Multicentre Phase II Study of XELOX with Bevacizumab in Late-stage Elderly Patients with Unresectable Advanced/Recurrent Colorectal Cancer: An ASCA Study

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We are conducting an open-label multicentre phase II study to evaluate the efficacy and safety of the combination therapy of XELOX and bevacizumab in late-stage elderly patients with unresectable advanced/recurrent colorectal cancer. The primary endpoint of the study is progression-free survival. The secondary endpoints are the toxicity, overall response rate, time to treatment failure and overall survival. Thirty-five patients are required for the study.

Key words: XELOX – bevacizumab – late-stage elderly – advanced/recurrent colorectal cancer

INTRODUCTION

5-Fluorouracil (5-FU) in combination with leucovorin (LV) (5-FU/LV) has been the standard systemic regimen for the treatment of unresectable advanced/recurrent colorectal cancer in most countries (1–4). Recently, more effective chemotherapies that include oxaliplatin or irinotecan {e.g. FOLFOX [folic acid (FOL), 5-fluorouracil (F) and oxaliplatin (OX)], XELOX (capecitabine plus oxaliplatin) (5–13) or FOLFIRI [folic acid (FOL), 5-fluorouracil (F) and irinotecan (IRI)] therapy (12–15)} have shown superior survival benefit when compared with 5-FU/LV, and led to a steady improvement in the median overall survival of patients with unresectable advanced/recurrent colorectal cancer. Many randomized clinical trials have shown the advantages of combining bevacizumab with 5-FU/LV (16,17), IFL [irinotecan (I), bolus-5-fluorouracil (F) and leucovorin (L)] (18) or FOLFOX4/XELOX (19,20); combinations of chemotherapeutic agents and monoclonal antibodies are used as standard first-line treatment.

With the increase in average life expectancy, the incidences of colorectal cancer among elderly people are gradually increasing in Japan, and this is an important issue in the field of solid tumours. A meta-analysis by Cassidy et al. (21) showed that age groups and the add-on treatment had no effect on the overall survival rate after treatment with bevacizumab [hazard ratio = 0.80 (95% confidence interval, 0.74–0.87) for all populations and 0.85 (0.74–0.97) for ages over and equal to 65 years]. On the other hand, it is well known that neutropenia occurs more frequently after FOLFOX therapy than after XELOX in elderly individuals (19,20,22). Furthermore, since capecitabine can be orally administered, XELOX therapy can be considered to be more favourable for elderly patients. However, there is no evidence of the safety and efficacy of the combination of chemotherapeutic agents and bevacizumab in elderly patients aged 75 years or more (officially referred to as ‘late-stage elderly’ by the Japanese government) with colorectal cancer.
We are, therefore, conducting an open-label multicentre phase II study to evaluate the efficacy and safety of the combination therapy of XELOX and bevacizumab in late-stage elderly patients with unresectable advanced/recurrent colorectal cancer.

PROTOCOL DIGESTS OF THE STUDY

OBJECTIVE

The ASCA (Avastin plus XELOX Strategy for late-stage elderly patients with metastatic colorectal CAncer) study is an open-label multicentre phase II study to evaluate the efficacy and safety of the combination therapy of XELOX and bevacizumab in late-stage elderly patients with unresectable advanced/recurrent colorectal cancer.

ENDPOINTS

The primary endpoint is progression-free survival (PFS). The secondary endpoints are the toxicity, overall response rate, time-to-treatment failure and overall survival. The progression will be evaluated based on response evaluation criteria in solid tumours (RECIST) ver.1.1 (23).

ELIGIBILITY CRITERIA

Inclusion Criteria

(i) Written informed consent before initiation of study-related procedures.
(ii) Age more than or equal to 75 years at the time of providing informed consent.
(iii) An Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
(iv) A life expectancy of more than 3 months.
(v) Histologically confirmed colorectal cancer.
(vi) Measurable disease based on RECIST ver.1.1 (however, the patients with two or more lung metastases of 5 mm or more are eligible).
(vii) No prior chemotherapy, or treatment of recurrent lesions only with 5-FU without adjuvant chemotherapy.
(viii) Adequate functioning of vital organs, including normal haematopoietic, liver and renal function, as confirmed by the following data obtained in the 2 weeks before registration:
   (a) white blood cell count ≥3000/mm³;
   (b) neutrocyte count ≥1500/mm³;
   (c) platelet count ≥100 000/mm³;
   (d) haemoglobin ≥9.0 g/dl;
   (e) total bilirubin level: 1.5 times the institutional upper normal limit;
   (f) aspartate aminotransferase and alanine aminotransferase levels: 2.5 times the institutional upper normal limit;
   (g) serum creatinine level: below the institutional upper normal limit or ≥50 ml/min.

Exclusion Criteria

(i) Uncontrolled pleural effusion or ascites.
(ii) Brain metastasis.
(iii) Presence of other active malignancies or a history of other malignancies within the past 5 years.
(iv) Clinically significant cerebrovascular disease or arterial thromboembolism, or a history of cerebrovascular disease or arterial thromboembolism within the past 1 year.
(v) A history of surgery, biopsy specimen with section or sutures in the past 4 weeks, and fine-needle aspiration biopsy within the past 1 week.
(vi) Surgery planned during the course of the trial.
(vii) Intake of anticoagulant within the past 10 days.
(viii) Bleeding tendency and coagulant disorder (International Normalized Ratio ≥1.5).
(ix) Uncontrolled peptic ulcer.
(x) Perforation of the digestive tract or history of perforation of the digestive tract in the past 6 months.
(xi) Untreated traumatic bone fracture.
(xii) Nephropathy for which medication or transfusion is required, or a urine protein level of greater than or equal to +2 within the past 2 weeks.
(xiii) Uncontrolled hypertension.
(xiv) Uncontrolled diabetes mellitus.
(xv) Clinically problematic cardiac disease [toxicity grade ≥2 based on Common Toxicity Criteria for Adverse Events (CTCAE) ver.4.0 within the past 12 months].
(xvi) History of hypersensitivity to fluorouracil or platinum agents.
(xvii) History of adverse events related to dihydropyrimidine dehydrogenase deficiency induced by fluorinated pyrimidines.
(xviii) Uncontrolled diarrhoea.
(xix) Severe pulmonary disease (interstitial pneumonia, pulmonary fibrosis, pulmonary emphysema, etc.).
(xx) Organ transplant that necessitates immunosuppressant therapy.
(xxi) Uncontrolled infection.
(xxii) History of bevacizumab use.
(xxiii) Inability of oral intake.
(xxiv) Any other medical condition that makes the patient unsuitable for inclusion in the study according to the investigator.

REGISTRATION

After written informed consent is obtained, an eligibility report form is sent to the registration centre at the Epidemiological and Clinical Research Information Network (ECRIN) where the eligible patients are enrolled for
participation in the trial. Information regarding the necessary follow-up tests is then sent from the registration centre.

**TREATMENT METHODS**

The treatment schedule of the combination therapy of XELOX and bevacizumab applied in this study is shown in Table 1. One cycle is conducted from day 1 to day 22. This treatment protocol is continued until disease progression is arrested or the patients can be operated on. The dose reduction or stopping criteria of drugs due to adverse events is defined based on the haematological toxicity (Grade 4 neutropenia, Grade 3 neutropenia with $38.5^\circ C$ or Grade 3 or more decrease in platelets) and Grade 3 non-haematological toxicity. Oxaliplatin will be stopped in case Grade 3 or more allergies occur, and reduced in case peripheral sensory neuropathy occurs. Capecitabine will be reduced in case the hand-foot syndrome occurs.

The protocol treatment will be discontinued if the following are observed: (i) inability to continue the protocol treatment because of an adverse drug reaction; (ii) an adverse drug reaction is causing the patient to refuse treatment; (iii) an adverse drug reaction is causing the clinician to discontinue treatment; (iv) death or (iv) protocol violation or the patient becomes ineligible after enrolment.

**FOLLOW-UP**

The ASCA Trial schedule and its data collection are shown in Table 2. Disease progression and occurrence of new diseases are monitored by using abdominal radiography, abdominal computed tomography (CT) or magnetic resonance imaging and thoracic CT, and by measuring levels of the tumour markers CEA and CA19–9 at the baseline and every 8 weeks during the treatment period (tumour markers levels are measured every 4 weeks). Blood tests and symptom checks (collecting adverse events) will be carried out throughout the treatment period. The follow-up period is 1 year after the registration of the last patient.

**STUDY DESIGN AND STATISTICAL METHODS**

This study was primarily designed to evaluate the effect of the combination therapy of XELOX and bevacizumab on PFS.

The NO16966 trial reported a median PFS of 9.4 months for the FOLFOX/XELOX treatment in combination with

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**Table 1. Treatment schedule of the combination therapy of XELOX and bevacizumab**

<table>
<thead>
<tr>
<th>Agents</th>
<th>Volume</th>
<th>Methods</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>7.5 mg/kg</td>
<td>div (90–60–30 min)</td>
<td>Day 1</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>130 mg/m²</td>
<td>div (120 min)</td>
<td>Day 1</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2000 mg/m²/day</td>
<td>p.o. (after breakfast and dinner)</td>
<td>Days 1–15</td>
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</tbody>
</table>

**Table 2. Trial schedule and data collection**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Course 1 (days 1–21)</th>
<th>Course 2 (days 22–43)</th>
<th>After course 3</th>
<th>Time of last follow-up or dropout</th>
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<tbody>
<tr>
<td>XELOX and bevacizumab</td>
<td>○</td>
<td>○</td>
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<td>Baseline characteristics</td>
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<tr>
<td>PS, weight, blood pressure</td>
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</tr>
<tr>
<td>Adverse effects</td>
<td></td>
<td></td>
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<td></td>
<td>○</td>
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<td>Arterial blood gases</td>
<td></td>
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<td></td>
<td></td>
<td>In case of dyspnoea</td>
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<tr>
<td>Chest X-ray</td>
<td></td>
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<td></td>
<td>In case of dyspnoea</td>
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<tr>
<td>12-lead electrocardiogram</td>
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<td>In case of arrhythmia</td>
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<tr>
<td>Brain MRI</td>
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<td>In case of suspected brain metastasis</td>
</tr>
</tbody>
</table>

PS, performance status; MRI, magnetic resonance imaging.
bevacizumab (11). In Japan, the JO19380 trial reported a median PFS of 11.0 months for the XELOX treatment in combination with bevacizumab (24). Taking these data into account, it was determined that the threshold and expected PFS of the present study would be 6.5 months and 10.5 months, respectively. On the basis of the assumptions of uniform accrual over time, no loss to follow-up, and exponentially distributed survival times under a 2-year enrolment period and 1 year of follow-up, 32 patients would be needed to achieve a power of 80% with one-sided significance of \( P < 0.05 \) (25). Taking possible dropouts into consideration, the target number of patients was set at 35.

The primary analysis in this study is aimed at estimating the median PFS. The PFS curves are constructed as time-to-event plots by using the Kaplan–Meier method (26), and the median PFS and its 95% confidence interval are estimated. Other time-to-endpoint data (overall survival and time to treatment failure) are also analysed in the same manner. The response rate and the toxicities are calculated as proportions with exact confidence intervals.

The ASCA Study Group

Principal investigator: M.M. (Donko Hospital, Nara, Japan).

Secretariat: T. Otsuji (Donko Hospital, Nara, Japan).

Advisory board: H.M. (Osaka National Hospital, Osaka, Japan), T.S. (Kinki University School of Medicine, Osaka, Japan).

Data and safety monitoring board: N.O. (Gunma University Graduate School of Medicine, Gunma, Japan), K.M. (Aichi Cancer Center Hospital, Aichi, Japan).

Data center: J.S. (Nagoya University Graduate School of Medicine, Nagoya, Japan), C. Abe (ECRIN, Kyoto, Japan).

Statistical advisor: K.O. (Hokkaido University, Hokkaido, Japan).

Participating institutions: Approximately 19 Japanese institutions and hospitals are participating in this trial: Kansai Medical University, Kansai Electric Hospital, Kyoritsu General Hospital, Kinki University Hospital, Kinki Daigaku Igakubu Nara Hospital, Hakodate Goryoukaku Hospital, Saiseikai Nara Hospital, Sanno Hospital, Jichi Medical University Hospital, Shizuoka Cancer Center, Sakai Municipal Hospital, Toyonaka Municipal Hospital, Tochigi Cancer Center, Donko Hospital, Nara Social Insurance Hospital, Fukui Saiseikai Hospital, Misatokenwa Hospital, Minoh City Hospital, Rinku General Medical Center.

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Conflict of interest statement

None declared.

References


