Clinical Trial

Combination chemotherapy with bevacizumab and S-1 for elderly patients with metastatic colorectal cancer (BASIC trial)

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Abstract Background: Chemotherapeutic regimens for elderly patients with metastatic colorectal cancer (mCRC), such as bevacizumab combined with 5-fluorouracil (5-FU) and leucovorin, often exclude oxaliplatin and irinotecan owing to the risk of toxicity. However, treatment with infusional 5-fluorouracil and leucovorin requires percutaneous port-catheter placement and other precautions, causing unnecessary stress for patients as well as healthcare workers.

Methods: We conducted a phase II study to evaluate the efficacy and safety of bevacizumab plus S-1 in elderly patients with previously untreated mCRC. Bevacizumab was given intravenously every two weeks, and S-1 was administered orally on days 1–28 of a 42-day cycle. The primary end-point was progression-free survival (PFS). The secondary end-points were time to treatment failure, response rate (RR), overall survival (OS), treatment completion status and safety.

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1. Introduction

The recent introduction of molecularly targeted chemotherapeutic agents has improved the outcomes of patients with advanced and recurrent colorectal cancer. Recent phase III clinical trials have reported a median survival time of longer than 2 years [1,2]. Combination regimens such as FOLFOX or FOLFIRI are similarly effective in younger patients, but tend to be associated with higher incidences of bone-marrow toxicity in elderly patients with advanced or recurrent colorectal cancer [3–8], requiring that these treatments are used with caution in older patients.

Combination therapy with 5-fluorouracil (5-FU) and bevacizumab has been demonstrated to be safe and effective. In the AVF0780 g trial, a randomised phase II study comparing 5-FU plus leucovorin (5-FU/LV) with 5-FU/LV plus bevacizumab [9,10], the progression-free survival (PFS) was 9.0–9.2 months in the 5-FU/LV plus bevacizumab group despite the absence of oxaliplatin, compared with 5.2–5.5 months in the 5-FU/LV group. While no study has directly compared FOLFOX plus bevacizumab with 5-FU/LV plus bevacizumab, the results of previous clinical trials [3,9,10] indicate that the median PFS is similar with these regimens, and that 5-FU/LV plus bevacizumab is better tolerated, with a lower incidence of adverse events. These clinical results suggest that it may be unnecessary to use oxaliplatin or irinotecan in combination with 5-FU as first-line treatment and that sequential chemotherapy based on 5-FU is useful.

In the phase III AVEX trial in elderly patients, bevacizumab and capecitabine were shown to be superior to capecitabine alone with PFS as the primary end-point. The main toxic effect of capecitabine is known to be frequent hand-foot syndrome [11].

S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) is an anticancer preparation that is widely used in Japan to treat advanced gastric, colon, pancreatic and lung cancer. S-1 combines the 5-FU prodrug tegafur (FT) with 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate [12]. Phase II studies of S-1 reported a response rate (RR) of 40%, a median PFS of 5.4 months and high safety in Japanese patients with unresectable or recurrent colorectal cancer [13,14].

The SOFT study showed S-1 and oxaliplatin plus bevacizumab, in terms of PFS, as first-line treatment for metastatic colorectal cancer (mCRC) [15]. To confirm and extend these results, we conducted a phase II study of S-1 plus bevacizumab in elderly patients with metastatic colorectal cancer.

2. Patients and methods

2.1. Patients

Patients with histologically confirmed colorectal cancer and measurable metastatic disease were eligible for enrolment in this study. Patients who had previously received chemotherapy, radiotherapy, or both for metastatic disease were excluded. Patients who had received oral adjuvant fluorouracil-based chemotherapy with drugs other than S-1 were eligible, provided that they had remained disease-free for at least 6 months after the completion of such therapy.

Other eligibility criteria were as follows: age ≥ 65 years; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2; treatment with FOLFIRI or FOLFOX was not indicated; ability to tolerate oral drug administration; electrocardiographic results within normal limits; adequate baseline bone-marrow function (white cell count, >3500/mL to <12,000/mL; neutrophil count, >1500/mL; haemoglobin concentration, >9.0 g/dL; and platelet count, >100,000/mL); adequate hepatic function (serum total bilirubin level, <1.5 mg/dL; serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels, <100 U/L); adequate renal function (serum creatinine, <1.2 mg/dL; creatinine clearance estimated by the Cockcroft–Gault equation, >50 mL/min); a life expectancy of at least 90 days; and written informed consent from the patient.

The main exclusion criteria were as follows: surgical procedures or open biopsy performed <28 days before study entry; current use of anticoagulant or thrombolytic therapy; severe drug allergy; treatment with aspirin (>325 mg/day) or non-steroidal anti-inflammatory drugs, except as required for cancer pain; treatment with steroids; the concurrent presence of another cancer, infection, serious pleural effusion or ascites.

The study was approved by the institutional review board of each participating centre and was registered in the Clinical Trials Government Registry (NCT00569699).
2.2. Treatment

Bevacizumab (5 mg/kg) was administered as a 90-, 60- or 30-min intravenous infusion every 2 weeks. The infusion time was chosen based on whether the patient showed any infusion-site reaction. S-1 was available in capsule and granule preparations containing 20 or 25 mg of tegafur, respectively. Patients received S-1 orally twice daily (after breakfast and dinner) from the evening of day 1 to the morning of day 29, followed by a 14-day rest. The dose of S-1 was based on body surface area (40 mg for <1.25 m²; 50 mg for 1.25–1.50 m²; or 60 mg for >1.50 m²). This 6-week cycle was repeated until onset of disease progression or a severe adverse event. No patient received premedication with a 5-hydroxytryptamine-3-receptor antagonist. All treatments were routinely given on an outpatient basis.

In patients with laboratory abnormalities, subsequent treatment was withheld until the neutrophil and platelet counts were >1500/mL and >75,000/mL, respectively; the AST or ALT was <100 IU/L; the total bilirubin level was <2.0 mg/dL; the serum creatinine level was <1.2 mg/dL; and any diarrhoea, stomatitis or hand-foot syndrome (HFS) had resolved to grade 0 or 1. The dose of S-1 was reduced by one step if the neutrophil count was less than 500/mL, the platelet count was less than 50,000/mL, the AST was 200 IU/L or higher, the ALT was 200 IU/L or higher or the serum creatinine level was 1.5 mg/dL or higher. In the event of grade 3 or higher non-haematological toxicity (excluding constipation, anorexia, fatigue and nausea), the dose of S-1 was reduced by one step. The protocol treatment was repeated until the onset of disease progression or a severe adverse event. Treatment with bevacizumab was withdrawn if patients developed bevacizumab-induced uncontrolled hypertension, proteinuria, bleeding, thrombosis, gastrointestinal perforation or hypersensitivity of grade 3 or higher.

2.3. Toxicity and response evaluation

Before enrolment, all patients underwent a physical examination, complete blood cell count (CBC) with differential counts, serum chemical analysis, electrocardiography, and computed tomography scanning or magnetic resonance imaging, including documentation of measurable disease. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0) [16].

During the study, all patients were evaluated weekly for signs and symptoms of toxicity. CBC and differential counts, liver function tests, measurements of blood urea nitrogen, creatinine, and electrolyte levels, and urinalysis were performed weekly. All toxic effects were evaluated weekly during the first cycle, and then every 2 weeks from the second cycle onward. Any serious adverse events or deaths were reported by the investigators, and the factors responsible were analysed. CT or MRI scans were performed every 8 weeks to evaluate lesions. Responses were evaluated according to the RECIST criteria, version 1.0 [17]. Treatment response and safety were assessed by the trial committee.

2.4. Statistical methods

The primary end-point was PFS. The secondary endpoints were safety, RR, overall survival (OS), relative dose intensity (RDI) and time to treatment failure (TTF). We calculated the required sample size for this study on the basis of a target PFS of 8.5 months and a minimum PFS of 5 months, with a one-sided α error of 0.05 and a β error of 0.2, and estimated that we needed to enrol 50 patients. Therefore, the required sample size for analysis, to compensate for mid-trial exclusions or ineligibility, was 55. OS was calculated as of September 2012. TTF, PFS and OS were analysed by the Kaplan–Meier method. RDI was calculated for each drug on the basis of four treatment cycles.

The association of PS (0 versus 1), alkaline phosphatase activity (ALP) (<300 versus ≥300) and the number of organs involved (1 versus ≥2) with PFS and OS were evaluated by univariate and multivariate analyses using a proportional hazards model as described by Köhne et al. [18].

3. Results

3.1. Patient characteristics

Between October 2008 and March 2010, we enrolled 56 patients with advanced colorectal carcinoma at eight hospitals in Japan. This study was approved by the institutional review board of each hospital. All patients gave written informed consent. The clinical characteristics of the eligible patients are shown in Table 1. The median age was 75 years (range, 66–85). The ECOG PS was 0 in 28 patients and 1 in 28 patients.

The median follow-up time was 34.6 months (range, 1.1–54.0 months). 56 patients received a total of 329 treatment courses (median, 5; range, 1–17). Thirty-five patients (63%) received second-line chemotherapy based on oxaliplatin (20 patients, 36%), irinotecan (10 patients, 18%), or combination therapy including bevacizumab (13 patients, 23%). After second-line therapy, nine patients (16%) received anti-epidermal growth factor receptor antibodies. Three patients received surgery for metastases after the completion of the study treatment.

3.2. Efficacy

Median PFS, the primary end-point of the study, was 9.9 months (95% confidence interval [CI], 7.9–
11.1 months) (Fig. 1). Results for the secondary endpoints were as follows: the median OS was 25.0 months (range, 19.4–31.6 months) (Fig. 2) and the median TTF was 7.5 months (95% CI, 5.9–9.1 months).

The response rate was 57% (95% CI, 43.2–70.3), with a disease control rate (DCR) of 96%. The confirmed response rate was 43%, with an associated confirmed DCR of 89%. The response was evaluated according to the protocol in all patients, but the confirmed response could not be evaluated in four patients (two who refused to continue treatment and two who discontinued treatment because of grade 1 or 2 gastrointestinal toxicity after evaluation of the initial response).

All 56 patients had at least one measurable lesion. The responses to treatment are shown in Table 2. One patient had a complete response (CR), 31 had an unconfirmed partial response and 22 had stable disease. The CR was achieved after 14 cycles of the protocol treatment in a patient with liver metastasis.

### 3.3. Toxicity

Toxicity was classified according to the worst grade per patient across the 329 courses of treatment (Table 3). The most common toxic effects were neutropenia, hypertension and diarrhoea, which were generally mild. With the exception of hypertension, the incidence of grade 3 or 4 toxicity was less than 10%.

One patient had thalamic haemorrhage (not shown in the table). There was no treatment-related death. The treatment protocol was discontinued owing to toxicity in 18 of the 56 patients.

### 3.4. Dose intensity

The median number of treatment cycles was five (range, 1–17). The mean RDI for both S-1 and bevacizumab was 80% (range, 8.9–100% and 33.3–100%, respectively).
3.5. Survival according to Köhne’s index

Fig. 3 shows the Kaplan–Meier curves of OS and median OS according to risk group as defined by Köhne’s index [18], based on PS (0 versus 1), ALP (<300 versus ≥300) and the number of organs involved (1 versus ≥2), which have been reported to be predictors of the response to fluoropyrimidine therapy. PS was 0 in 28 patients and one in 28. ALP was <300 in 32 patients and ≥300 in 24. The number of organs involved was one in 23 patients and ≥2 in 33. Our results showed that median OS according to Köhne’s index was longer in the low-risk group (35.3 months [95% CI: 22.3–not reached]) than in the high-risk group (14.4 months [95% CI: 7.5–25.0], hazard ratio 4.21 [95% CI: 1.83–9.91], P < 0.001; Fig. 3). Second-line chemotherapy was given to 12 (86%) of the 14 patients in the high-risk group, 10 (53%) of the 19 patients in the intermediate-risk group and 13 (57%) of the 23 patients in the low-risk group.

### Table 2

<table>
<thead>
<tr>
<th>Response rates.</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
<th>RR (%)</th>
<th>DCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconfirmed</td>
<td>1 (2)</td>
<td>31 (55)</td>
<td>22 (39)</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>57</td>
<td>96</td>
</tr>
<tr>
<td>Confirmed</td>
<td>1 (2)</td>
<td>23 (41)</td>
<td>26 (46)</td>
<td>2 (4)</td>
<td>4 (7)</td>
<td>43</td>
<td>89</td>
</tr>
</tbody>
</table>

*Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; RR, response rate; DCR, disease control rate.

* Not prespecified in the study protocol because the primary end-point in this study was progression-free survival.

### Table 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Grade</th>
<th>Any grade (%)</th>
<th>Grade ≥ 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Anaemia</td>
<td>14</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>24</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>29</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>18</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>20</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>24</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>12</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>8</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

4. Discussion

We conducted a phase II study to evaluate the efficacy and safety of combination chemotherapy with bevacizumab plus S-1 in elderly patients with untreated unresectable or recurrent colorectal cancer. Toxicity was tolerable, and efficacy outcomes in terms of RR and PFS were comparable to those reported for combination chemotherapy with 5-FU or capecitabine in combination with bevacizumab in a phase 3 trial [10,11].

This phase II trial may be considered as further confirmation that the S-1 compound can replace 5-FU or capecitabine in combination with bevacizumab, with or
without other drug combinations. Although as yet there has been no phase III trial of S-1 plus bevacizumab alone, the above conclusion is supported by the results of three randomised phase III trials in Asia, comparing S-1 plus oxaliplatin with capecitabine plus oxaliplatin [19], FOLFIRI with S-1 plus irinotecan [20], and FOLFOX plus bevacizumab with S-1/oxaliplatin plus bevacizumab [15]. All these trials demonstrate the non-inferiority of S-1 combination therapy compared with drug combinations containing 5-FU or capecitabine, suggesting that S-1 can replace 5-FU or capecitabine, at least in Asia.

The therapeutic usefulness of sequential chemotherapy with molecularly targeted drugs has yet to be validated in well-designed clinical trials. However, the FOCUS [21], CAIRO [22], and FFCD2000-05 [23] studies showed that OS does not differ significantly between sequential chemotherapy (with fluoropyrimidines alone as first-line therapy and oxaliplatin or irinotecan as second-line therapy) and combination chemotherapy (with fluoropyrimidines and oxaliplatin or irinotecan as first-line therapy), suggesting the non-inferiority of sequential chemotherapy.

5-FU monotherapy may be particularly useful in elderly or frail patients because of its low toxicity. Many patients with colorectal cancer are elderly (aged >65 years) and thus tend to have greater morbidity and a higher risk of adverse reactions [24]. Poor tolerability and severe adverse reactions may therefore preclude aggressive chemotherapy. Our study group is likely to have many subjects with reduced tolerance to chemotherapy because the protocol required that patients were 65 years or older. The proportion of the elderly patients enrolled in our study who were frail is unclear because detailed data on physical status were not collected. While the median OS obtained in the studies on S-1 plus bevacizumab therapy (AVF2192g trial) and capecitabine plus bevacizumab therapy (AVEX trial) was 16.6 and 20.7 months, respectively, our study achieved a considerably longer median OS of 25.0 months. However, while 8% and 9% of patients included in the AVF2192g and AVEX studies, respectively, had a PS ≥2, this particular group of patients was not included in our study [10,11]. It is therefore likely that this difference in patient background is a contributing factor in our favourable OS. The eligibility criteria required that treatment with FOLFOX and FOLFIRI was not indicated. However, our subjects included patients who did not want to receive intensive chemotherapy, as well as those who were ‘frail.’ Although treatment with FOLFOX and FOLFIRI was not indicated in our subjects, 30 patients subsequently received second-line chemotherapy with oxaliplatin- or irinotecan-based regimens after the protocol treatment. The reasons for using these second-line regimens are unfortunately not available for all patients. However, it is possible that some patients who refused FOLFOX or FOLFIRI as first-line therapy consented to second-line therapy with oxaliplatin- or irinotecan-based regimens because their physical and mental condition had improved. Since PS and other data were not collected at the initiation of second-line therapy, this can only be a supposition; however, such differences in patient status between the time of enrolment and the start of second-line therapy may have allowed patients to receive regimens including oxaliplatin or irinotecan.

Among patients’ demographic characteristics at enrolment, PS, WBC, ALP, and the number of organs involved, which are collectively known as Köhne’s index, have been reported to be predictors of the response to fluoropyrimidine therapy. Although none of our subjects had a PS of two or higher, our results are generally consistent with those reported by Köhne et al. regarding the prognostic factors for fluoropyrimidine therapy, suggesting that these factors may apply not only to 5-FU-based chemotherapy but also to other therapies. However, it should be noted that the correlation of OS with ALP and the number of organs involved might be a reflection of tumour burden rather than a direct effect of treatment.

The fact that 86% of high-risk patients received second-line chemotherapy suggests that such patients may require intensive chemotherapy. The results of a risk-stratified analysis based on the aforementioned prognostic factors suggested that the outcomes of combination therapy with fluoropyrimidines and bevacizumab agree with those of a previous study [18]. However, large prospective clinical studies and additional analyses may be necessary to verify this conclusion.

Combination chemotherapy with fluoropyrimidine and bevacizumab is currently positioned as one treatment option for elderly patients with metastatic or unresectable colorectal cancer, and new trials of this regimen are being performed by the North Central Cancer Treatment Group and Japanese Clinical Oncology Group [25]. Standard chemotherapy for elderly patients may change on the basis of the findings of these trials.

In conclusion, our results suggest that combination therapy with S-1 plus bevacizumab can be administered safely and continuously on an outpatient basis and may be therapeutically effective in elderly patients with advanced or recurrent colorectal cancer.

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Conflict of interest statement

Kazuhiro Yoshida is a member of Taiho advisory boards. All remaining authors have declared no conflicts of interest.
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References


[16] [Japanese translation of common terminology criteria for adverse events (CTCAE), and instructions and guidelines]. Int J Clin Oncol 2004;9(Suppl. 3):1–82.


