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A Multicenter Cohort Study for XELOX (Capecitabine, Leucovorin plus Oxaliplatin) Therapy as First-Line Treatment in Elderly Patients with Unresectable Colorectal Cancer

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Abstract

Oxaliplatin-based chemotherapy with bevacizumab is now widely used for colorectal cancer patients. This study evaluated the efficacy and tolerability of XELOX (capecitabine + oxaliplatin + leucovorin combined) therapy with or without bevacizumab in elderly patients. One hundred and seven patients, consisting of 52 elderly (>70 years of age) and 55 non-elderly, with unresectable colorectal cancer were enrolled in this multicenter cooperative group study using a database between October 2009 and March 2012. We evaluated the outcomes in terms of the median time to treat failure (TTF), overall response rate (ORR), disease control rate (DCR) and tolerability in both age groups. The median TTF for the XELOX + bevacizumab regimen was 7.1 months in the non-elderly group and 8.1 months in the elderly group (p = 0.838). There was no significant difference in TTF between the two groups. The ORR and DCR in the non-elderly group were 30.8% and 73.1%, respectively. In the elderly group, the ORR was 40.0% and the overall DCR was 90.0%. No severe or uncontrollable adverse events were observed in the two groups. These data indicated that the XELOX chemotherapy with or without bevacizumab has an equivalent efficacy in both groups, without increasing the adverse events even in the elderly population.

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Keywords

Colorectal Cancer, Oxaliplatin, Capecitabine, Bevacizumab, Elderly Patients

1. Introduction

Colorectal cancer (CRC) is one of the most common forms of cancer worldwide. The annual incidence of CRC increases considerably with age. There are several chemotherapy combinations with proven activity in unresectable CRC. Nevertheless, there is a fear of great susceptibility to severe adverse events in elderly patients due to limitations in the functional reserve of various organ systems associated with aging. Therefore, the number of elderly patients included in clinical trials remains limited.

Oxaliplatin, in combination with either 5-fluorouracil (5-FU) (FOLFOX) or capecitabine (XELOX), is now widely used in the treatment of CRC, both in the adjuvant and metastatic setting [1] [2]. In addition, the management of metastatic CRC has evolved substantially with the introduction of biologic agents. Bevacizumab, a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has produced clinically worthwhile improvements in efficacy [3]-[5]. Because oxaliplatin can lead to the development of specific cold-related dysesthesia and cumulative peripheral sensory neuropathy, many patients have to withdraw from oxaliplatin-containing regimens [6]. In addition, this neuropathy persists for a long time after the discontinuation of treatment. On the other hand, the primary adverse events associated with bevacizumab include thrombosis, hypertension, proteinuria and epistaxis. There are some reports that bevacizumab increases the risk of arterial thromboembolism (ATE) in patients with CRC or breast or lung cancer [7]. In addition, the risk of ATE is associated with a prior history of ATE and age (over 65 years).

There are many reports that elderly patients can receive the same regimens as non-elderly patient [8]-[10]. However, the population of elderly patients varies according to the locality. Furthermore, some reports have reported elderly patients to be underrepresented in clinical trials and less often treated according to the standard treatment [11] [12].

The Shimane Gastroenterological Cancer Study Group (SGCSG) has constructed a mutual database of patients with CRC in 2009 to survey the context of CRC treatment in Shimane prefecture, a rural region with quite a large elderly population in Japan, and then initiated several multicenter studies on the treatment of unresectable advanced/recurrent CRC. Since the impact of adding bevacizumab to doublet chemotherapy in elderly patients is unclear, we conducted a retrospective analysis of the efficacy and tolerability of XELOX with or without bevacizumab in elderly patients (≥70 years of age) in a large elderly population area. And we chose a retrospective cohort study to evaluate the actual clinical situation in one prefecture.

2. Patients and Methods

2.1. Study Population

A sample survey of CRC patients receiving chemotherapy was conducted by using the SGCSG database recorded in the Microsoft Access 2007 software program (Microsoft Japan Co., Ltd., Tokyo, Japan). All colorectal cancer patients who undertook chemotherapy for advance/recurrent CRC in our region were enrolled in this database. Once a patient is enrolled in this database, the information of this patient is collected prospectively. Patients registered into the SGCSG database between October 2009 and March 2012 were extracted and enrolled in this study. The eligibility criteria in this study were as follows: histologically proven unresectable colorectal adenocarcinoma; a tumor lesion > 1 cm or non-measurable assessable lesion according to the response evaluation criteria in solid tumors (RECIST) on a computed tomography scan [13]; an adequate function of the liver, kidney and bone marrow reserve (absolute neutrophil count > 15,000/L, hemoglobin > 8.5 g/dl, platelets > 100×10^9/L); an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of <2; an age > 20 years at the time of starting first-line chemotherapy; and an expected survival time of >3 months. Patients with multiple malignancies, a history of prior radiotherapy, pregnancy or lactation, or a history of serious drug hypersensitivity were excluded from the analysis. Since there is a consensus that the elderly patient population is defined by an age of 70 years or older, we categorized the patients into two groups: <70 years of age (non-elderly patients) and ≥70 years of age (elderly patients).

2.2. Treatment

In this study, chemotherapy with XELOX +/− bevacizumab was performed at any line of treatment. An outline of the administration method for XELOX therapy is shown in **Figure 1(a)** and **Figure 1(b)**. Briefly, the patients received a two-hour intravenous infusion of oxaliplatin at a dose of 130 mg/m^2 on day 1 plus oral capecitabine at a dose of 1000 mg/m^2 twice daily for two weeks every three weeks. Bevacizumab was administered at a dose of 7.5 mg/kg as a 30- to 90-minute intravenous infusion before the administration of oxaliplatin on Day 1.

The administration was continued until the patient showed progressive disease (PD), which included clinical PD or adverse events that made further administration difficult.

2.3. Evaluation Procedure

Before initiating chemotherapy, all patients were assessed using physical examinations, PS assessments and routine hematological and biochemical blood analyses. Computed tomography scans of measurable lesions were assessed within 28 days prior to the beginning of treatment and repeated every four cycles or three months. All adverse events were recorded before each cycle of chemotherapy. Toxicities were scored according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [14]. The primary assessment criterion was the time to treatment failure (TTF). The second criteria were the antitumor effects (ORR: overall response rate; and DCR: disease control rate) and safety in the elderly patients. The therapeutic efficacy was evaluated according to the RECIST guidelines (Version 1.1) [15].

2.4. Statistical Analysis

The chi-square test, Fisher's exact probability test and the Mann-Whitney U test were used to compare patient characteristics, treatment status, adverse events and antitumor effects. A probability (p) value of less than 0.05 was considered to be statistically significant for comparisons between the elderly and non-elderly groups. The Kaplan-Meier method was used to estimate the TTF. The statistical analyses were performed using the JMP ver. 9 software package (SAS institute Inc., Cary, NC).

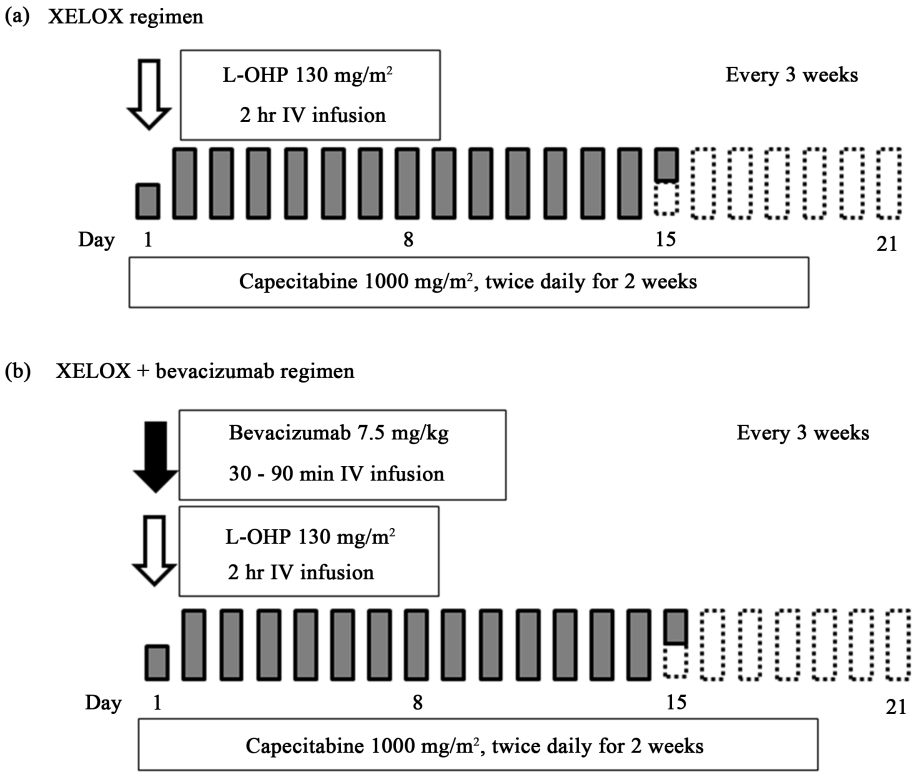

Figure 1. Chemotherapy regimens: (a) XELOX regimen; (b) XELOX + bevacizumab regimen.

3. Results

3.1. Patient Characteristics

A total of 107 patients were enrolled in this study, consisting of 55 non-elderly patients who were <70 years of age and 52 elderly patients who were ≥70 years of age. The median age was 69 years (range: 41 - 89); 61 years (range: 41 - 69) in the non-elderly group and 77 years (range: 70 - 89) in the elderly group. The baseline characteristics of the 107 eligible and treated patients are summarized in **Table 1**. Thirty-nine patients (70.9%) in the non-elderly group and 37 patients (71.2%) in the elderly group were male. The patients generally had a widespread disease, with the most frequent sites for distant metastasis in the liver, lymph nodes, lungs and peritoneum. The performance status was less than 2 in almost all patients. Twenty-nine patients (52.7%) in the non-elderly group and 29 patients (55.8%) in the elderly group had colon cancer as the primary tumor. Seven patients (12.7%) in the non-elderly group and 18 patients (34.6%) in the elderly group received oral and/or venous administration of adjuvant chemotherapy prior to this study. There were no significant differences in the baseline characteristics between the two study groups.

3.2. Treatment

At the cutoff date (March 31, 2012), the median follow-up time for the entire group was 16.4 months. Seventy-nine patients (73.8%) received XELOX with or without bevacizumab chemotherapy as first-line treatment, including 38 patients (69.2%) in the non-elderly group and 41 patients (78.9%) in the elderly group. As second-line chemotherapy, XELOX with or without bevacizumab treatment was performed in 13 patients (23.6%) in the non-elderly group and five patients (9.6%) in the elderly group.

Table 1. Baseline characteristics of the two study groups.

	<70 Years (n = 55)		≥70 Years (n = 52)	
	n	%	n	%
Age, y (median, range)	61	(41 - 69)	77	(70 - 89)
Male	39	(70.9%)	37	(71.2%)
Female	16	(29.1%)	15	(28.8%)
PS (ECOG)				
0	53	(96.4%)	44	(84.6%)
1	2	(3.6%)	6	(11.5%)
2	0	(0.0%)	2	(3.8%)
Primary tumor				
Colon	29	(52.7%)	29	(55.8%)
Rectum	26	(47.3%)	23	(44.2%)
Site of metastases				
Liver	25	(45.5%)	24	(46.2%)
Lymph nodes	16	(29.1%)	16	(30.8%)
Lung	12	(21.8%)	9	(17.3%)
Peritoneum	5	(9.1%)	10	(19.2%)
Other	5	(9.1%)	4	(7.7%)
Prior adjuvant chemotherapy	7	(12.7%)	18	(34.6%)

Abbreviations: PS, performance status; ECOG, Eastern Cooperative Oncology Group. Values in parentheses are percentages of row totals.

Chemotherapy with XELOX + bevacizumab was performed in 78 patients (72.9%), including 42 patients (76.4%) in the non-elderly group and 36 patients (69.2%) in the elderly group. Twenty-nine patients (27.1%) received XELOX chemotherapy, including 13 patients (23.6%) in the non-elderly group and 16 patients (30.8%) in the elderly group. Non-elderly patients received a median of nine cycles (range, 1 - 30 cycles) of XELOX + bevacizumab regimen and a median of four cycles (range, 3 - 9 cycles) of XELOX regimen. On the other hand, elderly patients received a median of seven cycles (range, 1 - 27 cycles) of XELOX + bevacizumab regimen and a median of three cycles (range, 1 - 11 cycles) of XELOX regimen.

In the XELOX + bevacizumab treatment group, 25 patients received further chemotherapy after disease progression, including 12 patients (60.0%) in the non-elderly group and 13 patients (81.3%) in the elderly group. In the XELOX treatment group, 14 patients received further chemotherapy after disease progression, including eight patients (66.7%) in the non-elderly group and six patients (60.0%) in the elderly group.

3.3. Efficacy

Seventy-nine (73.8%) of the 107 patients received XELOX with or without bevacizumab treatment as first-line chemotherapy. Fifty-eight (73.4%) of these 79 patients were assessable for a response. Twenty-one patients, including 14 patients in the non-elderly group and seven patients in the elderly group, were not assessable. Thirteen patients (6 in the non-elderly group and 7 in the elderly group) were not assessable because the duration after the administration of chemotherapy did not exceed 28 days when the examination was performed.

In the XELOX + bevacizumab group, two (7.7%) complete responses (CRs) and six (23.1%) partial responses (PRs) were observed among the non-elderly patients (**Table 2**). On the other hand, one (5.0%) CR and seven (35.0%) PRs were observed among the elderly patients. In addition, 11 patients (42.3%) in the non-elderly group and 10 patients (50.0%) in the elderly group were revealed to have stable disease (SD). Therefore, the overall response rate (ORR; CR + PR) was 30.8% in the non-elderly group and 40.0% in the elderly group. The overall disease control rate (DCR; CR + PR + SD) was 73.1% in the non-elderly group and 90.0% in the elderly group. There were no significant differences in the ORR ($p = 0.839$) and disease control rate DCR ($p = 0.514$) between the non-elderly and elderly groups.

When XELOX was performed as first-line chemotherapy, no CRs were observed in either the non-elderly or elderly groups. Three (15.8%) PRs and seven (36.8%) SDs were recorded in the non-elderly group. On the other hand, two (14.3%) PRs and two (14.3%) SDs were recognized in the elderly group. Therefore, the ORR was 15.8% and the DCR was 52.6% in the non-elderly group, while the ORR was 14.3% and the DCR was 28.6% in the elderly group. These differences were not statistically significant (ORR, $p = 0.78$; DCR, $p = 0.09$).

The median TTF for the XELOX + bevacizumab regimen was 7.1 months (95% CI: 5.4 to 10.5) in the non-elderly group and 8.1 months (95% CI: 5.4 to 14.0) in the elderly group ($p = 0.838$) (**Figure 2**). In addition, the median TTF for the XELOX regimen was 2.8 months (95%: CI 1.5 to 3.8) and 3.2 months (95% CI: 0.2 to 4.8) in the non-elderly and elderly groups, respectively ($p = 0.847$) (**Figure 3**).

3.4. Safety

Safety was evaluated in all patients who participated in this study. The incidence of primary toxic effects is summarized in **Table 3** and **Table 4** as the maximum grade per patient. The majority of treatment-related adverse events were mild to moderate in intensity.

Table 2. Best response to first line treatment according to RECIST criteria.

	XELOX + BEV regimen				XELOX regimen			
	<70 Years (n = 26)		≥70 Years (n = 20)		<70 Years (n = 19)		≥70 Years (n = 14)	
	n	%	n	%	n	%	n	%
Complete response	2	(7.7%)	1	(5.0%)	0	(0.0%)	0	(0.0%)
Partial response	6	(23.1%)	7	(35.0%)	3	(15.8%)	2	(14.3%)
Stable disease	11	(42.3%)	10	(50.0%)	7	(36.8%)	2	(14.3%)
Progressive disease	0	(0.0%)	2	(10.0%)	2	(10.5%)	3	(21.4%)
Not evaluated	7	(26.9%)	0	(0.0%)	7	(36.8%)	7	(50.0%)

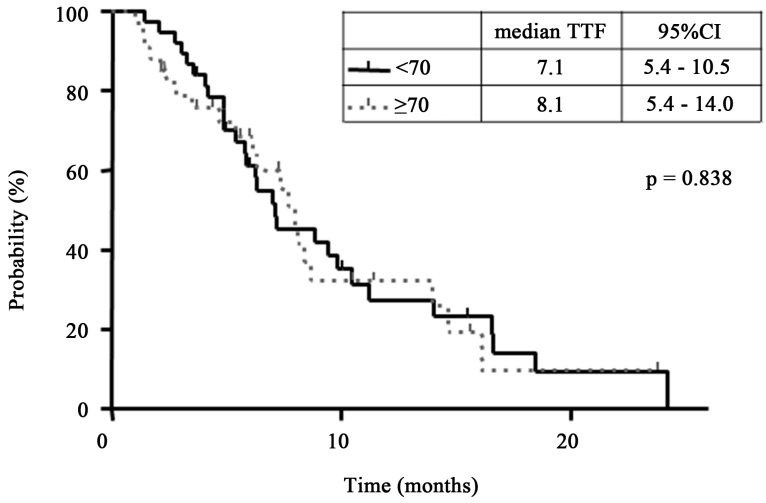

Figure 2. Kaplan-Meier curves of the time to treatment failure (TTF) in the XELOX + bevacizumab group. The median TTF was 7.1 months and 8.1 months in the non-elderly group (—) and elderly group (·····), respectively.

Table 3. Major adverse events of XELOX with bevacizumab treatment in all treatment lines (n = 78).

	<70 Years (n = 42)				≥70 Years (n = 36)				p Values*
	Grade 1 - 2		Grade ≥ 3		Grade 1 - 2		Grade ≥ 3		
	n	(%)	n	(%)	n	(%)	n	(%)	
Related to capecitabine and oxaliplatin									
Leukocytopenia	4	(9.5%)	6	(14.3%)	3	(8.3%)	2	(5.6%)	0.409
Thrombocytopenia	10	(23.8%)	0	(0.0%)	5	(13.9%)	0	(0.0%)	0.042
	Grade 1		Grade ≥ 2		Grade 1		Grade ≥ 2		
Nausea and vomiting	5	(11.9%)	3	(7.1%)	3	(8.3%)	3	(8.3%)	0.597
Fatigue	3	(7.1%)	1	(2.4%)	4	(11.1%)	1	(2.8%)	0.288
Aphtha	0	(0.0%)	0	(0.0%)	3	(8.3%)	0	(0.0%)	0.029
Diarrhea	3	(7.1%)	0	(0.0%)	2	(5.6%)	0	(0.0%)	0.775
Hand-foot syndrome	1	(2.4%)	8	(19.0%)	0	(0.0%)	6	(16.7%)	0.508
Peripheral neuropathy	13	(31.0%)	17	(40.5%)	10	(27.8%)	7	(19.4%)	0.054
Gastrointestinal perforation	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	-
Hemorrhage	0	(0.0%)	0	(0.0%)	1	(2.8%)	0	(0.0%)	0.211
Hypertension	1	(2.4%)	4	(9.5%)	1	(2.8%)	7	(19.4%)	0.446
Proteinuria	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	-
Thromboembolism	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	-
Wound dehiscence	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	-

The grade of adverse events was defined according to the CTCAE v4.0 guidelines. *p values were calculated using Fisher's exact probability test. The values in parentheses are percentages of the raw totals.

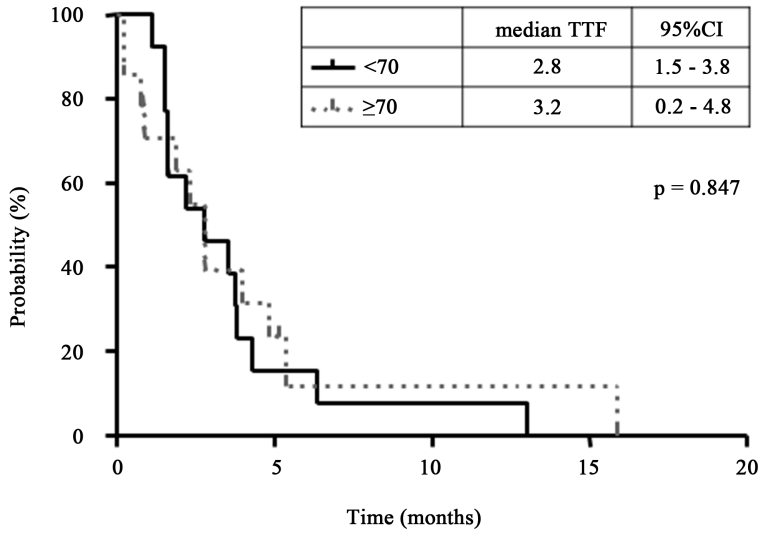

Figure 3. Kaplan-Meier curves of the TTF in the XELOX group. The median TTF was 2.8 months and 3.2 months in the non-elderly group (—) and elderly group (·····), respectively.

Table 4. Major adverse events of XELOX treatment in all treatment lines (n = 29).

	<70 Years (n = 13)				≥70 Years (n = 16)				p Values*
	Grade 1 - 2		Grade ≥ 3		Grade 1 - 2		Grade ≥ 3		
	n	(%)	n	(%)	n	(%)	n	(%)	
Related to capecitabine and oxaliplatin									
Leukocytopenia	2	(15.4%)	0	(0.0%)	1	(6.3%)	0	(0.0%)	0.421
Thrombocytopenia	2	(15.4%)	0	(0.0%)	2	(12.5%)	0	(0.0%)	0.823
	Grade 1		Grade ≥ 2		Grade 1		Grade ≥ 2		
Nausea and vomiting	2	(15.4%)	0	(0.0%)	1	(6.3%)	1	(6.3%)	0.411
Fatigue	1	(7.7%)	0	(0.0%)	2	(12.5%)	1	(6.3%)	0.483
Aphtha	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	-
Diarrhea	1	(7.7%)	0	(0.0%)	1	(6.3%)	0	(0.0%)	0.879
Hand-foot syndrome	0	(0.0%)	3	(23.1%)	0	(0.0%)	3	(18.8%)	0.775
Peripheral neuropathy	6	(46.2%)	1	(7.7%)	1	(6.3%)	1	(6.3%)	0.031

The grade of adverse events was defined according to the CTCAE v4.0 guidelines. *p values were calculated using Fisher's exact probability test. The values in parentheses are percentages of the raw totals.

Although there was no statistically significant difference, non-elderly patients showed a high incidence of neurotoxicity (71.5%) when compared to elderly patients (47.2%) ($p = 0.054$). In the XELOX + bevacizumab chemotherapy, severe neurotoxicity more than Grade 2 occurred in 40.5% of the non-elderly patients, being significantly higher than that observed in the elderly patients (19.4%) ($p = 0.045$). In addition, the incidence of neurotoxicity related with the XELOX treatment was significantly higher in the non-elderly group (53.8%) than in the elderly group (12.6%, $p = 0.031$). The common adverse events more than Grade 2 in the XELOX + bevacizumab treatment group were hand-foot syndrome (19.0% in the non-elderly group and 16.7% in the elderly group; $p = 0.508$) and hypertension (9.5% in the non-elderly group and 19.4% in the elderly group; $p = 0.446$). Severe diarrhea, nausea, vomiting, general fatigue and allergies were rarely observed.

4. Discussion

In general, CRC occurs frequently in elderly people and intensive chemotherapy is required for unresectable disease. However, there are no sufficient data regarding the selection of chemotherapy regimens for elderly CRC patients because little number of elderly patients are eligible in clinical trials [11]. Therefore, we conducted a retrospective cohort study for investigating the actual situation of standard triplet chemotherapy plus molecular targeted drugs in elderly patients with unresectable CRC. In the present study, the 2 study groups, elderly and non-elderly groups, were nearly equal in number. The main finding of this study was that the TTF of the elderly patients > 70 years of age was not different from that of the younger group, regardless of the use of bevacizumab. This finding indicates that older and younger patients could achieve an equivalent treatment benefits from intensive chemotherapy.

Although previous studies have reported that adding bevacizumab to chemotherapy has significant benefits for CRC patients [16] [17], some reports have shown that the benefits in elderly patients are reduced [18]. In this study, the median TTF for the XELOX + bevacizumab regimen was 7.1 months in the non-elderly group and 8.1 months in the elderly group, indicating that there is a similar benefit in adding bevacizumab to chemotherapy in all age groups. On the other hand, the TTF was significantly shorter in the XELOX regimen than in the XELOX plus bevacizumab regimen in both younger and elderly patient groups. In this study, each participating physician decided whether to add bevacizumab to the chemotherapy regimen. Therefore, the patients who did not receive bevacizumab may have had some contraindication for bevacizumab, such as thrombosis, hypertension, proteinuria, epistaxis and so on, as previously described [5]. At any rate, the patients who received bevacizumab treatment tended to have the benefit in terms of TTF in both two age groups.

Generally, the pharmacokinetics of a drug deteriorates in the elderly due to organ dysfunction associated with aging [19] [20]. There are some reports that the incidence of adverse events tends to increase with age [21] [22]. Therefore, dose reductions and treatment delays are usually performed in elderly patient because of safety concerns. However, all elderly patients were received same dose of younger patients in our study. In addition, the elderly and non-elderly patients did not differ in the incidence of adverse events and all adverse events were controllable even in the elderly patients. The complete administration of drugs as planned, including 5-FU/LV, irinotecan and oxaliplatin, prolongs survival in patients with colon cancer. Therefore, it is important that safe and effective regimens are used in elderly patients as first-line chemotherapy.

Although there was no statistical difference, the incidence of severe neuropathy was higher in the XELOX + bevacizumab group (42.9%) than in the XELOX group (3.6%) in our 56 patients with peripheral neuropathy. The XELOX + bevacizumab group, furthermore, the incidence of peripheral neuropathy was significantly higher in the non-elderly patients (40.5%) than in the elderly patients (19.4%) in our study. All patients received same planned administration of preventing drugs. The reason why this incidence was lower in the elderly patients is unclear. Therefore, further studies and research are needed.

Many CRC patients have to withdraw from oxaliplatin-containing regimens due to severe dysesthesia and cumulative peripheral sensory neuropathy. This neuropathy persists for a long time after withdrawing oxaliplatin treatment. There are some reports that a stop-and-go strategy can reduce the development of sensory neuropathy and has equivalent efficacy in comparison to the continuance of oxaliplatin-containing regimens until disease progression or the development of unacceptable toxicities [23]. Therefore, we are studying the safety and efficacy of a stop-and-go strategy with a XELOX + bevacizumab regimen in a Phase II study.

A previous study reported the benefits of adding bevacizumab to chemotherapy in medically fit patients > 65 years of age, with no increase in the risk of adverse events [16]. Although we defined an elderly patient as a patient ≥ 70 years of age in our study, the similar tendency was observed. Intensive chemotherapy can be administered in elderly patients with careful selection of patients and monitoring of adverse events.

In conclusion, the XELOX chemotherapy with or without bevacizumab has equivalent efficacy in the treatment of elderly and non-elderly patients with unresectable CRC, without increasing the incidence of adverse events in the elderly. Carefully selecting elderly patients and managing adverse events are required to administer combination chemotherapy in this patient population.

Conflict-of-Interest Notification Field

The authors declare that they have no conflict of interests.

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List of Abbreviations

XELOX: capecitabine + oxaliplatin + leucovorin combined chemotherapy;
TTF: median time to treat failure;
ORR: overall response rate;
DCR: disease control rate;
CRC: colorectal cancer.

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