

Capecitabine plus oxaliplatin compared with 5-fluorouracil plus oxaliplatin in metastatic colorectal cancer: Meta-analysis of randomized controlled trials

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Abstract. The aim of this study was to evaluate the curative effects and safety of capecitabine plus oxaliplatin compared with 5-fluorouracil (5-FU) plus oxaliplatin in patients with metastatic colorectal cancer (MCRC). We searched the Cochrane Central register of Controlled Trials (CENTRAL), PubMed, Ovid, ScienceDirect, EBSCO, EMBASE and conference proceedings for eligible trials. A meta-analysis was performed using Review Manager 5.0. A total of 3,603 cancer patients from 7 trials were analyzed, and the baseline patient characteristics were comparable in all studies. Curative effect outcomes including complete response (CR) (OR=0.78; 95% CI 0.47-1.31; $p=0.35$), partial response (PR) (OR=0.81; 95% CI 0.65-1.00; $p=0.05$) and the overall response rate (ORR) (OR=0.85; 95% CI 0.71-1.02; $p=0.08$) showed similar curative effects between the capecitabine plus oxaliplatin group and the 5-FU plus oxaliplatin group. Moreover, the median overall survival (OS) and progression-free survival (PFS) had no statistically significant differences. Regarding safety, hand-foot syndrome was more frequently observed in the capecitabine plus oxaliplatin group (OR=2.71; 95% CI 2.04-3.61; $p<0.00001$), while stomatitis and neutropenia were reversed. Other toxic effects had no statistically significant differences between the two groups. Our results showed that capecitabine plus oxaliplatin had similar curative effects to 5-FU plus oxaliplatin, however, it was safer in patients with MCRC.

Introduction

Colorectal cancer (CRC) is one of the most common causes of digestive system cancer-related mortality, and is the fourth main cause of cancer-related mortality worldwide (1). In Western countries, metastatic colorectal cancer (MCRC) is the second most frequently diagnosed form of malignant tumor. In recent years, the incidence of CRC has increased markedly, and 50% of patients eventually succumb to the disease due to metastatic spread of the cancer. Surgery is the standard treatment for resectable CRC if the disease has not spread prior to surgery. However, chemotherapy was required for MCRC patients to prolong the median survival. Numerous new drugs and chemotherapy regimens have been used in CRC therapy, which have improved the survival rate and reduced the adverse drug reactions.

Combinations of 5-fluorouracil/folinic acid (5-FU/FA) and oxaliplatin (FOLFOX regimens) are established standard regimens for the first-line treatment of MCRC (2). Capecitabine (Xeloda; Hoffmann-La Roche Inc., Nutley, NJ, USA) is an oral fluoropyrimidine that has similar efficacy to bolus 5-FU/FA as a monotherapy for the first-line treatment of MCRC, but has a high target-specific killing effect on tumor cells of the human body. Previous studies confirmed that capecitabine plus oxaliplatin is non-inferior to 5-FU/LV for the treatment of CRC (3). In this study, a large of database of patients with MCRC who were eligible for clinical trials was collected to assess the curative effects and safety of capecitabine plus oxaliplatin compared with 5-FU plus oxaliplatin in patients with MCRC.

Materials and methods

Search strategy. We searched the Cochrane Central register of Controlled Trials (CENTRAL), PubMed, Ovid, ScienceDirect, EBSCO, EMBASE and conference proceedings for eligible trials between January 2000 and April 2011. Searches were conducted using the following MESH terms: 'capecitabine', 'oxaliplatin', 'colorectal neoplasms', 'FOLFOX' and 'XELOX', as well as the text words: metastatic colorectal

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cancer, colorectal carcinoma and chemotherapy. Searches were limited to literature in English.

Inclusion criteria. Inclusion criteria for retrieved studies were: i) Studies were randomized controlled trials (RCTs), and published in English; ii) patients had histologically confirmed CRC; iii) in intervention studies, the experimental group patients underwent a capecitabine plus oxaliplatin regimen, consisting of a 2-h intravenous infusion of oxaliplatin 130 mg/m² on day 1 plus oral capecitabine 1,000 mg/m² twice daily on days 1 to 14 every 3 weeks; in the control group patients underwent a 5-FU plus oxaliplatin regimen. The chemotherapy dose and cycle of 5-FU and oxaliplatin were not limited as there were a number of regimens applied in various clinics, for example, FOLFOX4, FOLFOX6, FUFOX and FUOX (4). Original literature outcomes included overall response rate (ORR), progression-free survival (PFS), median overall survival (OS) and toxic effects evaluated according to National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE).

Exclusion criteria. Exclusion criteria for retrieved studies were: i) A lack of basic data necessary for our research or that the basic data were incomplete; ii) we chose the most recent literature if there was repetition of the same or similar reports.

Data collection. The two reviewers extracted data on: i) Basic patient characteristics, such as age, gender, the primary tumor sites, tumor status, number of metastatic sites and the Eastern Cooperative Oncology Group scale performance status (ECOG PS); ii) description of interventions, outcomes (CR, PR, ORR, OS, PFS and the adverse reaction of patients according to CTCAE) and lost to follow-up; iii) study design: Concealment of treatment allocation and blinding.

Quality assessment. The study quality was judged by the same two reviewers according to a modified Jadad score (4). Assessment scores were as follows: i) Randomization method: 2 points for appropriate, 1 point for not clear, 0 point for inappropriate; ii) blinding of outcomes: 2 points for appropriate, 1 point for not clear, 0 point for inappropriate; iii) description of follow-up situation if the patients were lost to follow-up, exit from or breach of the treatment regimen: 1 point for intention-to-treat analysis, 0 point for no description. Total scores were 1 to 5 points: studies with 1-2 points were classified as low quality studies, and those with 3-5 points were classified as high quality studies. Any disagreement in the extracted data was resolved by a third reviewer.

Statistical analysis. Statistical analyses were performed using the Review Manager 5.0 freeware package. The heterogeneity of trials was estimated by use of the Chi-square test. A random effects model was preferred for heterogeneous data and a Mantel-Haenszel fixed effects model for homogeneous data. The odds ratio (OR) and 95% confidence interval (95% CI) were used as summary statistics for categorical variables. Analyses were according to the intention-to-treat principle. Results were presented in all figures as conventional meta-analysis forest plots. A two-sided p-value of <0.05 was judged to indicate a statistically significant difference for all analyses.

Results

Search results and study selection. We searched more than 170 references in CENTRAL, PubMed, Ovid, ScienceDirect, EBSCO, EMBASE and conference proceedings. Following an initial screening of the title and abstract, 33 studies were thought to meet the inclusion criteria. Following further screening of full texts, we excluded 28 articles due to a lack of basic data or disagreement of outcome measures. Finally, seven studies published between 2000 and 2011, including 3,603 cancer patients, comprising 1,702 in the capecitabine plus oxaliplatin group (experimental group) and 1,901 in the 5-FU plus oxaliplatin group (control group), were included in the meta-analysis. The complete articles were retrieved. Trial characteristics are shown in Table I.

Seven RCTs were observed for PFS and OS (3,603 patients, intention-to-treat analyses) for the primary endpoints. With regard to the secondary endpoints, four trials were evaluated for CR and PR (1444 patients) and five trials for ORR (2071 patients).

Quality assessment. The Jadad scale assessed all RCTs and this information was listed in Table II. None of the trials had any description of concealment of treatment allocation and blinding methods, but they had described the randomization method and follow-up situation appropriately. Analyses were according to the intention-to-treat principle.

Curative effects analysis. Among the seven included trials, four studies reported on CR and PR. A meta-analysis was performed on the four studies. The heterogeneity test did not reveal any significant departure from the Chi-square test (CR: $p=0.06$, $I^2=59\%$; PR: $p=0.84$, $I^2=0\%$), thus, OR calculations were performed according to the fixed effects model. The results showed that there was no statistically significant difference between the two regimens on CR and PR (OR=0.78, 95% CI 0.47-1.31, $p=0.35$, Fig. 1; OR=0.81, 95% CI 0.65-1.00, $p=0.05$; Fig. 2).

ORR was selected as the outcome measure in the five included articles. No significant heterogeneity was present in ORR ($p=0.34$, $I^2=11\%$). Using a fixed effects model, the result showed that the differences between the capecitabine plus oxaliplatin group and the 5-FU plus oxaliplatin group were not statistically significant (OR=0.85, 95% CI 0.70-1.02, $p=0.08$; Fig. 3). Comprehensive analysis of these results showed the similar curative effects of capecitabine plus oxaliplatin compared with 5-FU plus oxaliplatin for MCRC.

PFS and OS analysis. We did not obtain information from each individual patient from every study. Furthermore, PFS and OS belong to the skewed distribution that cannot be studied by meta-analysis. Therefore, we only performed a descriptive statistical analysis of the data. All seven studies reported PFS and median OS (Table III).

Adverse reaction analysis. The most commonly reported chemotherapy-related adverse events were nausea, vomiting, diarrhea, fever, thrombocytopenia, neutropenia, stomatitis, hand-foot syndrome and peripheral neuropathy. There were five studies reporting the toxic effects of hand-food syndrome.

Table I. Characteristics of studies included in the meta-analysis.

Study (year, reference)	Interventions	No. of patients	Age range in years (mean)	Gender (M/F)	Primary tumor site			No. of metastatic sites		ECOG PS score		
					Colorectal	Colon	Rectum	1	≥2	0	1	2
Rothenberg ML <i>et al</i> 2008 (5)	XELOX	313	26-81 (60.7)	194/119	26	185	102	99	214	150	139	24
	FOLFOX-4	314	26-83 (59.7)	191/123	24	201	89	108	206	145	148	21
Porschen R <i>et al</i> 2007 (6)	CAPOX	241	32-81 (66)	150/91	NA	NA	NA	118	123	219	22	
	FUFOX	233	34-86 (64)	146/87				114	119	216	17	
Ducreux M <i>et al</i> 2010 (7)	XELOX	156	32-83 (66)	100/56	25	94	37		NA	144	12	
	FOLFOX-6	150	42-84 (64)	90/60	17	95	38			139	11	
Van Cutsem E <i>et al</i> 2009 (8)	XELOX	346	20-84 (60)	197/149	48	208	90	204	142	221	125	0
	FOLFOX	552	21-85 (59)	331/221	72	337	143	348	204	381	171	0
Diaz-Rubio E <i>et al</i> 2007 (9)	XELOX	171	32-80 (64)	107/64	12	110	49		NA		NA	
	FUOX	171	37-79 (65)	100/71	6	116	49					
Comella P <i>et al</i> 2009 (10)	OXXEL	158	39-84 (64)	104/54		114	44	79	79	96	57	5
	OX-AFAFO	164	37-79 (65)	89/75		115	49	74	90	99	59	6
Cassidy J <i>et al</i> 2008 (11)	XELOX	317	24-84 (61)	194/123	30	204	83	127	190	160	157	0
	FOLFOX-4	317	24-81 (62)	204/113	17	200	100	118	198	163	154	0

ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not available.

Table II. Quality assessment of studies included in the meta-analysis.

Study (year, reference)	Randomization	Blind	Exit/lose	ITT	Jadad score
Rothenberg ML <i>et al</i> 2008 (5)	Yes	NA	Yes	Yes	4
Porschen R <i>et al</i> 2007 (6)	Yes	NA	Yes	Yes	4
Ducreux M <i>et al</i> 2010 (7)	Yes	NA	Yes	Yes	4
Van Cutsem E <i>et al</i> 2009 (8)	Yes	NA	Yes	Yes	4
Diaz-Rubio E <i>et al</i> 2007 (9)	Yes	NA	Yes	Yes	4
Comella P <i>et al</i> 2009 (10)	Yes	NA	Yes	Yes	4
Cassidy J <i>et al</i> 2008 (11)	Yes	NA	Yes	Yes	4

NA, not available; ITT, intention-to-treat analysis; lose, lost to follow-up. Total Jadad scores 1-5. 1-2: low quality studies, 3-5: high quality studies.

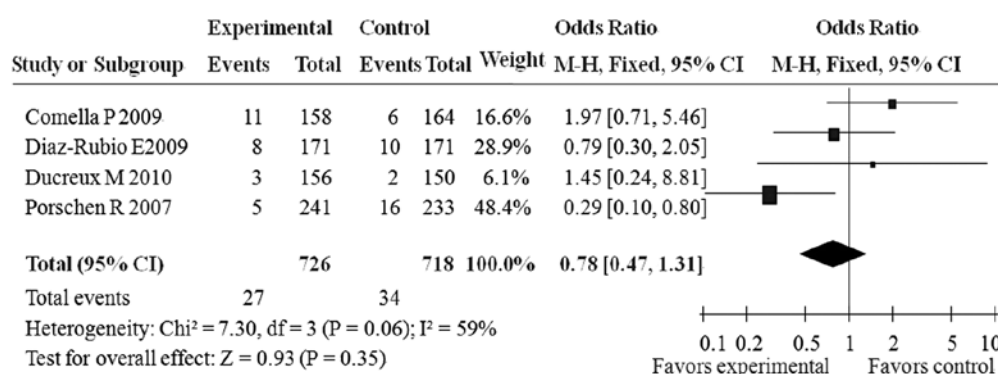


Figure 1. Meta-analysis of the complete response rate of capecitabine plus oxaliplatin compared with 5-fluorouracil plus oxaliplatin for metastatic colorectal cancer.

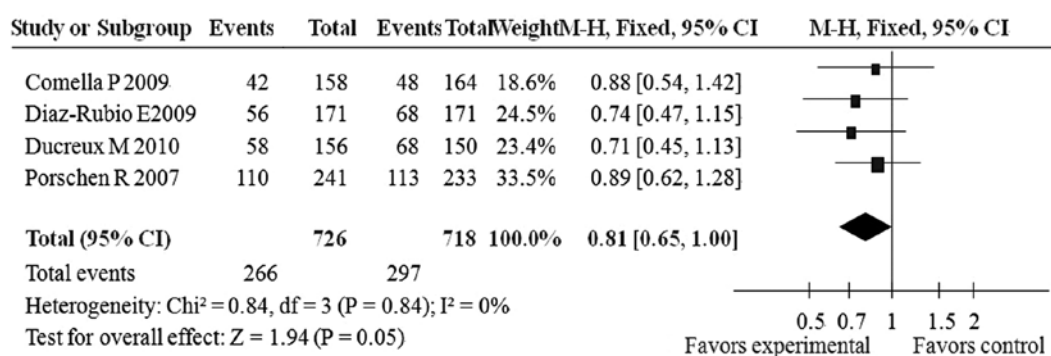


Figure 2. Meta-analysis of the partial response rate of capecitabine plus oxaliplatin compared with 5-fluorouracil plus oxaliplatin for metastatic colorectal cancer.

The heterogeneity test appeared to show no statistically significant difference ($p=0.05$, $I^2=58\%$); thus we confirmed that the difference between the capecitabine plus oxaliplatin group and the 5-FU plus oxaliplatin group was statistically significant by using the fixed effect model (OR=2.71, 95% CI 2.04-3.61, $p<0.00001$; Fig. 4), which revealed that the incidence of hand-foot syndrome in the capecitabine plus oxaliplatin group was markedly higher than that the 5-FU plus oxaliplatin group. Conversely, stomatitis and neutropenia were

more commonly observed in the 5-FU plus oxaliplatin group. The third and fourth trials, respectively, reported stomatitis and neutropenia. Significant differences were not found ($p=0.09$, $I^2=59\%$) in the adverse reaction of stomatitis by using a fixed effects model; the resulting difference between the two regimens was statistically significant (OR=0.51, 95% CI 0.38-0.70, $p<0.0001$; Fig. 5). Regarding neutropenia, we used a random effects model ($p<0.00001$, $I^2=89\%$) and received a similar result to stomatitis (OR=0.31, 95% CI 0.16-0.60,

Table III. Analytic results of median OS and PFS.

Study (year, reference)	PFS (month)			Median OS (month)		
	Experimental group	Control group	P-value	Experimental group	Control group	P-value
Rothenberg ML <i>et al</i> 2008 (5)	4.7	4.8	-	11.9	12.6	-
Porschen R <i>et al</i> 2007 (6)	7.1	8.0	0.117	16.8	18.8	0.26
Ducieux M <i>et al</i> 2010 (7)	8.8	9.3	-	19.9	20.5	-
Van Cutsem E <i>et al</i> 2009 (8)	10.8	11.3	-	23.0	25.9	-
Diaz-Rubio E <i>et al</i> 2007 (9)	8.9	9.5	0.153	18.1	20.8	0.145
Comella P <i>et al</i> 2009 (10)	6.6	6.5	0.699	16.0	17.1	0.883
Cassidy J <i>et al</i> 2008 (11)	8.4	8.5	-	19.8	19.6	-

PFS, progression-free survival; OS, overall survival.

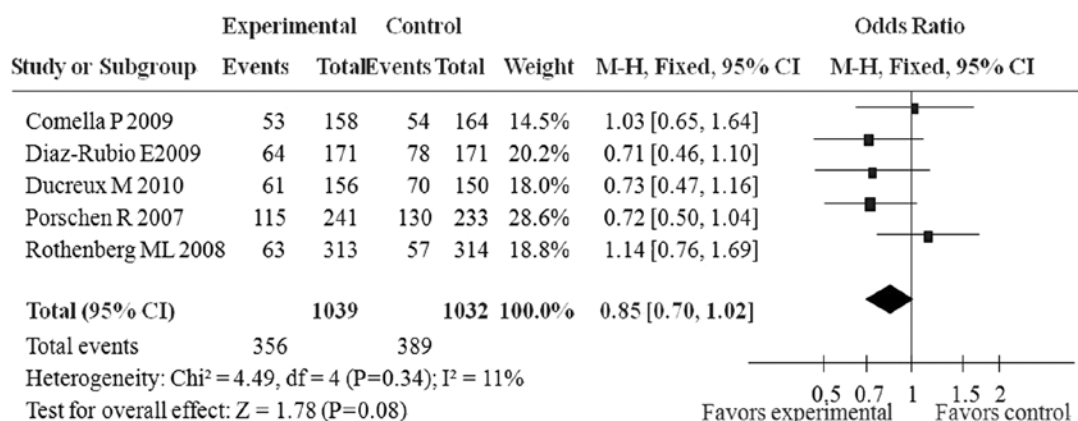


Figure 3. Meta-analysis of the overall response rate of capecitabine plus oxaliplatin compared with 5-fluorouracil plus oxaliplatin for metastatic colorectal cancer.

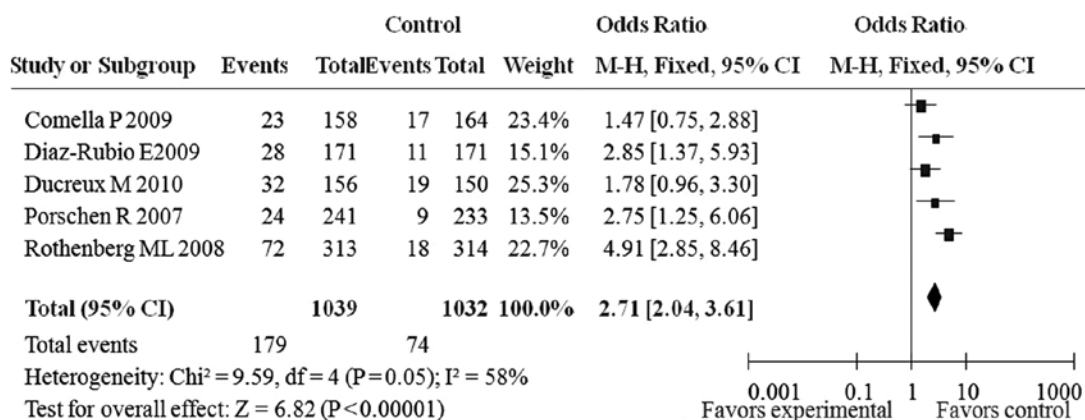


Figure 4. Meta-analysis of the incidence of hand-foot syndrome using capecitabine plus oxaliplatin compared with 5-fluorouracil plus oxaliplatin for metastatic colorectal cancer.

p=0.0005; Fig. 6). However, certain common toxic effects, for example, nausea, vomiting, diarrhea, fever, thrombocytopenia and peripheral neuropathy, occurred to a similar extent in the two regimens (p>0.05). Remaining data on adverse events are shown in Table IV.

Discussion

The drug 5-FU has been the main chemotherapy for colorectal carcinoma in clinical use as it was the only available drug. Recently, improved regimens combining 5-FU with oxaliplatin

Table IV. Meta-analysis of partial adverse events.

Adverse reaction	RCT (n)	Experimental group (n/N)	Control group (n/N)	Heterogeneity test		Effect model	OR	95% CI	P-value
				P-value	I ² %				
Nausea	3	357/640	360/635	0.02	73	Random	0.89	0.57-1.39	0.61
Diarrhea	4	417/798	420/799	0.0004	84	Random	0.91	0.55-1.51	0.71
Fever	3	124/640	130/635	0.99	0	Fixed	0.94	0.71-1.23	0.64
Thrombocytopenia	4	206/798	250/799	0.02	71	Random	0.73	0.48-1.13	0.16
Peripheral neuropathy	3	177/712	182/711	0.38	0	Fixed	0.97	0.75-1.24	0.79

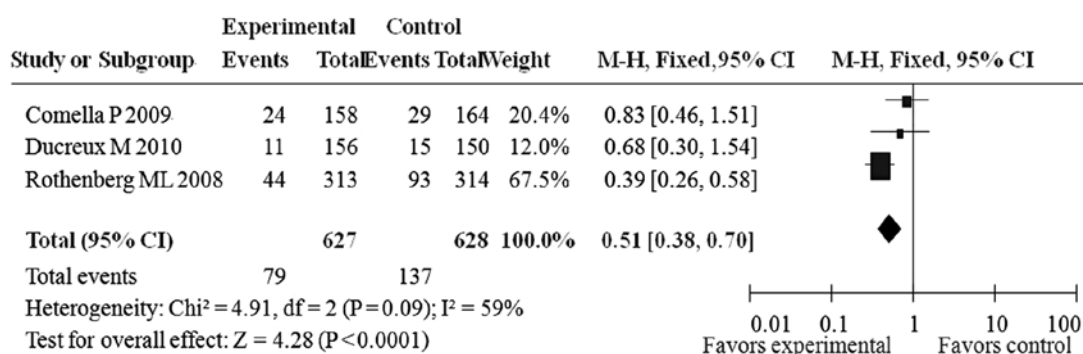


Figure 5. Meta-analysis of the incidence of stomatitis in capecitabine plus oxaliplatin compared with 5-fluorouracil plus oxaliplatin for metastatic colorectal cancer.

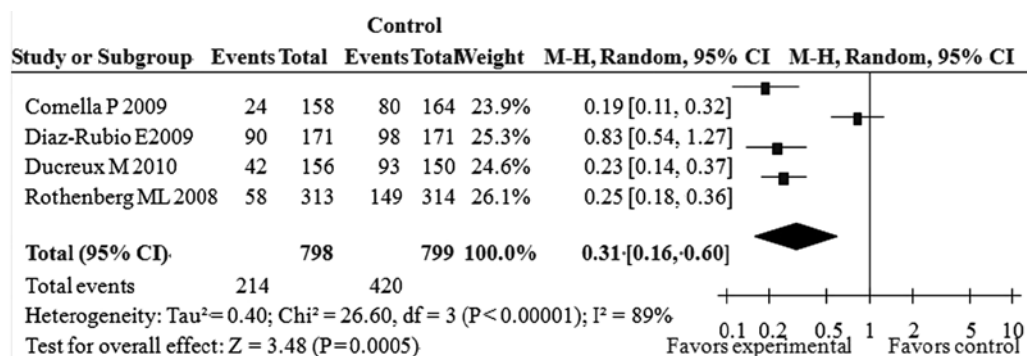


Figure 6. Meta-analysis of the incidence of neutropenia in capecitabine plus oxaliplatin compared with 5-fluorouracil plus oxaliplatin for metastatic colorectal cancer.

have been applied, which may be considered as more efficacious. Oxaliplatin is a third-generation cisplatin derivative with anti-cancer activity. The mechanism of action, platinum atom and DNA, form the platinum-DNA bulky adducts, which are capable of restraining DNA synthesis and repair, and activating the cell signaling pathway through intrastrand, interstrand and protein cross-linking with DNA. Oxaliplatin was found to be highly active as it was higher and firmer when combined with DNA than other platinum drugs. De Gramont *et al* demonstrated significantly higher activity of a combination of oxaliplatin plus 5-FU/LV compared with 5-FU/LV as first-line therapy in advanced CRC in a phase III trial (12). The combined regimen of oxaliplatin plus 5-FU/LV as first-line chemotherapy for advanced CRC also demonstrated good tolerance and more effective power of 34-67% (13).

Capecitabine (Xeloda; Hoffmann-La Roche Inc.), an oral prodrug of fluoropyrimidine, is absorbed from the gastrointestinal tract in an inactive form and generates fluorouracil by way of a three-step enzymatic cascade. The final stage of doxifluridine converted to fluorouracil is catalyzed by the enzyme thymidine phosphorylase (TP), which is present in tumors at a higher concentration than in normal tissue (14). Cassidy *et al* confirmed that oxaliplatin upregulates the expression of TP in a CFX280 xenograft model of human colon tumor tissue to increase the collaborative anti-cancer activity with capecitabine (15). Early phase II trials considering the XELOX (oxaliplatin 130 mg/m² on day 1 every 3 weeks) and CAPOX (oxaliplatin 70 mg/m² on days 1 and 8 every 3 weeks) regimens showed an ORR of 37-49%, and the endpoints of median TTP and median OS were 5.9 to 8.2 months and 15.8 to 20 months,

respectively (16-18). Recently, more attention has been paid to combination chemotherapy of CRC with the regimen of capecitabine and oxaliplatin for safe, reliable and convenient medication. In certain randomized studies it was concluded that XELOX is non-inferior in terms of efficacy to the FOLFOX regimen in the first-line treatment of MCRC (5-7,9,11). In addition, as a substitute of 5-FU, capecitabine did not require central venous catheterization, preventing infection, thromboembolism and certain other risks in elderly patients. Results of the study by Comella *et al* on 76 elderly patients with MCRC (mean age, 75 years) receiving the XELOX regimen, with an ORR of 41% (95% CI 30-53%), including 2 CR and 29 PR, showed the median PFS to be 8.5 months (95% CI 6.7-10.3 months), and the median OS to be 14.4 months (95% CI 11.9-16.9 months). Regarding adverse reactions during treatment, 5% of patients had Grade ≥ 3 hematologic toxicity, 8% of patients had Grade 3 peripheral neuropathy and 13% of patients had severe hand-foot syndrome (19). Similar results were obtained in another phase II trial that included a total of 50 patients aged >70 years with MCRC, using the XELOX regimen as first-line therapy. The authors observed that the ORR was 36% (95% CI 28-49%), with 3 CR and 15 PR. The median OS was 13.2 months (95% CI 7.6-16.9 months). There were 14 (28%) patients who exhibited Grade ≥ 3 adverse reactions including 11 (22%) with diarrhea, 8 (16%) with asthenia, 7 (14%) with nausea/vomiting, 3 (6%) with neutropenia, 3 (6%) with thrombocytopenia and 2 (4%) with hand-foot syndrome (20). Based on the data from these trials, capecitabine and oxaliplatin may be regarded as an appropriate treatment selection for elderly patients with MCRC. This combined therapy may be well tolerated and have reliable clinical efficacy.

Our study analyzed published trials comparing capecitabine plus oxaliplatin with 5-FU plus oxaliplatin in patients with MCRC in the last decade. Analyses were according to the intention-to-treat principle. The results revealed that CR, PR and ORR had similar curative effects between the capecitabine plus oxaliplatin group and the 5-FU plus oxaliplatin group, and the median OS and PFS had no statistically significant differences. Regarding safety, hand-foot syndrome was more frequently observed in the capecitabine plus oxaliplatin group, while stomatitis and neutropenia were reversed. Other toxic effects had no statistically significant differences between the two groups. Our findings have shown that capecitabine plus oxaliplatin had similar curative effects as 5-FU plus oxaliplatin, but was safer in patients with MCRC.

Since capecitabine is a prodrug of fluoropyrimidine, it is capable of reducing the systemic exposure of the active form of 5-FU to normal tissue. In 2001, a large Phase III randomized trial compared capecitabine with intravenous 5-FU in patients with MCRC (21). The toxicity of capecitabine mainly included hand-foot syndrome ($p<0.0001$), but resulted in lower incidences of Grade 3/4 stomatitis and neutropenia compared to 5-FU ($p<0.00001$). The results are consistent with our study. Results of another study (22) found that Grade 3 adverse events were more common in the capecitabine than those in the 5-FU/leucovorin group (38.1 vs. 34.1%; $p=0.16$), primarily due to Grade 3 hand-foot syndrome. However, Grade 4 adverse events were more frequent with 5-FU/leucovorin (3.0 vs. 5.1%; $p=0.078$), which was mainly ascribed to neutropenia and diarrhea. The incidence of Grade 3 or 4 chemotherapy-related

adverse events during the first treatment cycle was significantly higher in patients receiving 5-FU/leucovorin than capecitabine (22.6 vs. 9.1%; $p<0.001$) (22). However, in our study, the incidence of diarrhea had no significant difference between the two regimens. More studies with high quality and large samples are required to update the investigation into adverse events.

Our report has a number of limitations. Firstly, we did not obtain information from each individual patient for each trial. Furthermore, PFS and median OS belong to the skewed distribution that cannot be assessed by meta-analysis. Secondly, there is a potential bias in the studies included, as the dose and specification of chemotherapy drugs were not uniform. Thirdly, unpublished trials were not included. Finally, the result of the comparison between certain adverse effects is not stable and reliable enough due to the small number of inclusive studies. We believe that more results with improved methodological quality should be provided to update this study. Should findings of the present study be utilized as a reference, it would be necessary to make a reasonable adjustment for other research results, clinical experience and the individual patient characteristics in clinical practice.

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