We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

New Option for Metastatic Colorectal Cancer: Oxaliplatin and Novel Oral S-1 Combination Chemotherapy

Dae Young Zang

*Division of Hematology-Oncology, Department of Internal Medicine
Hallym University Medical Center and Hallym University College of Medicine, Anyang
South Korea*

1. Introduction

The combination of oxaliplatin or irinotecan with bolus and infusional fluorouracil (FU) and folinic acid (FA) is considered the standard regimen for the first-line treatment of metastatic colorectal cancer [1–4]. However, this regimen is inconvenient owing to its requirement for continuous infusion of FU via vascular access.

To overcome this drawback, oral fluoropyrimidines such as capecitabine have been used as a substitute for infused FU/FA [5], and recent data have shown that capecitabine plus oxaliplatin (XELOX) was not inferior to infused FU/FA plus oxaliplatin (known as FOLFOX-4 or FUOX) [6, 7]. S-1, a novel dihydropyrimidine dehydrogenase-inhibitory oral fluoropyrimidine, has been used widely in patients with gastric cancer. In phase II studies, S-1 as a single agent showed an overall response rate (ORR) of 19–40% with tolerable toxicities in the first-line treatment of metastatic colorectal cancer [8–10].

To explore the possibility of using S-1 to replace the continuous FU infusion of the FOLFOX regimen, Korean investigators carried out a phase II clinical trial [11] and Japanese investigators performed a phase I/II clinical trial [12] with a regimen of oxaliplatin plus S-1 (OS) for the first-line treatment of metastatic colorectal cancer, respectively.

2. Patients and methods

2.1 Eligibility

Eligible patients met all of the following criteria: presence of unresectable, metastatic, histologically confirmed colorectal cancer; age from 18 to 70 years [11] or from 20 to 74 years [12]; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 [11] or 0–1 [12]; estimated life expectancy of more than 3 months; and adequate hematological, renal, and hepatic functions. The presence of a unidimensionally measurable lesion was also required for the phase II studies. Patients with a previous history of chemotherapy (except adjuvant or neoadjuvant chemotherapy not including oxaliplatin or S-1), central nervous system metastasis, obvious bowel obstruction, serous gastrointestinal bleeding, or serious comorbid conditions were excluded from the study.

Each patient gave written informed consent before entering the study. The protocol was approved by the institutional review board of each center.

2.2 Pretreatment evaluations

Baseline evaluations included medical history, physical examination, ECOG PS, complete blood count with differential count, serum chemistry and electrolytes, urine analysis, and three-dimensional computed tomography.

2.3 Treatment scheme

In phase I part of the Japanese phase I/II study, oxaliplatin was administered at a dose of 100 mg/m² (level 1) or 130 mg/m² (level 2) on day 1, and S-1 (40–60 mg) was given twice daily for 2 weeks followed by a 1-week rest [12]. This schedule was repeated every 3 weeks. Level 2 was determined to be the recommended dose (RD) for the phase II part of the study. In two Japanese and Korean phase II studies, oxaliplatin 130 mg/m² mixed with 250 mL of dextrose solution was administered intravenously over 2 h on day 1, and S-1 40 mg/m² [body surface area (BSA) < 1.25 m², 40 mg; 1.25 ≤ BSA < 1.5, 50 mg; BSA ≥ 1.5, 60 mg] was administered orally, twice daily from day 1 to 14, followed by a 7-day rest period [11, 12]. The treatment was repeated every 3 weeks until progression of the disease, the development of unacceptable toxicity, or consent withdrawal by the patient.

2.4 Dose modifications

The dose of a specific agent was adjusted when the cause of toxicity could be distinguished [11]. When both agents were believed to have caused the toxicity, the doses of both were reduced. Treatment was interrupted in the case of grade 2 or higher toxicity and was not resumed until the toxicity resolved or had improved to grade 0 or 1. The dose of oxaliplatin was reduced by 25% of the initial dose for related grade 3 toxicities or for the second occurrence of same grade 2 toxicity. The dose of S-1 was reduced by 20 mg/day for related grade 3 toxicities or for second occurrence of the same grade 2 toxicity. The dose of oxaliplatin was reduced by 50% of the initial dose for related grade 4 toxicities or for the second occurrence of same grade 3 toxicity. The initial dose of S-1 was reduced by 40 mg/day for related grade 4 toxicities or for second occurrence of the same grade 3 toxicity. No dose increase was allowed. Treatment was discontinued if, despite the dose reduction, the same toxicity occurred for a fourth time at grade 2, a third time at grade 3, or a second time at grade 4. In addition, if the toxicity had not improved to grade 0 or 1 after 3 weeks to allow the continuation of treatment, the patient was removed from the study.

Dose-limiting toxicity (DLT) was defined as any of the following findings during cycle 1: (1) a neutrophil count of less than 500/mm³ for more than 4 days, (2) a platelet count of less than 50,000/mm³, (3) diarrhea of grade 3 or more that occurred despite adequate supportive therapy, (4) grade 3 or 4 non-hematologic toxicity, excluding nausea, vomiting, anorexia, and electrolyte imbalance, or (5) a treatment delay longer than 1 week due to drug-related toxicity in the phase I part [12]. If DLT occurred, the dose of oxaliplatin in the subsequent course was reduced to 75% of the initial dose and that of S-1 was reduced by one dose level: from 80 to 50, 100 to 80, and 120 to 100. S-1 intake was interrupted mid-cycle if there was a neutrophil count less than 1,000/mm³, a platelet count less than 75,000/mm³, diarrhea, stomatitis, or hand foot syndrome occurred at grade 1 or more, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 150 IU/L, total bilirubin more than 1.5 times the upper limit of normal, or creatinine more than the upper limit of normal. The treatment in the subsequent cycle could be resumed if these adverse events resolved within 3 weeks after the last S-1 treatment. If peripheral neuropathy persisted between courses, the next treatment cycle was started at 75% of the previous dose of oxaliplatin.

2.5 Response and toxicity evaluation

The Response Evaluation Criteria in Solid Tumors guidelines [13] were used to evaluate tumor responses, and the National Cancer Institute Common Toxicity Criteria (version 3.0) were used to assess toxicity. Complete response (CR) was defined as the disappearance of all target and nontarget lesions. Partial response (PR) was a 30% or greater decrease in the sum of the longest diameter of target lesions, referenced against the baseline sum of the longest diameter of target lesions together with stabilization or decrease in size of nontarget lesions. Progressive disease (PD) required a 20% or greater increase in the sum of the longest diameter of target lesions, an unequivocal increase in the nontarget lesions, or appearance of any new lesions. Stable disease (SD) was defined as insufficient shrinkage to qualify for partial response and insufficient increase to qualify for progressive disease. Tumor responses were evaluated every two cycles [11] or every month [12] by three-dimensional computed tomography and were determined by an independent response review committee. All partial and complete responses were confirmed not less than 4 weeks after the criteria for response were first met. After completion of the study treatment, patients were followed up every 2 or 3 months until disease progression or death.

2.6 Statistical analysis

The primary aim of these phase II studies was to assess the ORR, and the secondary endpoints were safety profile, time to progression (TTP) or progression free survival (PFS), overall survival time, and duration of response.

Simon's MinMax two-stage design [14] was used to calculate the sample size in the Korean study [11]. The first stage required at least seven of 19 patients to have a confirmed response, assuming $P_1 = 0.40$, $P_0 = 0.20$, $\alpha = 0.05$, and $\beta = 0.20$, before proceeding to the second stage. In the second stage, 20 additional patients were to be entered, to achieve a target sample size of 43 assessable patients. Assuming a dropout rate of 10%, 48 patients were initially enrolled for the study.

The sample size was calculated to be at least 28 patients on the assumption of the null hypothesis of overall response rate of $\leq 30\%$ versus the alternative hypothesis of overall response rate of $> 60\%$, power 80%, and a 2.5% (one-sided) in the Japanese study [12].

The duration of response, TTP, and survival time were estimated using the Kaplan-Meier method.

3. Results

3.1 Patient characteristics

Forty-eight patients were enrolled in the Korean study [11]. All patients were assessed for safety and survival. Response was evaluated in all patients, except one patient who died due to the rupture of an underlying aortic aneurysm after the second cycle but before the evaluation, and one patient who had only non-measurable lesions and peritoneal seeding with malignant ascites. Patient characteristics are listed in Table 1. There were 25 men, and the median age was 56 years (range, 24–70). Twenty-three (48%) had colon cancer, seven (15%) had rectosigmoid colon cancer, and 18 (38%) had rectal cancer. Thirty-one patients (65%) were diagnosed with metastatic disease. Seventeen patients (35%) had recurrent colorectal cancer that relapsed after surgery, with adjuvant chemotherapy or chemoradiotherapy. The most common metastatic sites were distant lymph nodes (56%), liver (56%), and lung (31%). The median number of metastatic organs was two (range, 1–6).

Twenty-nine patients were treated at the RD in the Japanese study [12]. All 29 patients were evaluated for toxicity. Efficacy was evaluated in 28 patients. One patient was excluded from the analysis of efficacy due to symptoms of brain metastasis suspected to have existed before enrolment. There are 20 men, and the median age was 57 years (range 34–71). Eighteen (62%) had colon cancer and 11 (38%) had rectal cancer. Four patients had received adjuvant oral fluorouracil based therapy.

Characteristic	No. of patients (%) [ref. 11]	No. of patients (%) [ref. 12]
Total number of patients	48 (100)	29 (100)
Gender		
Male	25 (52)	20 (69)
Female	23 (48)	9 (31)
Age, years		
Median	56	57
Range	24–70	34–71
Eastern Cooperative Oncology Group performance status		
0	39 (81)	26 (90)
1	8 (17)	3 (10)
2	1 (2)	
Primary disease site		
Colon	23 (48)	18 (62)
Rectosigmoid colon	7 (15)	
Rectum	18 (38)	11 (38)
Surgery and adjuvant therapy		
None	12 (25)	
Resection only	19 (40)*	25 (86)
Resection + chemotherapy	8 (17)	4 (14)
Resection + chemotherapy + radiotherapy	9 (19)	
Metastatic sites		
Liver only	9 (19)	10 (35)
Lung	8 (17)	3 (10)
Liver and other lesions	18 (38)	10 (35)
Others	13 (27)	6 (21)
No. of metastatic sites		
1	19 (40)	15 (52)
≥2	29 (60)	14 (48)

*Palliative surgery only.

Table 1. Patient characteristics

3.2 Efficacy

In total, 413 treatment cycles were administered to 48 patients, with a median of six cycles (range, 2–24) per patient in the Korean study [11]. Tumor response data are listed in Table 2. There were three CRs, 23 PRs, 17 cases of SD, and three cases of progression. The confirmed ORR in the intention-to-treat (ITT) population was 54% (95% CI, 40–68%) and in the per protocol (pp) population was 57% (95% CI, 43–71%). The median time to response was 1.5 months (95% CI, 1.3–1.7), and the median duration of response was 9.3 months (95% CI, 6.5–12.1). The median duration of follow-up was 21.2 months (95% CI, 17.9–23.6). The median TTP in the ITT population was 8.5 months (95% CI, 6.2–10.9). The median survival time was 27.2 months (95% CI, 20.3–34.0), and the 2-year survival rate in the ITT group was 53%. The median number of administered cycles was 6.5 (range: 2–14), and the total number of cycles for the 29 patients was 180 in the Japanese study [12]. The ORR was determined by the External Review Board. One of the 28 patients given the RD had CR and 13 patients had PRs, yielding a response rate of 50% (95% CI, 31–69%). In the 28 patients studied, the median PFS was 6.5 months (95% CI, 5.6–10.1). The median overall survival time was not reached when 1 year passed since the last patient enrolment, and the 1-year survival rate was 79% by the Kaplan–Meier method.

Response*	No. of patients [ref. 11]	% (95% CI)	No. of patients [ref. 12]	% (95% CI)
Total No. patients	48		29	
Overall response	26	57 (43–71)	14	50 (31–69)
Complete	3		1	
Partial	23		13	
Stable disease	17		9	
Disease control	43	93 (86–100)	23	82 (68–96)
Progression	3		5	
Not evaluable	2		1	
Median time to response (months)	1.5	(1.3–1.7)		
Median duration of response (months)	9.3	(6.5–12.1)		

* Response in evaluable patients.

Table 2. Analysis of response (independent response review committee assessed)

3.3 Safety

Safety was assessed in 48 patients based on a total of 413 cycles in the Korean study [11]. The adverse events are listed in Table 3. Thrombocytopenia, which developed in 13% of the patients, was the most common grade 3/4 adverse event. There was no case of symptomatic thrombocytopenia. Neutropenia, observed in 10% of the patients, was the second most common grade 3/4 toxicity, and febrile neutropenia developed in one patient. Anemia, observed in 6% of the patients, was the third most common grade 3/4 toxicity. Non-hematologic toxicities were usually mild (mostly grade 1/2) and manageable. The most

common non-hematologic toxicities were anorexia, neuropathy, nausea, asthenia, and hyperbilirubinemia.

Event	No. of patients (<i>n</i> = 48) [ref. 11]				No. of patients (<i>n</i> = 29) [ref. 12]			
	NCI-CTC grade, version 3				NCI-CTC grade, version 3			
	All	3	4	3/4 %	All	3	4	3/4 %
Leukopenia	31	0	0	0	20	0	0	0
Neutropenia	34	5	0	10	18	4	0	14
Anemia	49	3	0	6	18	1	0	3
Thrombocytopenia	28	5	1	13	27	7	1	28
Anorexia	41	0	0	0	26	0	0	0
Nausea	35	0	0	0	21	0	0	0
Vomiting	16	0	0	0	7	0	0	0
Diarrhea	10	0	0	0	17	1	0	3
Neuropathy	36	0	0	0	29	0	0	0
Abnormal AST/ALT	29	0	0	0	n/a			
Hyperbilirubinemia	23	1	0	2	n/a			
Asthenia/ fatigue	27	0	0	0	26	0	0	0
Allergic reaction	0	0	0	0	1	1	0	3

NCI-CTC, National Cancer Institute–Common Toxicity Criteria; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3. Observed adverse events according to number of patients

The median relative dose intensities (ratio of dose received to dose planned) of oxaliplatin and S-1 for all cycles administered were 0.82 (range, 0.46–1.00) and 0.82 (range, 0.52–1.00), respectively [11]. The mean relative dose intensities of oxaliplatin and S-1 for all cycles administered were 0.79 and 0.83, respectively. The mean relative dose intensities of both drugs in each cycle during one to nine treatment cycles are shown in Figure 1. The dose reductions and delays during one to nine treatment cycles (total, 311 cycles in 48 patients) were as follows. Oxaliplatin was reduced in 37 cycles (12%), primarily because of thrombocytopenia (18 cycles), neutropenia (10 cycles), and thrombocytopenia with neutropenia (9 cycles). S-1 was reduced in 28 cycles (9%), primarily because of thrombocytopenia (14 cycles), neutropenia (8 cycles), and thrombocytopenia with neutropenia (6 cycles). Eighty-six cycles (28%) were delayed owing to thrombocytopenia (39 cycles), neutropenia (34 cycles), thrombocytopenia with neutropenia (10 cycles), and other reasons (3 cycles).

After identification of tolerability at level 2 (130 mg/m²) of oxaliplatin, 29 other patients received the RD at 130 mg/m², including the phase I part patients, to further evaluate the tolerability and toxicity of the study regimen [12]. Oxaliplatin could be administered at the RD without dose reduction in 57% of 28 patients. At the RD, grade 3 neutropenia was observed in four patients (14%), and grade 3 and 4 thrombocytopenia in seven patients (24%) and one patient (3%), respectively. The median relative dose intensity was 0.83 for

oxaliplatin and 0.75 for S-1 at level 2. The causes of treatment discontinuation at the RD were PD in 13 patients (36%), delayed recovery from toxicity such as neutropenia, thrombocytopenia, and slight hyperbilirubinemia in 8 patients, discretion of the investigator in 2 patients, allergic reaction in 1 patient, and symptomatic deterioration in 1 patient. The treatment was discontinued due to prolonged thrombocytopenia in eight patients after a median of seven cycles (range, 3–8). No treatment-related death was observed.

Fig. 1. Mean relative dose intensities of oxaliplatin and S-1 in each cycle between the 1st and 9th treatment cycles.

Sensory neuropathy occurred in all patients [12]. However, no functional impairment was observed in this study. The most common non-hematologic toxicities were anorexia, nausea, and diarrhea. One patient had grade 3 diarrhea at the RD. Another mild adverse event related to treatment was injection site reactions (45%). One patient had severe allergic reactions such as skin rash and fever, which are typical platinum-related reactions during the sixth cycle.

4. Discussion

The primary outcome of these two studies was the ORR, and the secondary outcomes were safety, TTP or PFS, and overall survival time [11, 12]. These studies demonstrated an ORR of 57% [11] and 50% [12], a median TTP of 8.5 months [11] and PFS of 6.5 months [12], and a median survival time of 27.2 months [11] in patients with metastatic colorectal cancer treated with the combination of oxaliplatin with S-1. Although these two studies were phase II studies, these efficacy results compare favorably to an ORR of 37–54%, a PFS or TTP of 8.0–9.5 months, and a median survival time of 16.2–20.8 months obtained with infused FU/FA and oxaliplatin (FOLFOX or FUFOX) as first-line chemotherapy for metastatic colorectal cancer in phase III studies [1, 2, 6, 7, 15-17]. Capecitabine plus oxaliplatin (XELOX or CAPOX) is another regimen commonly used in treating colorectal cancer. When oxaliplatin 130 mg/m² (day 1) or 70 mg/m² (days 1, 8) was administered intravenously, and capecitabine 1,000 mg/m² was administered orally, twice daily on days 1–14, every 3 weeks, the ORR, median PFS or TTP, and median overall survival with the XELOX or CAPOX

regimen were 37–55%, 6.0–8.9, and 16.8–19.8 months, respectively [5–7, 16, 18–20]. Those efficacy data for oxaliplatin combined with infused 5-FU/FA or capecitabine are similar to the data for oxaliplatin combined with S-1 in the present studies [11, 12].

The median age of the subjects was 56 [11] and 57 years [12], which was relatively younger than in other studies, which typically had median ages between 60 and 66 years [6, 7, 15, 16, 18, 20]. The inclusion criterion for the age of the patients was 18–70 years old [11] and 20–74 years old [12], while the criterion used in many other studies was age ≥ 18 years old. This might explain the relatively young median age of 56 (range 24–70) years and 57 (range 34–71) years in Korean and Japanese studies, respectively [11, 12].

The treatment was generally well tolerated by most patients. The most common and second most common grade 3/4 adverse events were thrombocytopenia (13% [11] and 28% [12] of all patients) and neutropenia (10% [11] and 14% [12]), respectively. There was no symptomatic thrombocytopenia, and only one patient experienced febrile neutropenia [11]. Although peripheral neuropathy was commonly observed (75% [11] and 100% [12]), most cases were grade 1 or 2. Hand-foot syndrome was rarely observed in these studies. The toxicity profile observed in the present study is different from those of the FOLFOX/FUFOX and XELOX/CAPOX regimens. Diarrhea, neutropenia, and neuropathy are major toxicities of FOLFOX/FUFOX regimens, and diarrhea, hand-foot syndrome, and neuropathy occur most commonly with XELOX/CAPOX regimens [6, 7, 16]. There were few observed grade 3/4 non-hematologic toxicities, with just one grade 3 hyperbilirubinemia [11], and one grade 3 diarrhea and one grade 3 allergic reaction [12]. Possible explanations for the reduced occurrence of severe non-hematologic toxicities compared to other studies using the XELOX regimen include the younger patient population, greater dose reduction or delay, or real reduced toxicity of the OS regimen. In contrast, the median age was between 60 and 66 years (range, 24–88) in many other studies, while the median age in these studies was 56 and 57 years (range, 24–71) due to the lower upper limit for patient inclusion. Perhaps younger patients can better tolerate the treatment. In addition, strict dose modifications according to the toxicities in previous cycles might have reduced the chance of developing more severe toxicities in subsequent cycles. Large comparative studies are needed to confirm the more favorable toxicity profiles of the OS regimen.

As expected, the administration of the OS regimen was convenient for the patients. Unlike the inconvenient, 2-day, continuous infusion of 5-FU in the FOLFOX regimen, the OS regimen requires only a 2-h infusion of oxaliplatin and oral administration of S-1 every 3 weeks. Thus, the OS regimen was as convenient as the XELOX regimen and required fewer clinic visits than the FOLFOX regimen [21].

5. Conclusion

The OS regimen can be an effective, well tolerated, and convenient therapeutic strategy in patients with metastatic colorectal cancer. Two comparative clinical trials with the XELOX regimen in advanced colorectal cancer are ongoing in Korea.

6. References

- [1] de Gramont A, Figer A, Seymour M et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18: 2938–2947.

- [2] Giacchetti S, Perpoint B, Zidani R et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000; 18: 136–147.
- [3] Douillard JY, Cunningham D, Roth AD et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; 355: 1041–1047.
- [4] Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N Engl J Med* 2005; 352: 476–487.
- [5] Cassidy J, Tabernero J, Twelves C et al. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. *J Clin Oncol* 2004; 22: 2084–2091.
- [6] Cassidy J, Clarke S, Díaz-Rubio E et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008; 26: 2006–2012.
- [7] Díaz-Rubio E, Tabernero J, Gómez-España A et al. Phase III study of capecitabine plus oxaliplatin compared with continuous-infusion fluorouracil plus oxaliplatin as first-line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. *J Clin Oncol* 2007; 25: 4224–4230.
- [8] Ohtsu A, Baba H, Sakata Y et al. Phase II study of S-1, a novel oral fluoropyrimidine derivative, in patients with metastatic colorectal carcinoma. S-1 Cooperative Colorectal Carcinoma Study Group. *Br J Cancer* 2000; 83: 141–145.
- [9] Van den Brande J, Schöffski P, Schellens JH et al. EORTC Early Clinical Studies Group early phase II trial of S-1 in patients with advanced or metastatic colorectal cancer. *Br J Cancer* 2003; 88: 648–653.
- [10] Shirao K, Ohtsu A, Takada H et al. Phase II study of oral S-1 for treatment of metastatic colorectal carcinoma. *Cancer* 2004; 100: 2355–2361.
- [11] Zang DY, Lee BH, Park H et al. Phase II study with oxaliplatin and S-1 for patients with metastatic colorectal cancer. *Ann Oncol* 2009; 20: 892–896.
- [12] Yamada Y, Tahara M, Miya T et al. Phase I/II study of oxaliplatin with oral S-1 as first-line therapy for patients with metastatic colorectal cancer. *Br J Cancer* 2008; 98: 1034–1038.
- [13] Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92: 205–216.
- [14] Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; 10: 1–10.
- [15] Goldberg RM, Sargent DJ, Morton RF et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; 22: 23–30.
- [16] Porschen R, Arkenau HT, Kubicka S et al. Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in

- metastatic colorectal cancer: a final report of the AIO Colorectal Study Group. *J Clin Oncol* 2007; 25: 4217–4223.
- [17] Tournigand C, André T, Achille E et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; 22: 229–237.
- [18] Makatsoris T, Kalofonos HP, Aravantinos G et al. A phase II study of capecitabine plus oxaliplatin (XELOX): a new first-line option in metastatic colorectal cancer. *Int J Gastrointest Cancer* 2005; 35: 103–109.
- [19] Scheithauer W, Kornek GV, Raderer M et al. Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2003; 21: 1307–1312.
- [20] Shields AF, Zalupski MM, Marshall JL, Meropol NJ. Treatment of advanced colorectal carcinoma with oxaliplatin and capecitabine: a phase II trial. *Cancer* 2004; 100: 531–537.
- [21] Mayer RJ. Should capecitabine replace infusional fluorouracil and leucovorin when combined with oxaliplatin in metastatic colorectal cancer? *J Clin Oncol* 2007; 25: 4165–4167.

IntechOpen

Rectal Cancer - A Multidisciplinary Approach to Management

Edited by Dr. Giulio A. Santoro

ISBN 978-953-307-758-1

Hard cover, 410 pages

Publisher InTech

Published online 10, October, 2011

Published in print edition October, 2011

Dramatic improvements in medicine over the last few years have resulted in more reliable and accessible diagnostics and treatment of rectal cancer. Given the complex physiopathology of this tumor, the approach should not be limited to a single specialty but should involve a number of specialties (surgery, gastroenterology, radiology, biology, oncology, radiotherapy, nuclear medicine, physiotherapy) in an integrated fashion. The subtitle of this book "A Multidisciplinary Approach to Management" encompasses this concept. We have endeavored, with the help of an international group of contributors, to provide an up-to-date and authoritative account of the management of rectal tumor.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Dae Young Zang (2011). New Option for Metastatic Colorectal Cancer: Oxaliplatin and Novel Oral S-1 Combination Chemotherapy, Rectal Cancer - A Multidisciplinary Approach to Management, Dr. Giulio A. Santoro (Ed.), ISBN: 978-953-307-758-1, InTech, Available from: <http://www.intechopen.com/books/rectal-cancer-a-multidisciplinary-approach-to-management/new-option-for-metastatic-colorectal-cancer-oxaliplatin-and-novel-oral-s-1-combination-chemotherapy>

INTech
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen