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Reasearch Article

Both XELIRI And TEGAFIRI Together with Bevacizumab are Effective for Recurrent or Metastatic Colorectal Cancer: A Real-Life Experience

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2. Keywords

Bevacizumab; Colorectal cancer; Irinotecan; Overall survival; Progression-free survival; Tegafur-uracil

1. Abstract

1.1. Objective: To evaluate a surgeon's experience of combination chemotherapy comprising different regimens of fluorouracil with or without irinotecan together with bevacizumab with respect to response rate for patients with recurrent or metastatic colorectal cancer.

1.2. Methods: Metastatic or recurrent colorectal cancer patients treated with bevacizumab were retrospectively analyzed from January 2009 to March 2018. They were grouped according to the type of regimen: group I: fluorouracil together with bevacizumab every 2 weeks; group II: irinotecan with fluorouracil (FOLFIRI), with bevacizumab every 2 weeks; group III: irinotecan with tegafur-uracil and leucovorin (TEGAFIRI), with bevacizumab every 2 weeks; and group IV: irinotecan with capecitabine (XELIRI), with bevacizumab every 2 weeks. They were followed until September 2017 or death.

1.3. Results: The cohort comprised 140 patients: 15 (group I), 18 (group II), 36 (group III), and 71 (group IV). The median progression-free survival was 10.52 (group I), 8.00 (group II), 11.02 (group III), and 14.10 (group IV) months. Meanwhile, the median overall survival was 17.48 (group I), 20.52 (group II), 27.70 (group III), and 22.16 (group IV) months, without significant difference in the treatment cycle among the groups. The rate of diarrhea, and hand foot syndrome, and poor appetite was similar between groups III and IV, while that of oral ulcer was slightly higher in group IV than that in group III. One patient (0.71%) in group IV developed colon perforation after seven courses of chemotherapy but recovered well after emergent surgery.

1.4. Conclusions: Both XELIRI and TEGAFIRI with bevacizumab are feasible and yield acceptable outcomes for recurrent or metastatic colorectal cancer. This combination is advantageous because it does not require admission and additional apparatus for administration, has shorter infusion time, is well-tolerated by most patients, and has acceptable hematological and non-hematological side effects.

3. Mini Abstract

There are few articles to discuss the feasibility to combine XELIRI and TEGAFIRI with bevacizumab. However, these regimens do have benefit such as well-tolerated, shorter infusion time.

4. Introduction

Chemotherapy is currently the primary treatment modality for metastatic and recurrent cancer [1-3], with many patients with metastases or recurrence responding well to chemotherapy [1-5]. It has been suggested that multiple drugs result in a better response than therapy with a single agent. Irinotecan has a response rate of 25%-40% when combined with 5-Fluorouracil (FU) and Leucovorin (LV) in Western countries [3,5] and also in Asia, but oral Uracil-Tegafur (UFT) and capecitabine has been preferred over 5-FU as a combination agent by some physicians [6-8]. Some studies used capecitabine (Xeloda) with irinotecan (XELIRI) instead of folinic acid, fluorouracil, and irinotecan (FOLFIRI) for metastatic colorectal cancer [9,10]. Similarly, oral tegafur-uracil (UFUR) with LV and irinotecan (TEGAFIRI) was also used to treat metastatic and recurrent colorectal cancer [11-13]. One previous study suggested that TEGAFIRI with LV is an effective alternative regimen for the management of recurrent or metastatic colorectal cancer [14]. Additionally, adding biologics to the multidrug regimen has been reported to possibly result in a better response than chemotherapy alone [15,16].

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This study aimed to evaluate a single surgeon's experience of combination chemotherapy comprising different regimens of fluorouracil with or without irinotecan together with bevacizumab with respect to response rate in patients with recurrent or metastatic colorectal cancer.

5. Materials and Methods

5.1. Patients and Ethical Concerns

This retrospective study evaluated all patients with a history of histologically proven colorectal cancer and had not been previously treated with chemotherapy for metastatic disease. The inclusion criteria were (1) age at least 18 years, (2) at least one measurable lesion, and (3) an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients who had (1) previous chemotherapy for metastatic colorectal cancer, (2) central nervous system metastasis, and (3) a life expectancy of <3 months were excluded.

Patients were categorized into four groups according to the treatment regimen. Group I comprised patients who received fluorouracil together with bevacizumab every 2 weeks; group II, FOLFIRI together with bevacizumab every 2 weeks; group III, TEGAFIRI together with bevacizumab every 2 weeks; and group IV, XELIRI together with bevacizumab every 2 weeks.

All patients signed an informed consent before receiving chemotherapy treatment. The Institutional Review Board (IRB) of Mackay Memorial Hospital approved this study.

5.2. Chemotherapy Regimen

The chemotherapy regimens were standardized at irinotecan 150 mg/m^2 every 2 weeks with continuous intravenous infusion, oral capecitabine at 900 mg/m^2 twice daily for 10 days and then rest for 4 days every 2 weeks, and oral UFUR at 300 mg/m^2/day and oral LV at 45 mg/m^2/day continuously. Bevacizumab was given at a rate of 5 mg/kg via continuous intravenous infusion every 2 weeks. Premedication included 10 mg dexamethasone intravenously, 3 mg granisetron or 8 mg ondansetron intravenously, and 0.5 mg atropine subcutaneously before irinotecan infusion. Supportive care included loperamide administration, antiemetic agents, and oral cephradine for diarrhea of more than 48-h duration. Oxaliplatin-based regimen was allowed in cases of progression. Biologics such as cetuximab were routinely used as third-line therapy for patients with K-ras wild-type metastatic colon cancer, with reimbursement from the government health insurance system in Taiwan.

Patients were also allowed to receive salvage chemotherapy such as regorafenib if the disease progressed after treatment with all chemotherapy regimens and biologics.

5.3. Assessment of Treatment Response and Adverse Effects

Patient assessment included serum Carcinoembryonic Antigen (CEA) test, chest radiography, abdominal ultrasound, and computed tomography of the chest or abdomen every 3 months. Treatment response to chemotherapy was evaluated according to the Response Evaluation Criteria in Solid Tumors and was categorized into four grades as (1) complete response (i.e., disappearance of metastatic lesions and normal CEA), partial response (i.e., at least a 25% decrease of number or size of metastatic lesions or a decreased level of CEA), stable disease, and progressive disease (i.e., an increase of at least 25% in the number or size of metastatic lesions, the appearance of new lesions, or an increased level of CEA).

The severity of adverse effects was evaluated using the National Cancer Institute Toxicity Criteria (version 2.0). Treatment interruption or dose reduction was not indicated for reactions unlikely to become serious or life-threatening. No dose reduction was required for the first appearance of grade 2 toxicity, but treatment with chemotherapy and biologics was interrupted in cases of grade ≥3 toxicity and was not resumed until the toxicity had resolved or had improved to grade 1. When treatment was resumed, the chemotherapeutic dose was reduced.

5.4. Study End Points

The primary end points were Progression-Free Survival (PFS) and Overall Survival (OS). PFS was defined as the duration from treatment to disease progression or death from disease progression or unknown causes. OS was defined as the time from the start of irinotecan treatment to death. All the patients were followed until September 2018 or death.

5.5. Statistical Analysis

Descriptive statistics (median, percentile, and range) were calculated for the baseline characteristics of the patients. Cox regression analysis with the forward stepwise conditional method was used to identify factors associated with time to progression in the multivariate analysis. Survival curves were computed according to the Kaplan-Meier method and compared using log-rank test.

6. Results

6.1. Patient Characteristics

The cohort comprised 140 patients. Of these, 15, 18, 36, and 71 belonged to groups I, II, III, and IV, respectively. Patients in group I were older, and there were more patients with colon cancer in group IV than that in group III (84.51% vs 44.44%). Meanwhile, more patients previously received adjuvant chemotherapy in group III than those in group IV (55.56% vs 22.54%). However, the rate of metastasectomy was similar between group IV and group III (22.54% vs 55.56%) (Table 1). A few patients who were old and frail only received oral chemotherapy with bevacizumab without irinotecan.

6.2. Survival Outcomes

The median PFS was 10.52 months in group I, 8.00 in group II, 11.02 in group III, and 14.10 in group IV. Group IV had the highest

PFS (14.10 months), followed by group III (11.02 months), with the lowest PFS in group I (8.00 months) (Figure 1). Meanwhile, the median OS was 17.48 months in group I, 20.52 months in group II, 27.70 months in group III, and 22.16 months in group IV. Group III had the highest OS (27.70 months), followed by group IV (22.16 months), with the lowest OS in group I (17.48 months) (Figure 2).

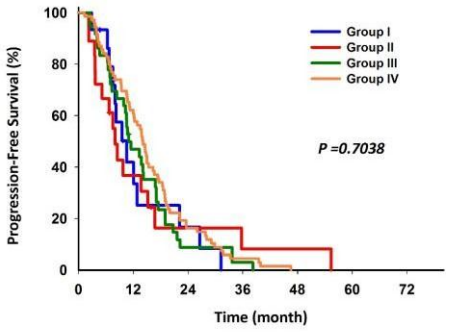
There was no significant difference in survival between patients with Right-Sided Colon Cancer (RSCC) and Left-Sided Colon Cancer (LSCC) (Figures 3 & 4). There was also no significance difference in the treatment cycle among groups(Table 2).

Table 1: Patient characteristics according to treatment group

	Group I Fluorouracil + bevacizumab		Group II FOLFIRI + bevacizumab		Group III TEGAFIRI + bevacizumab		Group IV XELIRI + bevacizumab		Total		
	n=15		n=18		n=36		n=71		N=140		
	n	%	n	%	n	%	n	%	n	%	P-value
Sex											0.2299
Female	6	40.00	12	66.67	14	38.89	30	42.25	62	44.29	
Male	9	60.00	6	33.33	22	61.11	41	57.75	78	55.71	
Age mean, SD	73.41 ± 11.73		57.75 ± 11.26		64.43 ± 9.78		61.44 ± 12.18		63.02 ± 12.05		0.0007
Primary tumor site											0.0003
Colon	10	66.67	12	66.67	16	44.44	60	84.51	98	70.00	
Rectum	5	33.33	6	33.33	20	55.56	11	15.49	42	30.00	
Pathological differentiation											0.0068
Well	1	6.67	4	22.22	0	0.00	1	1.41	6	4.29	
Moderately	10	66.67	9	50.00	31	86.11	58	81.69	108	77.14	
Poorly	2	13.33	4	22.22	3	8.33	9	12.68	18	12.86	
Unknown	2	13.33	1	5.56	2	5.56	3	4.23	8	5.71	
ECOG PS											
0	15	100.00	18	100.00	36	100.00	71	100.00	140	100.00	
RAS type											0.3029
mutation	6	54.55	10	58.82	13	39.39	24	36.36	53	41.73	
Wild-type	5	45.45	7	41.18	20	60.61	42	63.64	74	58.27	
Previous adjuvant CT											0.0045
No	12	80.00	12	66.67	16	44.44	55	77.46	95	67.86	
Yes	3	20.00	6	33.33	20	55.56	16	22.54	45	32.14	
Site of metastasis											0.4065
Single											
Liver only	6	40.00	2	11.11	10	27.78	27	38.03	45	32.14	
Lung only	3	20.00	3	16.67	6	16.67	8	11.27	20	14.29	
Others site	2	13.33	7	38.89	9	25.00	11	15.49	29	20.71	
Multiple											
Liver and lung	2	13.33	2	11.11	1	2.78	8	11.27	13	9.29	
Over 2 sites	2	13.33	4	22.22	10	27.78	17	23.94	33	23.57	
Surgical resection of metastatic disease											0.06
No	13	86.67	18	100.00	26	72.22	55	77.46	112	80.00	
Yes	2	13.33	0	0.00	10	27.78	16	22.54	28	20.00	

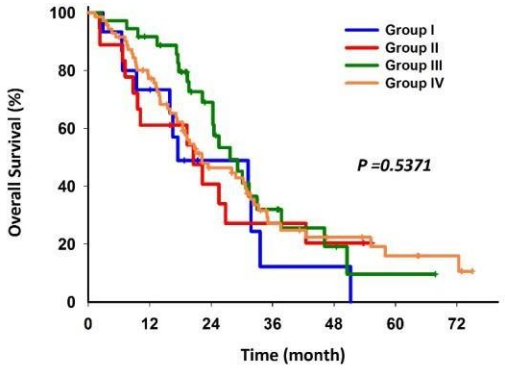
Table 2: Treatment cycles in the four groups

	Mean (cycles)	Standard deviation (cycles)	Median (cycles)	Range (cycles)
Group I (n=15) (Fluorouracil + A)	11.67	±5.69	11	5~22
Group II (n=18) (FOLFIRI + A)	12.06	±7.67	13	2~30
Group III (n=36) (TEGAFIRI + A)	14.14	±9.01	13	2~35
Group IV (n=71) (XELIRI + A)	14.89	±9.35	14	1~55
Total (n=140)	13.99	±8.74	13	1~55



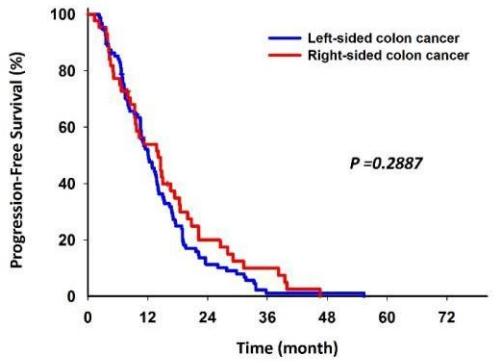
Regimen	n	MST	95% CI	
Fluorouracil + A (Group I)	15	10.52	6.69	22.13
FOLFIRI + A (Group II)	18	8.00	3.67	15.18
TEGAFIRI + A (Group III)	36	11.02	8.39	16.82
XELIRI + A (Group IV)	71	14.10	11.25	16.33

Figure 1:



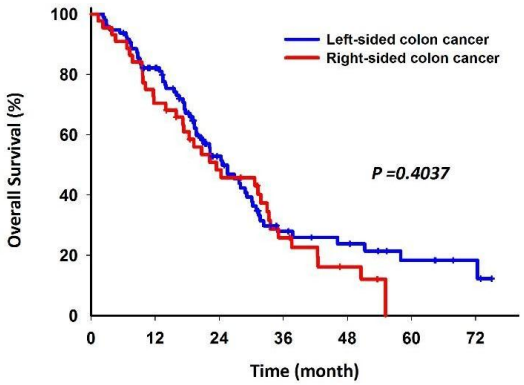
Regimen	n	MST	95% CI	
Fluorouracil + A (Group I)	15	17.48	6.69	33.54
FOLFIRI + A (Group II)	18	20.52	8.79	26.82
TEGAFIRI + A (Group III)	36	27.70	22.26	37.74
XELIRI + A (Group IV)	71	22.16	17.31	30.92

Figure 2:



	n	MST	95% CI	
Left-sided colon cancer	96	12.07	10.52	13.84
Right-sided colon cancer	44	14.10	9.38	17.38

Figure 3:



	n	MST	95% CI	
Left-sided colon cancer	96	24.56	19.67	30.10
Right-sided colon cancer	44	23.44	15.93	32.95

Figure 4:

6.3. Adverse Events

The rate of diarrhea, hand and foot syndrome, and poor appetite was similar between group III and group IV, but group IV had a slightly higher rate of oral ulcer than that of group III. One patient (0.71%) in group IV developed colon perforation after seven courses of chemotherapy, but this patient recovered well after emergent surgery. The adverse events are detailed in Table 3.

Table 3: Adverse events in the four groups

Adverse event	Group I Fluorouracil + bevacizumab	Group II FOLFIRI + bevacizumab	Group III TEGAFIRI + bevacizumab	Group IV XELIRI + bevacizumab	Total
Abdominal pain				2 (3%)	2 (1%)
Colon perforation				1 (1%)	1 (1%)
Diarrhea			3 (8%)	6 (8%)	9 (6%)
Dysuria	1 (7%)				1 (1%)
Fatigue			1 (3%)		1 (1%)
Hand foot syndrome	2 (13%)		1 (3%)	3 (4%)	6 (4%)
Severe hand foot syndrome	1 (7%)				1 (1%)
Insomnia		1 (6%)		2 (3%)	3 (2%)
Skin itching			1 (3%)		1 (1%)
Weight loss				1 (1%)	1 (1%)
Nausea			2 (6%)	3 (4%)	5 (4%)
Oral ulcer	1 (7%)	1 (6%)	1 (3%)	5 (7%)	8 (6%)
Poor appetite			7 (19%)	12 (17%)	19 (14%)
Shoulder pain				1 (1%)	1 (1%)
Stomatitis	1 (7%)				1 (1%)
Vomiting			2 (6%)	3 (4%)	5 (4%)
Total	6 (40%)	2 (11%)	18 (50%)	39 (55%)	65 (46%)

7. Discussion

Both the incidence and mortality rates of colorectal cancer are increasing worldwide [17,18], and colorectal cancer is the second leading cancer and the third leading cause of cancer-related death in Taiwan. The primary treatment strategy for colorectal cancer is curative resection, but cure is rarely achieved for metastatic colorectal cancer [19]. Chemotherapy is currently the main treatment for metastatic disease [1-4].

Irinotecan (TTY Biopharm, Taiwan) is a novel inhibitor of the DNA enzyme topoisomerase; it exerts cytotoxic activity by influencing DNA replication and transcription and has shown response rates of 25%-40% in patients with metastatic colorectal cancer when combined with 5-FU and LV in Western countries [3,5]. Some studies in Taiwan have also reported good response rates or survival in first-line and second-line therapy. Adding 5-FU or its precursors and LV is important for good response rates.

Meanwhile, capecitabine (Xeloda, F. Hoffmann-La Roche, Basel, Switzerland) is an oral fluoropyrimidine that generates 5-FU preferentially in the tumor tissue through a three-step enzymatic cascade [20]. The efficacy of capecitabine as a first-line treatmentfor

metastatic colorectal cancer compared with monthly bolus intravenous 5-FU/LV (Mayo Clinic regimen) has been demonstrated in terms of improved response rates (26% vs 17%) and at least equivalent PFS and OS [21].

Tegafur, an oral fluoropyrimidine, is metabolized to 5-FU in vivo and has been reported to be active and less toxic in the management of metastatic colorectal cancer. Uracil is a naturally occurring pyrimidine capable of incorporating into nucleic acids. Oral UFUR (TTY Biopharm, Taiwan) is comprised of tegafur, combined with uracil in 4:1 molar ratio. Preclinical studies showed that the combination of tegafur and uracil is associated with higher plasma levels of 5-FU than with tegafur alone, and this difference was associated with greater antitumor activity. Two phase III studies comparing tegafur-uracil/LV and intravenous 5-FU/LV have shown similar response rates, time to progression, and OS between the two regimens, with OS of 12 to 13 months. However, myelosuppression, diarrhea, nausea and vomiting, and stomatitis and mucositis were significantly less frequent in tegafur-uracil /LV [22,23].

UFUR has been preferred over 5-FU as an agent for combining with other chemotherapeutic agents such as irinotecan (the FOLFIRI regimen) by some physicians in Japan and Taiwan [8,24,25]. LV was reported to be capable of enhancing the anti-tumor efficacy of 5-FU in the treatment of metastatic colorectal cancer. Studies have shown that the combination of UFT with irinotecan is well-tolerated [12,26] and, in modulating with LV, the TEGAFIRI regimen demonstrated comparable efficacy and safety as with infusion regimens [11,13].

Vascular Endothelial Growth Factor (VEGF) is a key mediator of angiogenesis in normal tissues and binds two VEGF receptors (VEGF receptor-1 and VEGF receptor-2), which are expressed on vascular endothelial cells [27]. VEGF is also thought to be a key mediator of angiogenesis in cancer [28,29]. Avastin (bevacizumab, Roche, Hoffmann-La Roche, Basel, Switzerland) is a humanized monoclonal antibody that targets the VEGF molecule. It is hypothesized that bevacizumab works by both depriving tumors of the neovascularity they require to grow and sustain beyond a size of approximately 2 mm and improving local delivery of chemotherapy through alterations of tumor vasculature permeability and Starling forces [27-29]. Although it is not effective as monotherapy, clinical trials have demonstrated the capability of bevacizumab to enhance the effectiveness of chemotherapy for the treatment of metastatic colorectal cancer [27-30]. The most serious adverse events associated with bevacizumab include bowel ischemia, gastrointestinal perforation, wound healing complications, hemorrhage, and arterial thromboembolic events [28,30]. The occurrence of gastrointestinal complications relating to bowel ischemia prompted the issuance of a warning letter addressed to physicians by the manufacturer and changes in the FDA product labeling to reflect these risks [32,33].

It is generally recommended that surgery should not be performed for at least 4-8 weeks following cessation of bevacizumab treatment because of its known inhibitory effects on wound healing [29,34]. Wound healing is the result of a sequence of several basic processes including inflammation, cell proliferation, matrix formation and remodeling, angiogenesis, wound contraction, and epithelialization [35]. Perforation of the colon is among the serious adverse effects of bevacizumab. However, the rate of perforation of the colon was very low in this series, and this might be because all the primary colorectal tumors and most metastatic tumors (metastasectomy) were removed before the initiation of bevacizumab therapy.

Recently, whether the prognosis differs between LSCC and RSCC has gained research attention [36,37]. Although the survival difference between RSCC and LSCC remains controversial, there was no difference in the prognosis between LSCC and RSCC in this series.

Combination chemotherapy of irinotecan and capecitabine or irinotecan and tegafur-uracil together with bevacizumab is advantageous because it does not require admission or additional apparatus for administration, has shorter infusion time, is well-tolerated by most patients, and has acceptable hematological and non-hematological side effects. However, it also has disadvantages, including poor patient compliance for various reasons such as that nausea and vomiting associated with irinotecan might interfere with the desire to take oral medications and that the vomiting and diarrhea associated with irinotecan might decrease the actual amount of oral medications ingested. However, despite these disadvantages, both XELIRI and TEGAFIRI together with bevacizumab are effective regimens for recurrent or metastatic colorectal cancer. In elderly and frail patients, bevacizumab together with fluorouracil still offers some benefit with respect to prolonged survival.

8. Conclusions

The results of the study indicate that both XELIRI and TEGAFIRI together with bevacizumab are feasible and yield acceptable outcomes for recurrent or metastatic colorectalcancer.

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