Original Study

Effects of Proton Pump Inhibitors on FOLFOX and CapeOx Regimens in Colorectal Cancer

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Abstract

Proton pump inhibitors (PPIs) have been implicated in the impaired absorption of various oral oncologic therapies. Significantly reduced 3-year recurrence-free survival rates were seen in our retrospective chart review of stage II-III colorectal cancer patients who received PPIs concurrently with CapeOx (capecitabine, intravenous oxaliplatin) compared to non-PPI recipients. No significant differences were seen among FOLFOX-treated patients (intravenous 5-fluorouracil, leucovorin, oxaliplatin).

Background: First-line adjuvant chemotherapy options for early-stage colorectal cancer (CRC) include CapeOx (capecitabine, intravenous oxaliplatin) and FOLFOX (intravenous 5-fluorouracil, leucovorin, oxaliplatin). Capecitabine is an oral prodrug analog of 5-fluorouracil, and recent studies have suggested that proton pump inhibitors (PPIs) may detrimentally affect capecitabine efficacy. Conversely, some literature suggests that PPIs may negatively affect CRC itself. To gain insight into the nature of PPIs' effect on capecitabine and CRC, we investigated their effects on effectiveness of CapeOx versus FOLFOX chemotherapy. **Patients and Methods:** We conducted a retrospective chart review of 389 patients with stage II-III CRC who received adjuvant CapeOx or FOLFOX from 2004 to 2013. Information regarding PPI receipt, chemotherapy, and patient outcomes from medical records was analyzed. **Results:** Three-year recurrence-free survival was significantly lower in CapeOx-treated PPI recipients than non-PPI recipients (69.5 vs. 82.6%; $P = .029$). Unadjusted analysis showed that CapeOx-treated PPI recipients were twice as likely to experience cancer recurrence or death as CapeOx-treated non-PPI recipients (hazard ratio = 2.03; 95% confidence interval, 1.06-3.88; $P = .033$). FOLFOX-treated PPI recipients had a non–statistically significant difference in 3-year recurrence-free survival versus non-PPI recipients (82.9 vs. 61.7%; $P = .066$) and a non–statistically significant difference in recurrence/death (hazard ratio = 0.51; 95% confidence interval, 0.25-1.06; $P = .071$). No significant differences were seen in overall survival between groups. **Conclusion:** Our results suggest PPIs negatively affected recurrence-free survival in CapeOx-treated CRC patients and yielded no significant effects among FOLFOX-treated patients, potentially implicating a pharmacokinetic interaction between PPIs and capecitabine. No overall survival effects were seen. Given PPIs' widespread use, further studies are required to corroborate our findings.

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Introduction

Colorectal cancer (CRC) is the second most prevalent cancer in women and the third most prevalent in men worldwide, and is responsible for approximately 608,000 deaths per year.[1] Primary treatment for early stage (stage I-III) CRC is surgical resection.[2-4] After surgery, adjuvant chemotherapy is indicated for stage II colon cancer patients who are considered high risk. High-risk patients are those who possess at least one of the following criteria: lymphovascular invasion, poorly differentiated histology, tumor perforation, bowel obstruction, incompletely evaluated lymph nodes, or age < 40 years.[2,5] Additionally, adjuvant chemotherapy is indicated for stage III colon cancer and stage II-III rectal cancer patients.[2,3,5,6]

Adjuvant chemotherapy options for these patient populations include CapeOx (capecitabine, intravenous oxaliplatin) and FOLFOX (intravenous 5-fluorouracil [5-FU], leucovorin, oxaliplatin).[2,3,5-8] 5-FU is an intravenous pyrimidine analog antimetabolite

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that is transformed into 2 active metabolites, 5-fluorouridine triphosphate and 5-fluorodeoxyuridine monophosphate, which subsequently interfere with protein and DNA synthesis and repair.[9,10] Capecitabine is an oral prodrug analog of 5-FU that is hydrolyzed in tissues and the liver, then subsequently metabolized within cells into the same active metabolites as 5-FU.[11] Capecitabine is regarded as an equivalent therapy to 5-FU and leucovorin in metastatic CRC, and CapeOx has demonstrated improved disease-free survival rates comparable to 5-FU and leucovorin in stage III colon cancer.[12-14] Moreover, Park et al[15] observed no significant difference in disease-free survival between FOLFOX and CapeOx in a prospective multinational study of stage II-III colon cancer patients.

Proton pump inhibitors (PPIs) are a ubiquitously used class of medications for treating gastroesophageal reflux disease and other hypersecretory disorders.[16] These agents exert their therapeutic effects by inactivating H^+/K^+ adenosine triphosphatase pumps in parietal cells to reduce gastric acid secretion.[16] PPIs have been shown to impair oral anticancer agent absorption, potentially because of their acid-reducing properties.[17] This is of concern given their widespread use; Smelick et al[17] noted that 50% to 67% of patients with gastrointestinal cancers used acid-reducing agents, of which PPIs were the most prescribed. Recently, effects of PPIs on oral capecitabine were studied by Sun et al,[18] who found that concomitant PPI receipt was associated with detrimental effects on 5-year recurrence-free survival (RFS) in early-stage CRC patients. The proposed interaction was attributed to reduced capecitabine tablet disintegration due to gastric pH changes from concomitant PPI receipt, leading to decreased drug absorption. Conversely, some literature suggests that PPIs may affect progression of CRC itself, which could be responsible for these results. One proposed mechanism for this potential drug—disease interaction begins with PPI-induced hypergastrinemia, leading to increased colorectal mucosa proliferation.[16,19-21] Another theory involves gut bacterial overgrowth and toxic bile salt formation due to reduced acidity.[20]

The goal of this study was to gain insight into the nature of effects of PPIs on capecitabine and CRC. To accomplish this, we sought to investigate effects of PPIs on CapeOx versus FOLFOX chemotherapy. We compared 3-year RFS rates of CapeOx-treated stage II-III CRC patients who received therapy with PPIs to those of CapeOx-treated non-PPI recipients, and replicated this for recipients of FOLFOX. Should effects of PPIs be pharmacokinetic in nature, then lower RFS rates for CapeOx-treated PPI recipients versus non-PPI recipients would be expected, whereas no RFS differences between FOLFOX-treated PPI and non-PPI recipients would be seen. Conversely, if PPIs affect CRC as a disease, equally detrimental effects on RFS would be expected among both CapeOx- and FOLFOX-treated patients.

Patients and Methods

Study Design and Patient Population

We conducted a retrospective chart review of patients with stage II-III CRC who received adjuvant CapeOx or FOLFOX chemotherapy from our tertiary-care cancer treatment center in Edmonton, Alberta, from January 1, 2004, to December 31, 2013. This time frame of inclusion was based on implementation of the American Joint Committee on Cancer's collaborative staging system by the Alberta Cancer Registry in 2004, and to account for the introduction of over-the-counter omeprazole to the Canadian market in 2014.[22,23]

To identify eligible patients, a list of CRC patients who received surgery as an initial method of treatment was obtained from the Alberta Cancer Registry via Cancer Measurement, Outcomes, Research, and Evaluation from Alberta Health Services. This was cross-referenced with lists obtained from the tertiary-care center's pharmacy database of patients who received CapeOx or FOLFOX from 2004 to 2013. Data regarding PPI receipt was retrieved from the Data Integration, Measurement, and Reporting system, a data repository that collects information from the Alberta Netcare Electronic Health Record.[24] Electronic medical records and pharmacy dispensing databases were used to gather all other patient information.

This study received approval by the Health Research Ethics Board of Alberta Cancer Committee. Because of its retrospective nature, the need for informed consent was waived.

Patient Eligibility

Patients were included in the study if they were $\geq$ 18 years of age, were formally diagnosed with and received surgical treatment for CRC, had stage II-III disease at the time of CapeOx or FOLFOX initiation, and received their first cycle of adjuvant CapeOx or FOLFOX from January 1, 2004, to December 31, 2013. Per our site's treatment standards, patients with high-risk stage II colon cancer (who have at least one of the following: direct invasion into adjacent structures, tumor perforation, clinical obstruction, poorly differentiated histology, lymphovascular and/or perineural invasion, evaluation of $<$ 12 regional lymph nodes, or age $<$ 40 years), stage III colon cancer, and stage II-III rectal cancer are indicated to receive adjuvant chemotherapy.[2,3]

Patients with in-situ (stage 0) or localized (stage I) disease were excluded from the study because adjuvant systemic therapy is not recommended for this population.[2,3] Additionally, patients with metastatic disease (stage IV) were excluded, as palliative treatment without curative intent is the treatment of choice for these patients.[25] Patients receiving concurrent radiotherapy or who had information missing from their records were also excluded.

Study Outcomes

The primary end point of this study was the 3-year RFS rate among CRC patients who received adjuvant CapeOx or FOLFOX chemotherapy, with or without any concurrent PPI receipt. This was designated as such given that the current standard of practice within our facility is 3-year patient follow-up. In the literature, 2- to 3-year disease-free survival treatment-effect hazard ratios (HRs) have been shown to be predictive of 5- to 6-year overall survival (OS) hazard ratios in stage III colon cancer.[26]

Secondary end points in this study included 3-year OS and occurrences of dose reductions, dose delays, or premature treatment discontinuations. Treatment-related toxicities have been shown to be predictors of survival responses to capecitabine[14,27] and are managed through dose modifications via their respective protocols.[28-31] Thus, these end points were chosen as a surrogate means to assess treatment efficacy.

PPI recipients were defined as individuals who received PPIs at any time during their CapeOx or FOLFOX treatment, as determined by prescription fill data. Capecitabine dose delays were defined as delays in treatment of ≥ 7 days. Treatments were considered "discontinued early" if they were stopped before their intended duration, per written documentation by the patient's oncologist.

Statistical Analysis

Descriptive statistics were used to describe baseline characteristics of the study cohort. Averages and standard deviations were reported for continuous, normally distributed data. Categorical data were reported as frequencies or percentages, and log-rank tests were used to compare CapeOx-treated or FOLFOX-treated PPI recipients with non-PPI recipients, respectively. Three-year RFS and OS were calculated from the date of treatment initiation until disease recurrence/death, or date of death/date of last follow-up. Patients were censored at their last date of follow-up if no recurrence was experienced. Kaplan-Meier estimates and their corresponding 95% confidence interval (CI) were reported for survival outcomes.

The Cox proportional hazards regression model was used to conduct an unadjusted analysis of survival data. Binary logistic regression models were used to analyze categorical data associated with treatment modifications or early discontinuations. Chi-square tests were performed to assess for associations between categorical variables. SAS 9.3 software (SAS Institute, Cary, NC) was used for all statistical analysis, and a significance level of $P < .05$ was used for statistical testing.

Results

Nine hundred fifty-six patients who received CapeOx or FOLFOX during 2004 to 2013 were initially screened; of these, 389 patients met the inclusion criteria for the study. Lack of documented primary tumor resection (n = 442) and metastatic disease upon initiation of CapeOx or FOLFOX treatment (n = 97) were the 2 most frequent reasons for patient exclusion. Other reasons for exclusion included: stage 1 disease, concurrent radiotherapy, absent orders, completing treatment in other centers, or receiving both CapeOx and FOLFOX for a similar number of cycles.

Of the 389 patients included, 224 patients (57.6%) were male, 355 patients (91.3%) had stage III disease when CapeOx or FOLFOX treatment was initiated, and 252 patients (64.8%) had cancer specifically localized to the colon; these characteristics were similar among both CapeOx-treated and FOLFOX-treated groups. Concurrent PPI receipt was comparable between both groups as well (23.4% and 28.0%, respectively). Detailed baseline patient characteristics are reported in Table 1.

Patients who received PPIs concurrently with treatment had a lower 3-year RFS compared to CapeOx-treated non-PPI recipients (69.5 vs. 82.6%; $P = .029$; Tables 2 and 3, Figure 1). Unadjusted analysis demonstrated that CapeOx-treated PPI recipients were twice as likely to experience cancer recurrence or death as CapeOx-treated non-PPI recipients (HR = 2.03; 95% CI, 1.06-3.88; $P = .033$). Patients who received PPIs concurrently with FOLFOX appeared to have the opposite, but not statistically significant, difference in 3-year RFS rates compared to FOLFOX-treated non-PPI recipients (82.9 vs. 61.7%; $P = .066$). Among non-PPI recipients, patients treated with CapeOx were 59% less likely to experience cancer recurrence or death than FOLFOX-treated patients (HR = 0.41; 95% CI, 0.25-0.65; $P < .001$). No other differences in RFS were seen between patient groups.

Multivariate analysis considering sex, disease stage (stage II vs. III), and primary tumor location (colon vs. rectum) found that none of these factors had a significant effect on RFS individually, regardless of cancer treatment or PPI receipt. Cumulatively adjusting for these known prognostic factors in patients treated with CapeOx demonstrated an association between PPI receipt and increased cancer recurrence or death (HR = 2.20; 95% CI, 1.14-4.25; $P = .018$; Table 3). Conversely, adjusting for these same

Table 1 Baseline Characteristics of Stage II-III Colorectal Cancer Patients Who Received CapeOx or FOLFOX Adjuvant Chemotherapy

Demographic	CapeOx (N = 214)	FOLFOX (N = 175)	*P*
Age (years)	59.5 ± 1.1	59.4 ± 11.3	.941
Male sex	132 (61.7)	92 (52.6)	.070
BSA (m^2)	1.9 ± .3	1.9 ± .3	—[a]
Cancer Stage			.407
II	21 (9.8)	13 (7.4)	
III	193 (90.2)	162 (92.6)	
Cancer Location			.183[b]
Colon	132 (61.7)	120 (68.6)	
Rectal	52 (24.3)	29 (16.6)	
Rectosigmoid junction	29 (13.6)	26 (14.9)	
Colon + rectum	1 (0.5)	0	
Concurrent PPI Receipt			.296
Any overlapping receipt	50 (23.4)	49 (28.0)	

Data are presented as n (%) or mean (± standard deviation).
Abbreviations: BSA = body surface area; CapeOx = capecitabine, oxaliplatin; FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin; PPI = proton pump inhibitor.
[a]Same average, no difference.
[b]Fisher exact test.

Table 2 RFS Rates Among Stage II-III Colorectal Cancer Patients Who Received CapeOx or FOLFOX Chemotherapy With or Without Concurrent PPI

Adjuvant Chemotherapy	Concurrent PPI Receipt	3-Year RFS Rate (%)	*P* (Log-Rank Test)
FOLFOX	Any overlapping receipt (n = 49)	82.9	.066
	No overlapping receipt (n = 126)	61.7	
CapeOx	Any overlapping receipt (n = 50)	69.5	.029
	No overlapping receipt (n = 164)	82.6	

Abbreviations: CapeOx = capecitabine, oxaliplatin; FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin; PPI = proton pump inhibitor; RFS = recurrence-free survival.

Table 3 Unadjusted and Adjusted RFS Analysis Among Stage II-III Colorectal Cancer Patients Who Received CapeOx or FOLFOX Chemotherapy With or Without Concurrent PPI

Group	Unadjusted RFS Analysis		Adjusted RFS Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
CapeOx, PPI versus no PPI	2.03 (1.06-3.88)	.033	2.20 (1.14-4.25)	.018
FOLFOX, PPI versus no PPI	0.51 (0.25-1.06)	.071	0.51 (0.24-1.05)	.066
PPI, CapeOx versus FOLFOX	1.93 (0.77-4.84)	.161	2.02 (0.80-5.10)	.138
No PPI, CapeOx versus FOLFOX	0.41 (0.25-0.65)	< .001	0.41 (0.25-0.66)	< .001

Unadjusted RFS analysis provides Cox proportional hazards model of PPI effect; adjusted multivariate RFS analysis is adjusted for gender, stage (II vs. III), and primary tumor location (colon vs. rectum).
Abbreviations: CapeOx = capecitabine, oxaliplatin; CI = confidence interval; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; HR = hazard ratio; PPI = proton pump inhibitor; RFS = recurrence-free survival.

factors in patients treated with FOLFOX showed that PPI receipt was associated with an HR of 0.51 (95% CI, 0.24-1.05; $P = .066$).

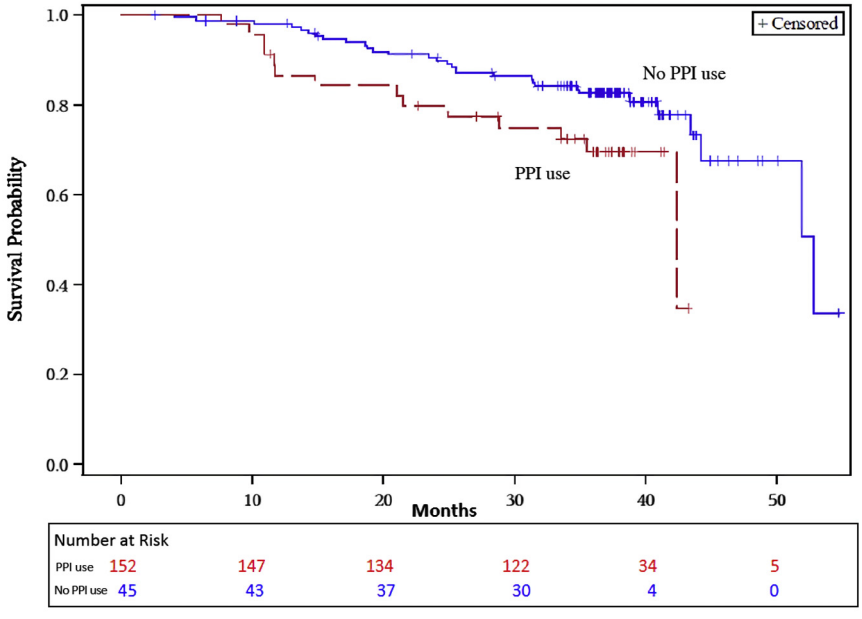
Multivariate analysis showed that PPI receipt did not have a significant effect on OS among those treated with either CapeOx or FOLFOX (Tables 4 and 5). Among non-PPI recipients, patients treated with CapeOx were 51% less likely to experience mortality than FOLFOX-treated patients (HR = 0.49; 95% CI, 0.27-0.89; $P = .020$; Table 5). FOLFOX-treated PPI recipients were more likely to require dose reductions as FOLFOX-treated non-PPI recipients (57.1 vs. 39.7%; $P = .037$; Table 6). No significant differences in dose delays occurred between PPI and non-PPI recipients regardless of FOLFOX or CapeOx treatment. Furthermore, no significant differences were found in the proportion of premature treatment discontinuations between any patient groups (Tables 6 and 7). With regard to secondary end points, no differences in OS were seen between CapeOx-treated PPI recipients versus non-PPI recipients (90.1 vs. 91.2%; $P = .345$), nor between FOLFOX-treated PPI recipients versus non-PPI recipients (77.4 vs. 80.1%; $P = .929$; Table 4).

Discussion

In this retrospective chart review, a statistically significant reduction in RFS was observed among stage II-III CRC patients who received concurrent CapeOx therapy and PPIs compared to CapeOx-treated non-PPI recipients. Notably, this difference was not replicated in FOLFOX-treated patients. These results suggest that PPIs may have adversely affected the efficacy of CapeOx but not FOLFOX treatment, and therefore affected capecitabine's efficacy.

Our results are generally concordant with the limited amount of published literature on this topic. Sun et al[18] found reduced 5-year RFS rates between early-stage CRC patients who received capecitabine monotherapy and concomitant PPIs compared to non-PPI recipients (HR = 1.89; 95% CI, 1.07-3.35; $P = .03$). Subsequently, Chu et al[32] observed reduced progression-free survival following a secondary analysis of metastatic gastroesophageal cancer patients receiving capecitabine, oxaliplatin, and concurrent PPIs in

Figure 1 Recurrence-Free Survival Rates Among Stage II-III Colorectal Cancer Patients Who Received CapeOx Chemotherapy With or Without Concurrent PPI



Abbreviations: CapeOx = capecitabine, oxaliplatin; PPI = proton pump inhibitor.

Table 4 OS Rates Among Stage II-III Colorectal Cancer Patients Who Received CapeOx or FOLFOX Chemotherapy With or Without Concurrent PPI

Adjuvant Chemotherapy	Concurrent PPI Receipt	3-Year OS Rate (%)	*P* (Log-Rank Test)
FOLFOX	Any overlapping receipt (n = 49)	77.4	.929
	No overlapping receipt (n = 126)	80.1	
CapeOx	Any overlapping receipt (n = 50)	90.1	.345
	No overlapping receipt (n = 164)	91.2	

Abbreviations: CapeOx = capecitabine, oxaliplatin; FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin; OS = overall survival; PPI = proton pump inhibitor.

the TRIO-013 trial (4.2 vs. 5.7 months; HR = 1.55; 95% CI, 1.29-1.81; $P < .001$). In their study of PPIs' chemosensitizing properties, Wang et al[33] observed improved survival outcomes with PPI receipt and concurrent FOLFOX treatment (relative risk = 0.67; 95% CI 1.10-2.05; $P = .01$), while no significant difference was seen with PPI receipt and CapeOx therapy. Notably, these authors speculated that their result might have been due to impaired capecitabine absorption as well. Interestingly, Zhang et al[34] observed improved tumor regression among patients who received omeprazole with oxaliplatin, capecitabine, and radiotherapy before radical surgery for rectal cancer. Patients with concurrent radiotherapy were excluded from our study, which may explain the discordant results.

Preceding these studies, literature addressing the use of acid reducers and capecitabine is sparse. In vitro experiments have shown that capecitabine is unstable under acidic conditions, and that the antacid Maalox (aluminum hydroxide and magnesium hydroxide) is capable of prolonging capecitabine tablet dissolution and disintegration times (from 50 to > 100 minutes and 20 to 40 minutes, respectively).[35,36] Reigner et al[36] examined the effects of Maalox when provided to 12 patients immediately or 2 hours after receipt of capecitabine and found no significant difference in plasma concentrations of its metabolites. However, these investigators noted that the Maalox doses used in this study were likely insufficient to induce an adequate rise in gastric pH to elicit effects on tablet disintegration seen in in vitro experiments. Given that PPIs are more potent acid reducers than antacids, PPIs may be capable of reducing efficacy of capecitabine (and by extension CapeOx) by altering gastric pH to a greater degree, thus impeding capecitabine absorption.[37] Moreover, similar drug–drug interactions have been observed between PPIs and molecularly targeted cancer medications, such as erlotinib, whose absorption has been shown to be pH dependent.[38]

Table 5 Unadjusted and Adjusted OS Analysis Among Stage II-III Colorectal Cancer Patients Who Received CapeOx or FOLFOX Chemotherapy With or Without Concurrent PPI

	Unadjusted OS Analysis		Adjusted OS Analysis	
Group	HR (95% CI)	*P*	HR (95% CI)	*P*
CapeOx, PPI versus no PPI	1.46 (0.66-3.24)	.348	1.68 (0.75-3.80)	.210
FOLFOX, PPI versus no PPI	0.97 (0.45-2.08)	.930	0.96 (0.44-2.08)	.918
PPI, CapeOx versus FOLFOX	0.82 (0.32-2.07)	.674	0.79 (0.30-2.04)	.619
No PPI, CapeOx versus FOLFOX	0.49 (0.27-0.89)	.020	0.48 (0.26-0.89)	.019

Unadjusted OS analysis provides Cox proportional hazards model of PPI effect; adjusted multivariate OS analysis is adjusted for gender, stage (II vs. III), and primary tumor location (colon vs. rectum).
Abbreviations: CapeOx = capecitabine, oxaliplatin; CI = confidence interval; OS = overall survival; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; HR = hazard ratio; PPI = proton pump inhibitor.

An alternatively proposed mechanism posits that PPIs may detrimentally affect CRC progression itself. However, in the present study, PPI receipt was not associated with significant effects on RFS among FOLFOX-treated patients. This suggests that the effect of PPIs on RFS of CapeOx-treated patients is not due to an effect on the disease but rather is the result of a treatment-specific drug–drug interaction with capecitabine. In the literature, Graham et al[20] retrospectively observed higher mortality risk between PPI-receiving CRC patients versus non-PPI recipients (HR = 1.34; 95% CI, 1.01-1.79; $P = .042$). Conversely, no statistically significant difference in CRC risk was observed with PPI and histamine-receptor antagonist use in a case–control study by Chubak et al.[21] Three other studies all failed to show significant links between prolonged PPI receipt and CRC.[16,19,39] Moreover, some literature suggests that PPIs may theoretically benefit CRC outcomes; postulated mechanisms include PPI-induced inhibition of vacuolar type H^+ ATPases, apoptosis of gastric cancer cells, and paradoxical antagonism of trophic effects of hypergastrinemia.[34,40,41] This may contribute to the statistically insignificant difference in RFS rates seen among FOLFOX-treated PPI recipients versus FOLFOX-treated non-PPI recipients in our study; however, further investigations are required to confirm this finding, as PPIs have also been associated with the chemosensitization of CRC HT29 and RKO cells to 5-FU.[33]

Unlike RFS, no significant difference in OS was seen between treatment groups in our study. Possible reasons for this discrepancy include reduced event incidence for this end point (as it solely accounts for survival and not recurrence) and efficacy of treatments for recurrent disease. Higher proportions of dose reductions were seen in FOLFOX-treated PPI recipients versus FOLFOX-treated non-PPI recipients; no other significant differences were noticed among patients who used PPIs throughout each treatment arm. An analysis of the specific reasons for these dose alterations may be warranted to clarify these outcomes. Another incidental finding suggests that CapeOx was associated with improved survival over FOLFOX among non-PPI recipients but not PPI recipients. This could imply that CapeOx yields survival benefits over FOLFOX in CRC, which PPI receipt subsequently negates; however, our study was not designed to detect survival differences between CapeOx and FOLFOX, so further investigations are needed to confirm these results.

Limitations

One limitation of our study is its retrospective design. Patient outcomes may have been affected by confounders such as

Table 6 Secondary End Points Among Stage II-III Colorectal Cancer Patients Who Received CapeOx or FOLFOX Chemotherapy With or Without Concurrent PPI

Secondary End Point	FOLFOX With:			CapeOx With:		
	Any Overlapping PPI Receipt (N = 49)	No Overlapping PPI Receipt (N = 126)	*P* (Chi-Square Test)	Any Overlapping PPI Receipt (N = 50)	No Overlapping PPI Receipt (N = 164)	*P* (Chi-Square Test)
Occurrence of dose reductions	28 (57.1)	50 (39.7)	.037	30 (60.0)	89 (54.3)	.475
Occurrence of dose delays	40 (81.6)	92 (73.0)	.235	36 (72.0)	104 (63.4)	.264
Occurrence of premature treatment discontinuation	12 (24.5)	25 (19.8)	.499	11 (22.0)	32 (19.5)	.700

Data are presented as n (%), with percentages expressed as percentage of patients who received CapeOx or FOLFOX with or without PPI treatment.
Abbreviations: CapeOx = capecitabine, oxaliplatin; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; PPI = proton pump inhibitor.

comorbidities, differences in baseline health status, concomitant medications, nutritional status, and compliance with PPI and capecitabine therapy. (Due to its intravenous administration, FOLFOX compliance was assured.) Inaccuracies in PPI data could have further affected our results, as it was not always possible to distinguish rebillings of the same prescription from distinct prescription fills or to view directions for use. For this reason, PPI receipt was characterized dichotomously as "any" or "no" overlapping receipt, as opposed to stratifying this by amount used, to yield a conservative estimate of effect. Additionally, some community pharmacies may not have uploaded data to the electronic health record database, resulting in missing records. Furthermore, the number of PPI recipients in each arm of our study was objectively low, thus limiting statistical power, though the proportions of PPI recipients seen (23.4% and 28.0% for CapeOx-treated and FOLFOX-treated patients, respectively) were similar to that in Sun et al[18] (25.8%). One additional limitation was lack of information regarding receipt of histamine-2 receptor antagonists and other over-the-counter acid reducers, as this is not typically captured in the Alberta Netcare Electronic Health Record because of their nonprescription status. Notably, receipt of these medications could have affected capecitabine pharmacokinetics similarly to PPIs. Moreover, pharmacokinetic studies were not performed to confirm effects of PPIs on capecitabine exposure; they remain an avenue for future study to confirm our findings.

Table 7 Binary Logistic Regression Model of PPI Effect on CapeOx or FOLFOX-Treated Patients: Secondary End Point Analysis

Secondary End Point	Patient Group Analyzed	OR (95% CI)	*P*
Occurrence of dose reductions	CapeOx, PPI versus no PPI	1.26 (0.66-2.41)	.476
	FOLFOX, PPI versus no PPI	2.03 (1.04-3.96)	.039
	PPI, CapeOx versus FOLFOX	1.13 (0.51-2.50)	.773
	No PPI, CapeOx versus FOLFOX	1.80 (1.13-2.89)	.014
Occurrence of dose delays	CapeOx, PPI versus no PPI	1.48 (0.74-2.97)	.266
	FOLFOX, PPI versus no PPI	1.64 (0.72-3.74)	.237
	PPI, CapeOx versus FOLFOX	0.58 (0.22-1.50)	.259
	No PPI, CapeOx versus FOLFOX	0.64 (0.39-1.06)	.084
Occurrence of premature treatment discontinuation	CapeOx, PPI versus no PPI	1.16 (0.54-2.52)	.701
	FOLFOX, PPI versus no PPI	1.31 (0.60-2.87)	.500
	PPI, CapeOx versus FOLFOX	0.87 (0.34-2.21)	.769
	No PPI, CapeOx versus FOLFOX	0.98 (0.55-1.76)	.944

Abbreviations: CapeOx = capecitabine, oxaliplatin; CI = confidence interval; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; OR = odds ratio; PPI = proton pump inhibitor.

Clinical Implications

The results of our study suggest that concurrent PPI and CapeOx receipt should be avoided to maximize chemotherapeutic efficacy. Moreover, our results support the provision of FOLFOX to patients in whom PPIs cannot be avoided. PPIs, while generally well tolerated and beneficial when indicated, are not benign medications, and other potential adverse effects include hypomagnesemia, bone fractures, and *Clostridium difficile* infections with long-term use.[42,43] Clinical PPI deprescribing guidelines were published in *Canadian Family Physician* in May 2017 and may be used to assist with PPI discontinuation.[44] Of interest, acidic beverages were shown to increase erlotinib bioavailability when administered to patients receiving concurrent PPIs during one recent study; however, the utility of this option to manage this potential drug interaction requires further investigation.[45]

Conclusion

This retrospective study demonstrated a significant association between reduced RFS and concurrent PPI receipt among CapeOx-treated stage II-III CRC patients. This effect was not seen in patients treated with FOLFOX, suggesting that there is a drug interaction between capecitabine and PPIs and no effect of PPIs on the underlying malignancy. Given the ubiquity of PPI receipt, more research is needed to investigate interaction profiles of these medications. Multicenter studies and pharmacokinetic trials should

be undertaken to corroborate our results and to guide optimization of treatment outcomes.

Clinical Practice Points

- Widely prescribed among cancer patients, PPIs are potent acid-reducing agents that have been shown to reduce absorption of various oral anticancer agents with pH-dependent solubility, such as erlotinib and dasatinib. Emerging studies have suggested that PPIs may detrimentally affect capecitabine efficacy via similar means. Conversely, other literature suggests that PPIs may negatively affect CRC itself. To investigate this further, our retrospective chart review sought to examine PPIs' effect on effectiveness of 2 comparable adjuvant chemotherapy regimens, CapeOx and FOLFOX, in stage II-III CRC patients.
- Results from our study suggest that PPIs negatively affected RFS in early-stage CapeOx-treated CRC patients while yielding no significant effect among FOLFOX-treated patients. To maximize chemotherapeutic efficacy, this suggests that concurrent PPI and CapeOx receipt should be avoided, and provision of FOLFOX to patients who must continue to receive PPIs may be considered.
- Practitioners should be cognizant of this potential drug–drug interaction between capecitabine and PPIs and should consider that long-term PPI receipt is associated with other potential adverse effects beyond this scope. Clinical PPI deprescribing guidelines are available to assist with PPI discontinuation, should this be the preferred method of management. Concurrent consumption of acidic beverages to mitigate this potential interaction requires further study.

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Disclosure

The authors have stated that they have no conflict of interest.

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