Safety and efficacy of cetuximab-chemotherapy combination in Saudi patients with metastatic colorectal cancer

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Abstract

BACKGROUND: Cetuximab-based combination chemotherapy (CBCC) proved safe and effective as second-line strategy for metastatic colorectal cancer (mCRC). This prospective phase-II study was designed to assess the efficacy and safety of CBCC as first-, second- or third-line among Saudi patients with mCRC. MATERIALS AND METHODS: Patients with mCRC were offered CBCC to assess time-to-disease progression (TTP), response rate and duration, overall survival (OS) and safety. RESULTS: Nineteen patients were eligible and their median age was 51 years. Seven patients received CBCC as first-line and 12 as second- or third-line. Responses: 11 (58%) partial responses, 5 (26%) stable disease and 3 (16%) disease progressions. The median response duration was 4.3 months [95% confidence interval (CI): 3.4-5.2 months]. The median TTP was 6.8 months (95% CI: 2-13.9 months) for all 19 patients compared to 9.3 months (95% CI: 3.9-14.6 months) for the seven patients who received CBCC as first-line. The median OS for the entire population was 12.3 months (95% CI could not be determined). On the other hand, while the median OS for those who received CBCC as first-line have not been reached, the median OS for those who received CBCC after failure of other salvage therapies was 12.3 months (95% CI: 3.2-21.4 months). CBCC was generally tolerable. One patient had a severe hypersensitivity reaction and another fatal cardiac arrest. CONCLUSION: CBCC is active with an acceptable safety profile. Until results from phase-III clinical trials are available, using CBCC as first-line is probably justified.

Key words: Cetuximab, chemotherapy, metastatic colorectal carcinoma, Saudi Arabia

Introduction

In the Kingdom of Saudi Arabia (KSA), colorectal cancer (CRC) is the second and third most common cancer in Saudi males and females, respectively.[1] Chemotherapy reliably enhances quality of life and prolongs both progression-free survival (PFS) and overall survival (OS) for patients with metastatic colorectal cancer (mCRC).[2] Until recently, 5-fluorouracil (5-FU) in combination with folinic acid (FA) was the recommended first-line treatment for mCRC. However, several trials investigating combination regimens with FU-FA plus irinotecan or oxaliplatin as first-line therapy have achieved an improvement of PFS and OS suggesting that combining these agents is advantageous.[3-5] Mainly owing to the introduction of irinotecan and oxaliplatin, in the past decade, the median duration of survival among patients with mCRC has increased from 12 months to about 20 months.[6,7] Chemotherapies, however, are limited by their lack of specificity and are often associated with frequent and potentially severe dose-limiting toxicities.

Therefore, there is an urgent need for more effective, tailored and better-tolerated treatments that specifically target the processes pivotal to tumorigenesis and metastasis. Further advances in the understanding of molecular biology have led to the development of
target-specific agents. The FDA approved two targeted agents: a vascular endothelial growth factor (VEGF) monoclonal antibody inhibitor, bevacizumab and a human epidermal growth factor receptor (EGFR) targeted monoclonal antibody, cetuximab as first- and second-line mCRC therapy, respectively.\[8\]

In a phase-II study that evaluated the activity and safety of weekly cetuximab plus irinotecan in patients with irinotecan-refractory CRC, the response rate was 17% in 121 patients, who had progressive disease on irinotecan.\[9\] Cetuximab alone was then compared with cetuximab plus irinotecan in patients with irinotecan-refractory CRC in a phase-III trial. The response rates were 10.8% for cetuximab alone and 22.9% for cetuximab plus irinotecan. Moreover, the 1-year survival rates in this group of heavily pretreated patients (29% in the combination therapy group and 32% in the cetuximab monotherapy group) were encouraging.\[10\]

To the best of our knowledge, there are no published data from the Middle East about the use of cetuximab. This prompted the reporting of our phase-II trial that evaluated the efficacy and safety of cetuximab-based combination chemotherapy (CBCC) as first-, second- or third-line for patients with mCRC.

**Materials and Methods**

This study was conducted at King Faisal Specialist Hospital and Research Center, Jeddah, KSA, between August 2005 and August 2007. Patients with histologically confirmed metastatic adenocarcinoma of the colon or rectum were enrolled in this prospective phase-II trial. Prior salvage chemotherapy was allowed up to a second-line. CBCC was allowed either as first-, second- or third-line; however, treatment with cetuximab prior to enrollment was not allowed.

Other eligibility criteria were: age 18 years or more; performance status (World Health Organization) 0-2; at least one bidimensionally measurable lesion; a life expectancy of at least 3 months; adequate hematologic parameters (absolute neutrophil count >1.5 x 10^9/l and platelets >100 x 10^9/l); creatinine level <1.5 x upper limit of normal (ULN) and total rise in bilirubin level <1.25 x ULN; absence of a second primary tumor. Patients with severe cardiac dysfunction, central nervous system metastases, liver metastases involving >50% of the liver parenchyma or prior irradiation affecting >30% of the active bone marrow were excluded. The study was approved by the Institutional Review Board. All patients gave written informed consent in order to participate in the study.

**Patient evaluation**

Pretreatment evaluation included a detailed medical history and physical examination, a complete blood cell count with differential and platelet count, whole-blood chemistry including creatinine, bilirubin, aspartate and alanine aminotransferases, carcino-embryonic antigen and computed tomography scans of the chest and abdomen. CT scan of the brain was done only if central nervous system metastases were suspected. ECG and echocardiography were also required for all patients. Pretreatment evaluation had to be carried out within 2 weeks before study entry.

**Chemotherapy**

If the patient failed prior oxaliplatin-based chemotherapy (FOLFOX or CAPOX), irinotecan-cetuximab-based combination was given (FOLFIRI-Cetuximab). If the patient did not receive prior oxaliplatin-based chemotherapy, either FOLFOX-Cetuximab or CAPOX-Cetuximab was given. Capecitabine-Cetuximab was given if combination chemotherapy was thought to be poorly tolerated.

Cetuximab (Erbitux® Merck KGaA, Darmstadt, Germany) was given at a loading dose of 400 mg/m^2 as 2-h i.v. infusion on day 1. Premedication with diphenhydramine 50 mg i.v. was used. Cetuximab was then further administered on a weekly basis at a dose of 250 mg/m^2. FOLFIRI regimen: irinotecan (Campto, Pfizer) 180 mg/m^2 i.v. on day 1, FA 200 mg/m^2 i.v. followed by 5-FU 400 mg/m^2 i.v. bolus and 600 mg/m^2 i.v. 22-h continuous infusion on days 1 and 2 every 2 weeks. FOLFOX regimen: oxaliplatin (Eloxatin; Sanofi-Aventis) 85 mg/m^2 i.v. on day 1, FA 200 mg/m^2 i.v. followed by 5-FU 400 mg/m^2 i.v. bolus and 600 mg/m^2 i.v. 22-h continuous infusion on days 1 and 2 every 2 weeks. CAPOX regimen: oxaliplatin 130 mg/m^2 i.v. on day 1, capecitabine (Xeloda; Hoffmann-La Roche) 1000 mg/m^3 orally twice daily from day 1 to day 14 every 3 weeks. Cetuximab regimen: capecitabine was administered orally, at the dose of 1250 mg/m^2 twice daily from day 1 to day 14 every 3 weeks.

Cetuximab dose was delayed in cases of skin toxicity grade ≥3 and was stopped in case of severe hypersensitivity reaction. Following standard practice, chemotherapy cycles were delayed or doses were adjusted due to toxicity or change in hematological parameters. Routine antiemetic prophylaxis with a 5-hydroxytryptamine-3-receptor antagonist and dexamethasone was used. Treatment was administered until disease progression or unacceptable toxicity or until the patient declined further treatment or for a maximum of 6 months whichever came first.
Response and toxicity assessment
The World Health Organization criteria for response assessment were used.[11] All objective responses were required to be confirmed by a follow-up CT scan at least 4 weeks following documentation of the response.[12]

Statistical considerations
The primary end point of the study was the time-to-disease progression (TTP). Secondary objectives were response rate and duration, OS and safety to be assessed continuously throughout the trial by monitoring adverse events. Toxic effects were assessed according to the National Cancer Institute Common Toxicity Criteria, version 3.[13]

The median time of response duration was calculated from the date of response registration to the date of disease progression or death. TTP was calculated as the period from the date of starting treatment to the first observation of disease progression or to death from any cause within 60 days after the start of treatment or the most recent tumor assessment. OS was calculated as the period from the date of starting treatment until death from any cause or until the date of the last follow-up, at which point data were censored. TTP and OS were both determined by Kaplan-Meier product-limit method,[14] and the confidence intervals (CIs) for response rates were calculated using methods for exact binomial CIs.[15]

Results
Between August 2005 and July 2007, 19 consecutive patients with mCRC were treated at King Faisal Specialist Hospital and Research Center, Jeddah, KSA. There were 10 males and 9 females. Their median age was 51 years (range, 31-65 years).

The main characteristics of our patients’ population are summarized in Table 1. CBCC was given as first-line in seven patients (37%); while in the remaining 12 (63%) patients, CBCC was given as second- or third-line. Noteworthy, four of our study patients had disease progression after receiving bevacizumab in combination with chemotherapy prior to cetuximab use.

Table 2 depicts the various chemotherapy regimens used in combination with cetuximab. The median number of chemotherapy cycles was six (range, 2-12), while the median cetuximab cycles was 10 (range, 2-26).

Efficacy analysis
For the intention-to-treat analysis, all 19 patients were evaluated for efficacy. The median follow-up was 11 months (95% CI: 7.9-14.3 months). The best objective responses were achieved as follows: 0 (0%) complete responses (CR), 11 (58%) partial responses (PR), 5 (26%) stable disease (SD) and 3 (16%) disease progressions. Therefore, disease control rate (partial response and disease stabilization) was 84%. Of the seven patients who received CBCC as first-line, 5 and 2 achieved PR and SD, respectively and none experienced disease progression. The median response duration was 4.3 months in the cohort of responding patients (95% CI: 3.4-5.2 months). The median TTP was 6.8
months (95% CI: 2-13.9 months) for all 19 patients, while it was 9.3 months (95% CI: 3.9-14.6 months) for the seven patients who received CBCC as first-line.

At the time of the analysis, six patients (32%) were dead while the remaining 13 patients (68%) were alive with evidence of disease. With the exception of one patient (see below), all deaths were disease-related. The median OS for the entire population was 12.3 months (95% CI could not be determined). On the other hand, while the median OS for those received CBCC as first-line have not been reached, the median OS for those who received CBCC after failure of other salvage therapies was 12.3 months (95% CI: 3.2-21.4 months). Figures 1 and 2 depict TTP and OS, respectively, for all 19 patients.

**Adverse events**

Cetuximab-based combination chemotherapy was generally well tolerated with most of the side effects limited to the skin [Table 4]. Only one patient had a severe hypersensitivity reaction during the second week (anaphylaxis) for which cetuximab therapy was discontinued (first-line CBCC).

One male patient aged 65 years had sudden cardiac arrest 48 h after the infusion of the seventh week of Cetuximab (first-line CBCC). The latter patient was diabetic and had a history of coronary heart disease. Our patients also experienced the expected adverse events that are related to chemotherapy with no incidence of chemotherapy-related mortality.

**Discussion**

Epidermal growth factor receptor is a transmembrane glycoprotein that is involved in signaling pathways affecting cellular growth, differentiation, proliferation and programmed cell death. Cetuximab is a monoclonal antibody against the extracellular binding

**Table 3: Clinicopathologic features and efficacy outcomes of patients who received cetuximab-based combination either as first-line or second-/third-line**

<table>
<thead>
<tr>
<th>Data</th>
<th>First-line</th>
<th>Second-/third-line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>7 Pts</td>
<td>12 Pts</td>
</tr>
<tr>
<td>Sex</td>
<td>6 Pts</td>
<td>4 Pts</td>
</tr>
<tr>
<td>Males</td>
<td>1 Pt</td>
<td>8 Pts</td>
</tr>
<tr>
<td>Females</td>
<td>4 (57%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Age ≥50 years</td>
<td>4/3</td>
<td>5/7</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Three sites</td>
<td>Two sites</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>5 (71%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Median number of metastatic sites</td>
<td>2 (25%)</td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>0</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>PR</td>
<td>4 (57%)</td>
<td>8 (67%)</td>
</tr>
<tr>
<td>SD</td>
<td>9.3 (3.9-14.6)</td>
<td>5.1 (4.3-5.9)</td>
</tr>
<tr>
<td>PD</td>
<td>Not reached</td>
<td>12.3 (3.2-21.4)</td>
</tr>
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**Progression following therapy**

<table>
<thead>
<tr>
<th>TTP: Median and 95% CI (ms)</th>
<th>OS: Median and 95% CI (ms)</th>
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</thead>
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| PR: Partial response; SD: Stable disease; PD: Progressive disease; TTP: Time-to-disease progression; OS: Overall survival; CI: Confidence interval
The dermatologic cetuximab-related adverse events patients faired better. Nevertheless, Table 3 shows that first-line those who received the combination as second- or third-line. Limited by the small number of patients in our study, no statistical comparison of outcome was attempted between those who received CBCC as first-line and those who received the combination as second- or third-line. Nevertheless, Table 3 shows that first-line patients fared better.

The dermatologic cetuximab-related adverse events observed in our study occurred at a frequency similar to that reported in other studies. The occurrence of a severe hypersensitivity reaction in one of the 19 patients (5%) is similar to the rate of 3% reported in larger series. The occurrence of sudden cardiac arrest in our male patient, 48 h after the seventh week of cetuximab, is probably a drug-related fatal event. However, the patient had several underlying medical risks. Cardiopulmonary arrest and/or sudden death occurred in 2% (4/208) of patients with squamous cell carcinoma of the head and neck treated with radiation therapy and cetuximab as compared to none of 212 patients treated with radiation therapy alone. The etiology of these events is not precisely known.

Acknowledgements

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References


<table>
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<th>Table 4: Cetuximab-related adverse events</th>
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<tbody>
<tr>
<td>Adverse events</td>
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<tr>
<td>---------------</td>
</tr>
<tr>
<td>Acne-like skin rash</td>
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<tr>
<td>Skin fissuring</td>
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<tr>
<td>Skin dryness</td>
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<tr>
<td>Hypersensitivity</td>
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<td>Sudden cardiac death</td>
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*Percentages were rounded


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   b. point to point clarifications on the comments
   c. revised article with text highlighting the changes done

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   • Authors should highlight the relation of complication to duration of diabetes.
     Authors’ Reply: The complications as seen in our study group has been included in the results section [Page 4, Table]