

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

Ibrahim Ezzeldin M, Zeeneldin Ahmed A, Al-Gahmi Aboelkhair M, Sallam Yasser A, Fawzi Ehab E¹, Bahadur Yasser A¹

Departments of Oncology and Hematology, Sections of Medical Oncology and ¹Radiation Oncology, King Faisal Specialist Hospital and Research Centre, Jeddah, Kingdom of Saudi Arabia

Correspondence to: Ezzeldin M Ibrahim, E-mail: ezzibrahim@kfshrc.edu.sa

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 $>1.5 \times 10^9/l$ and platelets $>100 \times 10^9/l$); creatinine level $<1.5 \times$ upper limit of normal (ULN) and total rise in bilirubin level $<1.25 \times$ ULN; aspartate and alanine aminotransferases $<3.0 \times$ 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/m² 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/m². FOLFIRI regimen: irinotecan (Campto, Pfizer) 180 mg/m² i.v. on day 1, FA 200 mg/m² i.v. followed by 5-FU 400 mg/m² i.v. bolus and 600 mg/m² i.v. 22-h continuous infusion on days 1 and 2 every 2 weeks. FOLFOX regimen: oxaliplatin (Eloxatin; Sanofi-Aventis) 85 mg/m² i.v. on day 1, FA 200 mg/m² i.v. followed by 5-FU 400 mg/m² i.v. bolus and 600 mg/m² i.v. 22-h continuous infusion on days 1 and 2 every 2 weeks. CAPOX regimen: oxaliplatin 130 mg/m² i.v. on day 1, capecitabine (Xeloda; Hoffmann-La Roche) 1000 mg/m² orally twice daily from day 1 to day 14 every 3 weeks. Capecitabine regimen: capecitabine was administered orally, at the dose of 1250 mg/m² 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

Table 1: Patient's characteristics (19 patients)

Patient's characteristics	Number of patients (%)*
Sex	
Male	10 (53)
Female	9 (47)
Primary tumor site	
Colon	9 (47)
Rectum	10 (52)
Stage at diagnosis	
II	3 (16)
III	7 (37)
IV	9 (47)
Prior surgery	
Colectomy	5 (26)
Low anterior resection	5 (26)
Abdomino-Perineal resection	3 (16)
Palliative colostomy	2 (11)
None	4 (21)
Prior chemotherapy	
Neoadjuvant	3 (16)
Adjuvant	7 (36)
First-line palliative	12 (63)
Second-line palliative	2 (11)
None	7 (37)
Prior radiotherapy	
Neoadjuvant	3 (16)
Adjuvant	7 (37)
Palliative	3 (16)
None	6 (32)
Number of metastatic sites	
1	2 (11)
2	8 (42)
3 or more	9 (47)
Sites of metastases	
Liver	17 (89)
Lung	11 (58)
Loco-regional	10 (53)
Bone	4 (21)
Other	3 (16)

*Percentages were rounded

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.^[16] Cetuximab is a monoclonal antibody against the extracellular binding

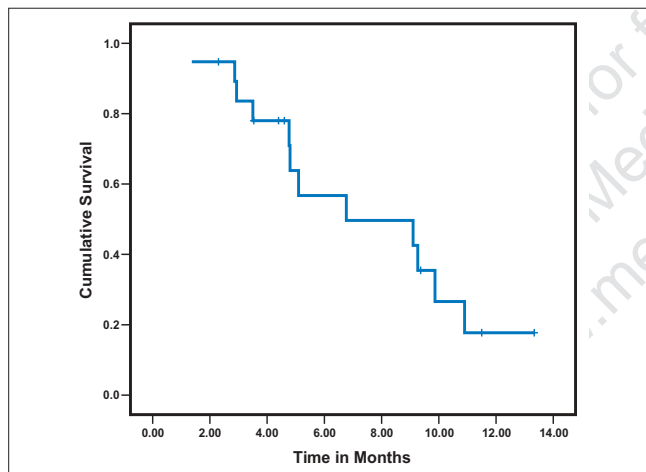


Figure 1: Kaplan-Meier survival curve for time to progression

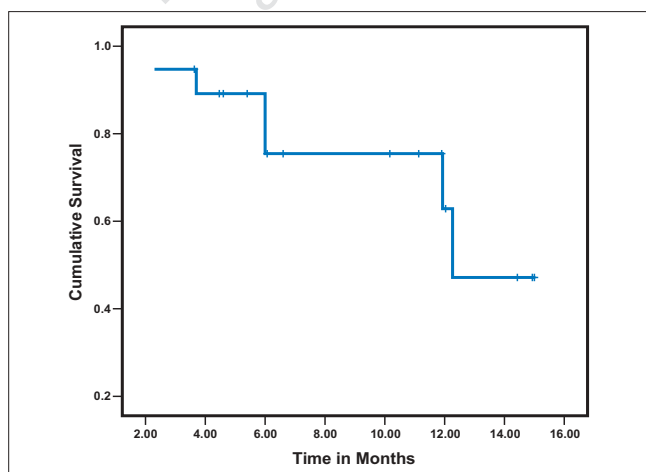


Figure 2: Kaplan-Meier survival curve for overall survival

Table 2: Cetuximab-based combinations

Regimens	Number of patients (%)*
FOLFIRI-CETUX	11 (58)
FOLFOX-CETUX	4 (21)
CAPOX-CETUX	2 (11)
CAPECITABINE-CETUX	2 (11)

*Percentages were rounded

FOLFIRI: 5-FU, folinic acid, irinotecan; CETUX: Cetuximab; FOLFOX: 5-FU, folinic acid, oxaliplatin; CAPOX: Capecitabine, oxaliplatin

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

Data	First-line	Second-/third-line
Number	7 Pts	12 Pts
Sex	6 Pts	4 Pts
Males	1 Pt	8 Pts
Females	4 (57%)	6 (50%)
Age ≥50 years	4/3	5/7
Diagnosis	Three sites	Two sites
Colon/rectum	5 (71%)	6 (50%)
Median number of metastatic sites	2 (29%)	3 (25%)
Response	0	3 (25%)
PR	4 (57%)	8 (67%)
SD	9.3 (3.9-14.6)	5.1 (4.3-5.9)
PD	Not reached	12.3 (3.2-21.4)

Progression following therapy

TTP: Median and 95% CI (ms)

OS: Median and 95% CI (ms)

PR: Partial response; SD: Stable disease; PR: Progressive disease; TTP: Time-to-disease progression; OS: Overall survival; CI: Confidence interval

Table 4: Cetuximab-related adverse events

Adverse events	Number of patients (%) [*]
Acne-like skin rash	14 (74)
Skin fissuring	8 (42)
Skin dryness	6 (31)
Hypersensitivity	1 (5)
Sudden cardiac death	1 (5)

^{*}Percentages were rounded

domain of the receptor and became the first such inhibitor to be approved in the United States for the treatment of mCRC.^[17,18]

We designed this trial to investigate the efficacy and safety of a CBCC. Our results showed a PR rate of 58% and a disease stabilization of 26%. Moreover, the median TTP was 6.8 months and the median OS for all 19 patients was 12.3 months. Despite that the majority of our patients were heavily pretreated and have multiple metastatic sites (42 and 47% had 2 and >3 sites, respectively), the results, by and large, appear superior to previously published data.^[8-10,19] The superior outcome was rather expected as more than one-third of our patients (seven patients) received CBCC as a first-line strategy. In the latter group, five patients achieved PR and two demonstrated SD. Moreover, in this cohort the OS has not been reached.

Cetuximab in combination with irinotecan has been approved in the USA and Europe for the treatment of patients with mCRC after failure of prior irinotecan-based cytotoxic therapy. The role of cetuximab in first-line therapy is still investigational. Preliminary studies in mCRC have provided evidence that the approach is safe and the results are encouraging.^[20-22] PR was achieved in 46-70% of patients, besides, additional 25-40% attained disease stabilization. In the study reported by Folprecht *et al.*, the median TTP was 9.9 months among 21 patients, while the median OS was 33 months.^[22] A phase III randomized trial comparing the addition of cetuximab, bevacizumab or both to combination chemotherapy (FOLFOX or FOLFIRI) for the first-line treatment of mCRC is under way.^[23]

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.^[9,10,19-22] 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.^[10] 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.^[24] The etiology of these events is not precisely known.

In conclusion, in this first study from the Middle East using cetuximab in mCRC, we found that CBCC is active with an acceptable rate of toxicity. Until the results from phase-III clinical trials are available, using CBCC as first-line is probably justified. Prudence, however, is required when cetuximab is used in patients with known coronary artery disease, congestive heart failure or arrhythmias.

Acknowledgements

We acknowledge the valuable support of Mr. M. Al-Zahrani and Ms. D. Al-Madani from the Oncology Data Unit, King Faisal Specialist Hospital and Research Centre, Jeddah, Kingdom of Saudi Arabia.

References

1. Saudi National Cancer Registry. Cancer Incidence Report, 2002. Available from: <http://www.kfshrc.edu.sa/NCR/>.
2. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan and oxaliplatin in the course of treatment. *J Clin Oncol* 2004;22:1209-14.
3. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, *et al.* Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;18:2938-47.
4. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, *et al.* Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomized trial. *Lancet* 2000;355:1041-7.
5. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, *et al.* A randomized controlled trial of fluorouracil plus leucovorin, irinotecan and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004;22:23-30.
6. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, *et al.* FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. *J Clin Oncol* 2004;22:229-37.
7. Kohne CH, van Cutsem E, Wils J, Bokemeyer C, El-Serafi M, Lutz MP, *et al.* Phase III study of weekly high-dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European Organisation for Research and Treatment of Cancer Gastrointestinal Group Study 40986. *J Clin Oncol*

- 2005;23:4856-65.
8. Venook A. Critical evaluation of current treatments in metastatic colorectal cancer. *Oncologist* 2005;10:250-61.
 9. Saltz B, Rubin M, Hochster H, Tchekmeydian S, Waksia HI, Needle N, *et al.* Cetuximab (IMC-C22 plus irinotecan (CPT-1 is active in CPT-11-refractory colorectal cancer (CRC) that expresses epidermal growth factor receptor (EGFR). *Proc Am Soc Clin Oncol* 2001;20:2a.
 10. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, *et al.* Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;351:337-45.
 11. Jaffe CC. Measures of response: RECIST, WHO and new alternatives. *J Clin Oncol* 2006;24:3245-51.
 12. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207-14.
 13. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). 2006 August 9. [Last cited on 2006 Sep 1]; v3. Available from: <http://ctep.cancer.gov/forms/CTCAEv3.pdf>.
 14. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
 15. Cox DR. *The Analysis of Binary Data*. London, UK: Methuen; 1970.
 16. Dei Tos AP. The biology of epidermal growth factor receptor and its value as a prognostic/predictive factor. *Int J Biol Markers* 2007;22:S3-9.
 17. Pfeiffer P, Qvortrup C, Eriksen JG. Current role of antibody therapy in patients with metastatic colorectal cancer. *Oncogene* 2007;26:3661-78.
 18. Galizia G, Lieto E, De Vita F, Orditura M, Castellano P, Troiani T, *et al.* Cetuximab, a chimeric human mouse anti-epidermal growth factor receptor monoclonal antibody, in the treatment of human colorectal cancer. *Oncogene* 2007;26:3654-60.
 19. Vincenzi B, Santini D, Rabitti C, Coppola R, Beomonte Zobel B, Trodella L, *et al.* Cetuximab and irinotecan as third-line therapy in advanced colorectal cancer patients: A single centre phase II trial. *Br J Cancer* 2006;94:792-7.
 20. Rougier P, Raoul JL, Van Laethem J. Cetuximab+FOLFIRI as first-line treatment for metastatic colorectal CA. *Proc Am Soc Clin Oncol* 2004.
 21. Tabernero J, Van Cutsem E, Sastre J. An international phase II study of cetuximab in combination with oxaliplatin/5-fluorouracil -FU)/folinic acid (FA) (FOLFOX- in the first-line treatment of patients with metastatic colorectal cancer (CRC) expressing Epidermal Growth Factor Receptor (EGFR): Preliminary results. *Proc Am Soc Clin Oncol*.
 22. Folprecht G, Lutz MP, Schoffski P, Seufferlein T, Nolting A, Pollert P, *et al.* Cetuximab and irinotecan/5-fluorouracil/folinic acid is a safe combination for the first-line treatment of patients with epidermal growth factor receptor expressing metastatic colorectal carcinoma. *Ann Oncol* 2006;17:450-6.
 23. Venook A. Protocol chair: Phase III randomized study of cetuximab and/or bevacizumab in combination with either oxaliplatin, fluorouracil and leucovorin calcium (FOLFOX) or irinotecan hydrochloride, fluorouracil and leucovorin calcium (FOLFIRI) in patients with previously untreated metastatic adenocarcinoma of the colon or rectum: Protocol ID: CALGB-C80405. Last modified: 8/24/2006. National Cancer Institute: Clinical Trials (database); 2006.
 24. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, *et al.* Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354:567-78.

Source of Support: King Faisal Specialist Hospital and Research Center, Jeddah, **Conflict of Interest:** None declared.

Author Help: Sending a revised article

- 1) Include the referees' remarks and point to point clarification to those remarks at the beginning in the revised article file itself. In addition, mark the changes as underlined or coloured text in the article. Please include in a single file
 - a. referees' comments
 - b. point to point clarifications on the comments
 - c. revised article with text highlighting the changes done
- 2) Include the original comments of the reviewers/editor with point to point reply at the beginning of the article in the 'Article File'. To ensure that the reviewer can assess the revised paper in timely fashion, please reply to the comments of the referees/editors in the following manner.
 - There is no data on follow-up of these patients.
Authors' Reply: The follow up of patients have been included in the results section [Page 3, para 2]
 - 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]