Oxaliplatin-based Chemotherapy in Patients Aged 75 Years or Older with Metastatic Colorectal Cancer

MINORU FUKUCHI, KEIICHIRO ISHIBASHI, YUSUKE TAJIMA, NORIMICHI OKADA, MASARU YOKOYAMA, NORIYASU CHIKA, SATOSHI HATANO, TAKEAKI MATSUZAWA, KENSUKE KUMAMOTO, YOUICHI KUMAGAI, HIROYUKI BABA, ERITO MOCHIKI and HIDEYUKI ISHIDA

Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, Saitama, Japan

Abstract. *Aim: To evaluate the tolerability and efficacy of oxaliplatin-based chemotherapy (OBC) in patients ≥75 years old with metastatic colorectal cancer (CRC). Patients and Methods: We reviewed the medical records of 126 patients with unresectable stage IV CRC in terms of OBC administered as first-line chemotherapy whenever feasible. Results: Use of first-line OBC was significantly less frequent in patients ≥75 years old (n=18) than in patients <75 years old (n=108) (46% vs. 81% p<0.01). When analysis was restricted to patients receiving OBC, the two age groups did not differ significantly in terms of response rate (44% vs. 36%, p=0.54), progression-free survival (18.7 months vs. 13.0 months, p=0.44), overall survival (25.4 months vs. 17.5 months, p=0.53), and frequency of grade 3-4 toxicity (72% vs. 58%, p=0.26). Conclusion: In selected patients aged 75 years or greater, the clinical outcomes of OBC seem equivalent to those of younger patients.*

With increases in the number of colorectal cancer cases and the geriatric population, the incidence of colorectal cancer (CRC) in the elderly is increasing in Japan (1). Accordingly, metastatic CRC in the elderly is being treated more frequently. Although modern chemotherapy, such as oxaliplatin-based chemotherapy (OBC), may be used in clinical practice in the elderly, the feasibility and safety for such patients have not been fully investigated. This retrospective observational study was performed to elucidate the response to first-line OBC, together with its feasibility, safety, and efficacy in patients ≥75 years old with metastatic CRC, who are usually excluded from clinical trials for modern chemotherapy regimens.

Correspondence to: Minoru Fukuchi, MD, Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, 1981, Kamoda, Kawagoe, Saitama, 350-8550, Japan. Tel: +81 492283619, Fax: +81 492228865, e-mail: mfukuchi@saitama-med.ac.jp

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Patients and Methods

This study was approved by the local Ethics Committee of Saitama Medical Center, Saitama Medical School.

Patients. We reviewed the medical charts of patients diagnosed with unresectable stage IV CRC in our institution between January 2006 and December 2010. The factors extracted from the charts included demographic, clinicopathological, and surgical factors, types of chemotherapy, response to chemotherapy and survival data. Patients allocated to clinical trials were excluded.

Systemic chemotherapy. Resection of the primary tumor was performed before first-line chemotherapy in selected patients to eliminate the potential risk of the chemotherapy regimen being stopped because of bleeding or obstruction. Patients with an Eastern Cooperative Oncology Group performance status (PS) of 0-2 were initially treated with the following regimens. (FOLFOX; available in Japan from March 2005) was mainly administered on an outpatient basis. Modified FOLFOX6 (mFOLFOX6) consisted of a 2-hour infusion of leucovorin (LV) (200 mg/m^2) and oxaliplatin (85 mg/m^2) on day 1, followed by a 5-fluorouracil (5-FU) bolus (400 mg/m^2) and a 46-h infusion of 5-FU (2,400 mg/m^2) over two days every two weeks. The CapeOX regimen (available in Japan from September 2009) consisted of oxaliplatin (135 mg/m^2) on day 1, oral capecitabine (1,000 mg/m^2) twice daily from the evening of day 1 to the morning of day 15, and then a 7-day treatment-free interval (a 3-week cycle). Bevacizumab (available in Japan from April 2007) was added in patients without cardiovascular complications. In principle, the second-line chemotherapy was FOLFIRI with bevacizumab whenever possible. FOLFIRI consisted of a 2-h infusion of LV (200 mg/m^2) and irinotecan (180 mg/m^2) on day 1, followed by a 5-FU bolus (400 mg/m^2) and a 46-hour infusion of 5-FU (2,400 mg/m^2) over two days every two weeks. Treatment was continued until disease progression or unacceptable toxicity occurred or until the patient chose to stop treatment. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria, version 4.0.

Table I. *Types of first-line and second-line treatments in the elderly group and the control group.*

	Elderly group n=39 (%)	Control group n=134 (%)
First-line chemotherapy		
Oxaliplatin-based	18 (46)	108 (81)*
mFOLFOX6	16	106
Cape OX	2	2
Combined use of Bev	6	33
Fluoropyrimidine-based	3	8
Best supportive care	18	17
Second-line chemotherapy		
FOLFIRI	13 (72)	61 (56)
Combined use of Bev	4	31

mFOLFOX, modified Folinic Acid (Leucovorin)/Fluorouracil/Oxaliplatin; CapeOX, Capecitabine/Oxaliplatin; Bev, Bevacizumab; *$p<0.01$.

Study parameters. When a patient had measurable lesions, the tumor response was assessed by computed tomography or colonoscopy every 2-3 months according to the Response Evaluation Criteria in Solid Tumors criteria, version 1.1.

Statistical analysis. Continuous variables are expressed as the median and range. Patient characteristics were compared by using the χ^2 test and the *t*-test or the Mann-Whitney test. Survival curves were drawn by the Kaplan-Meier method and compared with the log-rank test. Cumulative progression-free survival (PFS) and overall survival (OS) after first-line OBC were assessed by follow-up until March 2013, with the starting point being the first day of initial therapy. All statistical analyses were performed with JUMP 5.0 software (SAS Institute Inc., Cary, NC, USA). Significance set at $p<0.05$.

Results

Induction of first-line chemotherapy and subsequent treatment. There were a total of 173 patients. Among them, 126 patients were treated with first-line OBC (Table I). They included 18 out of 39 patients (46%) aged ≥75 years (elderly group) and 108 out of 134 patients (81%) aged <75 years (control group), with OBC given to a significantly lower percentage of the elderly group ($p<0.01$). Six patients (33%) in the elderly group and 33 patients (31%) in the control group received bevacizumab combined with first-line OBC, so there was no significant difference in the use of bevacizumab in the two groups ($p=0.81$). Eighteen patients (46%) in the elderly group and 17 patients (13%) in the control group received best supportive care because of a poor PS (≥3). Three patients (8%) in the elderly group and eight patients (6%) in the control group were given an oral fluoropyrimidine-based chemotherapy such as tegafur/uracil (UFT)/LV.

Table II. *Characteristics patients receiving first-line oxaliplatin-based chemotherapy.*

	Elderly group n=18 (%)	Control group n=108 (%)	*p*-Value
Gender			0.88
Male	11 (61)	64 (59)	
Female	7 (39)	44 (41)	
Primary tumor site	0.28		
Colon	14 (78)	70 (65)	
Rectum	4 (22)	38 (35)	
Histology			0.75
Well- or moderately-diff.	12 (67)	73 (68)	
Poorly-diff.	2 (11)	8 (7)	
Mucinous	2 (11)	7 (6)	
Unknown	2 (11)	20 (19)	
No. of metastatic organs			0.67
1	8 (45)	56 (52)	
2	6 (33)	37 (34)	
>2	4 (22)	15 (14)	
Performance status			0.18
0	6 (33)	60 (55)	
1	10 (56)	43 (40)	
2	2 (11)	5 (5)	
Primary tumor resection			0.32
Yes	15 (83)	78 (72)	
No	3 (17)	30 (28)	
Relative dose intensity for oxaliplatin (range)	69% (37-100%)	78% (38-100%)	0.16

diff., Differentiated adenocarcinoma; Mucinous, mucinous adenocarcinoma.

When analysis was restricted to patients given first-line OBC, 13 (72%) out of the 18 patients in the elderly group and 61 (56%) out of the 108 patients in the control group received FOLFIRI as second-line chemotherapy due to failure of OBC ($p=0.21$) (Table I). The frequency of using bevacizumab with FOLFIRI did not differ significantly between the two groups (31% *vs*. 55%, $p=0.11$).

Profile of patients receiving first-line OBC. The demographic and clinicopathological characteristics of patients who were given first-line OBC are shown in Table II. The median age of the 18 patients in the elderly group was 78 years (range=75-85 years), while the one of 108 patients in the control group was 61 years (range=31-74 years). No significant differences of the sex ratio ($p=0.88$), primary tumor site ($p=0.28$), histology ($p=0.75$), number of metastatic organ(s) ($p=0.67$), PS ($p=0.18$) and primary tumor resection ($p=0.32$) were observed between the two groups. The relative dose intensity of oxaliplatin was 69% (range=37-100%) in the elderly group *versus* 78% (range=38-100%) in the control group, showing no significant differences between the two groups.

Table III. *Adverse effects*.

Grade 3 or 4 toxicity	Elderly group n=18 (%)	Control group n=108 (%)	*p*-Value
All grade 3 or 4 toxicities	13 (72)	63 (58)	0.26
Neutropenia	8 (44)	46 (43)	0.88
Thrombocytopenia	1 (6)	2 (2)	0.40
Anemia	2 (11)	7 (6)	0.51
Nausea and vomiting	0 (0)	2 (2)	0.56
Diarrhea	0 (0)	2 (2)	0.56
Stomatitis	0 (0)	3 (3)	0.47
Mucositis	1 (1)	0 (0)	0.05
Neuropathy	2 (11)	8 (7)	0.61

Table IV. *Response to chemotherapy.*

	Elderly group n=18 (%)	Control group n=108 (%)	*p*-Value
Complete response	1 (6)	2 (2)	
Partial response	6 (33)	33 (31)	
Stable disease	5 (28)	37 (34)	
Progressive disease	4 (22)	26 (24)	
Not evaluable	2 (11)	10 (9)	
Response rate	7/16 (44)	35/98 (36)	0.54
Disease-control rate	12/16 (75)	72/98 (73)	0.90

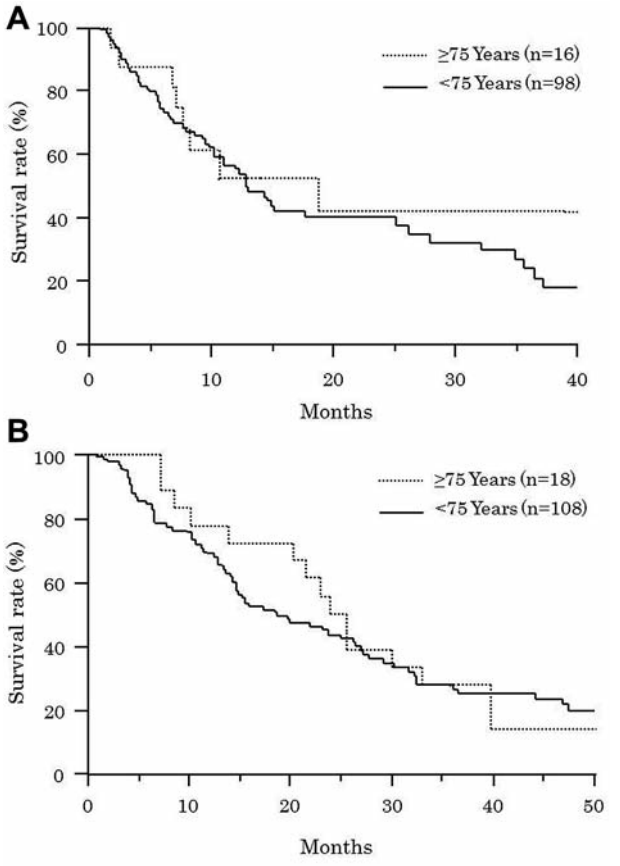

Figure 1. *Cumulative progression-free survival (PFS) (A) and overall survival (OS) (B) of 126 patients with metastatic colorectal cancer after first-line oxaliplatin-based chemotherapy. Cumulative PFS and OS of 18 patients aged ≥75 years were comparable to those of 108 patients aged <75 years (p=0.44 and p=0.53, respectively).*

Adverse effects. The frequency of grade 3 and 4 toxicities did not differ between the two groups (72% *vs*. 58%, p=0.26) (Table III). Among all grade 3 and 4 toxicities, the most frequent was neutropenia in both groups (44% *vs*. 43%, p=0.88). Oxaliplatin-related neurotoxicity also did not differ in frequency between the two groups (11% *vs*. 7%, p=0.61). Furthermore, other adverse events did not differ significantly between the two groups. All adverse events were manageable, and no toxic deaths occurred.

Response. Sixteen (89%) out of 18 patients in the elderly group and 98 patients (91%) in the control group were evaluable for response (Table IV). The response rate did not differ significantly between the two groups (44% *vs*. 56%, p=0.54), and the disease control rate also showed no significant difference (75% *vs*. 73%, p=0.9).

Survival. Survival curves for PFS and OS are shown in Figure 1. PFS was evaluable in 17/18 elderly patients (94%) and 98/108 control (91%). The median PFS did not differ significantly between the two groups (18.7 months *vs*. 13.0 months, p=0.44). The median OS also showed no significant difference between the two groups (25.4 months *vs*. 17.5 months, p=0.53).

Discussion

Although this single-center study was small in size and retrospective in nature, we obtained several important results. Firstly, we showed that the feasibility, safety, response rate, and survival were equivalent in the elderly group compared to the control group receiving first-line OBC, although this therapy was given to a significantly lower percentage of elderly patients. Considering that 46% of our elderly patients with metastatic CRC at initial diagnosis received first-line OBC, these results seem to reflect the general features of the elderly patient population rather than the specific features of a highly selected subgroup. In addition, the rate of using FOLFIRI as second-line chemotherapy did not differ significantly between the elderly and younger groups. Therefore, our findings suggest that first-line OBC followed by second-line chemotherapy is feasible and safe for approximately half of the patients aged ≥75 years old with metastatic CRC, achieving a comparable oncological outcome to the one of younger patients.

Whether elderly patients with a limited life expectancy should receive intensive modern chemotherapy such as OBC is controversial, even though the efficacy of fluoropyrimidine-based chemotherapy in patients with metastatic CRC who are aged >70 or >75 years has been well-validated (2-4). Because patients aged ≥75 years old have accounted for only 6% to 9% (5, 6) of the patients in previous randomized phase III studies of first-line OBC for metastatic CRC, useful information has not been demonstrated because of potential extreme selection bias. Two cohort studies of first-line OBC assessed feasibility, safety, response rate, and survival in patients ≥75 years old patients with metastatic CRC (7, 8), which were in agreement with ours. Nonetheless, these studies did not investigate the frequency of using OBC in unselected elderly patients. To address the issue, we limited the study population to patients with unresectable stage IV CRC, excluding patients who developed recurrence after curative colorectal resection because not all of the patients who underwent curative surgery were followed-up by our institution.

It is controversial whether resection of the primary tumor before chemotherapy is useful in patients with unresectable stage IV CRC, although this was outside the scope of our study. In a recent meta-analysis and a cohort study, resection of the primary tumor before chemotherapy led to better survival and fewer complications related to the primary lesion (9, 10). Generally, elderly patients have more complications after colorectal surgery than younger patients, especially those with metastatic CRC (11-13). In our study, primary tumor resection before chemotherapy was safe for elderly patients, although careful management is mandatory.

We selected OBC as the first-line therapy rather than irinotecan-based chemotherapy, although the efficacy does not differ significantly between these two strategies (5). Oxaliplatin was available in Japan at the time of this study; therefore, OBC was feasible for metastatic CRC at our institution. Because severe diarrhea due to irinotecan can occasionally require hospitalization of patients, oxaliplatin (which is unlikely to cause diarrhea) was more convenient to use at our institution, where chemotherapy is mainly performed on an outpatient basis.

Although this retrospective study was performed at a single center on a limited patient population, it still provides useful information to consider when developing a treatment strategy for elderly patients with metastatic CRC in clinical practice.

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