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Efficacy and safety of bevacizumab-based combination regimens in patients with previously untreated metastatic colorectal cancer: Final results from a randomised phase ii study of bevacizumab plus 5-fluorouracil, leucovorin plus irinotecan versus bevacizumab plus capecitabine plus irinotecan (FNCLCC ACCORD 13/0503 study)

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Abstract ***Background:*** The combination of bevacizumab and bolus 5-fluorouracil, leucovorin and irinotecan is highly effective in patients with metastatic colorectal cancer (mCRC). This randomised, multicenter, non-comparative phase II trial assessed the efficacy and safety of bevacizumab plus oral capecitabine plus irinotecan (XELIRI) or infusional 5-fluorouracil, leucovorin plus irinotecan (FOLFIRI) as first-line therapy for patients with mCRC.
Patients and Methods: Patients received bevacizumab 7.5 mg/kg on day 1 plus XELIRI (irinotecan 200 mg/m^2 on day 1 and oral capecitabine 1000 mg/m^2 bid on days 1–14) every 3 weeks or bevacizumab 5 mg/kg on day 1 plus FOLFIRI (5-fluorouracil 400 mg/m^2 on day 1 plus 2400 mg/m^2 as a 46-h infusion, leucovorin 400 mg/m^2 on day 1, and irinotecan 180 mg/m^2 on day 1) every 2 weeks. Patients aged $\geqslant$65 years received a lower dose of capecitabine (800 mg/m^2 twice daily). The primary endpoint was 6-month progression-free survival (PFS) rate.

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Results: A total of 145 patients were enrolled (bevacizumab–XELIRI, $n = 72$; bevacizumab–FOLFIRI, $n = 73$). The 6-month PFS rate was 82% (95% confidence intervals (CI) 71–90%) in the bevacizumab–XELIRI arm and 85% (95% CI 75–92%) in the bevacizumab–FOLFIRI arm. In both the bevacizumab–XELIRI and bevacizumab–FOLFIRI arms, median PFS and overall survival (OS) were 9 and 23 months, respectively. The most frequent toxicities were grade 3/4 neutropenia (bevacizumab–XELIRI 18%; bevacizumab–FOLFIRI 26%) and grade 3 diarrhoea (12% and 5%, respectively).

Conclusions: This randomised non-comparative study demonstrates that bevacizumab–XELIRI and bevacizumab–FOLFIRI are effective regimens for the first-line treatment of patients with mCRC with manageable toxicity profiles.

1. Introduction

Bevacizumab has been tested in combination with capecitabine-based regimens, particularly after several randomised phase III studies showed similar efficacy for capecitabine plus oxaliplatin (XELOX) and 5-fluorouracil/leucovorin (5-FU/LV) plus oxaliplatin.[1–4] Treatment with bevacizumab plus XELOX was highly effective and well tolerated in patients with metastatic colorectal cancer (mCRC) in the NO16966,[5] CAIRO2[6] and TREE2[7] studies, while Gruenberger and colleagues reported that this combination was tolerable when administered to patients with potentially resectable liver metastases.[8]

In contrast, capecitabine plus irinotecan (XELIRI) in the treatment of mCRC has been associated with some toxicity concerns, particularly diarrhoea,[9–11] although for two of these trials (European Organisation for Research and Treatment of Cancer (EORTC) 40015, BICC-C), this is now known to be due to the co-administration of celecoxib with XELIRI.[10,11] To date, the combination of bevacizumab with XELIRI has not been widely investigated in patients with mCRC, although small studies have reported that it is effective without excessive toxicity.[12–14]

The aim of the present randomised non-comparative phase II trial was to evaluate the efficacy and safety of bevacizumab in combination with either XELIRI or 5-FU/LV plus irinotecan (FOLFIRI) as first-line therapy for mCRC.

2. Patients and methods

2.1. Study design

This was a multicenter, randomised, open-label, non-comparative phase II study (clinicaltrials.gov identifier NCT00423696). Eligible patients were aged 18–75 years, with unresectable, histologically proven, measurable mCRC and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients were required to have adequate haematologic, renal and liver function. The study was approved by the Kremlin-Bicêtre Ethic Committee and all patients provided written informed consent.

Patients were excluded if they had untreated brain metastases or spinal cord compression; central nervous system disease; intestinal obstruction; uncontrolled hypertension; evidence of bleeding diathesis or coagulopathy; a serious non-healing wound or ulcer; major surgery <28 days before study entry or anticipated need for major surgery; or ongoing treatment with aspirin (>325 mg/day) or other medications known to predispose patients to gastrointestinal ulceration.

2.2. Treatment

Patients were randomised to treatment with either XELIRI (90-min intravenous infusion of irinotecan 200 mg/m^2 on day 1 and oral capecitabine 1000 mg/m^2 twice daily [bid] on days 1–14) followed by a 90-min intravenous infusion of bevacizumab 7.5 mg/kg on day 1 every 3 weeks for a maximum of eight cycles, or FOLFIRI as previously described[15] followed by a 90-min intravenous infusion of bevacizumab 5 mg/kg on day 1 every 2 weeks for a maximum of 12 cycles. After 6 months of chemotherapy and in the absence of disease progression, bevacizumab alone (7.5 mg/kg every 21 days) was given until disease progression in both treatment groups. Randomisation was stratified by centre, performance status (0/1 versus 2), age (<65 versus ⩾65 years) and number of metastatic sites (1 versus ⩾2). Patients aged ⩾65 years received a lower daily capecitabine dose (800 mg/m^2 bid). Dose modifications for grade 3/4 toxicities are described in the Supplementary material.

2.3. Assessments

Physical examination, ECOG performance status, blood pressure (BP), and routine blood/urine analysis, including carcinoembryonic antigen (CEA) and CA 19-9, were assessed within 8 days before starting study treatment. During treatment, physical examination, ECOG performance status, BP, and blood and biochemistry analyses were repeated every cycle. During bevacizumab maintenance, clinical examination, BP,