Real world outcomes for neoadjuvant capecitabine versus infusional 5-fluorouracil in the treatment of locally advanced rectal cancer

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/imj.15045

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Support: No funding was received for this article.

Disclosure: The named authors have nothing to declare in relation to this article.

Introduction

Rectal cancer is among the more common cancers worldwide and a leading cause of cancer-related death [1]. For patients diagnosed with locally advanced disease, where standard therapy includes initial long course chemoradiation followed by surgery [2], a 70% 5-year survival rate is achieved [3, 4]. In recent years capecitabine, an orally bioavailable fluoropyrimidine has become an alternative to the traditional use of infusional 5-FU, based on two large randomised trials demonstrating equivalence [5-7]. A more recent development has been the routine use of adjuvant oxaliplatin in patients that achieve a poor response to CRT, in part based on the overall survival benefit demonstrated in a randomised phase II study[8].

While capecitabine is an attractive option, being cheaper and more convenient than infusional 5FU [9], there remains a lack of data regarding the impact of this practice change in the real-world setting.

While it is important to evaluate the impact of any new therapy as it is adopted into the routine care setting, given the uncertain external validity of trial data, this is particularly important for oral therapies where patient compliance adds another element of uncertainty. Here we investigate the uptake of capecitabine at 3 large Australian hospitals and focus our analysis on pathological complete response rates, an early measure of CRT impact that is strongly linked with survival outcomes [10-12].

Methods

Eligibility

Patients from Melbourne Health, Eastern Health and Western Health in Melbourne, Australia who received neoadjuvant CRT for LARC from 1st January 2009 to 31st December 2018 were identified from the Australian Comprehensive Cancer Outcomes and Research Database (ACCORD). ACCORD, established in 2003, is a point of care database collecting prospective data on consecutive patients diagnosed with colorectal cancer at contributing hospitals. Magnetic Resonance Imaging (MRI) of the pelvis for initial local staging of rectal cancer was routinely used from 2009, having been incorporated into the Medicare Benefits Schedule that year, hence this was determined to be our first recruitment year. This study received approval from the Melbourne Health Ethics Review Board (approval number 201703/4).

Patients were included if they received neoadjuvant therapy with either capecitabine or infusional 5FU, proceeded to surgery and had a known pathological response. Data extracted included patient demographics, cancer stage, tumour site, treatment and outcomes. The IRSAD score (index of relative social disadvantage) was calculated based on postcode[13]. Pathological response was

determined as either complete (no evidence of invasive carcinoma) or incomplete (any remaining invasive carcinoma at the primary site or lymph nodes) based on routine histopathology from standard of care surgery, as reported by the local pathologist. Recurrence was determined by the clinician and could be based on clinical, biochemical or radiological findings. Recurrence free survival (RFS) was defined as the time from initial diagnosis until the date of recurrence, censored at the date of last review in the absence of an event.

Statistical Analysis

Demographics, disease and treatment characteristics were described using descriptive statistics and compared for patients who received neoadjuvant capecitabine versus infusional 5FU. Chi-square analysis and Fisher's exact tests were used for comparison of categorical variables, and the Mann-Whitney test for comparison of continuous variables. Univariable and multivariable logistic regression was used to estimate odds ratios for pCR. Multivariable analysis was performed on univariable factors where $p < 0.1$. The Kaplan-Meier method was used to calculate survival data, with log-rank and logistic regression tests being used to assess differences in survival rate. Analyses were performed with Stata 12.

Results

Demographics and disease characteristics

As shown in Figure 1a we initially identified 1663 patients with rectal cancer, with a final cohort of 657 eligible patients analysed. Demographics and disease characteristics are presented in Table 1. No differences in baseline characteristics were found between the capecitabine and 5-FU-treated groups. The median age was 62.6 and 63.9 years in the capecitabine and 5-FU groups respectively.

More than 90% of patients had a good performance status (ECOG 0 or 1). The bulk of tumours were in the lower (51%) and middle rectum (35%). Preoperatively, 83% of patients were stage T3-4 and 72% were N1-2.

Patient treatment

Figure 1b shows the trend in the use of capecitabine and 5-FU in neoadjuvant CRT over time. The proportional use of capecitabine increases after 2014, coinciding with the results of the NSABP protocol R-04 trial (first presented in January 2014 at the GI cancers Symposium, published in 2015) establishing capecitabine as a standard of care in the neoadjuvant setting [7] and the resultant pharmaceutical benefits derestriction of capecitabine in Australia in late 2014, making this widely available to patients in the routine care setting.

The use of chemotherapy agent did vary by treatment centre. All three centres contributed patients consistently across all years of the study, but with varying degrees of uptake in the use of capecitabine. In a subset analysis of 100 capecitabine-treated patients across all three sites, no significant deviation from the recommended dosage regimen (825mg/m^2 bd on days of radiotherapy) was found, with 90% of patients being dosed at a minimum of 80% of the recommended BSA-based dosage calculation. This subset was typical of the capecitabine–treated study population; a median age of 61.7 years, 72% male, 96% performance status 0-1 and split between 3 sites (A 15%, B 39%, C 46%). Where dose reductions occurred, these were due to mainly advanced age and/or significant co-morbidity. No analysis was made of 5FU dosing, but the standard protocol remained 5FU 225mg/m^2/day as a continuous infusion for the duration of the study period.

The standard radiation protocol was 50.4 Gy neoadjuvant radiotherapy in 28 fractions. Surgery was performed at a median of 9-10 weeks post completion of neoadjuvant therapy. A high number of

patients completed preoperative chemoradiotherapy across both groups. Time from completion of CRT to surgery was slightly longer in the capecitabine group (median 9.6 vs. 9 weeks). Most patients went on to receive adjuvant chemotherapy postoperatively, 70% in the 5FU group and 60% in the capecitabine group. Typically, the same fluoropyrimidine was used as in the neoadjuvant setting. There was a significantly higher usage of oxaliplatin doublet adjuvant therapy after neoadjuvant capecitabine versus after neoadjuvant 5FU (44% versus 6%, p = <0.01).

Pathology outcomes

The overall pCR rate was 21.3% (140/657), including 13.8% (n = 22/159) for the capecitabine group and 23.7% (n = 118/498) for the infusional 5-FU group (p = 0.0076). There was a numerically lower pCR rate for capecitabine across all three treatment sites (A: 21.7% vs 24.3%, B: 13.7% vs 25.3%, C: 11.8% vs 19.7%), but no statistically significant difference at any individual centre. Involved margins at surgery were seen in 3/159 (1.9%) of the capecitabine treated patients and 8/498 (1.6%) that received 5-FU.

As univariable analysis identified the neoadjuvant chemotherapy (capecitabine or 5-FU), treatment centre, IRSAD score and time to surgery as being associated with a pCR (p <0.1) these were included in a multivariable logistic regression model to assess their predictive value (Table 2). Results showed the chemotherapy agent and time from completion of CRT to surgery to be significant factors, with 5FU and longer wait times associated with a higher likelihood of pCR.

Recurrence outcomes

A total of 124 patients (18.9%) had a documented recurrence, 25 of whom were in the capecitabine group (at a median follow-up of 24.7 months) and 99 in the 5-FU cohort group (at a median follow-

up of 61.9 months). This included 22 patients (3.3% of all patients) having a locoregional recurrence as the initial site of relapse (with or without concurrent distant recurrence). No significant difference in 2-year recurrence free survival was observed, as shown in Figure 2**.** Overall survival data was not examined due to the relatively short follow-up.

Discussion

Standards of practice change as new therapeutic options become available, typically having been demonstrated in clinical trials to be equivalent or superior to existing standards. Our data demonstrates that, following the reporting of the pivotal trials in LARC, capecitabine has largely replaced infusional 5FU as a component of CRT, presumably driven by superior convenience and cost savings. Given this, our finding of inferior pCR rates in patients treated with capecitabine is of potential concern, particularly as it cannot be explained by any differences in the patient population treated.

The major finding of our study is that the pCR rate achieved with neoadjuvant oral capecitabine (13.8%) was significantly inferior ($p = 0.0076$) to that achieved with intravenous infusional 5-FU (23.7%). This difference is not explained by any observed differences in the two patient cohorts - including age, gender, pre-operative tumour stage and tumour location. The numerically lower pCR rate for capecitabine treated patients was also consistently seen across the three centres. Other Australian investigators also recently reported on a similar study to ours, using data from a single site, also finding a numerically lower pCR rate in capecitabine treated patients (9.5% vs 20%) but this difference was not statistically significant ($p = 0.082$)[14]. We were unable to find any other reports comparing outcomes for capecitabine versus 5FU in the routine care of LARC patients in the modern era where capecitabine appears to have been widely adopted as the standard fluoropyrimidine.

Among patients treated with capecitabine we did not find any suggestion of a patient subset where capecitabine should be avoided, with no evident impact of age or gender, and pCR rates were not worse in patients with a lower socioeconomic status as defined by the IRSAD score. Prompted by the unexpectedly low pCR rate in capecitabine treated patients we also reviewed a sample of 100 patients (63% of all capecitabine treated patients) to exclude the possibility of systematic underdosing of capecitabine. This analysis found a high proportion (90%) of patients were prescribed a minimum of 80% of the recommended standard body surface area-based dose suggesting underdosing was not responsible for the difference. One possible explanation that may be contributing to the low pCR rate is patient adherence, however we cannot explore this possibility further with our data set. A number of prior studies, using differing methods of adherence measurement, have reported capecitabine adherence to be between 67% and 100% [15-22], however in the absence of any precise measure of adherence these remain estimates of uncertain accuracy. More broadly across a range of oral antineoplastic agents, adherence varies widely across cancers and across methods of measurements, ranging from 16-100%, with adherence declining over time [23, 24].

Oral chemotherapy is considerably more convenient than intravenous-based therapy, with multiple studies showing that patients prefer oral administration provided there is no compromise in efficacy [25, 26]. Across a range of cancers over recent years the use of oral chemotherapy has been consistently rising [27, 28], with current approaches to adherence measurement including patient self-report, pill diaries, pill counting, pharmacy refill rates and Medication Event Monitoring System (MEMS)[29, 30]. However there remains no validated measure of adherence. The prospective randomised trial data finding similar pCR rates following the use of capecitabine versus infusional 5FU collected compliance data, but this is not achievable in a routine care setting [6]. Regardless, the efficacy of any

new therapy should be carefully evaluated in the real world setting as there are many factors beyond compliance that could impact efficacy and safety.

Limitations of our study include the different time periods over which the patients were treated, so we cannot exclude an unknown change in practice as a potential explanation. One evident impact of the different time periods where the majority of patients were treated is that while the proportions of patients receiving adjuvant chemotherapy remained steady, more capecitabine treated patients received post-operative oxaliplatin, which has emerged as a recent standard of care in high risk patients [8]. This may have modestly impacted the 2 year local recurrence rate in the group receiving neoadjuvant capecitabine and any interpretation of survival data will remain challenging in a non-randomised comparison. Another limitation of our data is that we relied on local pathology review but it is unclear how this could have impacted our findings. Scoring of tumour regression has been inconsistent over time, however the definition of pCR has remained consistent with consistent findings across all three sites.

Practice may also have evolved in other ways over the course of the study, but there was no evident practice change in terms of patient selection or radiation therapy delivery that would have impacted the rate of pCR. In recent years there has been much discussion of the watch and wait strategy but there is no evidence that this is being substantially adopted at these sites, with the patients not proceeding to surgery mostly being recorded as being unfit for the operation, with the occasional patient declining surgery against medical recommendation.

Conclusion

With no difference in baseline patient or tumour characteristics, the reason for decreased efficacy associated with capecitabine use, as measured by pCR rate, remains unclear. Compliance is one possible explanation. There is always some uncertainty as to the external validity of any clinical trial findings, due to the selected nature of the patients and centres involved. For any new oral therapy there is the uncertainty as to whether treatment compliance in the real-world setting will match that of the trial population, potentially compromising efficacy. This highlights the importance of not only careful patient selection when using oral chemotherapy, but also the need for patient education in multiple sessions and the implementation of an effective multidisciplinary adherence monitoring programs to ensure that patients are receiving the full benefit of the prescribed therapy [31]. Further prospective studies into compliance assessment and interventions to improve oral therapy compliance in cancer are required, as well as longer follow up to ascertain any detrimental effect in survival from lower pCR rates. This not only applies to oral capecitabine; it is applicable to all forms of oral therapy, an increasingly more available option in cancer medicine.

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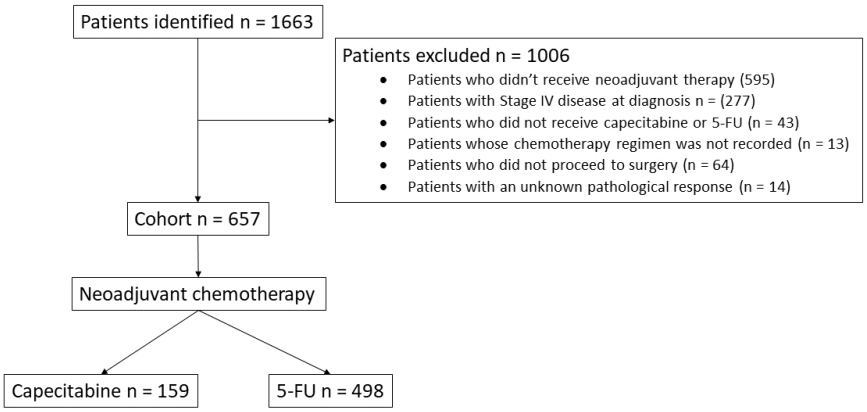

Figure 1a. CONSORT diagram describing neoadjuvant chemotherapy for ACCORD patients enrolled between 2009 and 2018

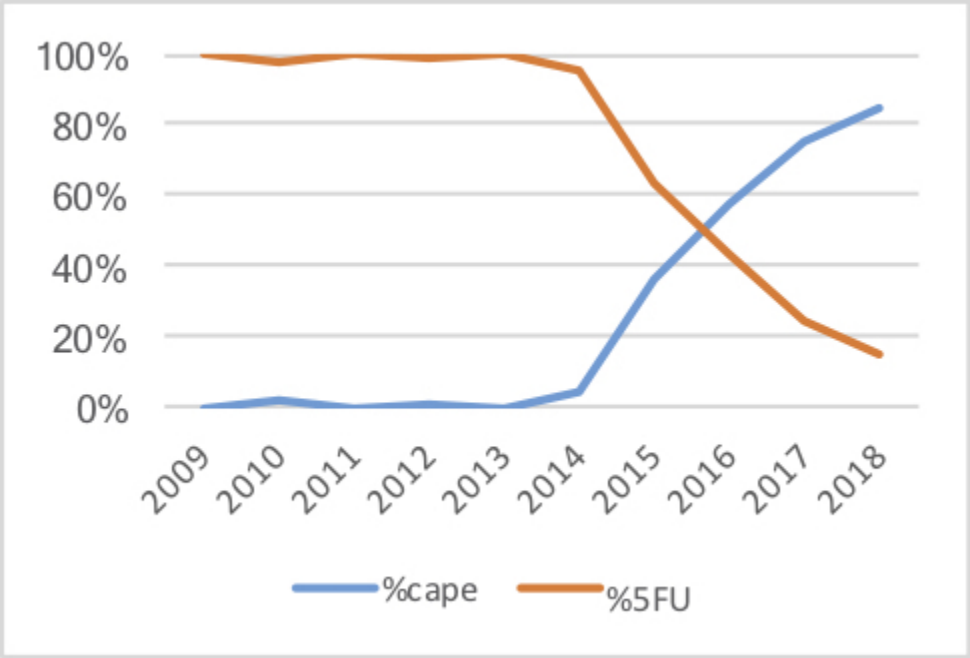

Figure 1b. Usage trends of capecitabine and 5-FU over time

	Capecitabine	5FU	*p* value
Total n (%)	159 (24.2)	498 (75.8)	
Demographics			
Age in Years (%)			
Median (IQR)	62.6 (52.9-73.6)	63.9 (55.6-73.2)	0.295
Gender (%)			
Male	108 (67.9)	326 (65.5)	
Female	51 (32.1)	172 (34.5)	0.631
Treatment Centre (%)			
A	23 (14.5)	136 (27.3)	
B	51 (32.1)	245 (49.2)	
C	85 (53.4)	117 (23.5)	<0.0001
ECOG at Baseline (%)			
PS 0-1	150 (94.3)	465 (93.4)	
PS >=2	8 (5.0)	28 (5.6)	
Not recorded	1 (0.6)	5 (1.0)	0.844
Clinical Features			
Tumour Site (%)			
Upper	14 (8.8)	47 (9.4)	
Middle	48 (30.2)	181 (36.3)	
Lower	81 (50.9)	257 (51.6)	
Not specified	16 (10.1)	13 (2.6)	0.710
Pre-operative Stage (%)			
II (T3,T4, N0)	31 (19.5)	106 (21.3)	
III (Any T, N+)	120 (75.5)	351 (70.5)	
Other/Not recorded	8 (5.0)	41 (8.2)	0.574
Treatment Characteristics			
Neoadjuvant Radiotherapy dose			
50.4 Gy	155 (97.5)	462 (92.8)	
Other	3 (1.9)	10 (2.0)	
Not recorded	1 (0.6)	26 (5.2)	1.000
Completed Neoadjuvant Chemoradiotherapy (%)			
Yes	151 (95.0)	455 (91.4)	
No	7 (4.4)	40 (8.0)	
Unknown	1 (0.6)	3 (0.6)	0.157
Time from Completion of Neoadjuvant Therapy to Surgery			
Median weeks (IQR)	9.6 (8.3-11.7)	9.0 (7.4-11)	0.0019
Surgery			
Anterior Resection	107 (67.3)	321 (64.5)	
Abdominoperineal Resection	39 (24.5)	156 (31.3)	
Other	13 (8.2)	21 (4.2)	0.059
Post-operative Chemotherapy Regimen (%)			
5FU	5 (5.3)	299 (85.9)	
Capecitabine	48 (50.5)	12 (3.5)	
Oxaliplatin doublet	42 (44.2)	22 (6.3)	
Other	0 (0)	4 (1.1)	<0.0001
Unknown	0 (0)	11 (3.2)	
Outcomes			
Complete Pathological Response (%)			
Yes	22 (13.8)	118 (23.7)	
No	137 (86.2)	380 (76.3)	0.0076
Margins Involved (%)			
No	142 (89.3)	478 (96.0)	
Not reported	14 (8.8)	12 (2.4)	
Yes	3 (1.9)	8 (1.6)	0.721
Local Recurrence (%)			
Yes	2 (1.3)	20 (4.0)	
No	157 (98.7)	477 (95.8)	
Not investigated	0 (0)	1 (0.2)	0.127

Table 1: Patient demographics, disease characteristics, treatment and outcome

Variable	Odds Ratio	*p* value	95% CI
Chemotherapy agent			
Capecitabine	-		
5-FU	1.9	0.016	1.13-3.19
Treatment Centre			
A	-		
B	0.83	0.434	0.51-1.33
C	0.72	0.249	0.42-1.25
IRSAD Score			
High	-		
Low	1.35	0.149	0.90-2.04
Time from Neoadjuvant Chemoradiotherapy to Surgery			
>median (>9.14 weeks)	-		
≤median (≤9.14 weeks)	0.67	0.045	0.45-0.99

Table 2. Multivariable logistic regression of independent predictors for pCR, n = 654

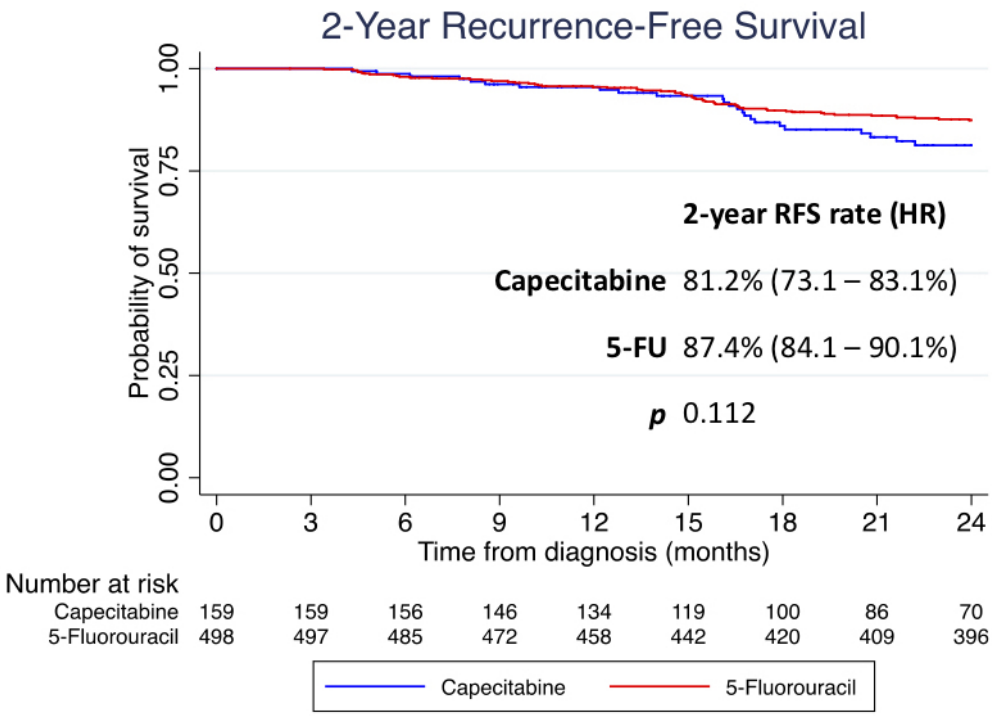

Figure 2. 2-year recurrence-free survival