International Journal of Clinical Oncology
https://doi.org/10.1007/s10147-020-01656-3

ORIGINAL ARTICLE

Phase II study of 5-fluorouracil–leucovorin plus bevacizumab for chemotherapy-naïve older or frail patients with metastatic colorectal cancer (OGSG 0802)

Takashi Ohta[1] · Takeshi Kato[2] · Hisato Kawakami[3] · Yasuhiro Miyake[4] · Masahiro Goto[5] · Shigeyoshi Iwamoto[6] · Toshio Otsuji[7] · Masato Nakamura[8] · Naotoshi Sugimoto[9] · Shu Okamura[10] · Masahito Kotaka[11] · Masaki Tsujie[12] · Yukihiko Tokunaga[13] · Hideyuki Mishima[6] · Taishi Hata[14] · Toshio Shimokawa[15] · Yukinori Kurokawa[16] · Taroh Satoh[16]

Received: 14 December 2019 / Accepted: 8 March 2020

Abstract

Background Older or frail patients are often underrepresented in clinical trials for metastatic colorectal cancer (mCRC). We here assessed the efficacy and safety of 5-fluorouracil (5-FU)–leucovorin plus bevacizumab in such patients.

Methods The study (OGSG 0802) was designed as a single-arm, open-label, multicenter phase II trial. Eligible patients had mCRC and at least one of the following: an age of ≥ 65 years, an Eastern Cooperative Oncology Group performance status of 1 or 2, a serum albumin level of ≤ 3.5 g/dL, incompatibility with oxaliplatin or irinotecan, and a history of abdominal or pelvic radiotherapy. Patients received 5-FU (600 mg/m^2) and l-leucovorin (200 mg/m^2) on days 1, 8, and 15 together with bevacizumab (5 mg/kg) on days 1 and 15 every 4 weeks. The primary end point was objective response rate (ORR), and secondary end points were progression-free survival (PFS), overall survival (OS), and safety.

Results Forty-one patients were enrolled and eligible. Median age was 76 years (range 56–90 years), and 51% of patients had a performance status of 0. The ORR was 36.6% [95% confidence interval (CI) 22.1–53.1%], median PFS was 9.4 months (95% CI 7.4–17.7 months), and median OS was 24.0 months (95% CI 19.9 months—not reached). The most common treatment-related adverse events of grade ≥ 3 were neutropenia (24%), anorexia (10%), leukopenia (7%), and mucositis/stomatitis (7%). There were no treatment-related deaths.

Conclusion Weekly 5-FU–leucovorin with biweekly bevacizumab may be a tolerable and effective treatment option for older or frail patients with mCRC.

Keywords 5-fluorouracil · Bevacizumab · Older · Frail · Metastatic colorectal cancer

Abbreviations

UFT	Uracil-tegafur
LV	Leucovorin
5-FU	5-Fluorouracil
NA	Not available
ECOG PS	Eastern Cooperative Oncology Group performance status
ORR	Objective response rate
PFS	Progression-free survival
OS	Overall survival
AE	Adverse event

Introduction

Colorectal cancer is the third most common malignancy worldwide, with more than 1.8 Mio. new cases in 2018 alone, and it is also the second most common cause of cancer-related deaths, with more than 880,000 deaths [1]. Attempts to improve the prognosis of metastatic colorectal cancer (mCRC) have led to the development of numerous treatment regimens consisting of chemotherapy combined with molecularly targeted agents [2–11]. Bevacizumab, a neutralizing antibody to vascular endothelial growth factor

Takashi Ohta and Takeshi Kato contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10147-020-01656-3) contains supplementary material, which is available to authorized users.

✉ Hisato Kawakami
kawakami_h@med.kindai.ac.jp

Extended author information available on the last page of the article

Published online: 26 March 2020

(VEGF), has been shown to extend the survival of patients with mCRC in association with limited toxicity and is thus considered a standard agent for the treatment of this condition.

At least 70% of patients with mCRC are thought to be 65 years or older, indicating that the disease arises predominantly in the older patients. This age distribution raises a practical problem in the treatment of mCRC, given that older patients are often not suitable for aggressive chemotherapy with 5-fluorouracil (5-FU) in combination with oxaliplatin and/or irinotecan because of age-related comorbidities and poor functional status [12]. A similar situation exists for so-called "frail" patients, who have a poor performance status (PS) as a result of disease progression or serious comorbidities. Despite the concerns with regard to chemotherapy in older or frail patients with mCRC, several studies [13–18] have demonstrated both the efficacy and safety of bevacizumab in combination with oral or infusional fluoropyrimidine in such patients. We have now conducted a single-arm phase II study to evaluate the efficacy and safety of bevacizumab plus weekly administration of the combination of 5-FU and leucovorin (known as the modified Roswell Park Memorial Institute [mRPMI] regimen) in chemotherapy-naïve older or frail patients with mCRC.

Materials and methods

Study design and treatment

This study by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG 0802) was designed as a non-randomized, multicenter, open-label phase II trial. Patients received the mRPMI regimen (5-FU at 600 mg/m^2 and l-leucovorin at 200 mg/m^2, each administered as a bolus, on days 1, 8, and 15) plus bevacizumab (5 mg/kg on days 1 and 15) every 4 weeks until disease progression or withdrawal from the study.

Patients

Eligible patients had histologically proven unresectable or metastatic colorectal cancer with measurable lesions and were not suitable for intensive chemotherapy. Individuals who had previously undergone adjuvant chemotherapy were eligible if the therapy had been completed > 180 days before initiation of the study treatment. Other eligibility criteria included a life expectancy of at least 3 months; adequate baseline hematologic function (hemoglobin level of ≥ 9.0 g/dL, white blood cell count of ≥ 3000/mm^3 and < 12,000/mm^3, neutrophil count of ≥ 1500/mm^3, platelet count of ≥ 100,000/mm^3), hepatic function (serum total bilirubin concentration of ≤ 1.5 mg/dL, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤ 100 U/L, or ≤ 200 U/L in the presence of liver metastasis), and renal function (serum creatinine concentration of ≤ 1.2 mg/dL); a normal electrocardiogram within the previous 28 days; and at least one of the following conditions: (1) an age of ≥ 65 years, (2) an Eastern Cooperative Oncology Group (ECOG) PS of 1 or 2, (3) a serum albumin concentration of ≤ 3.5 g/dL, (4) unsuitability for oxaliplatin or irinotecan treatment, or (5) a history of abdominal or pelvic radiotherapy. Exclusion criteria included an ECOG PS of 3 or 4; brain metastasis, interstitial pneumonia, or pulmonary fibrosis; carcinoma in situ of the portio or digestive tract treated with curative intent; a cerebral vascular disorder within the previous 12 months; surgery, open biopsy, or suturing of an injury within the previous 4 weeks; planned surgery during the trial; high susceptibility to bleeding or a coagulation disorder; history of thrombosis; uncontrollable peptic ulcer, hypertension, diarrhea, or infection; inflammation of abdominal organs; and severe allergy to 5-FU or levofolinate calcium.

End points and assessments

The primary end point of the study was objective response rate (ORR) based on the binominal distribution in the full analysis set (FAS), which was defined as all enrolled patients excluding those who were found to be ineligible after enrollment. Secondary end points were progression-free survival (PFS), overall survival (OS), and safety. Whereas efficacy outcomes were assessed in the FAS, toxicity was evaluated in the per protocol set (PPS), which was defined as all patients in the FAS who received at least one dose of protocol treatment and had no major protocol violations. Physical examinations and laboratory tests were performed at the time of each drug administration. Tumor response was evaluated by computed tomography or magnetic resonance imaging (abdomen and chest) every 8 weeks after initiation of the protocol treatment. Measurable lesions were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. No independent radiologic review was performed. The ORR was evaluated according to these response criteria. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. PFS was defined as the interval from the start of treatment to death from any cause or radiologic progression, as judged by the investigators. OS was defined as the interval from the start of treatment to death from any cause. Patients without progressive disease who were alive at the data cutoff date and those who were lost to follow-up were censored at the date of last evaluation.

Statistical analysis

The expected ORR was set at 35%, with 15% being assumed to be the minimum efficacy threshold, given that the ORR for the RPMI regimen was previously found to be 15.2% or 17.0% and that for the RPMI regimen plus bevacizumab to be 26.0%, 34.1%, or 40.0% in patients with mCRC [16–18]. The total required sample size was then calculated as 36 patients, with a one-sided alpha error of 0.05 and beta error of 0.10. Taking into account the possibility of patient withdrawal and ineligibility, we planned to include 40 patients in the study. The planned duration of accrual was 1 year, and the planned follow-up time was 1 year after registration of the last patient. Survival results were calculated by Kaplan–Meier analysis for estimation of incomplete data. All statistical analysis was performed with R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org).

Ethical conduct of the study

The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (no. 000002182), was performed in accordance with the Declaration of Helsinki and Japanese Good Clinical Practice Guidelines, and was 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 participation in the study.

Results

Patients

From 7 July 2009 to 24 December 2010, a total of 41 patients from 13 institutions was enrolled in the study. All patients were eligible for analysis of efficacy (FAS) and safety (PPS), and their principal clinical characteristics are shown in Table 1. The patients included 18 men and 23 women, with a median age of 76 years and age range of 56 to 90 years. *KRAS* mutation status was determined for 27 of the 41 patients, with 18 of these individuals being wild type and 9 harboring a *KRAS* mutation. Most patients had an ECOG PS of 0 or 1, and 19 of them had at least one comorbidity including hypertension, diabetes mellitus, Parkinson's disease, chronic hepatitis, asthma, and cerebral infarction. The most frequent conditions associated with older or frail was an age of ≥ 65 years ($n = 40$), followed by an ECOG PS of 1 or 2 ($n = 20$), unsuitability for oxaliplatin or irinotecan treatment ($n = 9$), a serum albumin concentration of ≤ 3.5 g/dL ($n = 4$), and a history of abdominal or pelvic radiotherapy ($n = 2$). As a result, 23 patients harbored two or more disadvantageous conditions. Metastatic sites included lymph nodes (43.9%), lung (39.0%), liver (29.3%), peritoneum (12.2%), and other (4.9%).

Table 1 Characteristics of the study patients ($n = 41$)

Median age (range), years	76 (56–90)
Sex, male/female	18/23
Median height (range), cm	154.8 (134–173)
Median weight (range), kg	51.8 (31–72)
ECOG performance status, 0/1/2	21/19/1
Primary tumor site	
Cecum	2
Colon	26
Rectum	13
Metastatic/recurrent sites	
Lymph node	18
Peritoneum	5
Liver	12
Lung	16
Bone	1
Local recurrence	1
KRAS status	
Unknown	14
Wild type	18
Mutant	9
Primary tumor site	
Present	6
Absent	35
Serum CEA (ng/mL), median (range)	15.5 (1.4–648.5)
Serum CA19-9 (U/mL), median (range)	25.3 (2.0–5471.9)
History of medical condition	
None	22
Cancer pain	1
Hypertension	10
Diabetes mellitus	8
Parkinson's disease	1
Chronic hepatitis	1
Asthma	3
Cerebral infarction	1

Data are *n* values unless indicated otherwise

ECOG Eastern Cooperative Oncology Group, *CEA* carcinoembryonic antigen

Efficacy

The ORR for the FAS was 36.6% (15/41). Twenty patients (48.8%) showed stable disease, whereas 3 patients (7.3%) progressed, yielding a disease control rate of 85.4% (35/41) (Table 2). With a median follow-up period of 730 days (range 62–1036 days), the median PFS was 9.4 months [95% confidence interval (CI) 7.4–17.7 months]

Table 2 Tumor response rate in the full analysis set

	Total	CR	PR	SD	PD	NE	ORR (95% CI)	DCR (95% CI)
Confirmed response	41	2	13	20	3	3	36.6% (22.1%–53.1%)	85.4%
Best response	41	2	21	12	3	3	56.1% (39.7%–71.5%)	85.4%

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* objective response rate (CR + PR), *DCR* disease control rate (CR + PR + SD), *CI* confidence interval

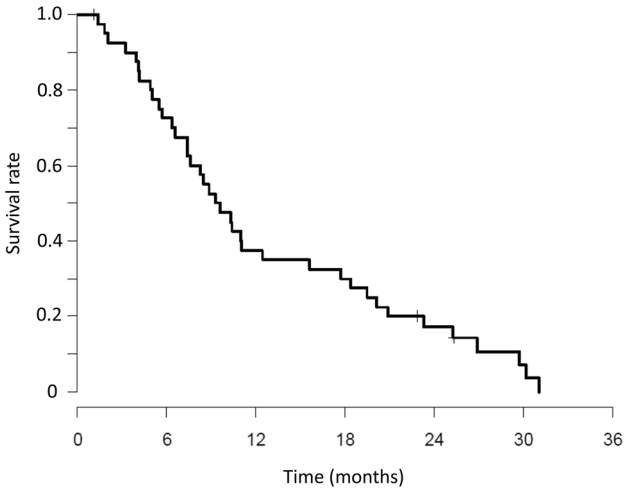

Fig. 1 Kaplan–Meier estimation of progression-free survival (PFS) in the full analysis set. Median PFS was 9.4 months (95% confidence interval, 7.4–17.7 months)

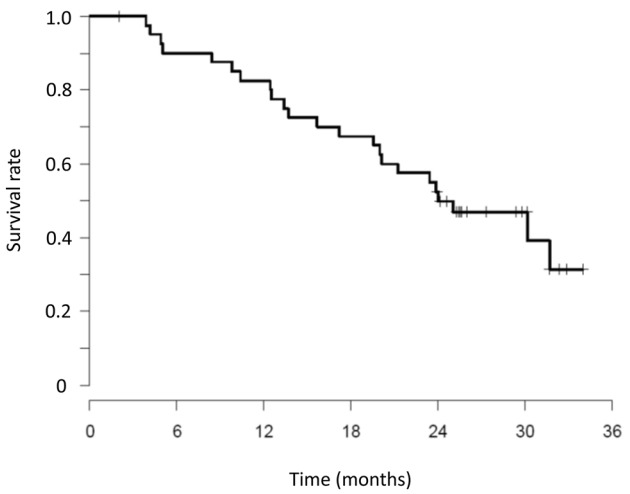

Fig. 2 Kaplan–Meier estimation of overall survival (OS) in the full analysis set. Median OS was 24.0 months (95% confidence interval, 19.9 months to not reached)

(Fig. 1) and the median OS was 24.0 months (95% CI 19.9 months to not reached) (Fig. 2). One patient showed a response to the study treatment consistent with conversion therapy.

Table 3 Principal adverse events based on the laboratory data for the per protocol set ($n = 41$)

	n (%)	
Adverse event	Any	Grade ≥ 3
Leukopenia	28 (68)	3 (7)
Neutropenia	25 (61)	10 (24)
Anemia	28 (68)	1 (2)
Thrombocytopenia	16 (39)	1 (2)
Hypoalbuminemia	15 (37)	0 (0)
AST increased	10 (24)	0 (0)
Creatinine increased	13 (32)	0 (0)
Hyper/Hypokalemia	9 (22)	0 (0)
Hyponatremia	4 (10)	0 (0)

AST aspartate aminotransferase

Treatment exposure and safety

The median number of treatment cycles was 7 (range 0–24). During the study period, 41 patients discontinued the study treatment for the following reasons: progressive disease in 22 patients (54%), severe or uncontrollable adverse events in 5 (12%), refusal by the patient or family in 7 (17%), investigator judgment in 6 (15%), and conversion surgery in 1 (2.4%). The severe or uncontrollable adverse events included diarrhea; depressed level of consciousness and febrile neutropenia; mucositis, anorexia, and hand–foot syndrome; anorexia; and seizure in one patient each.

Toxicities associated with treatment are listed in Tables 3 and 4. Leukopenia, neutropenia, anemia, and thrombocytopenia of all grades were apparent in 68%, 61%, 68%, and 39% of patients, respectively (Table 3). Hematologic toxicities of grade ≥ 3 included leukopenia (7%), neutropenia (24%), anemia (2%), and thrombocytopenia (2%). Nonhematologic toxicities of all grades included proteinuria (29%), anorexia (32%), nausea (32%), vomiting (12%), mucositis/stomatitis (29%), diarrhea (34%), fatigue (49%), rash (34%), hyperpigmentation (17%), hypertension (24%), alopecia (7%), epistaxis (29%), and seizure (2%) (Table 4). Nonhematologic toxicities of grade 3 or 4 included proteinuria (2%), anorexia (10%), mucositis/stomatitis (7%), diarrhea (5%), fatigue (5%), hypertension (5%), and seizure (2%). There were no treatment-related deaths.

Table 4 Principal adverse events based on the symptoms for the per protocol set ($n=41$)

Adverse event	*n* (%)	
	Any	Grade ≥ 3
Proteinuria	12 (29)	1 (2)
Anorexia	13 (32)	4 (10)
Nausea	13 (32)	0 (0)
Vomiting	5 (12)	0 (0)
Mucositis/stomatitis	12 (29)	3 (7)
Diarrhea	14 (34)	2 (5)
Fatigue	20 (49)	2 (5)
Rash	14 (34)	0 (0)
Hyperpigmentation	7 (17)	0 (0)
Hypertension	10 (24)	2 (5)
Alopecia	3 (7)	0 (0)
Epistaxis	12 (29)	0 (0)
Seizure	1 (2)	1 (2)

Poststudy treatment

Whereas 12 patients received only best supportive care after the study treatment, poststudy chemotherapy was administered in 28 patients (68%), including reintroduction of 5-FU-based therapy in 21 cases, an oxaliplatin-containing regimen in 12 cases, and an irinotecan-containing regimen in 11 cases. Bevacizumab was continued after the study treatment in 15 patients (37%), whereas antibodies to the epidermal growth factor receptor were administered in 5 patients (12%).

Discussion

Evidence suggests that older patients may be more prone than younger patients to the development of chemotherapy-related toxicities secondary to existing comorbidities, to the incompatibility of chemotherapy with other medications, and to a decline in the detoxification and elimination potential of the liver and kidneys. In addition, older patients represent a more heterogeneous population [19]. Chemotherapy regimens that can achieve a reasonable response rate with low toxicity are thus desirable for this subset of patients. To select such population, we adopted the eligibility criteria of this study mostly from that of AVF2192g trial [16] which has been known as the pivotal study for older and frail CRC patients. On the other hand, clinical trials including J-BLUE [13], AVEX [14], and XELAVIRI [15] took more moderate criteria compared with ours as shown in Supplementary Table 1. These suggest the difficulties to define the older and frail CRC patients in the clinical protocol as well as to interpret the data of these clinical trials.

In the present study, the most frequent severe nonhematologic toxicity was anorexia, with an incidence of 10%, which is higher than that reported in a similar previous study of fluoropyrimidine plus bevacizumab [13], as shown in Table 5. The frequencies of other 5-FU-induced gastrointestinal toxicities (such as nausea and vomiting) in the present study were similar to those of fluoropyrimidine-induced toxicities in previous studies of regimens including bevacizumab [13–16]. The incidence of mucositis/stomatitis and of diarrhea was lower in the present study than in comparator trials conducted in Western countries [14–16], consistent with previous findings [20]. Furthermore, whereas hand–foot syndrome of grade ≥ 3 developed in 16% of patients in clinical trials of capecitabine plus bevacizumab regimens [14, 15], no cases of this condition were observed in the present study, which may be an advantage of the mRPMI regimen plus bevacizumab for older patients in terms of their quality of life. With regard to bevacizumab-induced nonhematologic toxicities, the frequency of severe hypertension or fatigue was 5% and that of proteinuria was 2% in the present study. These findings thus suggest that the combination of bevacizumab with the mRPMI regimen was well tolerated in the study cohort, despite its high-risk nature.

There were no cases of treatment discontinuation due to hematologic toxicity in the present study, suggesting that the combination of bevacizumab plus the mRPMI regimen is feasible. However, neutropenia of grade ≥ 3 was apparent in 24% of patients, an incidence higher than that in previous studies of oral fluoropyrimidine plus bevacizumab [13, 14] (Table 5). This higher rate of neutropenia might has been attributable to a difference in the schedule of hospital visits between regimens. Whereas the mRPMI regimen requires weekly administration and a weekly blood examination, the other regimens consisting of fluoropyrimidine are administered bi- or triweekly. The weekly checkup required for the mRPMI regimen may actually be advantageous in the care of older or frail patients because it affords the opportunity for the early detection of toxicity and timely intervention, which may explain in part the lower rates of nonhematologic toxicities in the present study when compared with the other studies. Our data thus suggest that the careful monitoring associated with the weekly mRPMI regimen might contribute to the tolerability of the chemotherapy in older or frail patients with severe comorbidities.

Our data highlight the antitumor activity of the mRPMI regimen plus bevacizumab, with an ORR of 36.6%, which is similar to or even higher than that reported in the comparator trials [13–16] (Table 5). Of note, one patient underwent conversion surgery as a result of pronounced tumor shrinkage. The high antitumor efficacy of this combination also translated into survival, with the median PFS and OS being 9.4 months (95% CI 7.4–17.7 months) and 24.0 months (95% CI 19.9 months to not reached), respectively.

Table 5 Summary of and results for trials of first-line treatment with a fluoropyrimidine plus bevacizumab for older or frail patients with metastatic colorectal cancer

	J-BLUE study [13] ($n=52$)	AVEX study [14] ($n=140$)	XELAVIRI trial [15] ($n=212$)	AVF2192g trial [16] ($n=104$)	OGSG 0802 (present study) ($n=41$)
Regimen	UFT-LV + bevacizumab	Capecitabine + bevacizumab	(Capecitabine or 5-FU/LV) + bevacizumab	5-FU/LV + bevacizumab	5-FU/LV + bevacizumab
Age (years)					
Median	80	76	71	71.3	76
Range	75–87	70–87	NA	NA	56–90
ECOG PS (%)					
0	73	50	60	29	51
1	27	41	40	64	46
2	0	7	0	8	2
ORR (%)	40	19	36.8	26	36.6
Median PFS (months)	8.2	9.1	8	9.2	9.4
Median OS (months)	23	20.7	21.9	16.6	24
Discontinuation due to AE (%)	25	25	NA	10	17
Subsequent treatment (%)	65	37	63.2	~50	71
AEs of grade 3 or 4 (%)					
Leukopenia	0	NA	5.1	5	7
Neutropenia	2	1	15.5	NA	24
Febrile neutropenia	0	NA	0.9	NA	2
Anorexia	0	NA	NA	NA	10
Nausea	6	1	3.8	NA	0
Diarrhea	6	7	11.3	39	5
Hypertension	12	2	31.2	16	5
Proteinuria	0	1	NA	1	2
Hand–foot syndrome	0	16	16	NA	0

Of course, careful attention is needed for the cross-trial comparison above, especially for clinical trials for older or frail patients, as the differences in safety and efficacy potentially arise from those in the patient background including ethnic differences, which warrants further evaluation. Nonetheless, together with the mild toxicities, the efficacy results thus suggest that the mRPMI regimen plus bevacizumab is potentially suitable for older or frail patients with mCRC as a first-line treatment.

Regarding the subsequent therapy, only 5 out of 18 *KRAS* wild type patients were treated with anti EGFR antibody. In Japan, cetuximab, an anti-EGFR antibody was approved in July 2008 and mostly utilized in the 3rd line as shown in the Japanese treatment guideline at that time (https://www.jsccr.jp/guideline/2009/particular.html#no2). Given our study population, it is natural that only a limited number of patients could safely receive cetuximab containing treatment as the subsequent therapy.

Limitations of our phase II trial include the relatively small number of patients and the nonrandomized design. Furthermore, the study patients were all Japanese, which may limit the generalizability of our findings, especially with regard to toxicity. In addition, the information of primary tumor site was limited to colon *vs.* rectum, and not available for the sidedness. Moreover, oral fluoropyrimidines including capecitabine and S-1 have been widely adopted for older or frail CRC patients with high convenience and safety. However, we could not assess these agents in this setting as these oral fluoropyrimidines were not recommended in the 1st line treatment according to the treatment guideline at that time (https://www.jsccr.jp/guideline/2009/particular.html#no5).

In summary, bevacizumab plus weekly 5-FU and leucovorin (mRPMI regimen) was found to be safe and to show marked antitumor activity for older or frail patients with mCRC in the first-line setting. Together with the results of

previous trials, our data provide evidence that bevacizumab plus either infusional or oral 5-FU therapy is a potential standard option for the initial treatment of older or frail patients with mCRC.

Acknowledgements This work is dedicated in memory of Professor Hiroya Takiuchi. We thank all the patients, investigators, and medical staff who participated in this study, as well as the OGSG data center for their contribution.

Compliance with ethical standards

Conflict of interest T. Ohta has received lecture fees from Bristol-Myers Squibb Co. Ltd., Eli Lilly Japan K.K., Novartis Pharma K.K., Chugai Pharmaceutical Co. Ltd., and Teijin Pharma Ltd., T. Kato has received honoraria from Chugai Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., Bayer Yakuhin Ltd., Sanofi K.K., Yakult Honsha Co. Ltd., and research funding from Chugai Pharmaceutical Co. Ltd., H. Kawakami has received consulting fees from Bristol-Myers Squibb Co. Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical 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., 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., M. Nakamura. has received honoraria from Chugai Pharmaceutical Co. Ltd., Merck Biopharma Co. Ltd., Takeda Pharmaceutical Co. Ltd., Taiho Pharmaceutical Co. Ltd., Yakult Honsha Co. Ltd., Ono Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., Sanofi K.K., Bayer Yakuhin Ltd., and Otsuka Pharmaceutical Co. Ltd., N. Sugimoto has received research funding from MSD K.K., Ono Pharmaceutical Co. Ltd., Astellas Pharma Inc., and Daiichi Sankyo Co. Ltd., M. Kotaka has received honoraria from Chugai Pharmaceutical Co. Ltd., Yakult Honsha Co. Ltd., Kaken Pharmaceutical Co. Ltd., Taiho Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Merck Biopharma Co. Ltd., Takeda Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., Bayer Yakuhin Ltd., and Sanofi K.K. H. Mishima has received honoraria and research funding from Chugai Pharmaceutical Co. Ltd., T. Hata has received lecture fees from Daiichi Sankyo Co. Ltd., T. Satoh received research grants from Giliad; consulting fees from Daiichi Sankyo and Takeda Pharmaceutical, Co. Ltd.; consulting fees, honoraria and research grants from Merck BioPharm, Bristol-Myers K.K., Taiho pharmaceutical, Elli Lilly, MSD,, Sanofi, Bristol Myers-Squib; and departmental research grants, research grants, honoraria and consulting fees from Chugai Pharmaceutical Co. Ltd., Ono Pharmaceutical. Co. Ltd. and Yakult Honsha Co. Ltd. Y. Miyake, M. Goto, S. Iwamoto, T. Otsuji, S. Okumura, M. Tsujie, Y. Tokunaga, T. Shimokawa and Y. Kurokawa have no conflict of interest.

References

1. Bray F, Ferlay J, Soerjomataram I et al (2018) Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394–424
2. Saltz LB, Clarke S, Diaz-Rubio E et al (2008) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: as randomized phase III study. J Clin Oncol 26:2013–2019
3. Yamazaki K, Nagase M, Tamagawa H et al (2016) Randomized phase iii study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407g). Ann Oncol 27:1539–1546
4. Van Cutsem E, Kohne CH, Hitre E et al (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 360:1408–1417
5. Heinemann V, von Weikersthal LF, Decker T et al (2014) FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 15:1065–1075
6. Qin S, Li J, Wang L et al (2018) Efficacy and tolerability of first-line cetuximab plus leucovorin, fluorouracil, and oxaliplatin (FOLFOX-4) versus FOLFOX-4 in patients with ras wild-type metastatic colorectal cancer: the open-label, randomized, phase III TAILOR trial. J Clin Oncol 36:3031–3039
7. Schwartzberg LS, Rivera F, Karthaus M et al (2014) PEAK: A randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type kras exon 2 metastatic colorectal cancer. J Clin Oncol 32:2240–2247
8. Douillard JY, Siena S, Cassidy J et al (2014) Final results from PRIME: Randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol 25:1346–1355
9. Van Cutsem E, Tabernero J, Lakomy R et al (2012) Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 30:3499–3506
10. Cremolini C, Loupakis F, Antoniotti C et al (2015) FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol 16:1306–1315
11. Tabernero J, Yoshino T, Cohn AL et al (2015) Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol 16:499–508
12. Aparicio T, Pamoukdjian F, Quero L et al (2016) Colorectal cancer care in elderly patients: Unsolved issues. Dig Liver Dis 48:1112–1118
13. Nishina T, Moriwaki T, Shimada M et al (2016) Uracil-tegafur and oral leucovorin combined with bevacizumab in elderly patients (aged %3e/= 75 years) with metastatic colorectal cancer: a multicenter, phase II trial (joint study of bevacizumab, oral leucovorin, and uracil-tegafur in elderly patients [J-BLUE] study). Clin Colorectal Cancer 15:236–242
14. Cunningham D, Lang I, Marcuello E et al (2013) Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol 14:1077–1085
15. Modest DP, Weikersthal LF, Decker T et al (2019) Sequential versus combination therapy of metastatic colorectal cancer using fluoropyrimidines, irinotecan, and bevacizumab: a randomized, controlled study-XELAVIRI (AIO KRK0110). J Clin Oncol 37:22–32
16. Kabbinavar FF, Schulz J, McCleod M et al (2005) Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line

metastatic colorectal cancer: results of a randomized phase II trial. J Clin Oncol 23:3697–3705
17. Kabbinavar F, Hurwitz HI, Fehrenbacher L et al (2003) Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 21:60–65
18. Kabbinavar FF, Hambleton J, Mass RD et al (2005) Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. J Clin Oncol 23:3706–3712
19. Saif MW, Lichtman SM (2009) Chemotherapy options and outcomes in older adult patients with colorectal cancer. Crit Rev Oncol Hematol 72:155–169
20. Shirao K, Hoff PM, Ohtsu A et al (2004) Comparison of the efficacy, toxicity, and pharmacokinetics of a uracil/tegafur (UFT) plus oral leucovorin (LV) regimen between Japanese and American patients with advanced colorectal cancer: Joint United States and Japan study of UFT/LV. J Clin Oncol 22:3466–3474

Affiliations

Takashi Ohta[1] · Takeshi Kato[2] · Hisato Kawakami[3] · Yasuhiro Miyake[4] · Masahiro Goto[5] · Shigeyoshi Iwamoto[6] · Toshio Otsuji[7] · Masato Nakamura[8] · Naotoshi Sugimoto[9] · Shu Okamura[10] · Masahito Kotaka[11] · Masaki Tsujie[12] · Yukihiko Tokunaga[13] · Hideyuki Mishima[6] · Taishi Hata[14] · Toshio Shimokawa[15] · Yukinori Kurokawa[16] · Taroh Satoh[16]

1 Department of Clinical Oncology, Kansai Rosai Hospital, Amagasaki, Japan

2 Department of Surgery, Osaka National Hospital, Osaka, Japan

3 Department of Medical Oncology, Kindai University Faculty of Medicine, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589-8511, Japan

4 Department of Surgery, Osaka Minato Central Hospital, Osaka, Japan

5 Cancer Chemotherapy Center, Osaka Medical College, Takatsuki, Japan

6 Cancer Center, Aichi Medical University, Nagakute, Japan

7 Department of Internal Medicine, Dongo Hospital, Yamatotakada, Japan

8 Comprehensive Cancer Center, Aizawa Hospital, Matsumoto, Japan

9 Department of Clinical Oncology, Osaka International Center Institute, Osaka, Japan

10 Department of Surgery, Suita Municipal Hospital, Suita, Japan

11 Department of Surgery, Sano Hospital, Kobe, Japan

12 Department of Surgery, Tondabayashi Hospital, Tondabayashi, Japan

13 Department of Surgery, Japan Post Kyoto Teishin Hospital, Kyoto, Japan

14 Department of Surgery, Kansai Rosai Hospital, Amagasaki, Japan

15 Department of Clinical Study Support Center, Wakayama Medical University, Wakayama, Japan

16 Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Suita, Japan