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Phase I/II trial of dose-reduced capecitabine in elderly patients with advanced colorectal cancer

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ABSTRACT

Background Combination chemotherapy is associated with improved outcomes in trials of selected fit patients with advanced colorectal cancer (aCRC). For older or less-fit patients, combination chemotherapy is associated with greater toxicity and less benefit. Capecitabine monotherapy is a reasonable option for those patients, but the optimal dose remains controversial.

Methods A multicentre phase I/II trial of reduced-dose capecitabine (2000 mg/m^2, days 1–14 every 21 days) was conducted in 221 patients representing one or more of the following subsets: age greater than 65 years (n = 167), Eastern Cooperative Oncology Group (ECOG) performance status of 1 or greater (n = 139), elevated lactate dehydrogenase (LDH) (n = 105), or prior pelvic radiation (n = 54). Based on phase I results, patients with prior pelvic radiation received capecitabine 750 mg/m^2 twice daily. The goal was to ascertain efficacy in a design that was unlikely to cause high levels of toxicity.

Results Median age in the patient cohort was 72 years. A median of 5 and a mean of 8 capecitabine cycles were given (range: 0–50 cycles). Grade 3 or 4 toxicity occurred in 25% of patients during the first 3 cycles (8.1% hand–foot syndrome, 7.7% diarrhea). The response rate was 13.6%, with a 69.7% disease control rate. Median progression-free survival (PFS) was 5.6 months. Post progression, 56 patients received further capecitabine monotherapy (median of 4 additional cycles). Median overall survival duration for the patients was 14.3 months. Median survival was significantly higher for those who, at baseline, had an ECOG performance status of 0 (compared with 1 or more) and normal LDH (compared with elevated LDH).

Conclusions Toxicity is less with dose-reduced capecitabine than with historical full-dose capecitabine, with only a small trade-off in efficacy, seen as a lower objective response rate. The improved tolerability could lead to an increased number of cycles of therapy, and PFS appears to be consistently higher at the lower dose. Those observations should, in the absence of a head-to-head clinical trial, be viewed as compelling evidence that 1000 mg/m^2, or even 750 mg/m^2, twice daily is an appropriate dose in elderly or frail patients with aCRC.

Key Words Colorectal cancer, advanced; capecitabine; elderly patients; frail patients; sequential monotherapy

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INTRODUCTION

Colorectal cancer (CRC) is a major cause of morbidity and mortality, and the 2nd most common cause of cancer death in industrialized countries[1,2]. The incidence of CRC increases with age, with more than 50% of cases occurring in individuals more than 70 years of age, and 40% occurring in those more than 75 years of age[1,3]. Approximately a quarter of elderly patients present with advanced disease, and about half will develop metastasis at some point in their disease course[4,5]. Despite the fact that elderly patients with CRC benefit from chemotherapy in both the adjuvant and metastatic settings, they are less likely than their younger counterparts to receive chemotherapy[6,7]. Elderly patients are underrepresented in CRC clinical trials, comprising about 15%–20% of

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patients enrolled[8,9]. Furthermore, the elderly patients enrolled in trials often have a good performance status (PS) and limited comorbidities. As a result, uncertainty is increased with respect to dose, safety, and efficacy for elderly or frail patients.

For more than 40 years, 5-fluorouracil (5FU) has been a mainstay in the treatment of CRC, and it is included in most chemotherapy regimens for advanced disease (ACRC)[8,10–14]. The use of bolus 5FU and leucovorin (LV) was previously the "gold standard" in the treatment of ACRC. Bolus 5FU–LV, the Mayo regimen, has also been shown to be more toxic and less active than infusional 5FU–LV[15]. Trials have supported the addition of any or all of irinotecan, oxaliplatin, and bevacizumab to 5FU in that setting[14,16–20]. In addition to intravenous bolus and continuous-infusional 5FU, there is also an oral option: capecitabine.

Capecitabine is an oral fluoropyrimidine that is enzymatically converted to 5FU by cytidine deaminase and thymidine phosphorylase, which are found in higher concentrations within some solid tumours[21]. Surgically excised CRC tumour samples from patients pretreated with a short course of capecitabine showed that levels of 5FU within the tumour were 3.2 times those in adjacent tissues, and 20 times those measured in plasma[22]. However, plasma levels of capecitabine and its metabolites are not useful for assessing dose adjustments, safety, or efficacy, meaning that clinic trials are required to assess dose in specific populations[23]. Oral capecitabine offers an advantage to elderly or frail patients, who often depend on family and caregivers, in that less time is spent travelling to treatment centres. Oral palliative chemotherapy was preferred by 95% of patients, assuming that such treatment did not compromise the response rate[24,25].

Capecitabine was initially assessed at a dose of 1250 mg/m^2 twice daily for the first 14 days of a 21-day cycle. In two phase III trials comparing capecitabine with bolus 5FU–LV in ACRC, capecitabine was associated with improvements in overall response rate (ORR) and in toxicity profile[26,27]. Significant decreases were observed in grades 3 and 4 diarrhea, stomatitis, nausea, and alopecia, with the only increased toxicity being cutaneous hand–foot syndrome[28]. When comparing capecitabine with continuous infusional 5FU for the first-line treatment of ACRC, capecitabine is associated with a significant increase in diarrhea and hand–foot syndrome, but with significantly less neutropenia and other hematologic toxicities[29]. Capecitabine has also been validated as a substitute for 5FU in the FOLFOX4 regimen (5FU–LV–oxaliplatin) in the first- and second-line treatment of ACRC[30,31].

Data with respect to the treatment of elderly or frail patients with ACRC are limited and come mostly from subgroup analysis of phase II and III trials. Systemic chemotherapy offers both a survival and quality-of-life (QOL) benefit to elderly patients with ACRC[32]. The efficacy from 5FU-based therapy experienced by elderly and less-fit patients with ACRC is similar to that experienced by their younger counterparts, with PS being the most important predictive factor[10].

Capecitabine has been shown to be an effective and well-tolerated treatment in elderly and unfit patients with ACRC who are not suitable candidates for combination chemotherapy[33]. In elderly and less-fit patients, combination therapy with capecitabine and oxaliplatin or bevacizumab has also demonstrated tolerability, efficacy, and the appropriateness of capecitabine as a substitute for intravenous 5FU[11,14,34–36]. Capecitabine toxicity has been reduced by lowering the starting dose to 1000 mg/m^2 twice daily in combination therapies and by lowering the dose a further 20%–25% in patients with a creatinine clearance of 30–50 mL/min[34,37].

The optimal capecitabine dose is not known[13]. Many physicians use capecitabine monotherapy at a starting dose of 1000 mg/m^2 twice daily without a demonstration of efficacy at that dose in evidence from formal trials[14,35]. The initial trials validating capecitabine monotherapy in ACRC, and the subsequent trials assessing capecitabine use in elderly patients, reported that 30%–50% of patients required capecitabine dose reductions while on study[14,38,39]. A recent report by Chang and colleagues[40] assessing adjuvant capecitabine dosing in elderly patients used a dosing strategy that started at 1000 mg/m^2 twice daily and increased to 1250 mg/m^2 twice daily for the second cycle if the first was well tolerated. The higher dose was sustainable in fewer than half the patients who met the criteria for dose escalation.

Capecitabine offers an efficacious substitute for intravenous 5FU in ACRC. Its favourable tolerability and oral administration make it ideal for elderly and less-fit patients with ACRC. However, considering the frequency of capecitabine dose reductions in published trials, the optimal starting dose is not yet established. Here, we report a phase I/II study of capecitabine in patients not known to benefit from, or be suitable for, combination chemotherapy. Our primary endpoint was the response rate to capecitabine monotherapy, using a starting dose of 1000 mg/m^2 twice daily, with subgroup analyses of patients by age, PS, lactate dehydrogenase (LDH), prior pelvic radiotherapy (RT), and liver function tests. Secondary endpoints included time to progression (TTP), overall survival (OS), QOL score on the Functional Assessment of Cancer Therapy–General (FACT-G), toxicity rates during the first 3 cycles, and the influence of prognostic factors on the foregoing secondary endpoints.

METHODS

Patients

Eligible patients had histologically proven ACRC deemed not curable by resection, including hepatic metastasectomy or receipt of RT. Enrolled participants had not previously received chemotherapy for metastatic disease. Patients were either too unfit or not known to benefit from combination chemotherapy, specifically the Saltz IFL regimen (irinotecan–5FU–LV), the "gold standard" at the time of recruitment[19]. From August 2001 to March 2005, 221 patients were enrolled. Patients were required to meet at least one of the following five criteria: age greater than 65 years; Eastern Cooperative Oncology Group (ECOG) PS of 1 or 2; LDH above the upper limit of normal; prior pelvic radiation (because such patients were excluded from studies showing benefit with combination chemotherapy); or abnormal liver function tests

or enzymes (total bilirubin > 34.2 mol/L, or aspartate aminotransferase > 3 times the upper limit of normal without liver metastasis or > 5 times the upper limit of normal with liver metastasis). Patients were ineligible if their ECOG PS was 3 or greater; if they had significant comorbidities that would not allow them to comply with the requirements of the trial; or if they had relapsed within 6 months after completion of the last adjuvant chemotherapy.

Study Design and Treatment

Phase I

Initially 6 patients were accrued in each subgroup, with 39 patients eventually being included in 1 or more of the 5 subgroups. If fewer than 2 of 6 patients in a subgroup experienced dose-limiting toxicities during the first 3 cycles, then that dose was advanced and tested in the phase II portion of the trial. If 2 or more patients experienced dose-limiting toxicities, the dose for that subgroup would be lowered one level, to 750 mg/m^2 twice daily and then to 500 mg/m^2 twice daily, until a safe dose could be established and advanced to phase II.

Phase II

The 188 patients accrued were each included in 1 or more of the 5 subgroups: age 65 year or greater (n = 167), ECOG PS of 1 or greater (n = 139), elevated LDH (n = 105), prior pelvic radiation (n = 54), and abnormal liver function tests (n = 5). Patients received capecitabine 1000 mg/m^2 orally twice daily for days 1 through 14 of a 21-day cycle.

Dose Reductions and Delays

For patients experiencing grade 2 or greater hematologic toxicities, the capecitabine dose was delayed until the toxicities reached grade 1 or less. Patients experiencing grades 0–2 nausea or vomiting received antiemetics and supportive care, but proceeded at the discretion of the physician. In patients with grade 3 nausea or vomiting, a 25% capecitabine dose reduction was implemented; in patients with grade 4 nausea or vomiting, the dose reduction was 50%. For diarrhea or mucositis at grade 1 or less, patients proceeded; for diarrhea or mucositis at grade 2 or greater, patients waited until symptoms reached grades 0–1 before proceeding. When grade 2 diarrhea or mucositis occurred, patients proceeded without dose reductions once the symptoms resolved. For grade 3 diarrhea or mucositis, or any second episode of diarrhea or mucositis, patients received a 25% dose reduction. After grade 4 diarrhea or mucositis, a second occurrence of grade 3 symptoms, or a third occurrence of grade 2 symptoms, patients received 50% of the capecitabine dose. Management of hand–foot syndrome was the same as that for diarrhea or mucositis. Patients with a creatinine clearance of 30–40 mL/min received 75% of the capecitabine dose, and patients with a creatinine clearance below 30 mL/min were excluded. Patients with an increase in angina from their baseline or with acute coronary syndrome discontinued therapy.

Safety and Efficacy Assessments

The primary endpoint of the study was the ORR. Secondary endpoints included TTP, OS, FACT-G score, and toxicity rates. The effects of prognostic factors on response, progression, survival, and toxicity were examined. Response and progression were defined using the Response Evaluation Criteria in Solid Tumors, version 1.0. Toxicity assessments were completed every 3 weeks using NCIC toxicity criteria.

Tumours were evaluated after 2 cycles and again after each additional 2 cycles by computed tomography imaging or chest radiography (or both) while on trial. The TTP and OS were measured from initiation of treatment. Disease control was defined as the sum of complete response, partial response, and stable disease. The response rate was defined as complete responses plus partial responses. Between-group comparisons of response used the chi-square test. The OS and TTP were estimated using the Kaplan–Meier method, and between-group comparisons used Cox regression.

The FACT-G questionnaires were completed at enrolment, after each cycle of capecitabine, and once after protocol completion if possible. Patients were excluded from the QOL analysis in the absence of completion of a baseline FACT-G questionnaire and at least 1 further questionnaire. The minimal important difference for the FACT-G has previously been validated as 5–6[41]. Here, a meaningful improvement in QOL is reported as an increase of 6 or more on the FACT-G (the upper bound value of the validated range).

RESULTS

Our phase I and II trials included, respectively, 39 and 182 patients with previously untreated ACRC. Table I presents their baseline characteristics. Of the 221 patients accrued, 1 did not start treatment, but is included in the analysis. In 69 patients (31%), adjuvant chemotherapy had already been given for the initial presentation of CRC (stage III or less). Most patients, 96%, had previously undergone colorectal surgery; only 54 patients, 24%, had received prior pelvic RT.

Phase I

Five subgroups (age ≥ 65, ECOG PS ≥ 1, LDH > the upper limit of normal, prior pelvic RT, abnormal liver function tests) of 6 patients who would have been excluded from the Saltz IFL trial were given 1000 mg/m^2 capecitabine twice daily to assess for tolerability. The abnormal liver function tests group failed to accrue 6 patients in the phase I portion of the study. In the prior pelvic RT group, more than the pre-specified permitted number of patients experienced a dose-limiting toxicity (all diarrhea). All other groups tolerated the starting dose of capecitabine. Patients who had received prior pelvic RT tolerated capecitabine at the first planned incremental reduction (750 mg/m^2 twice daily).

Phase II

Patients received a median of 5 cycles of treatment, with a range of 0–50 cycles and a mean of 8 cycles. Most patients (n = 175, 79%) received a starting dose of 1000 mg/m^2 of capecitabine twice daily. Dose reductions were required for 35% of patients over the entire study, although reductions were needed for only 14% of patients in the first 4 cycles. Dose delays occurred in 49% of patients, with 26% of the delays occurring in the first 4 cycles.

The overall response rate was 13.6%, and the disease control rate was 69.7% (Table II). Median time to progression was 5.6 months [Figure 1(A)]. The PFS rate was 47% at 6 months, 21.6% at 12 months, and 4.3% at 24 months; 4 patients (2.1%) had not experienced progressive disease at 3 years. The median OS duration was 14.3 months [Figure 1(B)]. The OS rate was 55.0% at 1 year, 27.7% at 2 years, 13.6% at 3 years, and 6.3% at 5 years.

Treatment was generally well tolerated. In cycles 1–3, 21.7% of patients experienced grade 3 or 4 toxicity (Table III). Hand–foot syndrome was the most frequent treatment-related adverse event, with 9.5% of patients experiencing that toxicity at grade 3 or 4; diarrhea was next most frequent at 7.7%, and fatigue, at 4.5%. Treatment-related adverse events were generally the same in the subgroups (Table III). As already stated, patients with prior pelvic RT received capecitabine 750 mg/m^2 twice daily because of the higher rates of diarrhea that occurred at 1000 mg/m^2 twice daily. Only 1 patient experienced acute coronary syndrome related to treatment, and no patient experienced coronary vasospasm, although one third of the group had prior exposure to 5FU.

Subgroup analyses revealed that an age of 65 or older was not a significant prognostic factor [hazard ratio (HR): 0.76; 95% confidence interval (CI): 0.52 to 1.10; $p = 0.149$].

TABLE I Baseline characteristics of the study patients

Characteristic	Value
Patients (*n*)	221
Phase [*n* (%)]	
I	39 (17.6)
II	182 (82.4)
Starting dose[a] [*n* (%)]	
1000 mg/m^2	175 (79.2)
750 mg/m^2	46 (20.8)
Sex [*n* (%) men]	142 (64.3%)
Age	
Median (years)	72
>65 Years [*n* (%)]	173 (78.3)
ECOG PS ≥ 1 [*n* (%)]	145 (65.6)
Elevated LDH [*n* (%)]	106 (48.0)
Prior treatment [*n* (%)]	
Pelvic radiation	54 (24.4)
Surgery	206 (93.2)
Chemotherapy	69 (31.2)

[a] Given twice daily.
ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase.

TABLE II Best tumour response in the study patients (*n* =221)

Response type	Patients [*n* (%)]
Overall	30 (13.6)
Complete	4 (1.8)
Partial	26 (11.8)
Stable disease	124 (56.1)
Disease control rate	154 (69.7)
Progressive disease	47 (21.3)
Unknown	20 (9.0)

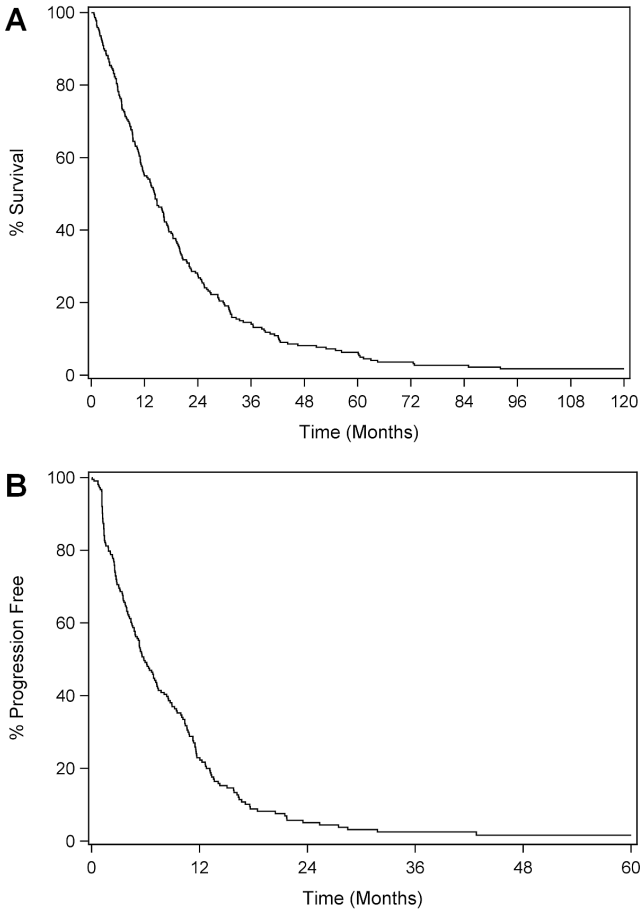

FIGURE 1 (A) Progression-free and (B) overall survival in the study cohort of elderly patients receiving reduced-dose capecitabine.

TABLE III Grade 3 or greater treatment-related events

Event	Incidence (%)	
	Cycles 1–3	Any cycle
Any	25.3	37.1
Diarrhea	7.7	12.2
Hand–foot syndrome	8.1	15.8
Nausea	2.1	3.9
Anorexia	2.1	2.5
Vomiting	1.6	2.5
Hematologic	0	0
Renal dysfunction	0	0
Acute coronary syndrome or coronary vasospasm	0.5	0.9

In patients who initiated therapy with elevated LDH, median survival duration was lower at 10.8 months compared with 17.5 months for patients with normal LDH [HR: 1.85; 95% CI: 1.32 to 2.59; $p < 0.001$; Figure 2(A)]. Compared with patients having an ECOG PS of 0, those with an ECOG PS of 1 or greater at the start of therapy did significantly worse [HR: 1.89; 95% CI: 1.29 to 2.75; $p = 0.001$; Figure 2(B)]. Elevated LDH and an ECOG PS of 1 or greater were both significant negative prognosticators by multivariate analysis (HR: 1.75; 95% CI: 1.18 to 2.58; $p = 0.005$; and HR: 1.69; 95% CI: 1.09 to 2.62; $p = 0.019$ respectively).

Of the 221 patients in the phase I and II portions of the study, 175 (79%) started with a capecitabine dose of 1000 mg/m^2 twice daily. Of the patients with prior pelvic RT, 46 received capecitabine 750 mg/m^2 twice daily, and 8 patients received 1000 mg/m^2 twice daily in the phase I portion of the study. The ORR was 19.4% for patients receiving a starting dose of 1000 mg/m^2 twice daily and 17.3% for those at the reduced dose. The disease control rate was 73.1% for patients starting at 1000 mg/m^2 twice daily; it was 63.0% for those starting at 750 mg/m^2 twice daily (Table IV). Patients receiving a starting dose of 1000 mg/m^2 twice daily had a median PFS duration of 5.9 months; the PFS duration was 4.7 months for patients receiving a starting dose of 750 mg/m^2 twice daily. The 1-year PFS in those groups was 23.0% and 22.3% respectively ($p = 0.416$).

Most patients who progressed on capecitabine monotherapy went on to receive post-protocol chemotherapy [125 of 188 patients (66.5%)]. The subsequent monotherapy or combination chemotherapy contained capecitabine 35% of the time (44 of 125 patients), 5FU 32% of the time, irinotecan 46% of the time, and oxaliplatin 3% of the time. A large proportion of patients [86 of 188 (45.7%)] went on to receive third-line chemotherapy. Third-line regimens included 5FU 55% of the time, irinotecan 48% of the time, oxaliplatin 26% of the time, and capecitabine 9% of the time. Of those patients, 56 (30%) received post-protocol capecitabine monotherapy (median: 4 cycles; average: 7.8 cycles; range: 1–40 cycles; 27% received 10 cycles or more).

Of the 182 phase II patients, 137 (75.3%) completed a baseline and at least one additional FACT-G questionnaire. The mean baseline score, out of a maximum of 108, was 81.6 (median: 85.9). The mean score peaked at 92.0 after cycle 10 (47 responses, Table V). The mean change from baseline was always positive, with the largest change, 4.0, occurring after cycle 12 (Table V). Patient scores reflecting a meaningful improvement in QOL ranged from 30% to 45% throughout each cycle. In 30.7% of the patients, the last recorded FACT-G score was 6 or more points higher compared with their personal baseline, the defined minimal important difference.

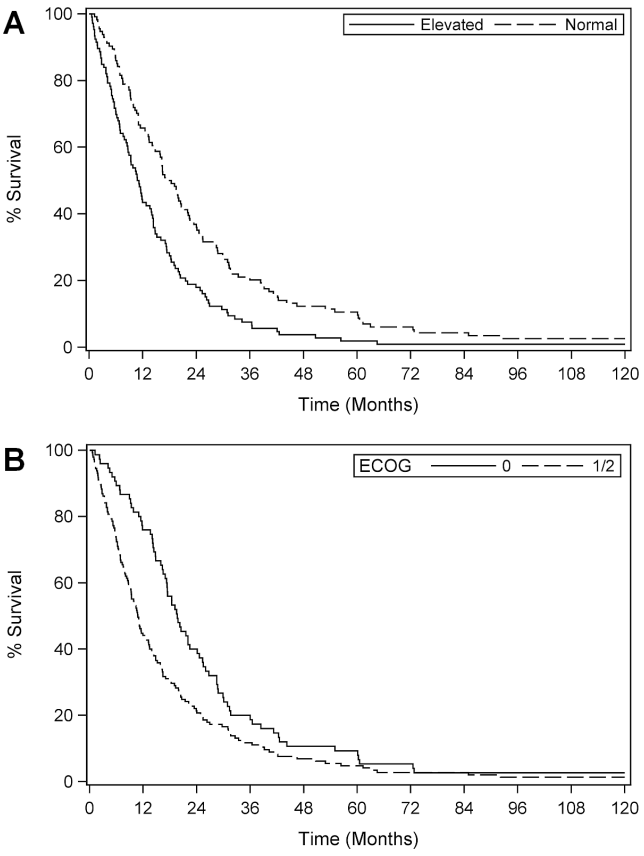

FIGURE 2 (A) Overall survival for elderly patients having normal lactate dehydrogenase (LDH) compared with those having elevated LDH [hazard ratio (HR): 1.85; 95% confidence interval (CI): 1.32 to 2.59; $p < 0.001$]. (B) Overall survival for patients having an Eastern Cooperative Oncology Group (ECOG) performance status of 0 compared with those having a performance status of 1 or greater (HR: 1.89; 95% CI: 1.29 to 2.75; $p = 0.001$).

TABLE IV Tumour response, survival, and toxicity by starting dose of capecitabine

Variable	Dose group (twice daily)	
	750 mg/m^2	1000 mg/m^2
Patients (*n*)	46	175
Response type [*n* (%)]		
Complete	2 (4.3)	3 (1.7)
Partial	6 (13.0)	31 (17.7)
Stable disease	21 (45.7)	94 (53.7)
Progressive disease	12 (26.1)	26 (14.9)
Not evaluable	5 (10.9)	21 (12.0)
Outcome		
1-Year PFS (%)	22.3	23.0
Median PFS duration (months)	4.7	5.9
1-Year OS (%)	56.5	54.6
2-Year OS (%)	30.4	27.0
3-Year OS (%)	8.7	15.5
Median OS duration (months)	14.3	14.3
Toxicity [*n* (%)]		
Hand–foot syndrome (cycles 1–3)		
Any grade	14 (30.4)	81 (46.3)
Grade 3 or greater	3 (6.5)	15 (8.6)
Diarrhea (any cycle)		
Any grade	20 (43)	77 (44)
Grade or greater	1 (2)	23 (13)[a]

[a] $p = 0.033$ by Fisher exact test.
PFS = progression-free survival; OS = overall survival.

TABLE V Scores for the study cohort on the Functional Assessment of Cancer Therapy–General

Time of completion	Patients (*n*)	Mean score	Median score	Mean change from baseline[a]	MID[b] (%)
Baseline	137	81.58	85.9	—	—
Cycle 2	118	83.16	86	+1.57	30.5
Cycle 4	83	85.71	87	+1.64	41
Cycle 6	74	87.88	87.1	+2.96	37.8
Cycle 8	57	90.75	93.3	+2.70	31.6
Cycle 10	47	92.03	96	+3.00	34
Cycle 12	39	88.86	93	+4.00	35.9
Cycle 14	29	88.32	93	+3.42	44.8
Last record	137	81.85	84	+0.26	30.7

[a] Change from that cohort's baseline score.
[b] Percentage of patients in that cohort with a score of 6 or greater above their baseline score.
MID = minimal important difference.

DISCUSSION

Our large single-armed multicentre phase I/II clinical trial evaluated capecitabine at a reduced dose. The initial capecitabine trials validated a dose of 1250 mg/m^2 twice daily in a younger population, and reductions from that dose level are common in elderly or frail patients[14,37,38].

Preliminary data from our trial were presented at the 2005 American Society of Clinical Oncology annual meeting, and that report has frequently been referenced by publications about the treatment of CRC in elderly patients. The primary endpoint of the phase II portion of the present study was to assess the response rate at 1000 mg/m^2 twice daily (dose-reduced capecitabine) or 750 mg/m^2 twice daily in patients with prior pelvic RT, as determined in the phase I portion. The response rate of 13.6% was less than the 25.7% reported by Van Cutsem[28] in the meta-analysis of the initial capecitabine efficacy studies, which had a younger and fitter population of more than 600 patients; however, the disease control rate in our trial was 70.0% compared with the 74.0% reported by Van Cutsem. Feliu and colleagues[33] conducted a single-arm trial with 51 elderly patients receiving capecitabine at 1250 mg/m^2 twice daily (full-dose capecitabine) and reported an ORR of 24% and a disease control rate of 67%, further suggesting that, with dose-reduced capecitabine in elderly or frail patients, the ORR decreases, but without a loss of disease control. Those rates are consistent with rates in other reports involving elderly patients with untreated metastatic CRC containing an arm with full-dose capecitabine[42,43].

The paucity of reported data verifying the appropriateness—or even the superiority (when considering toxicity and quality of life)—of using dose-reduced capecitabine was highlighted by the U.K. Medical Research Council's FOCUS2 trial[14], in which patients in the capecitabine arm received a dose of 1000 mg/m^2 twice daily for the first 6 weeks and then moved up to a "full dose" if they had no toxicities rated grade 2 or greater and if they consented. The use of dose-reduced capecitabine is common outside of trials—an approach that is exemplified by the Australasian Gastrointestinal Trials Group MAX trial[35], in which the capecitabine arm was protocoled at full dose, but clinicians could elect to commence patients at 1000 mg/m^2 twice daily. Of 37 patients, 32 were given dose-reduced capecitabine. There are a number of examples of control arms in trials using capecitabine at 1000 mg/m^2 twice daily[44]. The AVEX trial[45], which started accruing patients later than the aforementioned trials, protocoled its capecitabine-alone arm to 1000 mg/m^2 twice daily, consistent with how capecitabine is prescribed to elderly patients in practice. The AVEX trial's capecitabine-alone arm contained 140 patients, representing the largest reported group of elderly or frail patients with advanced CRC taking capecitabine until our study was reported.

Here, we report a TTP of 5.6 months, which is 1 month longer than the TTP of 4.6 months reported by Van Cutsem and colleagues[28], whose patients received full-dose capecitabine. Hong *et al.*[42] reported a PFS of 4.4 months in elderly or frail patients receiving full-dose capecitabine. The median PFS durations in reports by Seymour[14], Cunningham[45], and Price[35] and their colleagues were 5.8, 5.1, and 5.8 months respectively, for trials in which almost all patients received dose-reduced capecitabine. Those results demonstrate that, although dose-reduced capecitabine is associated with a lower ORR, the disease control rate is preserved, and disease progression might actually be better. In our study, patients received a median of 5 cycles of capecitabine; in contrast, the Van Cutsem and Hong groups both reported a median of 4 cycles when using full-dose capecitabine. Cunningham *et al.* and Price *et al.*, two other studies using mostly dose-reduced capecitabine, reported medians of 6 and 7 cycles of capecitabine respectively. One possible explanation for the improved TTP is that dose-reduced capecitabine is more tolerable, and thus patients stay on therapy longer.

Toxicity data are particularly difficult to compare from trial to trial, which is a limitation in a single-arm study. We report a 12.2% frequency of grade 3 or greater diarrhea at any point during our study, and a 15.8% frequency of grade 3 or greater hand–foot syndrome. Cassidy *et al.*[38] reported slightly higher rates of diarrhea (13.1%) and hand–foot syndrome (17.1%) from a meta-analysis of the original two capecitabine trials, which used full-dose capecitabine. The capecitabine arm of the AVEX trial, at 1000 mg/m^2 twice daily, reported lower levels of grade 3 or greater diarrhea and hand–foot syndrome (6% and 7% respectively). If those levels represent the true toxicity of dose-reduced capecitabine, toxicity would therefore be halved, with disease progression actually appearing to be better. That postulation represents a contradiction to the usual efficacy-for-toxicity tradeoff[46]. Even considering the loss in ORR, observations in the foregoing studies would imply a favourable gearing effect in decreasing the toxicity, with only a small trade-off in efficacy[46]. Furthermore, patients who started at 750 mg/m^2 twice daily had only a slightly lower disease control rate of 63% compared with the 73.1% for patients who started at 1000 mg/m^2 twice daily. In our trial, toxicity dropped considerably when the capecitabine dose was lowered from 1000 mg/m^2 to 750 mg/m^2 twice daily—for example, from 46% to 30% respectively for any grade of hand–foot syndrome.

Our study also revealed that a large proportion of patients remained on capecitabine therapy after progressive disease (53 of 188 total patients, and 53 of 125 patients who received subsequent chemotherapy). In the metastatic setting, progressive disease by the Response Evaluation Criteria in Solid Tumors does not equate to treatment failure, and the number of subsequent therapies is limited; thus, moving to subsequent therapy before true failure can be detrimental to a patient[47]. That scenario has best been demonstrated in *EGFR*-mutated lung cancer, but is used frequently outside of clinical trials[48]. The reported median of 4 cycles of post-protocol capecitabine monotherapy, with more than a quarter of patients receiving at least 10 cycles, suggests that capecitabine might be both effective and tolerable after technical disease progression.

CONCLUSIONS

Capecitabine is commonly used at a reduced dose in elderly or less robust patients, with a paucity of data demonstrating its efficacy and tolerability at that dose. In the present report, we suggest that, compared with historical full-dose capecitabine, dose-reduced capecitabine is associated with less toxicity, with only a small trade-off in efficacy, seen as a lower ORR. However, if capecitabine has improved tolerability, its use at the lower dose could lead to an increased number of cycles of therapy received and a PFS that seems consistently higher. Those observations should, in the absence of a head-to-head clinical trial, be viewed as compelling evidence that 1000 mg/m^2, or even 750 mg/m^2, twice daily is an appropriate dose in this trial population.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SW has received speaker honoraria from Roche, and MV has received consultancy meeting fees and speaker honoraria from Roche. The trial was an independent initiative by the principal investigator (MV), and the sponsor had no influence on trial design, data analysis, or manuscript preparation.

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