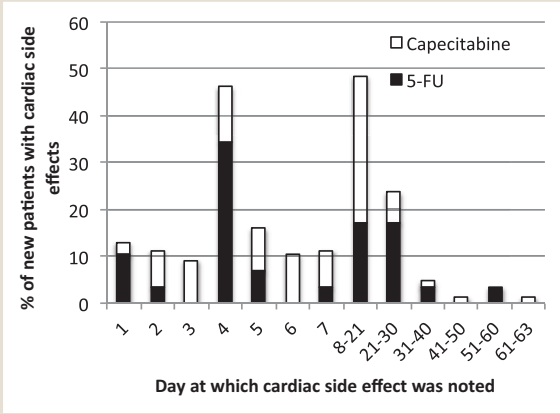
Efficacy of Substituting 5-FU/Capecitabine With Raltitrexed

The median PFS and OS of all patients in the study were 36.0 (95% CI, 26.5-48.6) and 44.3 months (95% CI, 33.1-56.8), respectively. The 5-year survival for early stage GI malignancies (n = 140) was 62% (95% CI, 50.1-71.9). As expected, 5-year survivals were 73.5% (95% CI, 58.8-83.7) and 17.6% (95% CI, 3.6-40.4) when divided into lower and upper GI malignancies, respectively. Median PFS and OS were not reached in the early stage group (interquartile range = 38.4 months to NR).

The median PFS and OS for all the advanced stage GI cancers were 18.8 months (95% CI, 11.9-25.7) and 23.7 months (95% CI, 17.0-26.9), respectively. Five-year survival was 16.3% (95% CI, 9.5-24.7) for advanced stage GI cancers. Significant differences were noted in the median PFS (HR = 3.7; 95% CI, 2.6-5.3; $P < .001$) and OS (HR = 4.1; 95% CI, 2.8-6.0; $P < .001$) of early and advanced stage GI (Figure 2). Interestingly, significant PFS (HR = 1.9; 95% CI, 1.1-3.2; $P = .02$) and OS (HR = 4.0; 95% CI, 2.4-6.6; $P < .001$) rate differences were also noted, depending on the site (upper vs. lower) of the evaluated cancer. Upper GI cancers had significantly worse outcomes compared to lower GI cancers (Figure 3). Efficacy details for all examined subgroups are provided in Table 4.

There was one death attributed to myocardial infarction after treatment with raltitrexed. Patients were followed up for a median period of 47.1 months (interquartile range = 32.4-65.7 months).

Figure 1 Cardiac AEs After Initiating 5-FU or Capecitabine Therapy



Abbreviations: AE = adverse event; 5-FU = 5-fluorouracil.

Table 3 Cardiac Toxicity Associated With Raltitrexed Treatment

Characteristic	All (N = 247)	5-Fluorouracil/Capecitabine (N = 155)	Cardiovascular Risk Factors (N = 92)
Total no. of patients with cardiac adverse events	13 (5.3%)	8 (5.2%)	5 (5.4%)
Angina	5	3	2
Arrhythmia	3	3	0
Palpitations	2	1	1
Myocardial infarction	2	1	1
Myocardial infarction and death	1	0	1

Discussion

This retrospective study represents what is to our knowledge the largest examination of GI cancer patients with preexisting cardiac risk factors or CV toxicities due to FPs treated with raltitrexed-based therapy. Consistent with previously published literature, these data demonstrate the safety of this approach. The unique and novel aspect of this study is that we present efficacy data of raltitrexed-based therapy in this high-risk patient population encompassing early and advanced upper and lower GI malignancies.

Figure 2 Kaplan-Meier Survival Estimates for (A) Progression-Free Survival and (B) Overall Survival for Early Stage and Advanced Stage Gastrointestinal Malignancies

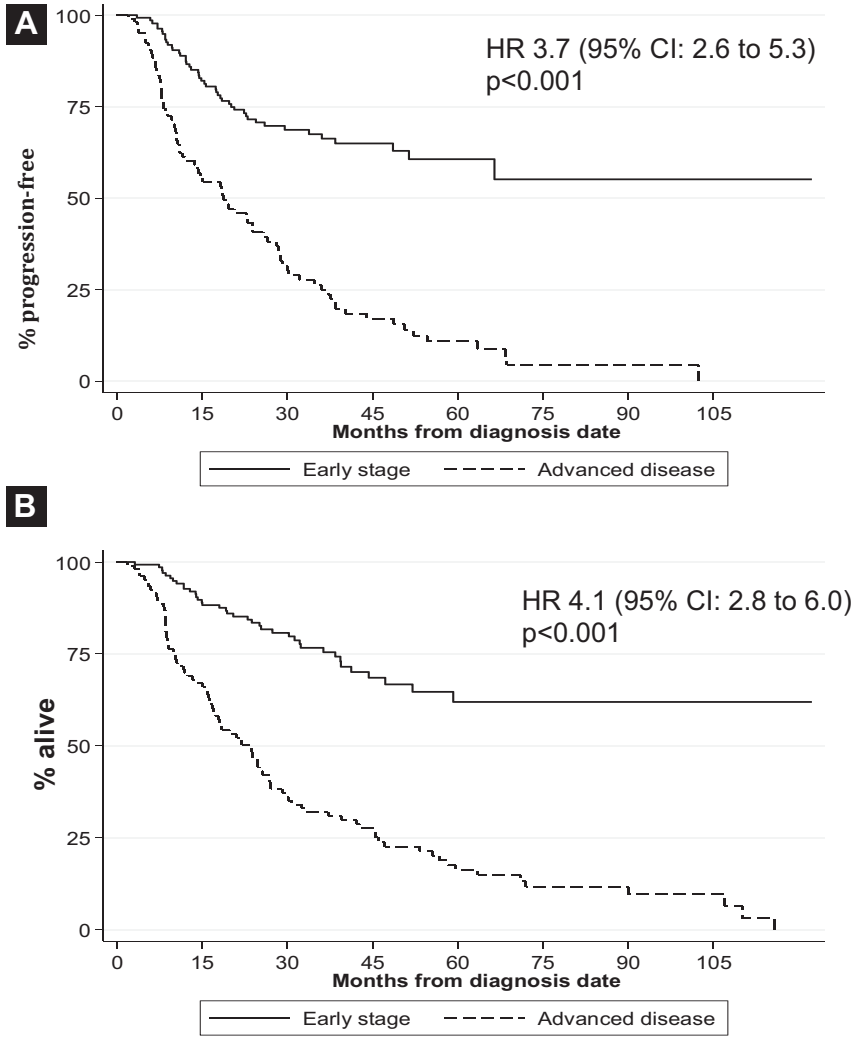
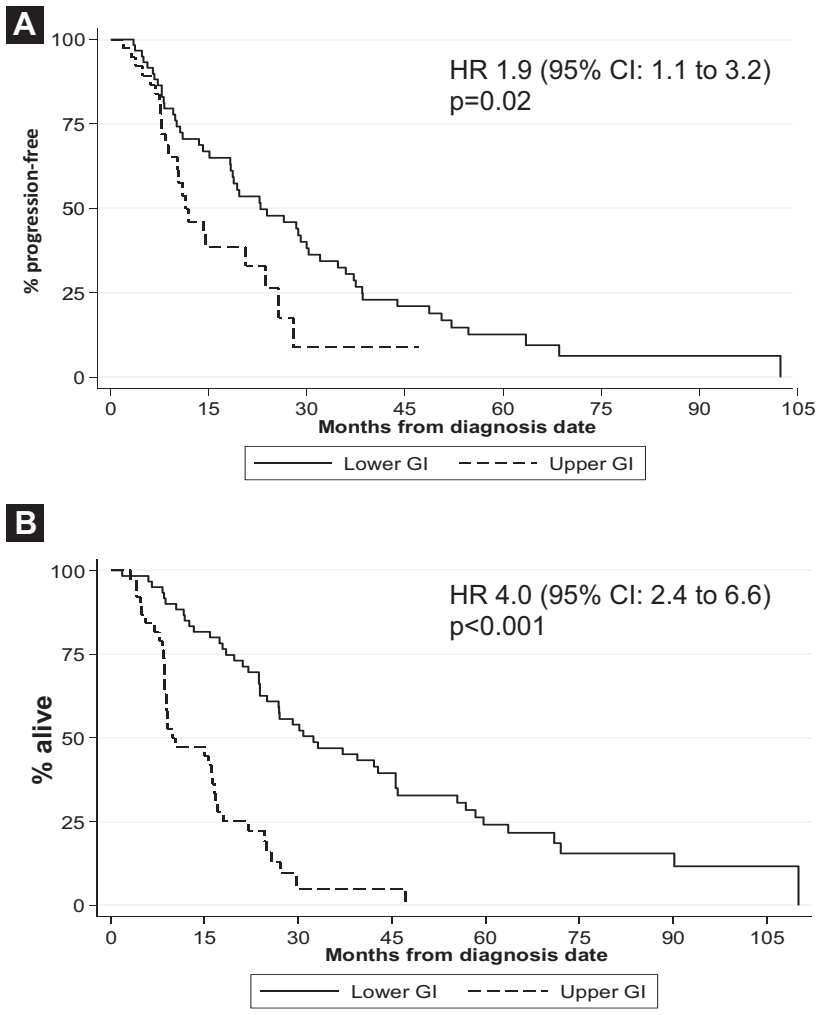


Figure 3 Kaplan-Meier Estimates of for (A) Progression-Free Survival and (B) Overall Survival for Upper and Lower Gastrointestinal Malignancies



It is well documented that raltitrexed treatment and its dosing schedule are convenient to patients.[21] We found that raltitrexed was well tolerated by the majority of patients. Only 5% of the treated patients developed cardiac toxicity, and more than half of these patients were able to continue treatment without further cardiac complications. Our data suggest that the standard dose of 3 mg/m^2 is safe in this high-risk population and that the cardiac AEs of raltitrexed were not found to be dose dependent. We have shown that appropriate dose adjustments based on renal function may be necessary for a better safety profile; however, precautionary dose

Table 4 Efficacy of Raltitrexed Based Therapy in All Study Participants

Cancer Type	5-Year PFS (95% CI)	5-Year OS (95% CI)
All cancers	36.9% (29.1-44.7)	38.7% (30.9-46.4)
Early stage upper GI cancers	24.7% (8.2-45.9)	17.6% (3.6-40.4)
Advanced stage upper GI cancers	0	0
Early stage lower GI cancers	71.1% (58.7-80.4)	73.5% (58.8-83.7)
Advanced stage lower GI	12.6 (5.3-23.3)%	24.1% (13.4-36.5)
Advanced miscellaneous	12.5% (0.7-42.3)	25% (3.7-55.8)
All early stage cancers	60.7% (49.9-69.8)	62% (50.1-71.9)
All advanced stage cancers	10.9% (5-19.2)	16.3% (9.5-24.7)

Abbreviations: GI = gastrointestinal; OS = overall survival; PFS = progression-free survival.

reduction in view of previous cardiac adverse events (AEs) or high-risk factors is not required.

Raltitrexed-related deaths have raised concerns about the safety of this treatment,[15,18,22] although other studies have not demonstrated similar treatment-related death rates.[23-27] One large phase 3 study reported 26 deaths (3.8%) causally related to raltitrexed.[18] When examined in detail, 17 of 26 deaths were associated with a major protocol variation when the raltitrexed dose was not adjusted according to renal function.[18,19] Because the kidney accounts for 40% to 50% of the drug's clearance,[21] special care should be exercised in patients with a creatinine clearance rate of < 65 mL/min.[7] In our high-risk cohort, only one treatment-related death was noted.

Given that our study revealed large differences in the incidence of CV AEs between patients who received FPs and those who received raltitrexed, it is likely that there are mechanistic differences underlying the development of cardiotoxicity between the 2 types of drug. Raltitrexed-induced CV AEs were generally observed in patients who had already received a few cycles of treatment. Intriguingly, relatively more patients presented with palpitations rather than 5-FU/capecitabine-induced chest pain, suggesting coronary artery vasospasm to be the main mechanim behind FP-related CV toxicity. Consistent with this observation, when coronary angiography was performed, it was found to be unremarkable in most of the patients in the current study. It is thus possible that cardiac AEs seen in patients who received raltitrexed are manifestation of indirect effects as a result of hyperdynamic states resulting from chemotherapy or renal impairment rather than direct cardiotoxicity. Indeed, randomized controlled trials assessing raltitrexed have provided no evidence for the direct cardiotoxicity of raltitrexed.[19]

The efficacy of raltitrexed-containing regimens in our cohort can be compared favorably with contemporaneous treatment options in lower GI malignancies.[28-30] It is interesting to note that all the previous studies comparing raltitrexed with 5-FU have also shown similar efficacy in lower GI malignancies.[15-18,31] However, none of these studies focused on a high-risk patient population, as reported in the current study. The efficacy outcomes for early upper GI malignancies in our cohort were somewhat variable. Although perioperative chemotherapy with surgery resulted in a 5-year survival of 36% (95% CI, 29.5-43.0) in the MAGIC trial,[32] in our cohort the 5-year survival was found to be 17.6% (95% CI, 3.6-40.4). However, in advanced upper GI malignancies, the results with raltitrexed were comparable with other existing treatment options.[33] These data overall provide a strong rationale for use of raltitrexed-based therapy in patients with CV risk/toxicities in all lower GI and advanced upper GI malignancies. However, raltitrexed-based treatment in early upper GI malignancies should be considered with caution, specially within the context of new available perioperative chemotherapy options.[34]

Although our study provides valuable information on the relative cardiac safety of raltitrexed versus 5-FU/capecitabine, we recognize that our analysis has some limitations. The main limitation is its retrospective nature along with its associated biases. However, given the stark differences in the incidence of cardiac AEs in patients receiving raltitrexed versus those receiving FPs, a prospective trial in high-risk CV patients would be ethically questionable. The lack of treatment options for such patients would also mean that prospective trials would be difficult to design and recruit. Our analysis may have also underestimated the incidence of cardiac AEs that would occur if all patients without a clear indication for raltitrexed dose reduction (eg, those with renal failure) had been offered the full dose. However, in all likelihood, patients with renal impairment would have received appropriate dose reduction with other chemotherapies as well, thus making our results applicable to such patients.

Conclusion

This study demonstrated the safety and efficacy of raltitrexed in upper and lower GI cancer patients who either experienced mild to moderate cardiac toxicity after FPs or those who had significant cardiac risk factors. Allowing extrapolation of data and comparison with available contemporaneous regimens, we recommend use of raltitrexed-based therapy in high-risk CV patients with all lower and advanced upper GI malignancies. In patients with early stage GI malignancies and curative treatment options, the use of raltitrexed-based therapy should be restricted to patients for whom no alternative therapeutic options are available.

Clinical Practice Points

- This study represents the largest examination of raltitrexed-treated GI cancer patients with CV toxicities after FPs or with CV risk factors precluding them from receiving or continuing with FP-based therapy.
- Consistent with previously published literature, we demonstrate the safety of this approach, with < 5% cardiac toxicity and low fatality (< 0.1%).
- The novel aspect of this study is that efficacy data with long median follow-up in a patient population with significant cardiac toxicities or risk factors were found to be comparable to the contemporaneous standard of care: 5-FU/capecitabine-based regimens.
- Despite the retrospective nature of our study, the findings support the use of raltitrexed-based regimens in a patient population with limited systemic therapy options.

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Disclosure

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Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2018.09.010.

References

1. Papanastasopoulos P, Stebbing J. Nuts and cancer: where are we now? *Lancet Oncol* 2013; 14:1161-2.
2. Wilson PM, Danenberg PV, Johnston PG, Lenz HJ, Ladner RD. Standing the test of time: targeting thymidylate biosynthesis in cancer therapy. *Nat Rev Clin Oncol* 2014; 11:282-98.
3. Moertel CG. Chemotherapy for colorectal cancer. *N Engl J Med* 1994; 330:1136-42.
4. Hirsch BR, Zafar SY. Capecitabine in the management of colorectal cancer. *Cancer Manage Res* 2011; 3:79-89.
5. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: colon cancer, 2013. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx.
6. Van Cutsem E, Van de Velde C, Roth A, et al. Expert opinion on management of gastric and gastro-oesophageal junction adenocarcinoma on behalf of the European Organisation for Research and Treatment of Cancer (EORTC)-Gastrointestinal Cancer Group. *Eur J Cancer* 2008; 44:182-94.
7. Deboever G, Hiltrop N, Cool M, Lambrecht G. Alternative treatment options in colorectal cancer patients with 5-fluorouracil– or capecitabine-induced cardiotoxicity. *Clin Colorectal Cancer* 2013; 12:8-14.
8. Jensen SA, Hasbak P, Mortensen J, Sorensen JB. Fluorouracil induces myocardial ischemia with increases of plasma brain natriuretic peptide and lactic acid but without dysfunction of left ventricle. *J Clin Oncol* 2010; 28:5280-6.
9. Sudhoff T, Enderle MD, Pahlke M, et al. 5-Fluorouracil induces arterial vasocontractions. *Ann Oncol* 2004; 15:661-4.
10. Kosmas C, Kallistratos MS, Kopterides P, et al. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. *J Cancer Res Clin Oncol* 2008; 134:75-82.
11. Polk A, Vistisen K, Vaage-Nilsen M, Nielsen DL. A systematic review of the pathophysiology of 5-fluorouracil–induced cardiotoxicity. *BMC Pharmacol Toxicol* 2014; 15:47.
12. Kelly C, Bhuva N, Harrison M, Buckley A, Saunders M. Use of raltitrexed as an alternative to 5-fluorouracil and capecitabine in cancer patients with cardiac history. *Eur J Cancer* 2013; 49:2303-10.
13. Saif MW, Tomita M, Ledbetter L, Diasio RB. Capecitabine-related cardiotoxicity: recognition and management. *J Support Oncol* 2008; 6:41-8.
14. Becker K, Erckenbrecht JF, Haussinger D, Frieling T. Cardiotoxicity of the antiproliferative compound fluorouracil. *Drugs* 1999; 57:475-84.
15. Maughan TS, James RD, Kerr DJ, et al. Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2002; 359:1555-63.
16. Cunningham D, Zalcberg JR, Rath U, et al. Final results of a randomised trial comparing "Tomudex" (raltitrexed) with 5-fluorouracil plus leucovorin in advanced colorectal cancer. "Tomudex" Colorectal Cancer Study Group. *Ann Oncol* 1996; 7:961-5.
17. Gravalos C, Salut A, Garcia-Giron C, et al. A randomized phase II study to compare oxaliplatin plus 5-fluorouracil and leucovorin (FOLFOX4) versus oxaliplatin plus raltitrexed (TOMOX) as first-line chemotherapy for advanced colorectal cancer. *Clin Transl Oncol* 2012; 14:606-12.
18. Popov I, Carrato A, Sobrero A, et al. Raltitrexed (Tomudex) versus standard leucovorin-modulated bolus 5-fluorouracil: results from the randomised phase III Pan-European Trial in Adjuvant Colon Cancer 01 (PETACC-1). *Eur J Cancer* 2008; 44:2204-11.
19. Ransom D, Wilson K, Fournier M, et al. Final results of Australasian Gastrointestinal Trials Group ARCTIC study: an audit of raltitrexed for patients with cardiac toxicity induced by fluoropyrimidines. *Ann Oncol* 2014; 25:117-21.
20. Khan KH, Athauda A, Aitken K, et al. Survival outcomes in asymptomatic patients with normal conventional imaging but raised CEA levels in colorectal cancer following PET-CT imaging. *Oncologist* 2016; 21:1502-8.
21. Young A, Topham C, Moore J, et al. A patient preference study comparing raltitrexed ("Tomudex") and bolus or infusional 5-fluorouracil regimens in advanced colorectal cancer: influence of side-effects and administration attributes. *Eur J Cancer Care (Engl)* 1999; 8:154-61.
22. Mackay HJ, McInnes A, Paul J, et al. A phase II study of epirubicin, cisplatin and raltitrexed combination chemotherapy (ECT) in patients with advanced oesophageal and gastric adenocarcinoma. *Ann Oncol* 2001; 12:1407-10.
23. Seitz JF, Bennouna J, Paillot B, et al. Multicenter non-randomized phase II study of raltitrexed (Tomudex) and oxaliplatin in non-pretreated metastatic colorectal cancer patients. *Ann Oncol* 2002; 13:1072-9.
24. Aparicio J, Vicent JM, Maestu I, et al. Multicenter phase II trial evaluating a three-weekly schedule of irinotecan plus raltitrexed in patients with 5-fluorouracil-refractory advanced colorectal cancer. *Ann Oncol* 2003; 14:1121-5.
25. Rosati G, Rossi A, Germano D, Reggiardo G, Manzione L. Raltitrexed and mitomycin-C as third-line chemotherapy for colorectal cancer after combination regimens including 5-fluorouracil, irinotecan and oxaliplatin: a phase II study. *Anticancer Res* 2003; 23:2981-5.
26. Feliu J, Salud A, Escudero P, et al. Irinotecan plus raltitrexed as first-line treatment in advanced colorectal cancer: a phase II study. *Br J Cancer* 2004; 90:1502-7.
27. Sato A, Kurihara M, Horikoshi N, et al. Phase II study of raltitrexed (Tomudex) in chemotherapy-pretreated patients with advanced colorectal cancer. Tomudex Cooperative Study Group. *Anticancer Drugs* 1999; 10:741-8.
28. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009; 27:3109-16.
29. Kerr RS, Love S, Segelov E, et al. Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial. *Lancet Oncol* 2016; 17:1543-57.
30. Khan K, Cunningham D, Chau I. Targeting angiogenic pathways in colorectal cancer: complexities, challenges and future directions. *Curr Drug Targets* 2017; 18:56-71.
31. Cocconi G, Cunningham D, Van Cutsem E, et al. Open, randomized, multicenter trial of raltitrexed versus fluorouracil plus high-dose leucovorin in patients with advanced colorectal cancer. Tomudex Colorectal Cancer Study Group. *J Clin Oncol* 1998; 16:2943-52.
32. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; 355:11-20.
33. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; 358:36-46.
34. Al-Batran SE, Homann N, Pauligk C, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: the AIO-FLOT3 trial. *JAMA Oncol* 2017; 3:1237-44.

Supplemental Data

Supplemental Table 1 Intent of Chemotherapy in Different Groups

Characteristic	5-Fluorouracil Pretreatment	Capecitabine Pretreatment	Cardiovascular Risk Factors	Total
Neoadjuvant	1	8	13	22
Neoadjuvant + radiochemotherapy	2	13	14	29
Radiochemotherapy	0	2	3	5
Adjuvant	23	35	26	84
Palliative chemotherapy	19	52	36	107

Supplemental Table 2 Cardiac Background for Patients Considered to Have High Cardiovascular Risk Factors

Condition	Frequency
Angina	9
Heart failure	1
Cardiomegaly + arrhythmia	1
Ischemic heart disease + heart failure	3
Ischemic heart disease + atrial fibrillation	7
Cardiomyopathy	3
Heart block	1
Angina + atrial fibrillation	1
Palpitations	1
Arrhythmia	4
Atrial fibrillation	6
Paroxysmal atrial fibrillation	6
Myocardial infarction	23
Ischemic heart disease	22
Arrhythmia + ischemia heart disease/myocardial infarction	3
Pacemaker	1
Total	92