Addition of Bevacizumab or Cetuximab to First Line Chemotherapy in the Treatment of K-ras Wild type metastatic Colorectal Carcinoma

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Abstract

Purpose: Mutations in *K-ras* gene are found in 30–40% of colorectal carcinoma (CRC) and are associated with poor response to Cetuximab or Panitumumab. Thus, *K-ras* testing is mandatory for patients with metastatic CRC (mCRC) but genotyping mistakes can be a result of many factors. The combination of Capecitabine with Irinotecan (XELIRI) was proven effective and addition of Bevacizumab as well as Cetuximab was studied with good tolerance and promising results. The aim of this study was to compare the efficacy and safety of XELIRI-Bevacizumab with that of XELIRI-Cetuximab in the first-line treatment of K-ras wild type mCRC.

Patients and methods: This is pilot study including 20 patients with mCRC K-ras wild type treated at Saudi German hospital, KSA & private center in Cairo, Egypt. The primary objective was to confirm non-inferiority of XELIRI-Bevacizumab compared with XELIRI-Cetuximab for progression-free survival (PFS).

Results: At median follow up of 12 months, the overall response rate (ORR) was 45% with 1-year PFS 75%. Comparing the 2 arms, ORR was 50% in Arm 1 compared to 40% in Arm 2 (p=0.952) while clinical benefit was 60% in both arms. PFS at 1-year was 80% in Arm 1 versus 70% in Arm 2 (p=0.612) with HR 0.63 (95%CI 0.10 - 3.79).

Conclusion: Adding Bevacizumab to XELRI is not inferior to adding Cetuximab to the same regimen in 1st line therapy of K-ras wild mCRC with acceptable and manageable toxicity profiles and maybe preferable in absence of accurate and reliable K-ras testing.

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide in both males and females, and is the second leading cause of cancer related mortality in western countries.[1] In Egypt, it is the 7th common malignancy with an annual incidence of 3.3%.[2]

Despite improvements in the screening programs, 20% of patients present with metastatic tumors.[1]

K-ras, an essential component of the EGFR signaling cascade, can acquire mutations in exon 2, isolating the pathway from the effect of EGFR thus rendering EGFR inhibitors ineffective. Mutations in the *K-ras* gene are found in 30%–40% of colorectal tumors [3] and are associated with a poor response to Cetuximab or Panitumumab.[4] Independent reanalysis of eight randomized clinical trials showed inadequate response for these drugs when a *K-ras* codon 12 or codon 13 mutation was present [5]. As a result, *K-ras* testing is now mandatory at the presentation of metastatic disease in patients with CRC.[6-7] *K-ras* mutation in CRC were found to have relations to the patients' age and sex; with the *K-ras* mutations being much less frequent in male than female patients at younger ages (< 40 years, odds ratio < 0.014). The low frequency might indicate that a different, ras-independent, pathway to neoplasia is dominating in the colon of younger males.[8]

For decades, treatment of mCRC was limited to 5-fluorouracil (5FU) / Leucovorin (LV), with a median OS of about 12 months.[9] Oral fluoropyrimidines (Capecitabine, Uracil) showed better response rates (RR) and better tolerability, as compared to the infusional 5FU, with comparable OS benefits.[10-11]

Two other chemotherapy agents, i.e. Irinotecan and Oxaliplatin, have shown activity in the treatment of mCRC when combined to fluoropyrimidine backbone, providing a variety of regimens (FOLFOX, FOLFIRI, IFL, XELOX, XELIRI…), with improvements in RR, progression free survival (PFS) and OS as compared to 5FL/LV only.[12-15]

Recently, the introduction of targeted therapies in the treatment of mCRC has greatly improved the outcomes. Two types of monoclonal antibodies were approved for the clinical use in mCRC; the anti vascular endothelial growth factor (VEGF) receptor antibody, bevacizumab and the anti epidermal growth factor receptor (EGFR) antibodies: Cetuximab and Panitumumab.[16-18] The combination of Capecitabine with Irinotecan (CAPIRI) was proven effective and safe in a large randomized trial.[19] Addition of Bevacizumab to XELIRI was shown to be not inferior to FOLFIRI-Bev in randomized studies.[20-22] Also, Cetuximab was studied in addition to XELIRI with good tolerance and promising results.[23]

The aim of this study was to compare the efficacy and safety of XELIRI-Bevacizumab with that of XELIRI-Cetuximab in the first-line treatment of K-ras wild type metastatic colorectal carcinoma (mCRC).

Patients and methods

This pilot study included 20 patients with metastatic K-ras wild type colorectal carcinoma treated at Saudi German hospital, KSA & a private center in Cairo, Egypt. The primary study objective was to confirm non-inferiority of XELIRI-Bevacizumab compared with XELIRI-Cetuximab for progression-free survival (PFS) in patients with K-ras wild type mCRC.

Inclusion criteria:

1. Pathologically proven adenocarcinoma of colorectal origin
2. metastases radiologically documented that couldn't be resected with curative intent
3. No detected mutations in codon 12 and 13 of K-ras gene by real time PCR on primary resection block or metastatic disease if feasible.
4. at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria
5. Previous adjuvant chemotherapy (FOLFOX) more than 6 months prior to enrollment.
6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0-2.
7. Age : 18 years or more .
8. Gender : both male and females.
9. Good cardiac, renal & hepatic functions.
10. written informed consent.

Exclusion criteria:

1. Evidence of any CNS metastases.
2. Bleeding tendency.
3. Severe co-morbid disease including uncontrolled hypertension.
4. Patients with second malignancy.
5. History of anti-cancer agents in the last 6 months.

All patients underwent complete history taking, physical examination, laboratory investigations including: complete blood count, serum creatinine, prothrombin time & concentration, ALT, AST, serum albumin, total & direct bilirubin. Imaging investigations included: C.T scanning of chest, abdomen & pelvis for assessment of metastatic disease

All patients were treated for 1st line metastatic disease with systemic chemotherapy XELIRI (Capecitabine PO 1700 mg/m^2/d in 2 divided doses at days 1-14 plus Irinotecan 200 mg/m^2 over 90 minutes i.v infusion on day 1 only) every 3 weeks plus either Bevacizumab 7.5 mg/Kg every 3 weeks (Arm 1) or Cetuximab weekly (initially 400 mg/m^2 I.V. [120 minutes], subsequently 250 mg/m^2 [30 minutes]) (Arm 2). Routine antiemetic prophylaxis with a 5-hydroxytryptamine-3-receptor antagonist was used in both arms. Treatment was administered until disease progression, unacceptable toxicity or consent withdrawal.

Patients were assessed for toxicity before each cycle using the National Cancer Institute Common Toxicity Criteria version 3.0.[24] Chemotherapy was delayed until recovery if neutrophils were less than 1.5×10^9/L or platelets less than 100×10^9/L, or for significant (more than grade-II) persisting non-hematologic toxicity.

Response to treatment was evaluated using CT scan with contrast every 9 weeks according to the RECIST criteria.[25]

Statistical analysis

The primary endpoint of the study was PFS. Secondary endpoints were clinical benefit and safety profile.

PFS was defined as the interval from the time of enrolment to the date of first documented disease progression or patient's death from any cause. Clinical benefit was defined as partial or complete response in addition to stable disease. The primary analysis of PFS was of the non-inferiority of Arm 1 to Arm 2, as measured by the hazard ratio $HR_{Arm1/Arm2}$ with a non-inferiority margin of 1.40; H_0 was rejected if the upper limit of the 95% confidence interval (CI) was less than the non-inferiority margin. The Kaplan–Meier method was used to estimate PFS curves, and log-rank test was used to compare curves. Cox proportional hazards modeling was used to calculate hazard ratio (HR) and confidence intervals (CIs). X^2-*tests* were used to compare toxicity and response rates. *P*-values less than 0.05 were considered statistically significant for all comparisons. SPSS program (version 17.0) was used for all analyses.

Results

From June 2009 to December 2010, twenty patients with unresectable mCRC were enrolled into the study. The median age for the studied patients was 56.5 years (range 43 - 69) with 65% of them had PS 0-1 at presentation. Liver was the most common site of metastasis in both arms (80% in Bevacizumab arm versus 100% in Cetuximab arm). Both arms were well balanced with no difference regarding age, PS as well as sites of metastasis. Detailed clinicopathological characteristics are shown in table (1).

At a median follow up of 12 months, the overall response rate (ORR) was 45%. Comparing the 2 arms, the ORR was 50% in Arm 1 compared to 40% in Arm 2 (p=0.952) while clinical benefit was 60% in both arms [table 2].

Regarding survival, 1-year PFS for the whole group was 75%. Comparing both arms, 1-year PFS was 80% in Arm 1 versus 70% in Arm 2 (p=0.612) with HR 0.63 (95%CI 0.10 - 3.79) [Figure 1].

Concerning toxicity, both regimens were well tolerated; diarrhea was the most encountered adverse event in both arms (50% in Cetuximab arm & 20% in Bevacizumab arm) while hand & foot skin reaction was encountered in 10% of patients in each arm. [Table 3]

Discussion

Median survival of patients with metastatic CRC has been considerable improved with FOLFIRI or FOLFOX regimens.[13-15]

Addition of monoclonal antibodies targeting either VEGF or EGFR to Irinotecan combination chemotherapy in mCRC has demonstrated an increase in RR, PFS and mOS compared with chemotherapy alone.[18,26]

Moreover, the use of the oral fluoropyrimidine Capecitabine with Irinotecan (XELIRI) in combination with Bevacizumab or Cetuximab has been reported to be safe and effective in the first-line treatment for metastatic CRC.[27-30]

To the best of our knowledge, the current study is the first randomized trial comparing Bevacizumab versus Cetuximab in combination with the outpatient XELIRI regimen. The primary endpoint was met as no statistically significant difference has been observed between the two treatment arms.

The efficacy parameters of XELIRI-Bevacizumab are in same range with that reported in previous trials. ORR was 50% with 1 year PFS 80% in our study trial compared to 40% and 43% in Souglakos et al[20]; same as regard XELIRI-

Cetuximab regimen, ORR was 40% with 1-year PFS 70% similar to Uygun et al[22] who reported ORR of 41.2% and 1-year PFS 55.4%.

Earlier trials evaluating chemotherapy regimen with Capecitabine and Irinotecan had showed that XELIRI regimen was associated with unacceptable incidences of severe gastrointestinal adverse effects with grade 3-4 diarrhea up to 36% of patients.[19,31] These effects were not seen in recent studies that used lower doses of both Capecitabine and Irinotecan without compromising efficacy which we used in our study.

Drugs targeting EGFR had improved survival in metastatic colorectal cancer. However, these therapies are effective only in patients harboring a tumor with a wild-type *KRAS* gene.[17,32-33] Thus, the appropriate selection of patients with colorectal cancer for treatment with anti-EGFR drugs is a major challenge. Genotyping mistakes can be a result of many factors. A very important factor is the starting material as the type of fixative used has an impact on the quality of the assay. Some fixatives such as non buffered formalin do not allow molecular testing as it leads to low DNA quality.[34] This might be the cause of false results. Another important issue in *K-ras* genotyping is the method used for testing. Two basic methods are predominantly used for *KRAS* testing: DNA sequencing and allele-specific PCR. Sequencing is usually used to detect point mutations but its major disadvantage is that it is less sensitive, and in samples with low tumor content, analysis might be difficult.[35] Allele-specific PCR is more sensitive but tests for only a subset of the most common mutations, whereas sequencing can detect all possible mutations.[36] Thus, in the absence of a national external quality assessment scheme, accurate and reliable K-ras testing is questionable and hence drugs depending on that test should be used with caution.

The major limitations of our study were the small number of patients included as well as the short follow up time, which might have influenced our findings and resulting in broad confidence intervals.

Although our results should be confirmed by prospective, randomized, phase-III trial, we think that they contribute to the literature because efficacy of Bevacizumab in comparison to anti-EGFR Cetuximab or Panitumumab in K-ras wild type mCRC was never studied until the recent presentation of results of FIRE-3 study in ASCO 2013 which was presented as Late breaking abstract showing better response rate of FOLFIRI-Cetuximab compared to FOLFIRI-Bevacizumab (72.2% vs 63.1%) but with no difference in PFS.

In conclusion, adding Bevacizumab to outpatient regimen XELIRI is not inferior to adding Cetuximab to the same regimen in the 1st line therapy of K-ras wild type mCRC with acceptable and manageable toxicity profiles and maybe preferable in absence of accurate and reliable K-ras testing.

Conflict of Interest: All authors declared no conflict of interest.

Tables

Table 1: Patients' characteristics according to treatment arm

Characteristics		XELIRI-Bevacizumab N = 10	XELIRI-Cetuximab N = 10	p- value
Age (years)	Mean (SD)	54 (7.6)	58 (8.8)	0.31
	Median (range)	55 (43 – 68)	61 (45 – 69)	
PS	0-1	8	5	0.16
	2	2	5	
Site of metastasis	Liver	8	10	0.136
	Bone	4	5	0.653
	Lung	2	1	0.531

Table 2: Response according to treatment arm

	XELIRI-Bevacizumab N= 10 (%)	XELIRI-Cetuximab N= 10 (%)	p- value
Complete response	1 (10)	1 (10)	0.952
Partial response	4 (40)	3 (30)	
Stable disease	3 (30)	3 (30)	
Disease Progression	2 (20)	3 (30)	
Objective response	5 (50)	4 (40)	0.653
Clinical benefit	8 (80)	7 (70)	0.606

Table 3: Adverse events according to treatment arm

	XELIRI-Bevacizumab N= 10 (%)	XELIRI-Cetuximab N= 10 (%)	p- value
Diarrhea	2 (20)	5 (50)	0.160
Vomiting	2 (20)	0 (0)	0.136
Hand & Foot Syndrome	1 (10)	1 (10)	0.763
Neutropenic fever	1 (10)	0 (0)	0.305

Figures

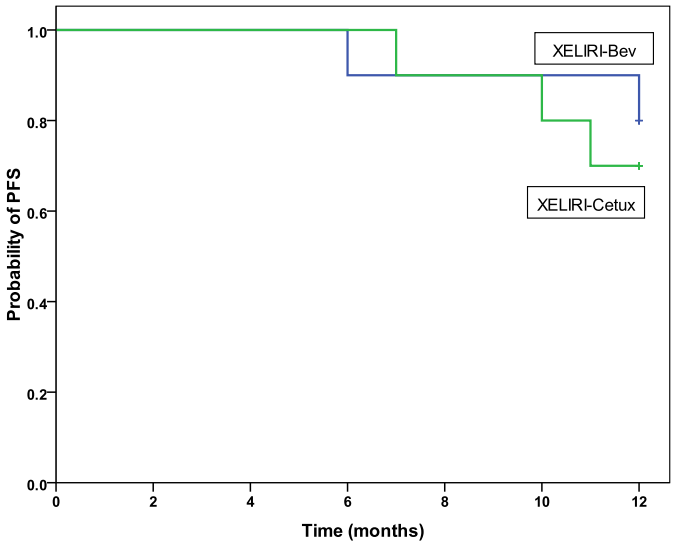

Fig 1: Progression Free Survival according to treatment arm.

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