Original Study

Capecitabine Plus Oxaliplatin and Bevacizumab, Followed by Maintenance Treatment With Capecitabine and Bevacizumab for Patients Aged > 75 Years With Metastatic Colorectal Cancer

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Abstract

The CAPOX/Bev (capecitabine plus oxaliplatin and bevacizumab) regimen has previously shown efficacy for patients with metastatic colorectal cancer (mCRC). Data on the efficacy and safety of CAPOX/Bev, followed by maintenance capecitabine and bevacizumab for elderly patients with mCRC, are limited. The present small study has shown that CAPOX/Bev, followed by maintenance capecitabine and Bev is safe and effective for mCRC patients aged > 75 years.

Background: The aim of the present study was to evaluate the efficacy and safety of the combination of CAPOX-Bev (capecitabine [Cap] plus oxaliplatin and bevacizumab [Bev]), followed by maintenance Cap and Bev, for patients with metastatic colorectal cancer (mCRC) and aged > 75 years. **Patients and Methods:** The regimen consisted of intravenous oxaliplatin 130 to 100 mg/m^2 on day 1, oral Cap 750 to 1000 mg/m^2 twice daily on days 1 to 14, and Bev 7.5 mg/kg on day 1, every 3 weeks. After 4 cycles of CAPOX-Bev, the patients without evidence of disease progression received maintenance treatment with Cap 1000 to 1250 mg/m^2 twice daily on days 1 to 14 and Bev 7.5 mg/kg on day 1, every 3 weeks, until disease progression or unacceptable toxicity. The primary endpoint was the 9-month disease control rate. Progression-free survival (PFS), overall survival (OS), and safety were the secondary endpoints. **Results:** Overall, 36 patients were enrolled from March 2012 to April 2017 at our institution. After completion of CAPOX/Bev, 15 patients (41.7%) had a partial response, 18 (50.0%) had stable disease, and 3 (8.3%) had progressive disease. Thirty-three patients (91.7%) received the Cap/Bev regimen as maintenance treatment for a median of 8.6 cycles (range, 3-14 cycles). The 9-month DCR was 58.3% (95% confidence interval [CI], 40.8-74.5), the median PFS was 8.8 months (95% CI, 6.7-10.3 months), and the median OS was 20.8 months (95% CI, 16.1-25.4 months). With the CAPOX/Bev regimen, the most common grade 3 toxicity included neutropenia (11.1%), diarrhea (5.5%), nausea/vomiting (2.8%), and fatigue (2.8%). Grade 3 neurotoxicity was not observed. With Cap/Bev maintenance therapy, grade 3 hand-foot syndrome was observed in 2 patients (6.0%). **Conclusion:** CAPOX/Bev, followed by Cap/Bev as maintenance treatment, is safe and effective in terms of PFS and OS for elderly patients aged > 75 years with mCRC.

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Introduction

Colorectal cancer (CRC) is the third most common malignancy and the fourth leading cause of cancer mortality worldwide.[1] More than one third of CRC diagnoses occur in patients aged ≥ 75 years.[2] Nevertheless, clinical trials designed to include the elderly population are still limited, as is the evidence supporting the treatment of advanced CRC for this specific population.[3]

Despite surgical resection currently representing the only chance of long-term cure, a variable proportion of patients develop recurrence or present at diagnosis with locally advanced or metastatic CRC (mCRC) and thus are candidates for systemic chemotherapy. Of the available chemotherapy agents, the fluoropyrimidines 5-fluorouracil (5-FU) and capecitabine (Cap) are the most active and conventionally administered drugs for mCRC.[4] In the past, large randomized trials demonstrated that oxaliplatin (L-OHP) combined with 5-FU (FOLFOX) or Cap (CAPOX) and the anti-angiogenic agent bevacizumab (Bev) significantly improved progression-free survival (PFS) and overall survival (OS) for patients with mCRC.[5,6] In most analyses, FOLFOX or CAPOX, plus Bev were administered for ≥ 12 or 8 cycles, respectively, or until progressive disease or unacceptable toxicity developed. Grade 3/4 hematologic and nonhematologic adverse events occur frequently. In particular, peripheral sensory neuropathy (PSN), a cumulative dose-limiting toxicity of L-OHP, often requires drug discontinuation before disease progression.[5-7] Alternative treatment strategies, such as "stop and go" or intermittent chemotherapy, have been evaluated to minimize the severity of adverse events.[8,9] A phase II study led by our research group showed promising results in terms of PFS and a very low incidence of grade 3 PSN for mCRC patients treated with FOLFOX stop and go and Cap as maintenance chemotherapy.[10] In addition, the activity of FOLFOX or CAPOX, plus Bev, followed by leucovorin/5-FU or CAP with Bev as maintenance treatment was reported in other recent studies.[11,12] However, in most trials, the population included was aged < 75 years and had a good performance status (PS), on average; hence, data suggesting the most effective chemotherapy regimen for elderly and vulnerable patients are limited. Older adults with mCRC often have comorbidities that complicate the administration of aggressive treatments; thus monochemotherapy or best supportive care alone are often recommended for patients aged > 75 years. However, elderly patients with a good PS and considered fit using a comprehensive geriatric assessment might benefit from the administration of a multidrug treatment regimen.[13]

The present study evaluated the clinical efficacy and tolerability of induction chemotherapy with CAPOX/Bev followed by Cap/Bev as maintenance treatment in nonfrail patients aged > 75 years.

Patients and Methods

Eligibility Criteria

For the present prospective observational study, patients aged > 75 years with histologically proven and radiologically measurable mCRC were enrolled at our institution. No previous chemotherapy for advanced disease was allowed. Adjuvant chemotherapy, if administered, had to have been completed ≥ 6 months before study entry. The other eligibility criteria included Eastern Cooperative Oncology Group PS of 0 to 2, a life expectancy of ≥ 3 months, adequate hematologic parameters (absolute neutrophil count, ≥ 1.5 × 10^9/L; platelet count, ≥ 100 × 10^9/L), creatinine < 1.5 times the upper limit of the normal range, total bilirubin < 3 times the upper normal limit, aspartate and alanine aminotransferase < 3 times the upper normal limit, and the absence of a second primary tumor other than nonmelanoma skin cancer or in situ cervical carcinoma. The exclusion criteria were histologic evidence of predominantly squamous cell cancer, a history of gross hemoptysis (≥ 2.5 mL), brain metastases or previous treatment of brain metastasis, uncontrolled pleural or pericardial effusion or ascites, pregnancy or lactation, a history of documented hemorrhagic diathesis or coagulopathy, therapeutic anticoagulation, the regular use of aspirin (> 325 mg/d), nonsteroidal anti-inflammatory agents known to inhibit platelet function, radiation therapy within 21 days before enrollment or major surgery within 28 days before enrollment, clinically significant cardiovascular disease, and medically uncontrolled hypertension.

Using a baseline geriatric assessment that included evaluation of activities of daily living, instrumental activities of daily living, and the Charlson score for comorbidities,[14] the patients were classified as fit, vulnerable, or frail. Specifically, subjects with activities of daily living limitations and > 2 comorbidities were classified as frail and were excluded from the present study.[15] All the included patients provided their written informed consent.

Patient Evaluation

Patients were seen at the start of every chemotherapy cycle for a physical examination, monitoring of symptoms and toxic effects, assessment of renal function, and a complete blood count. mCRC was reassessed after completion of 4 cycles of CAPOX/Bev and thereafter at 3-month intervals until evidence of disease progression (PD). The objective tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors, version 1.1.

Treatment Delivery

Induction chemotherapy consisted of 4 cycles of intravenous L-OHP 100 to 130 mg/m^2 on day 1 plus oral Cap 750 to 1000 mg/m^2 twice daily on days 1 to 14 and intravenous Bev 7.5 mg/kg on day 1 every 3 weeks. Given the advanced age of our study population, L-OHP and Cap were administered at a full-dose solely to fit patients aged ≤ 80 years and at a reduced dose (100 mg/m^2 for L-OHP and 750 mg/m^2 twice daily for Cap) to vulnerable patients and subjects aged > 80 years to minimize the occurrence of L-OHP– and Cap-related adverse events. Maintenance treatment consisted of Cap 1250 mg/m^2 twice daily on days 1 to 14 (1000 mg/m^2 twice daily for vulnerable patients) and Bev at a dose of 7.5 mg/kg.

Toxicity

Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.02. Treatment was delayed if, on the planned day of treatment, the neutrophil count was < 1500/mm^3, the platelet count was < 100,000/mm^3, or the patient had persistent diarrhea or stomatitis of grade > 1. Any patient who required > 2 weeks for recovery from adverse reactions was excluded from the present study. In the event of grade 4 hematologic or any other severe

(grade ≥ 3) organ toxicity, the chemotherapeutic drug doses were reduced by 25% for subsequent courses.

Statistical Analysis

The primary endpoint was the 9-month disease control rate (DCR), defined as the percentage of patients with stable disease (SD) or partial (PR) or complete response within 9 months after the start of induction treatment. Fluoropyrimidines can be considered reference drugs for elderly patients with advanced CRC, and most studies investigating these agents as monochemotherapy have suggested that ~20% of patients will still be progression free at 9 months after treatment onset.[4] The hypothesis for the present study was that using CAPOX/Bev as induction chemotherapy and Cap/Bev as maintenance treatment ≥ 40% of patients would be progression free 9 months after the start of chemotherapy. We calculated that a total of 33 patients should be recruited to yield an 80% probability to correctly select the treatment when it was superior by an absolute difference of 20% in the 9-month DCR (Simon's minimax design).[16]

The secondary endpoints included safety, PFS (calculated as the time from the first chemotherapy infusion to PD, death from any cause, or censored at the last follow-up visit, whichever came first), OS (measured from the date of treatment start to the date of death or the last follow-up visit), and the objective response rate (the proportion of patients achieving a PR or complete response). The Kaplan-Meier method was used to evaluate the distributions of PFS and OS, including the median time-to-event and 95% confidence intervals (CI). Statistical analyses were conducted using STATAiC software.

Results

Patient Characteristics

From March 2012 to April 2017, 36 patients with newly diagnosed mCRC who were aged > 75 years were enrolled in the present study. The baseline demographic and clinical characteristics of patients are presented in Table 1. Their median age was 79 years (range, 76-87 years), and more than one third (13 of 36; 36.1%) of the patients were aged > 80 years. The vast majority of patients (33 of 36; 91.7%) had an Eastern Cooperative Oncology Group PS of 0 or 1 and approximately two thirds (24 of 36; 66.7%) of the patients were classified as fit. Twenty-eight patients (77.7%) had undergone previous surgery with curative intent and were offered our treatment protocol after documentation of unresectable locally advanced or metastatic disease. Sixteen patients (44.4%) had previously received adjuvant chemotherapy. Twenty-six patients (72.2%) had liver metastases. At baseline, all the patients had ≥ 1 comorbidity, and most (23 of 36; 63.9%) had > 1 (Table 2). The most frequent concomitant illnesses were cardiovascular disease (16 of 36; 44.4%).

Table 1 Patient Characteristics (n = 36)

Characteristic	n (%)
Age, y	
Median	79
Range	76-87
Patients aged > 80 y	13 (36.1)
Gender	
Male	22 (61.1)
Female	14 (38.9)
ECOG PS	
0	14 (38.9)
1	19 (52.8)
2	3 (8.3)
Geriatric assessment	
Fit	24 (66.7)
Vulnerable	12 (33.3)
Charlson comorbidity index	
Median	1
Range	0-2
Primary tumor	
Colon	27 (75.0)
Right	7 (19.4)
Left	20 (55.5)
Rectum	9 (25.0)
Primary tumor resection	
Colon	21 (58.3)
Rectum	7 (19.4)
KRAS status	
Mutated	23 (63.9)
Wild type	13 (36.1)
Metastatic sites	
Liver	26 (72.2)
Lymph nodes	10 (27.8)
Peritoneum	7 (19.4)
Lung	9 (25.0)
Other	3 (8.3)
> 1 Metastasis	14 (38.9)
Primary adjuvant chemotherapy	
No	20 (55.5)
Yes	16 (44.4)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance status.

Efficacy

All 36 enrolled patients completed 4 cycles of induction chemotherapy and were evaluable for response and toxicity. The starting L-OHP dose was 130 mg/m^2 for 17 fit patients aged ≤ 80 years and 100 mg/m^2 for 12 vulnerable patients and 7 fit patients aged ≥ 80 years. Of the 36 patients, 15 (41.7%) had a PR and 18 (50.0%) had SD as the best response to therapy after initial CAPOX/Bev (Table 3). The 33 patients (91.7%) with a PR or SD after induction chemotherapy with CAPOX/Bev received maintenance chemotherapy with Cap and Bev for a median of 8.6 cycles (range, 3-14 cycles). The objective response rate for Cap/Bev maintenance treatment was 15%. Twenty-seven patients discontinued maintenance chemotherapy because of PD. For 7 of these patients, who were fit and aged ≤ 80 years, L-OHP was reintroduced. One patient was lost to follow-up 10 months after the onset of induction chemotherapy. One patient was continuing maintenance treatment at the last follow-up visit. The 9-month DCR was 58.3% (95% CI, 40.8%-74.5%), and median PFS was 8.8 months (95% CI, 6.7-10.3 months). Finally, 21 patients (58.3%)

Table 2 Patient Comorbidities

Comorbidities	Patients, n (%)
Cardiovascular	16 (44.4)
Hypertension	12 (33.3)
Coronary artery disease	5 (13.9)
Arrhythmia	4 (11.1)
Diabetes mellitus	5 (13.9)
Dyslipidemia	5 (13.9)
Respiratory	8 (22.2)
Genitourinary	4 (11.1)
> 1 Comorbidity	23 (63.9)

received irinotecan-based chemotherapy as second-line treatment, and 9 patients (25%) received regorafenib as third-line therapy.

At a median follow-up period of 31.5 months (range, 7.3-41.9 months), 28 patients had died, and the median OS was 20.8 months (95% CI, 16.1-26.4 months). The PFS and OS for the 36 enrolled patients are illustrated in Figure 1.

Treatment Toxicity

The toxicity occurring during the CAPOX/Bev induction regimen is summarized in Table 4. Grade 3 adverse events included neutropenia (11.1%), diarrhea (5.5%), nausea/vomiting (2.8%), and fatigue (2.8%). Four patients (11.1%) required ≥ 1 L-OHP and Cap dose reductions because of toxicity, and 13 cycles (9.0%) were delayed for ≥ 1 week.

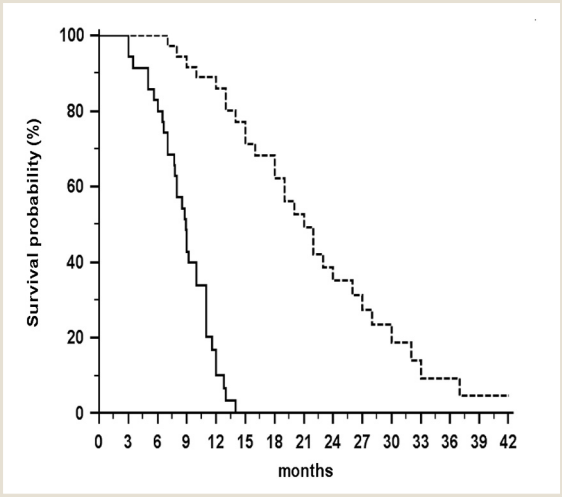
Toxicity during maintenance treatment was mild. Two patients (6.0%) experienced grade 3 hand-foot syndrome, one (3.0%) developed grade 3 diarrhea, one (3.0%) had grade 3 hypertension, and one (3.0%) developed grade 3 venous thrombosis (Table 5). No patient experienced grade 3 proteinuria or epistaxis. A dose reduction of Cap was required for 4 patients. Bev administration was definitively interrupted for 1 patient aged 83 years 3 months after the onset of maintenance treatment because of the occurrence of cognitive impairment. The neurologic symptoms, after neurologic examination and encephalic magnetic resonance imaging, was attributed to prolonged exposure to Bev, and the patient completely recovered ~6 weeks after Bev discontinuation.

Table 3 Results

Variable	n (%)
Objective response	
Complete response	0 (0)
Partial response	15 (41.6)
Stable disease	18 (50.0)
Progressive disease	3 (8.3)
9-mo DCR, % (95% CI)	58.3 (40.8-74.5)
PFS, mo (95% CI)	8.8 (6.7-10.3)
OS, mo (95% CI)	20.8 (16.1-25.4)

Abbreviations: CI = confidence interval; DCR = disease control rate; OS = overall survival; PFS = progression-free survival.

Figure 1 Progression-Free Survival (Solid Line) and Overall Survival (Dashed Line) for 36 Enrolled Patients



Discussion

Although favorable results have been reported previously for the addition of Bev to standard first-line chemotherapy for mCRC patients, increased toxicity has also been observed in association with this combination; thus, particular caution should be exercised when using it for the treatment of elderly patients.[17] A reasonable approach for nonfrail patients aged > 75 years with mCRC seems to be an initial short-term combination chemotherapy regimen, followed by a fluoropyrimidine associated with a biologic agent as maintenance therapy.[18,19] To the best of our knowledge, the

Table 4 Adverse Events With CAPEOX/Bev

Adverse Event	Grade, n (%)	
	2	3
Hematologic		
Neutropenia	5 (15.1)	4 (11.1)
Anemia	4 (11.1)	1 (2.8)
Thrombocytopenia	5 (15.1)	0 (0)
Nonhematologic		
Nausea	3 (8.3)	1 (2.8)
Vomiting	1 (2.8)	0 (0)
Fatigue	8 (22.2)	1 (2.8)
Stomatitis	3 (8.3)	0 (0)
Sensory neuropathy	9 (25.0)	0 (0)
Diarrhea	7 (19.4)	2 (5.5)
Constipation	8 (22.2)	1 (2.8)
Hypertension	6 (16.7)	0 (0)
Proteinuria	1 (2.8)	0 (0)
Epistaxis	0 (0)	0 (0)
Cognitive	0 (0)	0 (0)

No grade 4 events developed in any of the 36 patients.
Abbreviations: Bev = bevacizumab; CAPEOX = capecitabine, oxaliplatin.

Table 5 Adverse Events With Cap/Bev Maintenance Treatment

Adverse Event	Grade, n (%)	
	2	3
Cap-associated		
Neutropenia	2 (6.0)	0 (0)
Anemia	2 (6.0)	0 (0)
Thrombocytopenia	1 (3.0)	0 (0)
Nausea/vomiting	1 (3.0)	0 (0)
Abdominal pain	3 (9.0)	0 (0)
Diarrhea	3 (9.0)	1 (3.0)
Hand-foot syndrome	3 (9.0)	2 (6.0)
Bev-associated		
Hypertension	3 (9.0)	1 (3.0)
Proteinuria	2 (6.0)	0 (0)
Epistaxis	2 (6.0)	0 (0)
Cognitive	1 (6.0)	0 (0)
Venous thrombosis	2 (6.0)	1 (3.0)

Abbreviations: Bev = bevacizumab; Cap = capecitabine.

present study is the first to suggest that CapOX/Bev for 4 cycles, followed by Cap/Bev as maintenance treatment, is feasible and active for mCRC patients aged > 75 years. Albeit with the limitations of a small study, the 58.3% 9-month DCR, 8.8-month PFS, and 20.8-month median OS compare well with the results commonly reported with the most active combination chemotherapy regimens in younger populations.[5,6] The results of the present study are also in line with the best results previously observed in patients aged > 65 years with mCRC receiving CAPOX/Bev or FOLFOX/Bev.[20,21] A recent study demonstrated a 74.4% DCR, 7.9-month PFS, and 20.1-month OS for elderly patients with mCRC receiving Bev combined with modified CAPOX for a maximum of 12 cycles.[22] However, most of those patients were aged < 75 years, but all our patients were aged ≥ 75 years. Thus, although the median OS of 20.8 months in the present study might seem lower than expected, especially with the use of the newer agents available for patients with mCRC, 36.1% of our enrolled patients were aged > 80 years (5 were aged > 85 years), and 38.9% of our patients had > 1 metastatic site, including 19.4% of the patients with peritoneum involvement. In addition, the DCR was only 38% with irinotecan-based chemotherapy as second-line treatment, and only 4 of 13 patients with wild-type tumors could receive anti-EGFR agents (7 had a primary right tumor). Finally, regorafenib, which could be administered as third-line therapy for only 9 patients owing to a poor PS, resulted in a median PFS of 4.3 months.

In addition, the findings of our analysis are similar to those reported in recent studies that highlighted the role of oral fluoropyrimidines combined with Bev as maintenance therapy after initial induction combination chemotherapy.[23,24] In particular, the large randomized trial CAIRO 3 (Maintenance Treatment Versus Observation After Induction in Advanced Colorectal Carcinoma) reported a greater median PFS than that observed in the present study (11.7 vs. 8.8 months, respectively) and similar median OS (21.6 vs. 20.8 months, respectively) for the CAP/Bev maintenance group after 6 cycles of initial CAPOX/Bev. Although the CAIRO 3 trial included patients aged ≤ 81 years, the median age of the 279 subjects enrolled in the maintenance group was only 63 years.[23] Furthermore, a recent randomized phase III study reported an OR of 66.7, a PFS of 8.3 months, and an OS of 23.8 months for mCRC patients treated with CAPOX plus Bev for 6 cycles, followed by Cap/Bev as maintenance treatment. The median age of that study population was 56 years and in our study, was 79 years.[25] Compared with the present analysis, better results have been recently reported for a group of 52 Japanese patients with mCRC treated with a stop and go strategy of CAPOX and Bev for 6 cycles, followed by Cap/Bev as maintenance (OR, 55.8; PFS, 12.4 months; OS, 30.6 months). However, only a few patients were aged > 75 years, and the median age was 66 years. Moreover, grade 3 PSN was observed in 2 patients (3.8%), probably resulting from the planned reintroduction of L-OHP.[26]

Although favorable results with the combination of Bev and Cap as maintenance therapy have also been reported previously,[23,24] to the best of our knowledge, our analysis is the first to enroll patients aged > 75 years. Furthermore, other maintenance approaches have been previously tested in mCRC. Bev alone used as maintenance treatment after induction chemotherapy did not improve survival compared with no treatment (observation; median OS, 21.7 vs. 22.0 months) in a recent randomized phase III trial.[27] In contrast, single-agent capecitabine might be considered an appropriate maintenance treatment option after XELOX or FOLFOX induction regimens for mCRC patients with acceptable toxicities.[18] Capecitabine alone as maintenance treatment resulted in longer median OS in a group of 136 patients (25.6 months) compared with that for the observation-only group (23.3 months). However, the result was not statistically significant ($P = .2247$). Furthermore, the median age of the Cap-treated cohort (56 years) was much lower than that of our study population (79 years).[18]

Despite the advanced median age and potential frailty of our study population, the treatment was well tolerated and no unexpected toxic effects developed in the present study. The starting dose of L-OHP and Cap was for many patients lower than the conventional starting dose of 130 mg/m^2 and 2000 mg/m^2, respectively. However, such dose reductions were determined owing to the high rates of patients classified as vulnerable (33.3%) or presenting with > 1 concomitant comorbidities (63.9%) in our analysis. Possibly also for this reason, grade 3 neutropenia occurred in only 11.1% of patients, and the severity of nausea and vomiting was mild during initial CAPOX/Bev. In contrast, PSN, which is related to the cumulative L-OHP dose, developed in several patients in the present study (grade 2 in 25%) but never reached grade 3. This safety profile is similar to, or even better than, that usually reported with conventional CAPOX or FOLFOX-4 combined with Bev for younger patients and could be partly attributed to the shorter exposure to L-OHP, the accurate selection of nonfrail patients, and the starting dose reductions of L-OHP and Cap. Thus, although no consensus has yet been reached regarding the definition of frailty status, we deemed that patient age < 85 years, the ability to perform activities of daily living, < 3 concomitant comorbidities, and no cognitive impairment were the factors that can best determine a nonfrail patient. A reasonable approach that could be applied

by practicing clinicians could be the use at baseline of a screening tool such as the G8 questionnaire, which allows for a quick distinction between fit and nonfit patients. Nonfit subjects could be further evaluated using a comprehensive geriatric assessment, which can discriminate vulnerable and frail patients.[28,29]

The toxicities associated with Cap/Bev during maintenance treatment were consistent with the known adverse events associated with these drugs, especially for long-term use, and were grade 1 to 2 in most cases. However, a good safety profile is often the main advantage of a treatment strategy that includes maintenance treatment after induction chemotherapy before PD. The proportion of grade 3 Cap/Bev-related adverse events in the present study was lower than that reported in the AVEX clinical trial [a study of bevacizumab (Avastin) in combination with capecitabine (Xeloda) in elderly patients with metastatic colorectal cancer], which evaluated Cap/Bev versus Cap alone for patients aged > 70 years with mCRC (hand-foot syndrome, 6% vs. 16%; diarrhea, 3% vs. 7%; venous thromboembolic events, 3% vs. 8%, respectively).[30] This difference might have simply resulted from the small size of the present study and/or better selection of the enrolled patients (in the AVEX trial, patients were not considered fit for combination chemotherapy). Finally, Bev was interrupted in 1 patient aged > 80 years owing to the development of cognitive impairment. Although the findings from the present study and other reports suggest that appropriately selected older patients can tolerate well the addition of Bev to chemotherapy, caution should be observed for patients aged > 80 years, who are commonly at risk of developing cognitive decline, with consequent deterioration of their quality of life.[31]

The potential shortcomings of our study included the single-arm design, relatively small sample size, and long study duration of 5 years. The latter was chiefly the consequence of the single-institution experience that included only very elderly patients, which clearly delayed recruitment. Although clinical trials are warranted to confirm our results in a larger population, our data could aid treatment decision making for nonfrail patients aged > 75 years with mCRC.

Conclusion

The results of the present study suggest that CAPOX/Bev, followed by Cap/Bev as maintenance treatment, is safe and active as first-line treatment for nonfrail mCRC patients aged > 75 years and can achieve encouraging results in PFS and OS.

Clinical Practice Points

- In the past, several studies showed the efficacy of FOLFOX or CAPOX, plus Bev, induction chemotherapy, followed by 5-fluorouracil/leucovorin or Cap/Bev as maintenance treatment, for patients with mCRC.
- However, most studies included patients aged < 75 years with good PS.
- Therefore, data on the efficacy and safety of this regimen for elderly patients with mCRC are limited.
- Also, because patients aged > 75 years commonly present with comorbidities, monochemotherapy or best supportive care have typically been preferred.
- In the present prospective observational study, we reported the efficacy and tolerability of CAPOX/Bev as induction treatment, followed by Cap/Bev as maintenance therapy, for 36 patients with newly diagnosed mCRC aged > 75 years and screened as nonfrail.
- On completion of the CAPOX/Bev regimen, more than one third of the patients had a PR, one half had SD, and only few had developed disease progression.
- Nearly all patients received the Cap/Bev regimen as maintenance treatment.
- The 9-month DCR, median PFS, and median OS compared well with those observed in several studies evaluating similar regimens for younger populations.
- During CAPOX/Bev regimen and Cap/Bev maintenance treatment, grade 3 adverse events were not common, in particular, grade 3 neurotoxicity was not observed.
- Therefore, CAPOX/Bev, followed by maintenance Cap/Bev, can be safely proposed as first-line treatment for nonfrail patients with mCRC aged > 75 years.

Disclosure

The authors declare that they have no competing interests.

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