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ORIGINAL PAPER

Capecitabine-based chemotherapy for metastatic colorectal cancer

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Abstract
Purpose Metastatic colorectal cancer (MCRC) remains a significant public health concern. The objectives of present study are to investigate the efficacy and safety profile of capecitabine-based chemotherapy in the treatment of MCRC.
Materials and methods We performed a computerized search using combinations of the following keywords: "metastatic colorectal cancer," "Xeloda," "chemotherapy," "capecitabine," or "5-fluorouracil."
Results Treatment with capecitabine chemotherapy was associated with a significantly prolonged progression-free survival (WMD = 1.24; 95% CI, 0.04–2.44; $P = 0.04$), whereas overall survival was not statistically significant (WMD [random] = 0.29; $P = 0.75$). Patients in both capecitabine and 5-fluorouracil groups had equal 1-, 2-, and 3-year survival (OR = 0.82, 95% CI: 0.59–1.12, $P = 0.21$; OR = 0.84, 95% CI: 0.61–1.15, $P = 0.27$; OR = 1.26, 95% CI: 0.78–2.05, $P = 0.34$; respectively). The analysis also demonstrates that the response rate of capecitabine-based chemotherapy was comparable to 5-fluorouracil-based chemotherapy (OR = 1.02, 95% CI, 0.90–1.14; $P = 0.80$). When comparing single-agent capecitabine against 5-fluorouracil/leucovorin, our results showed an overall OR of 1.56 (95% CI, 1.16–2.09) in favor of the capecitabine arm. When toxicity was evaluated, a statistically significant benefit with capecitabine-based therapy was seen, especially for grade 3/4 neutropenia (OR, 0.80; 95% CI, 0.71–0.91; $P = 0.00005$).
Conclusions Capecitabine-based chemotherapy demonstrated a significantly superior progression-free survival, equivalent overall survival, and comparable response rate with 5-fluorouracil-based chemotherapy. These observations support the use of capecitabine-based chemotherapy in the treatment of MCRC as a first-line or as a neoadjuvant modality.

Keywords Capecitabine · 5-fluorouracil · Metastatic colorectal cancer · Meta-analysis

Introduction

Despite advances in early diagnosis and treatment, colorectal cancer (CRC) remains a significant public health concern and is the third leading cancer in both men and women. Upon diagnosis, 19% of colorectal cancer cases are metastatic. The overall 5-year survival rate for patients with colorectal cancer is 63%, whereas the rate drops to 10% or even less in patients with metastatic disease (Jemal et al. 2005). For more than four decades, 5-fluorouracil (5-FU) in combination with folinic acid (leucovorin, LV) had been the mainstay of palliative therapy for metastatic colorectal cancer (MCRC), with median survival at approximately 12 months. Current standard first-line regimens for MCRC are FOLFOX (infusional 5-FU/LV with oxaliplatin) and FOLFIRI (infusional 5-FU/LV with irinotecan). A drawback of the infusional 5-FU regimen is the

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inconvenience associated with portable pumps for continuous infusion. Continuous infusion increases the cost of this palliative treatment and probably decreases the quality of life of the patients.

Single-agent capecitabine (N4-pentyloxycarbonyl-5′-deoxy-5-fluorocytidine) (Xeloda; F. Hoffmann-La Roche, Basel, Switzerland), an oral tumor-selective fluoropyrimidine, has established efficacy in the treatment of metastatic colorectal cancer, achieving tumor-selective activation via a triple enzymatic cascade. It appears to be a reasonable substitute for infusional 5-FU/LV in combination regimens or as a single-agent therapy, with the added advantage of reducing the inconvenience of long infusion time (Hoff et al. 2001; Van Cutsem et al. 2001). Most importantly, in view of the indirect costs caused by the treatment, hospitalization was significantly reduced with capecitabine in comparison with i.v. 5-FU/LV. Medical resource use and associated costs were lower with capecitabine in both settings. These impressive results provided strong support for the conduct of several randomized controlled studies evaluating capecitabine-based chemotherapy applied to metastatic colorectal cancer. In these trials, capecitabine-based regimens have been evaluated in a range of different administration schedules and doses with no evidence of major overlapping key toxicities.

To compare the efficacy of capecitabine and 5-FU/LV in the treatment of MCRC with sufficient statistical power, we conducted the present meta-analysis to overcome the statistical limitations (for instance, low case load) of the individual trials and to investigate the treatment effects and safety profiles of the various treatment combinations.

Materials and methods

Search for trials

We performed a computerized search of the MEDLINE database, the Cochrane Central Register of Controlled Trials, Highwire Press, the Online Proceedings of the American Society of Clinical Oncology (ASCO) Annual Meetings and the European Cancer Conference (ECCO), using combinations of the following keywords: "metastatic colorectal cancer," "Xeloda," "chemotherapy," "capecitabine," or "5-fluorouracil." No language limits were applied. We also manually searched oncology journals known to publish a large number of clinical trials and reference lists of published trials and relevant review articles. We contacted experts in the field of colorectal cancer treatment to broaden our yield of potentially eligible trials. Abstracts or unpublished data were included if sufficient information was available. The deadline for trial inclusion was March 31, 2010.

Selection of trials

Study selection, data extraction, and data entry were performed by three authors (Jie Fan, Yuan Ma, and Yue Ma) independently. Differences were resolved by consensus with a forth author (Tao Yu). The availability of adequate response and survival data was an inclusion criterion for the selected randomized Phase III trials and for metastatic colorectal cancer. Consequently, all studies performed in the adjuvant setting were excluded. Trials had to fulfill the following inclusion criteria: (1) patients were randomly assigned to each treatment group; (2) capecitabine-based chemotherapy and infusional 5-FU-based chemotherapy were compared in the study; and (3) only patients with the diagnosis of MCRC were included. To avoid potential bias, information for all randomly assigned patients, including those who had been excluded from the final analysis, was required.

Statistical analysis

The primary endpoints in the meta-analysis were overall survival, defined as the time between the treatment randomization and the date of the last follow-up or of the patient's death. Living patients were counted at the date of last follow-up. The secondary endpoint were overall response rate, defined as the sum of partial and complete response rates (according to World Health Organization criteria), and toxicity, which was graded according to the NCI Common Toxicity Criteria (CTC). Data were obtained directly from included articles or calculated using the data in each article.

The meta-analysis was performed using a Review Manager Version 4.2 (Nordic Cochran Centre, Copenhagen). Heterogeneity between the trials was assessed to determine which model should be used. To assess statistical heterogeneity between studies, the Cochran Q test was performed, with a predefined significance threshold of 0.1 (Wagner et al. 2005) The odds ratios (ORs) were the principle measurements of effect and were presented with a 95% confidence interval (CI). P values of <0.05 were considered statistically significant. All reported P-values result from two-sided versions of the respective tests. The revision of funnel plots did not reveal any indications of major publication bias.

Results

Selection of the trials

Twenty-two trials with MCRC were initially identified, from which 10 trials were secondarily considered ineligible

for different reasons (one for cross-over design, nine for non-randomized controlled trials [RCTs]). Next, two trials were excluded. Among them, one trial reported by Tyagi and Grothey (2006) fulfilled the selection criteria but had to be excluded, as information was available only in an abstract and insufficient for appropriate efficacy and survival hazard analysis. Another additional trial was excluded because it compares the outcomes of first-line treatment in elderly versus young patients (Sastre et al. 2009).

Characteristics of the ten randomized trials within the meta-analysis

After the selection procedure (Fig. 1), ten eligible trials (Cassidy et al. 2008; Comella et al. 2009; Diaz-Rubio et al. 2007; Hoff et al. 2001; Kohne et al. 2008; Martoni et al. 2006; Porschen et al. 2007; Rothenberg et al. 2008; Skof et al. 2009; Van Cutsem et al. 2001) were identified, and the respective electronic databases were obtained for all of them. The quality scores of the RCTs were assessed according to the Jadad scale (Jadad et al. 1996) and ranged from 2 to 4 (5-point scale), with a mean of 3.3.

The analysis was conducted on the individual data of 5,260 patients with MCRC who were enrolled in ten trials and were randomly assigned to receive capecitabine-based (2,630 patients) chemotherapy or 5-FU-based chemotherapy (2,630 patients). All of the ten trials were randomized phase III trials. None were placebo-controlled, double-blinded trials. One trial differed from the others as it evaluated a second-line chemotherapy regimen (Rothenberg et al. 2008). Another trial differed from the others as it evaluated regimens in neoadjuvant settings (Skof et al. 2009).

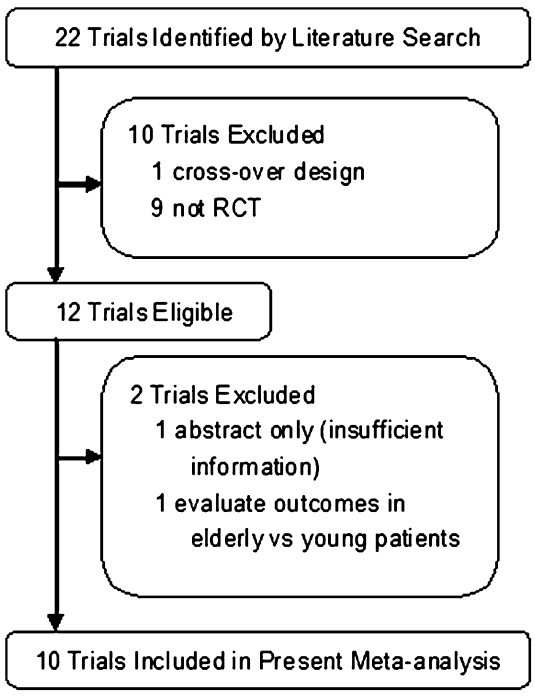

Fig. 1 Flow diagram of the study selection process

Two large randomized trials (Hoff et al. 2001; Van Cutsem et al. 2001) compared capecitabine with bolus 5-FU/LV (Mayo Clinic protocol) as first-line chemotherapy in metastatic colorectal cancer. In both these trials, capecitabine was used at a dose of 1,250 mg/m^2 bid d_{1-14}. Eight trials compared capecitabine and 5-FU when they were used in combination with other chemotherapeutic agents (oxaliplatin or irinotecan). Two of the ten trials (Cassidy et al. 2008; Kohne et al. 2008) included other treatment arms, in addition to the two arms considered for the meta-analysis. In combination settings, capecitabine dose was 1,000 mg/m^2.bid d_{1-11} in one trial (Comella et al. 2009), 1,000 mg/m^2.bid d_{1-14} in six trials (Cassidy et al. 2008; Diaz-Rubio et al. 2007; Kohne et al. 2008; Martoni et al. 2006; Porschen et al. 2007; Rothenberg et al. 2008), and 1,000 mg/m^2.bid d_{2-15} in one trial (Skof et al. 2009).

Baseline characteristics of the individual trials, including gender, performance status (ECOG performance status 0–1 or Karnofsky performance status (KPS) 70–100%), median age, and tumor characteristics are listed in Table 1. The distribution of baseline patient characteristics within the respective 10 trials was found to be quite homogeneous. However, between the different trials, a considerable degree of variation can be detected. For example, the median age of patients ranges from 59.7 to 67, while the fraction of good performance status patients varies from 89 to 100%. Most patients in these trials have good compliance. The length of follow-up ranged from 21.0 to 50.0 months.

Survival

The reported median progression-free survival (PFS) and median overall survival (OS) for each trial are listed in Table 2. Six trials contributed individual patient data on tumor progression (involving 2,928 patients). Moreover, there was not statistical significant heterogeneity in six trials ($df = 10$; $P < 0.0001$), and random effect model was used in this analysis. Treatment with capecitabine chemotherapy was associated with a significantly prolonged progression-free survival (PFS) (WMD [random] = 1.24; 95% CI, 0.04–2.44; $P = 0.04$), whereas overall survival shows statistical non-significance (WMD [random] = 0.29; $P = 0.75$) (Table 3).

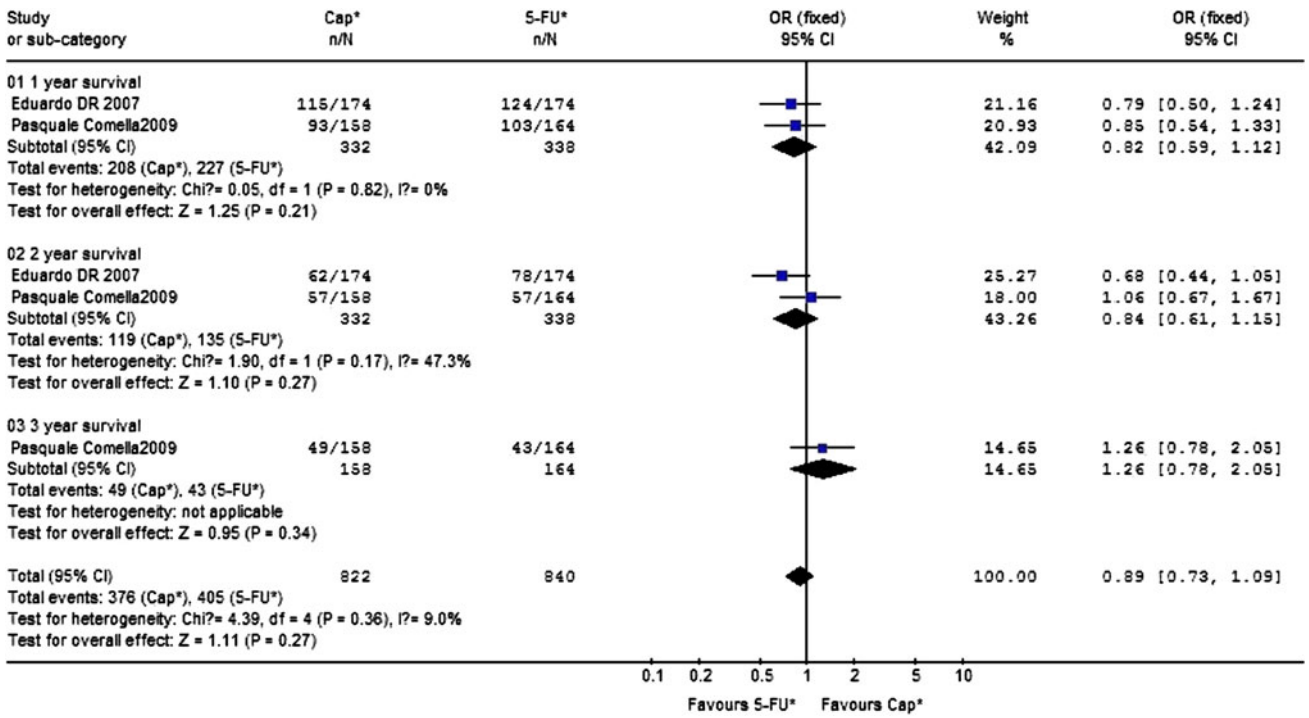

Fig. 2 Comparison of 1-, 2-, and 3-year survival between capecitabine group and 5-FU group in two trials. OR = odds ratio; Cap* = capecitabine-based chemotherapy; 5-FU* = 5-FU-based chemotherapy

Response rate

Both for the total and the subgroup analyses, the appropriate tests do not reveal any major heterogeneity between the results comparing the response rate. Accordingly, the fixed-effects meta-analysis model (Peto's method) was used in this analysis. Each trial is represented by a square, the center of which gives the odds ratio for that trial. The size of the square is proportional to the information in that trial. The ends of the horizontal bars denote a 95% CI. The black diamond gives the overall odds ratio for the combined results of all trials. The center of it denotes the odds ratio, and the extremities denote the 95% CI. All studies or subcategories are shown in Figs. 3, 4, 5, and 6. For all figures, values higher than one indicate that capecitabine has a beneficial effect in the treatment of metastatic colorectal cancer.

Capecitabine-based chemotherapy versus 5-FU-based chemotherapy

The total analysis of 10 randomized trials involving 5,260 patients demonstrates that capecitabine-based chemotherapy is not inferior in response to 5-FU-based chemotherapy in the treatment of MCRC. The odds ratio (95% CI; *P* value), expressed as the capecitabine group over the 5-FU group, was 1.02 (0.90, 1.14; $P = 0.80$), and the difference was not statistically significant (Fig. 3). Furthermore, only one of these trials showed that the overall objective tumor response rate was significantly higher in the capecitabine group (24.8%) than in the 5-FU/LV group (15.5%; $P = 0.005$) (Rothenberg et al. 2008). The results from the other nine trials showed that capecitabine and 5-FU regimens had equivalent response rates for metastatic colorectal cancer.

Capecitabine single agent versus 5-FU/LV

Two eligible studies including 1,207 patients were included in this meta-analysis (Fig. 4). Both studies compared RR (response rate) of capecitabine single agent versus 5-FU/LV in first-line treatment of metastatic colorectal cancer. The overall HR of 1.56 (95% CI, 1.16–2.09) in favor of the capecitabine arms demonstrates a convincing benefit in disease control ($P = 0.003$). Heterogeneity was non-significant ($P = 0.31$).

Capecitabine/oxaliplatin combinations versus 5-FU/oxaliplatin combinations

This meta-analysis was based on 3,923 patients in six randomized trials (Fig. 5). The resulting OR for response rate of 0.93 (95% CI, 0.82–1.06) demonstrates a statistically non-significant benefit ($P = 0.28$). Allocation concealment was adequate in all six studies included in this comparison, and heterogeneity was non-significant ($P = 0.59$).

Table 1 Characteristics of eligible trials included in the meta-analysis

Study (time periods)	Tumor characteristics	No. of patients	Median age (range)	Arms	No. of patients	Regimens	Compliance no*
Kohne et al. (2008)	MCRC	43	65 (43–78)	CAPIRI	21	Iri 250 mg/m^2 i.v. $d_{1,22}$, Cap 1,000 mg/m^2 bid $d_{1–15,22–36,}$ q6w	0
(2003.5 to 2004.4)	(first-line)		60.5 (45–75)	FOLFIRI	22	Iri 180 mg/m^2 $d_{1,15,22}$, LV 200 mg/m^2, 5-FU 400 mg/m^2 i.v. bolus, then 600 mg/m^2 infusion for 22 h, $d_{1,2,15,16,29,30}$, q6w	0
Eduardo 2007	MCRC	348	64 (32–38)	XELOX	174	Cap 1,000 mg/m^2 bid $d_{1–14}$, Oxa 130 mg/m^2 d_1, q3w	3
(2002.4 to 2004.8)	(first-line)		65 (35–81)	FUOX	174	5-FU 2,250 mg/m^2 CIV 48 h $d_{1,8,15,22,29,36}$, Oxa 85 mg/m^2 $d_{1,15,29}$, q6w	3
Van Cutsem et al. (2001)	MCRC	602	64 (29–84)	Capecitabine	301	Cap 1,250 mg/m^2 bid $d_{1–14}$, q3w	20
(1996.10 to 1998.2)	(first-line)		63.5 (36–86)	5-FU/LV	301	LV 20 mg/m^2, 5-FU 425 mg/m^2 bolus injection d1–5, q4w	20
Skof et al. (2009)	MCRC	87	63 (47–75)	XELIRI	41	Cap 1,000 mg/m^2 bid $d_{2–15}$, Iri 250 mg/m^2 d_1, q21d	0
(2004.1 to 2006.12)	(neoadjuvant)		62 (34–75)	FOLFIRI	46	Iri 180 mg/m^2, 5-FU 400 mg/m^2, LV 200 mg/m^2, 5-FU 2,400 mg/m^2 46 h infusion, q14d	0
Cassidy et al. (2008)	MCRC	2,034	61 (24–83)	XELOX	1,017	Cap 1,000 mg/m^2 bid $d_{1–15,}$ Oxa 130 mg/m^2 i.v. d_1, q3w	0
(2003.7 to 2004.5)	(first-line)		61 (24–84)	FOLFOX4	1,017	FOLFOX-4 regimen was administered as previously described	1
Rothenberg et al. (2008)	MCRC	627	60.7 (26–81)	XELOX	313	Cap 1,000 mg/m^2 bid $d_{1–15,}$ Oxa 130 mg/m^2 i.v. d_1, q3w	2
(2003.7 to 2005.5)	(second-line)		59.7 (26–83)	FOLFOX4	314	FOLFOX-4 regimen was administered as previously described	6
Martoni et al. (2006)	ACRC	118	67 (25–79)	XELOX	62	Cap 1,000 mg/m^2 bid $d_{1–14}$, Oxa 130 mg/m^2 d_1, q3w	1
(2001.12 to 2005.3)	(first-line)		64 (41–79)	pviFOX	56	pvi5-FU 250 mg/m^2 $d_{1–21}$, Oxa 130 mg/m^2 d_1, q3w	1
Comella et al. (2009)	MCRC	322	64 (39–84)	OXXEL	158	Cap 1,000 mg/m^2 bid $d_{1–11}$, Oxa 100 mg/m^2 i.v. d_1, q3w	16
(2004.5 to 2007.5)	(first-line)		65 (37–79)	OXAFAFU	164	LV 250 mg/m^2 i.v., 5-FU 850 mg/m^2 i.v. $d_{2,}$, Oxa 85 mg/m^2 i.v. d_1, q3w	13
Hoff et al. (2001)	MCRC	605	64 (23–86)	Capecitabine	302	Cap 1,250 mg/m^2 bid, q3w	3
(1996.9 to 1998.2)	(first-line)		63 (24–87)	5-FU/LV	303	LV 20 mg/m^2, 5-FU 425 mg/m^2 bolus injection d1–5, q4w	9
Porschen et al. (2007)	MCRC	474	66 (32–81)	CAPOX	241	Cap 1,000 mg/m^2 bid $d_{1–14}$, oxaliplatin 70 mg/m^2 $d_{1,8}$, q22d	5
(2002.8 to 2004.8)	(first-line)		64 (34–86)	FUFOX	233	LV 500 mg/m^2, FU 2,000 mg/m^2 CIV, Oxa 50 mg/m^2, $d_{1,8,15,22}$, q36d	2

Cap, capecitabine; Iri, irinotecan; CIV, continuous-infusion; Oxa, oxaliplatin; No*, number of patients did not accomplish treatment

Capecitabine/irinotecan combinations versus 5-FU/irinotecan combinations

Summarizing the results for the comparison of capecitabine/irinotecan chemotherapy and infusional 5-FU/irinotecan chemotherapy results in an OR of 1.06 (95% CI, 0.53–2.01, $P = 0.88$) (Fig. 6). This meta-analysis, which included 130 patients in two studies, once again confirms that capecitabine and 5-FU regimens were equally active in metastatic colorectal cancer. There was non-significant heterogeneity ($P = 0.95$).

Table 2 Survival in the nine trials included in the meta-analysis

Trial (reference)	No. of patients (per regimen)	PFS/TTP (months)	HR[a] (95% CI)	P^b	Median Survival (months)	R[a] (95% CI)	P^b
Kohne et al. (2008)	21 (CAPIRI)	5.9	0.76 (0.48–1.21)	NA*	14.75	0.31 (0.14–0.71)	NA*
	22 (FOLFIRI)	9.6			19.9		
Eduardo 2007	174 (XELOX)	8.9	1.18 (0.90–1.50)	NA*	18.1	1.22 (0.90–1.60)	.145
	174 (FUOX)	9.5			20.8		
Van Cutsem et al. (2001)	301 (Cap*)	5.2	0.96 (0.81–1.14)	NA*	13.2	0.92 (0.78–1.09)	.330
	301 (5-FU/LV)	4.7			12.1		
Skof et al. (2009)	41 (XELIRI)	10.3	NA*	.784	30.7	NA*	.160
	46 (FOLFIRI)	9.3			16.6		
Cassidy et al. (2008)	1017 (XELOX)	8.0	1.04 (0.93–1.16)	NA*	19.8	0.99 (0.88–1.12)	NA*
	1017 (FOLFOX4)	8.5			19.6		
Rothenberg et al. (2008)	313 (XELOX)	4.7	0.97 (0.83–1.14)	NA*	11.9	1.03 (0.87–1.23)	NA*
	314 (FOLFOX4)	4.8			12.5		
Martoni et al. (2006)	62 (XELOX)	9.0	NA*	NA*	NA*	NA*	NA*
	56 (pviFOX)	7.0			NA*		
Comella et al. (2009)	158 (OXXEL)	6.6	1.12 (0.88–1.45)	.354	16.0	1.01 (0.74–1.38)	.883
	164 (OXAFAFU)	6.5			17.1		
Hoff et al. (2001)	302 (Cap*)	4.3	1.03 (0.87–1.22)	.720	12.5	1.00 (0.84–1.18)	.970
	303 (5-FU/LV)	4.7			13.3		
Porschen et al. (2007)	241 (CAPOX)	7.1	1.17 (0.96–1.43)	.117	16.0	1.12 (0.92–1.38)	.260
	233 (FUFOX)	8.0			18.8		

* Cap = Capecitabine

[a] HR = hazard ratio; CI = confidence interval; NA = not applicable

[b] Two-sided *P* values were calculated using log-rank test

Table 3 Comparison of OS and DFS between capecitabine arms and 5-FU arms in trials included in this analysis

Survival	No. of trials	No. of patients		WMD	Weight (%)	*P* value
		Cap*	5-FU*			
OS	5	696	709	0.29	43.23	0.75
DFS	6	758	765	1.24	56.77	0.04

Cap* = capecitabine-based chemotherapy; 5-FU* = 5-FU-based chemotherapy

As is shown in Forest plot (Fig. 2), the results of the meta−analysis of individual patient data included in 2 trials showed that patients in both groups had a equally 1-, 2-, and 3-year survival (OR = 0.82, 95% CI: 0.59–1.12, $P = 0.21$; OR = 0.84, 95% CI: 0.61–1.15, $P = 0.27$; OR = 1.26, 95% CI: 0.78–2.05, $P = 0.34$; respectively). No evidence of statistical heterogeneity was found across two trials ($df = 4$, $P = 0.36$). The absolute difference in survival was 4.5% at 1 year (62.7 vs. 67.2%), 4.1% at 2 years (35.8 vs. 39.9%), and 5% at 3 years (31 vs. 26%) when comparing the capecitabine group with the 5-FU group. Cap* = Capecitabine-based-chemotherapy; 5-FU* = 5-fluorouracil-based chemotherapy

Toxicity

For the assessment of safety of capecitabine-based regimen versus 5-FU-based regimen, the adverse effects of chemotherapy were analyzed as grade 3 and 4 toxicity according to National Cancer Institute Common Toxicity Criteria. On the whole, analysis showed that overall treatment-related severe adverse events affected significantly fewer patients in the capecitabine-based therapy arm than in the 5-FU-based therapy arm (10 trials including 5,257 patients; OR, 0.73; 95% CI, 0.59–0.92; $P = 0.007$) (Fig. 7). According to the Comella 2008 trial, baseline single item and global health status/quality of life scores also did not significantly differ between the two arms. Excluding constipation ($P = 0.001$) and financial item score ($P = 0.004$), no other significant differences among the single scores were observed between the two arms during these trials. However, in another identical trial conducted in the United States, Canada, Mexico, and Brazil, which included 605 patients receiving first-line therapy for metastatic colorectal cancer (Hoff et al. 2001), the analysis demonstrated a statistically significant difference favoring capecitabine, with a lower overall incidence and later onset of these grade 3 or 4 adverse reactions with capecitabine throughout the entire treatment period ($P = 0.0037$, log-rank test).

Treatment-related deaths were reported in seven of 10 studies included in this comparison. The overall rate of

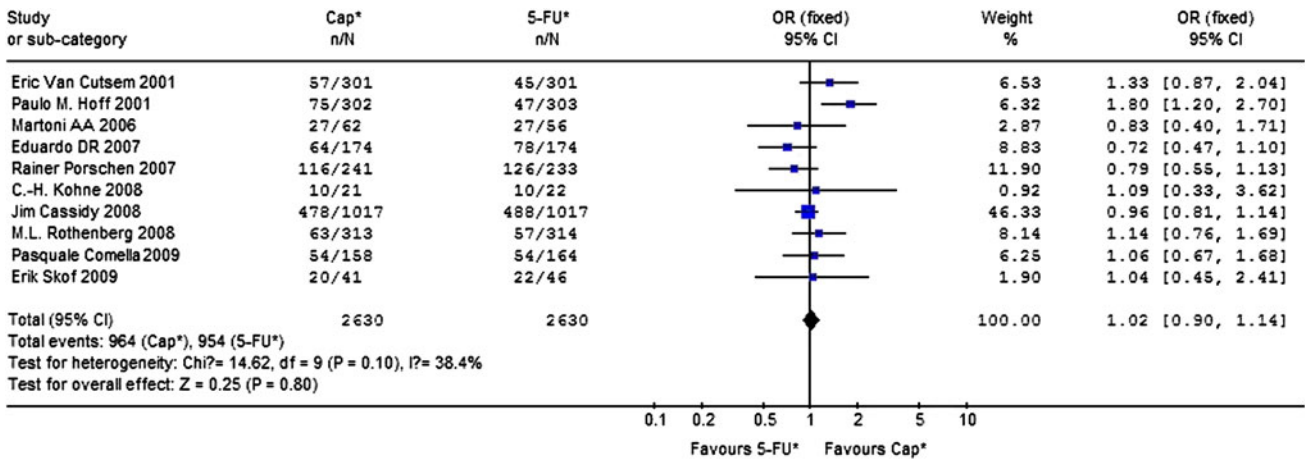

Fig. 3 Forest plot for RR (response rate). Each study is shown by the point estimate of the risk ratio (square proportional to the weight of each study) and 95% confidence interval for the risk ratio (*extending lines*); the summary risk ratio and 95% confidence interval by fixed-effects calculations are shown by diamonds. Cap*, capecitabine-based chemotherapy; 5-FU*, fluorouracil-based chemotherapy

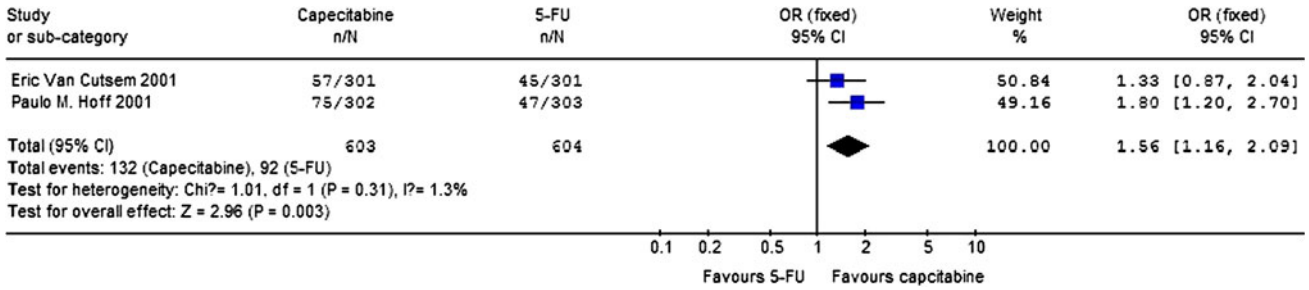

Fig. 4 Efficacy of capecitabine single agent versus 5-FU/LV on RR (response rate). Hazard ratios were analyzed with the fixed-effects model

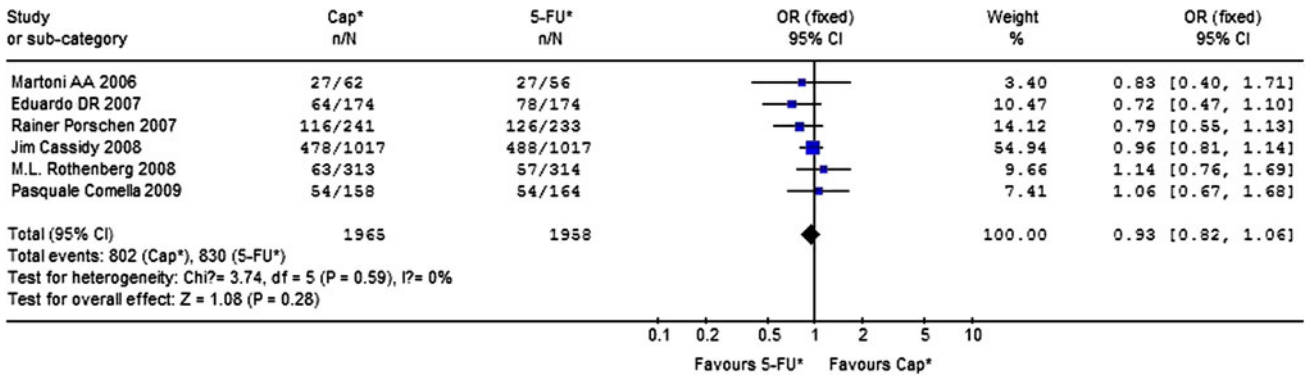

Fig. 5 Effect of capecitabine/oxaliplatin combinations versus 5-FU/oxaliplatin combinations. Hazard ratios were analyzed with the fixed-effects model. Cap* = capecitabine + oxaliplatin; 5-FU* = 5-fluorouracil + oxaliplatin

treatment-related deaths in these six studies combined was 2.0% for capecitabine therapy versus 1.8% for 5-FU therapy. This difference was not statistically significant (OR, 1.11; 95% CI, 0.73–1.68; $P = 0.63$) (Fig. 8). The most common causes of treatment-related mortality were gastrointestinal necrosis, pulmonary embolism, and myocardial infarction in the capecitabine group and cardiac failure, renal tubular necrosis, sepsis, and enterocolitis in 5-FU group.

Toxicity needed full consideration. In the follow-up subgroup analysis (Table 4), occurrence of severe neutropenia

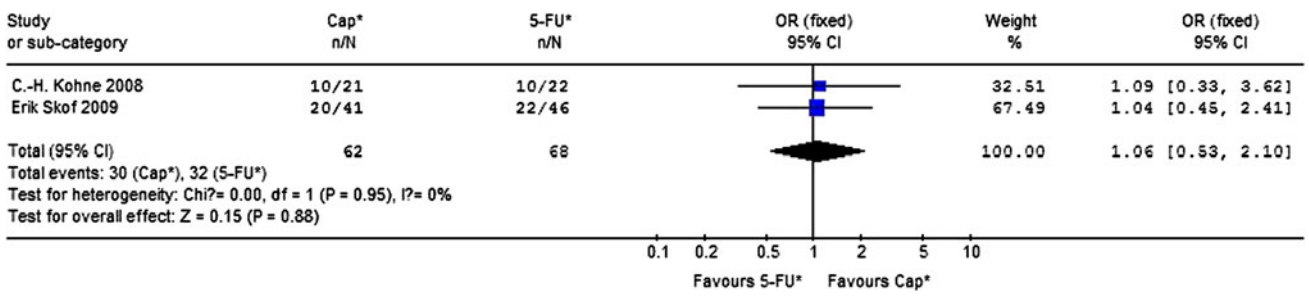

Fig. 6 Effect of capecitabine/irinotecan combinations versus 5-FU/irinotecan combinations. Hazard ratios were analyzed with the fixed-effects model. Cap* = capecitabine + irinotecan; 5-FU* = FOLFIRI (5-fluorouracil + irinotecan)

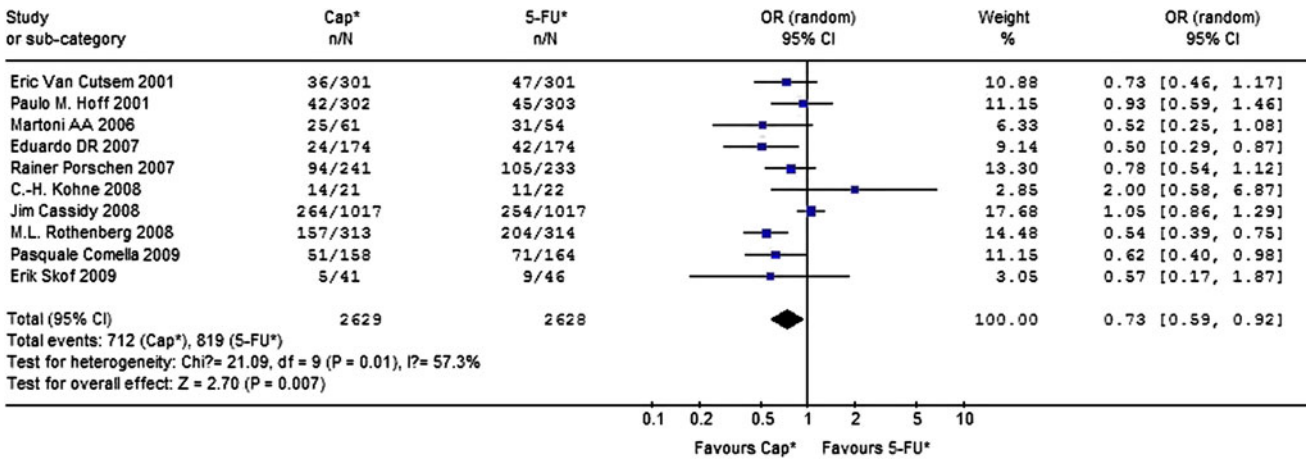

Fig. 7 Comparison of G3/4 toxicity between capecitabine arms and 5-FU arms in trials included in this analysis. OR = odds ratio; Cap* = capecitabine-based chemotherapy; 5-FU* = 5-FU-based chemotherapy

(9 trials including 4,786 patients; OR, 0.15; 95% CI, 0.12–0.18; $P < 0.0001$) was significantly lower with the capecitabine arm treatment, while frequencies of grade 3/4 diarrhea (10 trials including 5,260 patients; OR, 1.35; 95% CI, 1.16–1.57; $P = 0.0001$) were increased in the capecitabine group. No statistically significant difference was found for nausea/vomiting (8 trials including 4,668 patients; OR, 1.06; 95% CI, 0.84–1.33; $P = 0.62$), thrombocytopenia (6 trials including 2,622 patients; OR, 1.45; 95% CI, 0.82–2.55; $P = 0.20$), and neuropathy (7 trials including 2,266 patients; OR, 1.04; 95% CI, 0.82–1.32; $P = 0.76$). In the analysis of heterogeneity, the P values were significant for neutropenia ($P < 0.0001$) and diarrhea ($P < 0.0001$), whereas they were non-significant for thrombocytopenia ($P = 0.93$), nausea/vomiting ($P = 0.29$), and neuropathy ($P = 0.73$).

Discussion

5-FU remains one of the most important drugs in the treatment of metastatic colorectal cancer. It has been shown that the continuous infusion of 5-FU is superior to bolus i.v. injection, with improved anticancer activity as well as reduced toxicity. However, continuous infusion requires an indwelling central venous catheter with the associated increased risk of infection and thrombosis. The development of effective oral fluoropyrimidine is a desirable goal in the treatment of advanced colorectal cancer.

Capecitabine (Xeloda) is an oral precursor of 5′-deoxy-5-fluorouridine (5′-DFUR), with predictable bioavailability and promising efficacy as first-line treatment in colorectal cancer. Capecitabine is absorbed as an intact molecule through the intestinal mucosa and is then sequentially converted to cytotoxic fluorouracil by three enzymes, as follows: (1) conversion to 5′-deoxy-5-fluorocytidine (5′DFCR) by carboxylesterase in the liver; (2) 5′-DFCR is metabolized to 5′-DFUR by cytidine deaminase, an enzyme located primarily in the liver and tumor tissue; and (3) 5′-DFUR is converted to 5-FU by thymidine phosphorylase, which appears to be expressed at higher levels in tumor cells. There is strong evidence that the increased levels of thymidine phosphorylase in tumor cells selectively increases fluoropyrimidine concentrations, resulting in enhanced efficacy and reduced systemic toxicity.

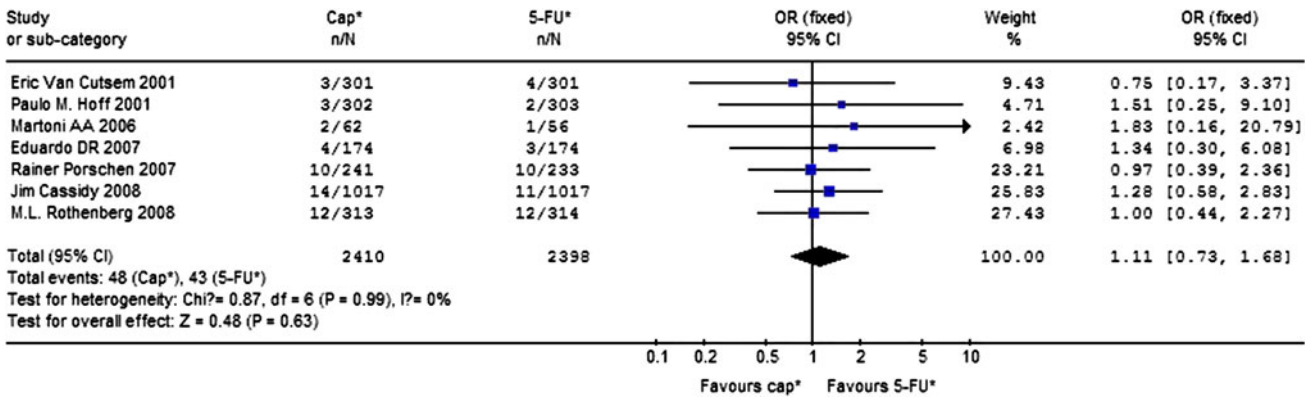

Fig. 8 Comparison of mortality between capecitabine arms and 5-FU arms in trials included in this analysis. OR = odds ratio; Cap* = capecitabine-based chemotherapy; 5-FU* = 5-FU-based chemotherapy

Table 4 Grade 3/4 (according to the National Cancer Institute Common Toxicity Criteria) toxicity in trials included in the meta-analysis

SAE	No. of trials	No. of patients		OR	95% CI	*P* value
		Cap*	5-FU*			
Neutropenia	9	2,389	2,397	0.15	0.12–0.18	<0.00001**
N–V	8	2,327	2,341	1.06	0.84–1.33	0.62
Diarrhea	10	2,360	2,360	1.35	1.16–1.57	0.0001**
Throm	6	1,310	1,312	1.45	0.82–2.55	0.20
Neuropathy	7	2,266	2,259	1.04	0.82–1.32	0.76

N–V nausea and vomiting, throm thrombocytopenia, *OR* odds ratio, *CI* confidence interval, *SAE* severe adverse events, *Cap** Capecitabine-based-chemotherapy, *5-FU** 5-fluorouracil-based chemotherapy, ** Statistical significant

Therefore, oral capecitabine offers an advantage over infusional fluorouracil/leucovorin in terms of convenience, practicality, and cost of health care. The question of whether continuous-infusion 5-FU might be replaced by capecitabine is the subject of many investigations. The results from some of these studies showed that capecitabine has an improved tolerability profile, higher tumor response rates, and at least equivalent time to disease progression and OS compared to intravenous (i.v.) bolus fluorouracil/leucovorin with the added convenience of oral administration.

Sumpter et al. reported that the replacement of continuous-infusion FU by capecitabine does not impair efficacy in the treatment of advanced gastric cancer (Sumpter et al. 2005). To compare efficacy of capecitabine and 5-FU/LV in the treatment of metastatic colorectal cancer with sufficient statistical power, we conducted the present meta-analysis to overcome the statistical limitations of the individual trials and to investigate the treatment effects, toxicity, and survival in various combination groups.

This systematic review revealed three major findings. First, treatment with capecitabine chemotherapy was associated with a significantly prolonged progression-free survival (PFS) (WMD [random] = 1.24; 95% CI, 0.04–2.44; $P = 0.04$), whereas overall survival shows statistical non-significance (WMD [random] = 0.29; $P = 0.75$). Patients in both groups had equal 1-, 2-, and 3-year survival (OR = 0.82, 95% CI: 0.59–1.12, $P = 0.21$; OR = 0.84, 95% CI: 0.61–1.15, $P = 0.27$; OR = 1.26, 95% CI: 0.78–2.05, $P = 0.34$; respectively).

Second, total analysis of response rates of 10 randomized trials involving 5,260 patients demonstrates capecitabine-based chemotherapy was as active as 5-FU-based chemotherapy in the treatment of MCRC. The odds ratio (95% CI; *P* value), expressed as the capecitabine group versus the 5-FU group, was 1.02 (0.90, 1.14; $P = 0.80$), and the difference was not statistically significant ($P = 0.80$). In an additional study (NO16966), which was excluded from the analysis because of insufficient information, the efficacy data showed that XELOX was as effective as FOLFOX4 (progression-free survival [PFS; intent-to-treat population]: HR = 1.04; 97.5% CI, 0.93–1.16) (Tyagi and Grothey 2006). A study by Skof et al. (2009), which included 87 patients investigating XELIRI regimen as neoadjuvant treatment for patients with unresectable liver-only metastases of MCRC, showed that the rate of radical R0 resection was 24% in both arms of patients. Thirty-seven percent of patients in the XELIRI and 26% of patients in the FOLFIRI arm were clinically disease-free (CR + R0 resection) ($P = 0.56$) at the end of treatment. Furthermore, analysis comparing the efficacy of single-agent capecitabine versus 5-FU/LV for the first-line treatment of metastatic colorectal cancer showed an overall OR of 1.56 (95% CI, 1.16–2.09) in favor of the capecitabine arm. This demonstrates a convincing benefit in disease control ($P = 0.003$) in single-agent chemotherapy.

Finally, when the toxicity of capecitabine-based regimens was compared with 5-FU-based regimens, a

statistically significant benefit with capecitabine-based therapy was seen, especially in grade 3/4 neutropenia. In the following subgroup analysis (Table 4), occurrence of severe neutropenia (9 trials including 4,786 patients; OR, 0.15; 95% CI, 0.12–0.18; $P < 0.0001$) was significantly lower with the capecitabine arm treatment, while frequencies of grade 3/4 diarrhea (10 trials including 5,260 patients; OR, 1.35; 95% CI, 1.16–1.57; $P = 0.0001$) were increased in capecitabine group. No statistical difference was found for nausea/vomiting (8 trials including 4,668 patients; OR, 1.06; 95% CI, 0.84–1.33; $P = 0.62$), thrombocytopenia (6 trials including 2,622 patients; OR, 1.45; 95% CI, 0.82–2.55; $P = 0.20$), and neuropathy (7 trials including 2,266 patients; OR, 1.04; 95% CI, 0.82–1.32; $P = 0.76$) between the two treatment groups. The analysis indicates that an improvement in toxicity profile might be expected to be associated with an improvement in overall quality of life during capecitabine-based chemotherapy. Information was not sufficient on the distribution of treatment-related toxicity according to age-group or on whether doses were routinely reduced for elderly patients within these trials. The overall rate of treatment-related deaths in seven studies was 2.0% for capecitabine therapy versus 1.8% for 5-FU therapy. This difference was not statistically significant (OR, 1.11; 95% CI, 0.73–1.68; $P = 0.63$).

On the contrary, Arkenau and Cao reported their different findings. In Arkenau's report, capecitabine-based chemotherapy resulted in lower response rate, but did not affect PFS and OS, while thrombocytopenia and hand–foot syndrome were consistently more prominent in the capecitabine-based regimens (Arkenau et al. 2008). Cao et al. (2010) reported that the efficacy of capecitabine plus oxaliplatin regimen is similar to 5-FU plus oxaliplatin regimen as first-line treatment for MCRC, but offers advantages of simplicity and convenience of administration. The difference of these results may be due to the selection of the trials included in meta-analysis (Arkenau's report: 6 trials, 3,494 patients; Cao's report: 6 trials, 2,196 patients). The less included trials and case load could be one of the reasons resulting in different conclusions. However, the present analysis including 10 trials with 5,260 patients suggested once again that capecitabine-based chemotherapy demonstrates a significantly superior PFS, equivalent OS and response rate, which is similar to most of the previous reports. Another analysis evaluated capecitabine-based combination and infused 5-FU-based combination chemotherapy for the treatment of oesophagogastric cancer (Okines et al. 2009). In this report, OS was superior in patients treated with capecitabine combination compared with 5-FU combination. Poor performance status, age <60, and metastatic disease were independent predictors of poor survival. There was no statistical difference in PFS. However, assessable patients treated with capecitabine combinations were more likely to have an objective response to treatment (OR, 1.38; 95% CI, 1.10–1.73; $P = 0.006$).

Satif and Narasimhan reported occurrence of serious HFS in African American patient treated with capecitabine, suggesting inter-race variations for adverse effect of capecitabine (Narasimhan et al. 2004; Saif and Sandoval 2008). Reigner compared the pharmacokinetics of capecitabine and its metabolites in Japanese and Caucasian patients with cancer and found no clinically relevant differences in the pharmacokinetics of capecitabine and its key metabolites 5′-DFUR, 5′-DFCR, and 5-FU between Japanese and Caucasian patients (Reigner et al. 2003). However, there is a lack of larger clinical trial to compare the efficacy and adverse effects of capecitabine among different races.

Compliance was previously thought to be a major issue with oral drugs like capecitabine. Oral drugs, while more convenient, do have their own problems like compliance and thus could be a major barrier to efficacy. In the analysis, data integrated from 10 clinical trials indicated that most patients had good compliance for capecitabine-based therapy when compared to 5-FU-based chemotherapy and were able to accomplish the prescribed course of chemotherapy (Table 1).

Conclusions

In general, the integrated analysis confirmed the results of the individual trials in terms of both efficacy and safety. Capecitabine-based chemotherapy demonstrated a significantly superior PFS, equivalent OS, and response rate. Furthermore, overall treatment-related severe adverse events affected significantly fewer patients in the capecitabine-based therapy arm than in the 5-FU-based therapy arm. These observations support the use of capecitabine-based chemotherapy in the treatment of advanced colorectal cancer as both first-line and neoadjuvant options.

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M.D. Anderson Cancer Center, USA; Dr Porschen R, Hospital Bremen, Germany.

Conflict of interest The authors declare that they have no competing interests.

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