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Sequential Treatment Strategy Using Fluoropyrimidine plus Bevacizumab Followed by Oxaliplatin for Metastatic Colorectal Cancer: A Phase II Study (OGSG 1107)

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Keywords
Metastatic colorectal cancer · Sequential therapy · Quality of life · Cytotoxic agents

Abstract

Introduction: Previous prospective studies suggest that the sequential use of cytotoxic agents, such as oxaliplatin, in patients with metastatic colorectal cancer (mCRC) has the potential to improve prognosis and maintain quality of life than combination chemotherapy. The purpose of this study was to investigate the feasibility and effectiveness of a sequential treatment strategy consisting of an initial therapy (capecitabine, S-1, or 5-fluorouracil with leucovorin [LV/5-FU] plus bevacizumab) and subsequent therapy (i.e., initial therapy plus oxaliplatin) for mCRC. ***Methods:*** The primary endpoint was second progression-free survival (2nd PFS) between the start of initial therapy and tumor progression after sequential therapy; secondary endpoints were PFS after initial treatment, overall survival (OS), objective response rate (ORR), and safety. ***Results:*** Sixty-six patients were planned to be recruited. However, owing to a slow accrual rate, recruitment was terminated when only 19 patients were enrolled between 2011 and 2015; 4, 10, and 5 patients were administered capecitabine plus bevacizumab, S-1 plus bevacizumab, and LV/5-FU plus bevacizumab, respectively. The proportions of those with a *KRAS* status (wild-type/mutant/unknown) were 26%, 21%, and 53%, respectively. The median 2nd PFS and OS were 19.1 months and not reached, respectively. The ORR was 45.5% in the initial therapy and 16.7% in the subsequent therapy. Grade 3/4 toxicities included neutropenia (5%), proteinuria (5%), and hypertension (47%). ***Conclusion:*** Although our data are limited and preliminary, the sequential treatment strategy may provide a survival benefit in patients with mCRC. Further investigation of this treatment approach is warranted.

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Introduction

Advanced metastatic colorectal cancer (mCRC) is the second most common cause of death due to cancer worldwide, after lung cancer [1]. The treatment of mCRC has significantly advanced in the last 20 years, mainly through the introduction of novel, active agents in clinical practice. However, for most patients with mCRC, the aim of chemotherapy is not to cure the disease but to prolong survival or at least to preserve the quality of life. Therefore, minimizing the side effects of chemotherapy is important.

In the therapeutic development of chemotherapy for mCRC, the continuous infusion of 5-fluorouracil (5-FU) was found to improve the median overall survival (OS) from 12 to 15 months in clinical trials [2–4], leading to the use of 5-FU as a standard of care for patients with mCRC for over decades. Subsequently, combination therapies of 5-FU with leucovorin (LV/5-FU) and either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) were found to further improve survival, with a median OS of 30 months, and became the main chemotherapeutic treatment option for mCRC [5–7]. However, compared with LV/5-FU, combination regimen such as FOLFOX are more likely to be associated with more frequent toxicities, such as bone marrow toxicity, diarrhea, and peripheral neuropathy in patients with mCRC; thus, caution must be exercised for maintaining quality of life and toxicity management [4, 5].

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has been shown to extend the survival of patients with mCRC, particularly in combination with cytotoxic chemotherapy. Several previous studies demonstrated the efficacy and safety of bevacizumab in combination with either oral or infusion 5-FU in patients with mCRC [8–12].

The results of previous clinical trials indicated that the median progression-free survival (PFS) and OS in patients treated with the fluoropyrimidines plus bevacizumab regimen were comparable with those in patients treated with FOLFOX plus bevacizumab or irinotecan, bolus fluorouracil, and leucovorin (IFL) plus bevacizumab, among which the 5-FU plus bevacizumab regimen was better tolerated, with a lower incidence of adverse events [12–14]. In another key trial (N9741 trial), FOLFOX was superior to IFL, and the addition of bevacizumab to IFL significantly improved efficacy when compared with that of IFL alone (trial AVF2107g) [13, 15]. However, the effect of bevacizumab on tumor response was relatively smaller than that on PFS and OS, particularly in comparison with conventional chemotherapy. A meta-analysis of the AVF2107g and N9741 trials demonstrated survival benefits of bevacizumab as a first-line treatment for mCRC and identified that the tumor response was not a predictive factor for PFS and OS [16]. Moreover, several randomized prospective trials have indicated that combination chemotherapy for mCRC did not significantly improve OS when compared with the sequential use of cytotoxic agents [17, 18].

On the basis of these data, we hypothesized that non-intensive or sequential therapy could be a treatment option for mCRC patients with low tumor volume, no imminent tumor symptoms, and in whom conversion surgery is not a primary treatment goal, to achieve long-term survival with minimal side effects caused by chemotherapy. To test this hypothesis, we conducted a multicenter phase II study to evaluate the effectiveness of a sequential therapy consisting of initial therapy (capecitabine or S-1 or LV/5-FU plus bevacizumab) and subsequent therapy (initial therapy plus oxaliplatin) for mCRC.

Patients and Methods

Study Design and Treatment

This study was conducted by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG 1107), and it was designed as a nonrandomized, multicenter, open-label phase II trial. Figure 1 presents the study design of the sequential treatment strategy consisting of initial therapy (fluoropyrimidine plus bevacizumab) and subsequent therapy (addition of oxaliplatin to the initial regimen) for mCRC.

Initial Therapy

The initial therapy regimen was decided by each investigator. Initial therapy consisted of capecitabine (1,000 mg/m^2 orally twice a day on days 1–14) with bevacizumab (7.5 mg/kg intravenously on day 1) every 3 weeks (C-group), S-1 (40–60 mg/m^2 orally twice daily on days 1–14) with bevacizumab (7.5 mg/kg intravenously on day 1) every 3 weeks (S-group), and LV/5-FU2 (200 mg/m^2 of leucovorin administered via continuous intravenous infusion over 2 h, followed by 400 mg/m^2 of 5-FU administered via a bolus injection, delivered at an initial loading dose of 2,400 mg/m^2 over 46 h) with bevacizumab (5 mg/kg intravenously on day 1) every 2 weeks (F-group). The protocol therapy was repeated until the onset of first disease progression (1st PD) or any severe adverse events. In this study protocol, if first-line capecitabine/S-1/5-FU plus bevacizumab combination therapy (initial therapy) required dose reduction due to adverse events, subsequent treatments (after the first PD) were recommended to be started at the same reduction dose. Protocol treatment with bevacizumab was withdrawn if the patients developed bevacizumab-induced uncontrolled bleeding, hypertension, proteinuria, thrombosis, or hypersensitivity of ≥ grade 3 (Fig. 1).

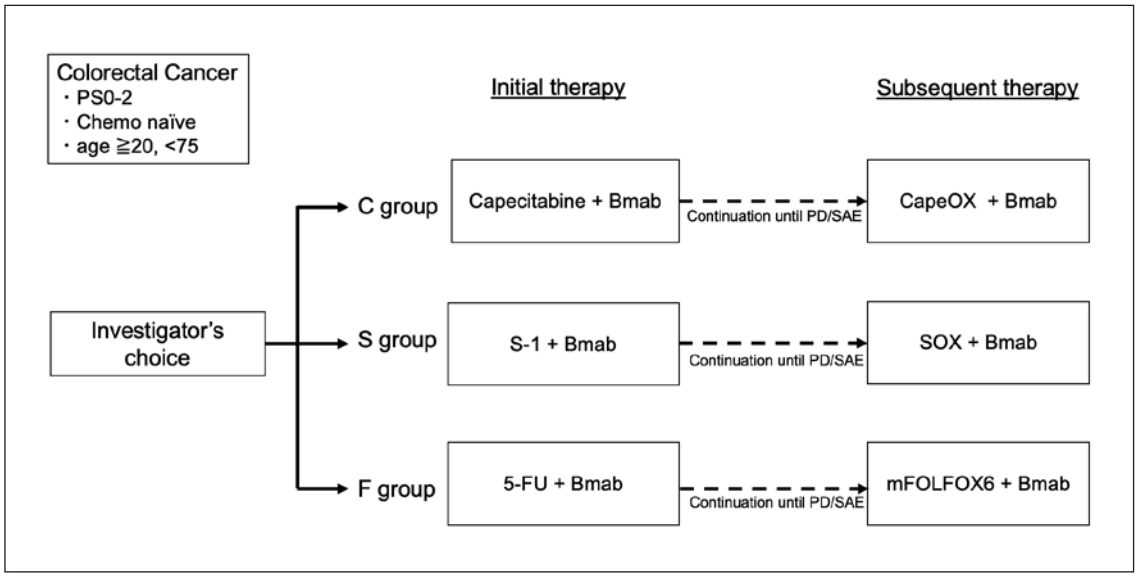

Fig. 1. Study design of the sequential treatment strategy. Bmab, bevacizumab; PD, progressive disease; SAE, severe adverse event.

Subsequent Therapy (after 1st PD)

The C-group was treated with capecitabine (1,000 mg/m^2 orally twice a day on days 1–14) plus oxaliplatin (130 mg/m^2 intravenously on day 1) with bevacizumab (7.5 mg/kg intravenously on day 1) every 3 weeks; S-group, S-1 (40–60 mg/m^2 orally twice daily on days 1–14) plus oxaliplatin (130 mg/m^2 intravenously on day 1) with bevacizumab (7.5 mg/kg intravenously on day 1) every 3 weeks; and F-group, mFOLFOX6 (200 mg/m^2 of leucovorin administered via continuous intravenous infusion over 2 h, followed by 400 mg/m^2 of 5-FU administered via a bolus injection, delivered at an initial loading dose of 2,400 mg/m^2 over 46 h, 85 mg/m^2 of oxaliplatin intravenously on day 1) with bevacizumab (5 mg/kg intravenously on day 1) every 2 weeks. This protocol therapy was repeated until either the onset of second disease progression (2nd PD) or any severe adverse events. Bevacizumab was recommended unless the patients developed bevacizumab-induced uncontrolled bleeding, thrombosis, bleeding, thrombosis, or hypersensitivity of ≥grade 3.

Patients

The mCRC patients with histologically confirmed adenocarcinoma with evaluable lesions were eligible for the study. Patients who had received postoperative adjuvant fluoropyrimidine-based chemotherapy drugs were eligible if they had remained disease-free for at least 6 months after the completion of adjuvant therapy. Patients who had previously received radiotherapy and chemotherapy for mCRC were excluded. Other eligibility criteria were as follows: Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, age 20–75 years, adequate baseline bone marrow function (white cell count, >3,000/mL; neutrophil count, ≧1,500/mL; hemoglobin concentration, ≧9.0 g/dL; and platelet count, ≧100,000/mL), adequate renal function (serum creatinine, ≦1.2 mg/dL), and adequate hepatic function (serum total bilirubin level, ≦1.2 mg/dL; serum aspartate alanine aminotransferase, and aminotransferase levels: within 3 times of normal range of the hospital). The main exclusion criteria were as follows: open biopsy or surgical procedures performed <4 weeks before study, severe drug allergy, infection, severe pleural effusion or ascites, and symptoms due to brain tumor.

Endpoints and Assessments

The primary endpoint of the study was PFS between the start of enrollment and progression of second-line treatment (2nd PFS) based on the full analysis set. The secondary endpoints were PFS of first-line treatment, overall response rate, OS, and safety.

Safety was evaluated in the per-protocol set. The physical examinations and laboratory data were performed at the first protocol treatment. Measurable lesions were assessed according to the Response Evaluation Criteria in Solid Tumors version 1.0. Tumor response was evaluated using either computed tomography every 8 weeks after the protocol treatment. No independent radiologic review was performed. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events version 4.03. PFS is defined as the time from assignment in a clinical trial to disease progression or death from any cause. OS is defined as the interval from the start of treatment to death. The patients with loss of follow-up were defined as a censored case.

Statistical Analysis

We calculated the sample size for the present study based on 1st plus 2nd PFS of 13 months and minimum 2nd PFS of 8 months, with a one-sided of 0.05, a power of 0.8, and estimated that we needed 59 patients. OS and PFS were analyzed using the Kaplan-Meier method. The planned duration of accrual and follow-up time were 2 years. All statistical analyses were performed using the SWOG statistical tool.

Table 1. Patient characteristics

	All (n = 19)	C-group (n = 4)	S-group (n = 10)	F-group (n = 15)
Age, median (range), years	65 (35–73)	67.5 (58–71)	65 (47–73)	65 (35–72)
Sex, *n* (%)				
Male	8 (42)	3	4	1
Female	11 (58)	1	6	4
ECOG PS, *n* (%)				
0	13 (68)	3	7	3
1	6 (32)	1	3	2
2	0	0	0	0
Histology, *n* (%)				
Intestinal	15 (79)	4	8	3
Diffuse	4 (21)	0	2	2
Location, *n* (%)				
Colon	11 (58)	3	5	3
Rectal	7 (37)	1	5	1
Multiple	1 (5)	0	0	1
Metastasis site, *n* (%)				
Liver	7 (37)	2	4	1
Lung	4 (21)	0	2	2
Other	8 (42)	2	4	2
Primary tumor site, *n* (%)				
Absent	17 (90)	4	9	4
Present	2 (10)	0	1	1
Post-adjuvant chemotherapy, *n* (%)				
Absent	14 (74)	1	9	4
Present	5 (26)	3	1	1
Post-adjuvant chemotherapy regimens				
Capecitabine	1	0	0	1
TS-1	1	0	1	0
UFT/LV	3	3	0	0
Comorbidities, *n* (%)				
Hypertension	6 (32)	1	3	2
Diabetes	7 (37)	1	4	2
Thrombosis	0	0	0	0
Other	7 (37)	1	4	2
KRAS status, *n* (%)				
Wild-type	5 (26)	0	4	1
Mutant	4 (21)	2	2	0
Unknown	10 (53)	2	4	4

ECOG, Eastern Cooperative Oncology Group; C-group, capecitabine plus bevacizumab; S-group, S-1 plus bevacizumab; F-group, sLV/5-FU2 plus bevacizumab; UFT/LV, uracil and tegafur/leucovorin; PS, performance status.

Ethical Conduct of the Study

The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (no. 000008190), performed in accordance with the Declaration of Helsinki and Japanese Good Clinical Practice Guidelines, and approved by the Institutional Review Board at each participating center. An independent committee monitored the safety of the patients throughout the study period. All patients provided written informed consent to participate in the study.

Results

Patient Characteristics

From December 2, 2011, to February 18, 2015, a total of 19 patients from three Japanese institutions were enrolled in the study. Although the planned number of patients was 66, recruitment was terminated, owing to slow accrual when 19 patients were enrolled. Among these, 4 patients were allocated to the C-group, 10 to the S-group,

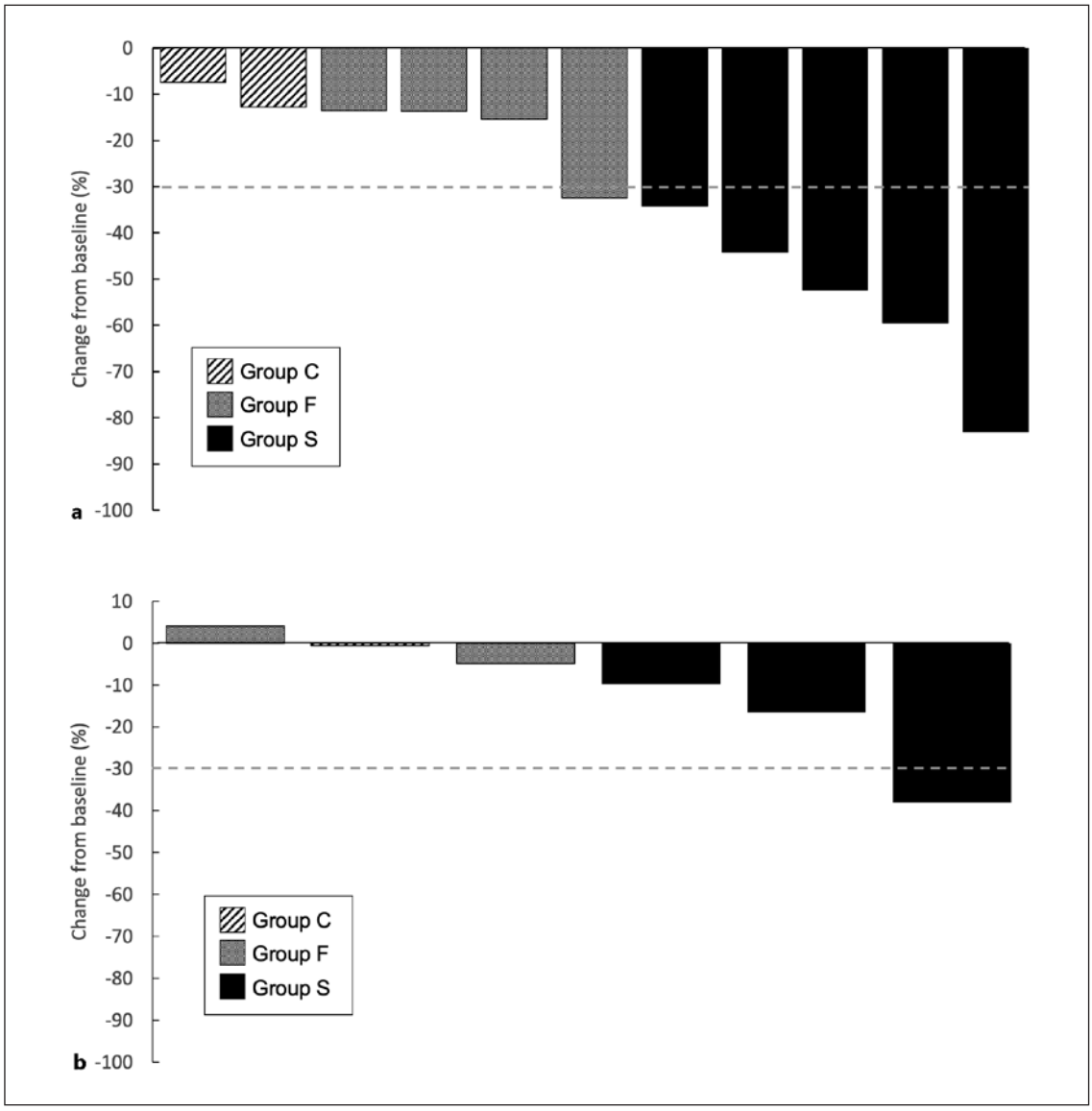

Fig. 2. Waterfall plot of initial therapy (**a**) and subsequent therapy (**b**).

and 5 to the F-group. All 19 patients were eligible, and their characteristics are shown in Table 1. Other comorbidities were prostatic hypertrophy (n = 1, C-group), rheumatoid arthritis (n = 1, S-group), bronchial asthma (n = 1, S-group), hyperlipidemia (n = 1, F-group), and arrhythmia and osteoporosis (n = 1, S-group).

Efficacy

At the data cutoff date (May 1, 2017), 14 of 19 (73%) patients experienced disease progression (1st PD), and 9 (47%) were administered an oxaliplatin-containing regimen as the subsequent therapy after the 1st PD. After the 1st PD, 2 patients (11%) were administered other regimens outside the protocol such as second-line chemotherapy, 2 patients were not administered subsequent chemotherapy because they refused, and 1 patient received best supportive care. Of the 19 patients, 11 had measurable lesions in the initial treatment phase. The objective response rate (ORR) for the initial treatment was 45.5% (5/11) (Fig. 2a). The other 6 patients showed stable disease, yielding a disease control rate of 100%. Of the 9 patients who were administered oxaliplatin-containing treatment, six had measurable lesions. The ORR for the follow-up treatment was 16.7% (1/6). Five patients

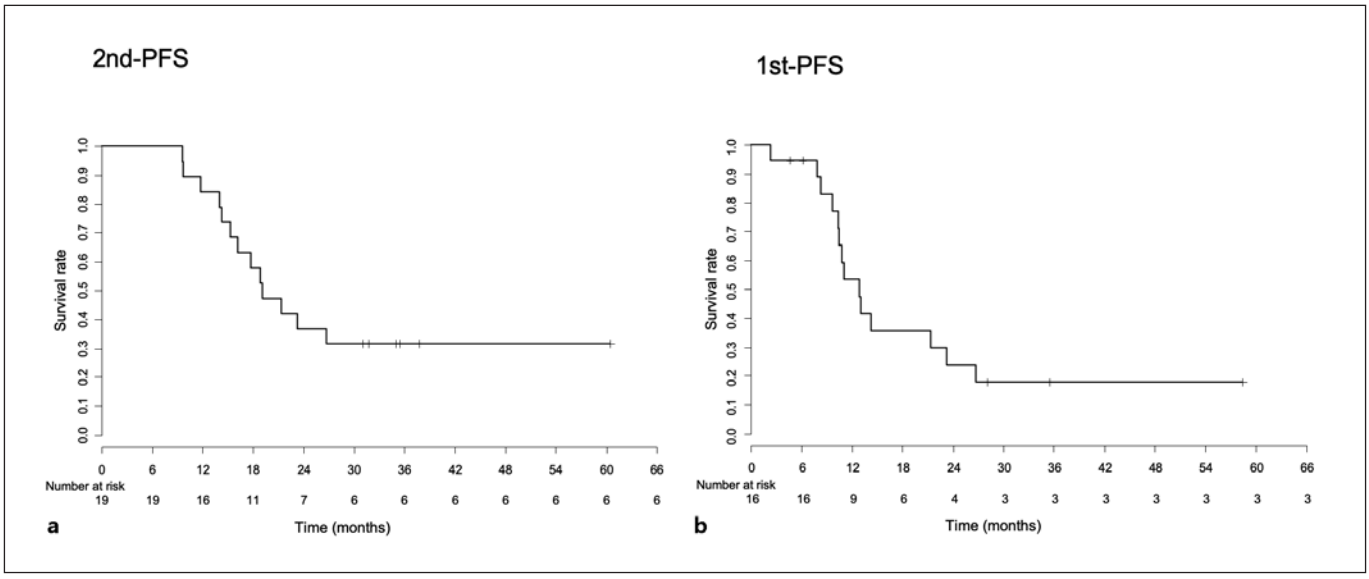

Fig. 3. Kaplan-Meier analysis of PFS. **a** Kaplan-Meier analysis of PFS in 2nd PD. The median 2nd PFS is 19.1 months (95% CI: 16.1 – NR). **b** Kaplan-Meier estimation of PFS in 1st PD. The median 1st PFS is 12.8 months (95% CI 10.4–26.7). PD, progressive disease.

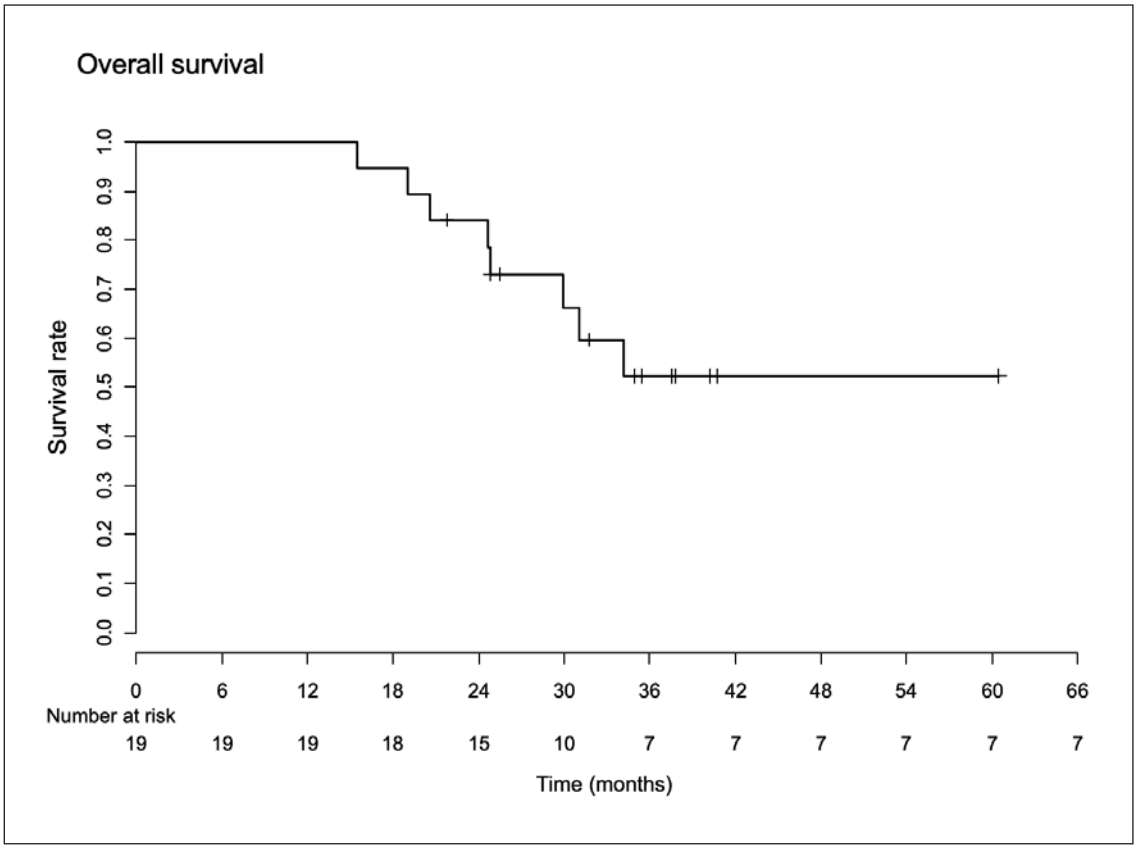

Fig. 4. Kaplan-Meier analysis of the OS. The median OS did not reach in all patients. The 2- and 3-year OS rates are 84.2% (95% CI 69.3–100.0) and 52.2% (95% CI: 32.6–83.8), respectively.

Table 2. Principal adverse events based on laboratory data and symptoms during the initial therapy (*n* = 19)

Adverse event	Any, *n* (%)	Grade ≥3, *n* (%)
Leukopenia	2 (10)	0
Neutropenia	12 (63)	1 (5)
Anemia	14 (73)	0
Thrombocytopenia	9 (47)	1 (5)
Hypoalbuminemia	18 (95)	0
AST increased	2 (10)	0
ALT increased	7 (37)	1 (5)
Hyperkalemia	7 (37)	1 (5)
Hyponatremia	3 (16)	0
Anorexia	13 (10)	4 (21)
Nausea	12 (63)	1 (5)
Vomiting	5 (26)	0
Diarrhea	8 (42)	1 (5)
Fatigue	10 (53)	1 (5)
Stomatitis	13 (10)	2 (10)
Hand-foot syndrome	16 (84)	0
Hypertension	17 (89)	9 (47)
Thrombosis	2 (10)	1 (5)
Neuropathy	2 (10)	0
Proteinuria	8 (42)	4 (21)

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3. Principal adverse events based on laboratory data and symptoms during the subsequent therapy (*n* = 9)

Adverse event	Any, *n* (%)	Grade ≥3, *n* (%)
Leukopenia	2 (22)	1 (11)
Neutropenia	6 (66)	1 (11)
Anemia	7 (78)	0
Thrombocytopenia	6 (66)	0
Hypoalbuminemia	8 (89)	0
AST increased	6 (66)	0
ALT increased	3 (33)	0
Hyperkalemia	1 (11)	0
Hypernatremia	1 (11)	0
Anorexia	9 (100)	2 (22)
Nausea	5 (55)	0
Febrile neutropenia	1 (11)	1 (11)
Diarrhea	1 (11)	0
Fatigue	7 (77)	0
Stomatitis	7 (77)	0
Hand-foot syndrome	3 (33)	0
Hypertension	6 (66)	2 (22)
Thrombosis	1 (11)	0
Neuropathy	6 (66)	1 (11)
Proteinuria	2 (22)	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

(54.5%) showed stable disease, yielding a disease control rate of 100% (Fig. 2b).

The median 1st PFS and 2nd PFS were 12.8 months (95% confidence interval [CI] 10.4–26.7) and 19.1 months (95% CI: 16.1 – not reached [NR] months) (Fig. 3a, b), respectively. The median 1st PFS was 17.2 months (95% CI: 11.1 – NR) in the C-group, 10.8 months (95% CI: 10.4 – NR) in the S-group, and 11.2 months (95% CI: 7.8 – NR) in the F-group. The median 2nd PFS was 20.2 months (95% CI: 15.3 – NR) in the C-group, 20.5 months (95% CI: 14.3 – NR) in the S-group, and 18.9 months (95% CI: 11.7 – NR) in the F-group. The median OS was NR in all patients. Two-year and 3-year OS rates were 84.2% (95% CI: 69.3–100.0) and 52.2% (95% CI: 32.6–83.8), respectively (Fig. 4).

Safety

Initial Therapy

Toxicities associated with the initial therapy are listed in Table 2. Neutropenia and thrombocytopenia of all grades were observed in 63% and 47%, respectively. The hematologic toxicities of grade ≥3 included thrombocytopenia (5%) and neutropenia (5%). The nonhematologic toxicities of grade ≥3 included anorexia (21%), proteinuria (21%), diarrhea (5%), nausea (5%), fatigue (5%), hypertension (47%), skin ulceration (5%), and thromboembolic events (5%). There were no treatment-related deaths.

Subsequent Therapy

Toxicities with subsequent therapy are listed in Table 3. Anemia, neutropenia, and thrombocytopenia of any grades were observed in 78, 66, and 66%, respectively. The hematologic toxicities of grade ≥3 included leukopenia (11%) and neutropenia (11%). Nonhematologic toxicities of grade ≥3 included anorexia (22%), hypertension (22%), febrile neutropenia (11%), and peripheral neuropathy (11%). There were no treatment-related deaths.

Post-Study Treatment

While 2 patients had received only the best supportive care after the study treatment, post-study chemotherapy was administered to 13 patients (68%), including reintroduction of 5-FU-based therapy in 3 cases, an oxaliplatin-containing regimen in 2 cases, an irinotecan-containing regimen in 6 cases, TAS-102 in 1 case, and unknown in 1 case. Beyond bevacizumab use after the protocol therapy in 6 patients (31%), antibodies of the epidermal growth factor receptor were received in 2 patients (10%).

Discussion

The present phase II study investigated the efficacy and safety of sequential treatment strategies consisting of initial therapy (fluoropyrimidine plus bevacizumab) and subsequent therapy (addition of oxaliplatin to initial therapy) for mCRC. Overall, 19 patients were enrolled from 2011 to 2015. The toxicity was tolerable, and efficacy outcomes in terms of ORR and PFS were comparable to those of previous reports in which, fluorouracil-based combination therapy with bevacizumab was administered [19–21].

In the days before the development of bevacizumab, three pivotal randomized phase III trials for sequential treatment strategy were conducted. The CApecitabine, IRinotecan, and Oxaliplatin in advanced CRC (CAIRO), FFCD-2000-05, and FOCUS trials were conducted to determine the efficacy of sequential treatment strategies [17, 18, 22]. These trials showed that the combination treatment did not significantly improve OS when compared with the sequential use of cytotoxic drugs in mCRC, suggesting the utility of sequential treatment strategy.

For the development of sequential treatment strategies with bevacizumab, the XELAVIRI (AIO KRK0110) trial and C-cubed trials were conducted [23, 24]. The XELAVIRI study investigated the efficacy of sequential treatment with a fluoropyrimidine plus bevacizumab, followed by the addition of irinotecan compared with the upfront use of fluoropyrimidine plus irinotecan plus bevacizumab. Noninferiority was not observed for a sequential treatment strategy when compared with the upfront use of combination therapy. In contrast, C-cubed trials investigated the efficacy and safety of fluoropyrimidine plus bevacizumab, followed by the addition of oxaliplatin compared with the upfront use of combination therapy for the first-line treatment of mCRC. The study showed that the sequential strategy was comparable to the upfront combination strategy.

Our data demonstrated a good antitumor activity of fluoropyrimidine (S1, capecitabine, and 5-FU) plus bevacizumab as the initial treatment for patients with mCRC with an ORR of 45.5%, which was similar to or even higher than that previously reported in clinical trials [19–21]. The high antitumor efficacy of this combination also translated into prolonged PFS, with the median PFS of first-line treatment and 2nd PFS of 12.8 months (95% CI: 10.4–26.7) in 1st PD and 19.1 months (95% CI: 16.1 – NR), respectively. Furthermore, the most frequent grade 3/4 hematologic toxicities in the initial treatment were neutropenia and thrombocytopenia, with an incidence of 5% (1/19), which was comparable with that reported in a similar previous study of fluoropyrimidine plus bevacizumab [19–21]. Febrile neutropenia and peripheral neuropathy were not observed in the induction treatment. In contrast, 11% of grade 3/4 nonhematological toxicities, including febrile neutropenia and peripheral neuropathy, were observed in a subsequent treatment with oxaliplatin.

These findings thus suggest that the sequential treatment strategy for mCRC was well tolerated, especially in the initial period, and that more careful attention to the patients may be needed during the subsequent therapy phase. The advantage of sequential treatment strategy is that patients with no tumor-related symptoms and a low risk of rapid tumor progression can be treated without accumulating toxicities such as peripheral neuropathy or severe bone marrow suppression. In contrast, rapid disease progression or severe side effects may prevent the patients from being treated with oxaliplatin, the key drug for mCRC treatment. Our data also suggest that the benefit of sequential strategy is potentially limited to patients without tumor-related symptoms and a risk of rapid tumor progression. Indeed, 5 of the 14 patients failed to be treated with second-line oxaliplatin, owing to the following reasons: 1 patient received best supportive care, two denied treatment, and two selected other regimens. Therefore, in sequential treatment, the timing of treatment escalation according to tumor progression and adverse events might be important.

Limitations of the present study include the small sample size and nonrandomized single-arm design. Each treatment was selected according to the physician's choice, which may have introduced a selection bias. Second, the RAS/BRAF status was not known in all patients, which may have affected the prognosis in each treatment group. Third, the information of the primary tumor site was limited to the colon and rectum, which was unable to the collection of information on the sidedness. Fourth, the dose intensity could not be calculated due to the lack of detailed medication records. Finally, the duration of treatment-related adverse events was not collected.

In conclusion, although our data were limited and preliminary, the sequential treatment strategy that consists of induction therapy (fluoropyrimidine plus bevacizumab) and subsequent therapy (initial therapy plus oxaliplatin) may provide a survival benefit in patients with mCRC. Further investigation of the efficacy and safety of this treatment approach is warranted.

Acknowledgments

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Statement of Ethics

The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (no. 000008190), performed in accordance with the Declaration of Helsinki and Japanese Good Clinical Practice Guidelines, and approved by the Institutional Review Board at each participating center (no. 0925, Osaka Medical college IRB). An independent committee monitored the safety of the patients throughout the study period. All patients provided written informed consent to participate in the study.

Conflict of Interest Statement

T.Y. reports grants and personal fees from Ono Pharmaceutical; grants, personal fees, and other from Chugai Pharmaceutical; and grants, personal fees, and other from Yakult Honsha, outside the submitted work. H.K. has received consulting fees from Bristol Myers Squibb Co., Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., and Taiho Pharmaceutical Co., Ltd.; honoraria from Bristol Myers Squibb Co., Ltd., AstraZeneca K.K., Bayer Yakuhin Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Co., Ltd., Merck Biopharma, Co., Ltd., and Taiho Pharmaceutical Co., Ltd.; lecture fees from Bristol Myers Squibb Co., Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Taiho Pharmaceutical Co., Ltd.; and research funding from Chugai Pharmaceutical Co., Ltd. and Eisai Co., Ltd., outside the submitted work. D.S. reports grants and personal fees from Ono Pharmaceutical; grants, personal fees, and honoraria from Chugai Pharmaceutical; grants, personal fees, and other from Yakult Honsha; and honoraria from Daiichi Sankyo Co., Ltd., outside the submitted work. T.S. reports grants and personal fees from Ono Pharmaceutical; grants, personal fees, and other from Chugai Pharmaceutical; grants, personal fees, and other from Yakult Honsha; grants and personal fees from Eli Lilly; grants and personal fees from MSD; grants from Gilead Sciences; grants from Palexell; grants and personal fees from Bristol Myers Squib; grants and personal fees from Astellas; grants from Daiichi Sankyo; grants and personal fees from Taiho Pharmaceutical; personal fees from Takara Bio; and personal fees from Sanofi-Aventis, outside the submitted work. All the other authors have no conflicts of interest to declare.

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Author Contributions

Conception and design: T.Y., M.Y., and M.G.; data acquisition: M.Y., T.K., H.H., T.M., T.T., F.S., M.Y., and M.G.; data interpretation: Y.K., T.S., and D.S.; analysis and development of the new software used: T.S.; manuscript drafting and substantive revision: T.Y., H.K., and T.S. All the authors have approved the final manuscript for submission.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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