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The Value of Target Therapy in Metastatic Cancer Colon

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ABSTRACT

Background: Colorectal cancer is the third leading cause of cancer-related deaths in the United States when men and women are considered separately, and the second leading cause when both sexes are combined It is expected to cause about 49,700 deaths during 2015.

Aim of the Work: The present work was aimed to study the efficacy of treatment of metastatic cancer colon (KRAS wild type) with chemotherapy plus anti-EGFR (Erbitux) and chemotherapy alone.

Patients and Methods: This phase II prospective study included a total of 37 patients of metastatic cancer colon (KRAS wild type) treated with chemotherapy plus anti-EGFR (Erbitux) and chemotherapy alone for (KRAS wild type) attending at Police Hospital. This study was conducted between September 2016 and August 2018.

Results: We have studied the value of adding target therapy in the metastatic colon cancer patients. Some of them received chemotherapy with cetuximab as target therapy versus patients received chemotherapy alone. In the current study, median progression-free survival (PFS) of the whole studied sample (n =37) was 10.0 months (range.3.0.-.21.0). Median survival was significantly higher in the chemotherapy and cetuxumab group (P: less than 0.001). Using cox regression analysis group with cetuximab associated with better survival (P=0.047) with protective hazard ratio of 0.974. The cumulative PFS proportion is presented at 12 months. Median overall survival of whole studied samples (n=37) was 21.0 months (range 18-23 months) and there were 25 cases dead and all cases progressed. Median OS was higher in chemotherapy with cetuximab group and was of a significant difference (P=0.001). There were others factors studied their relation to OS like age but no significant difference bit older patient had better OS by (34.8 % vs 28.6 %), also PS no significant difference but patient with PS =0 had better OS by (41.7% vs 28%) according to RT and LT colon there was LCC with better OS than RCC but no significant difference but LT site of colon had better survival by (42.9 %vs 18.8%).

Conclusion: Cetuximab was beneficial in down-staging programs and significantly improve progression-free survival and response rates and overall survival for patients with metastatic colorectal cancer

Keywords: Target Therapy, Metastatic Cancer Colon

INTRODUCTION

Excluding skin cancers, colorectal cancer is the third most common cancer diagnosed in both men and women in the United States. The American Cancer Society's estimates for the number of colorectal cancer cases in the United States for 2015 are: 93,090 new cases of colon cancer and 39,610 new cases of rectal cancer. Colorectal cancer is the third leading cause of cancer-related deaths in the United States when men and women are considered separately, and the second leading cause when both sexes are combined It is expected to cause about 49,700 deaths during 2015 **(1)**.

Prognosis is dependent on stage at presentation with five-year survival rates varying from 93% in stage I (T1-2 N0) to only 44% in stage IIIC disease (N2) **(2)**.

Although patients with early stage CRC commonly undergo potentially curative resection, disease recurrence may occur and is thought to arise from occult micrometastases that are present at the time of surgery **(3)**.

This is the premise to offer adjuvant chemotherapy for those who present with stage III or II with high-risk features as it could potentially eradicate micrometastatic disease **(4)**.

Despite embarking on adjuvant chemotherapy, approximately 30-35% of the patients with stage III CRC eventually relapse **(5)**. Although some patients may have either an isolated metastases or a local recurrence that is curable via surgery, most patients with metastatic CRC (mCRC) are incurable The treatment in this setting generally consists of palliative chemotherapy with the goal of prolonging overall survival (OS) and maintaining quality of life The median OS for patients with unresectable mCRC who receive best supportive care alone is approximately five to six months while patients on chemotherapy in the modern era routinely live longer than two years **(6)**.

In Egypt colorectal cancer has no age predilection and more than one - third of tumors affect a young population The high prevalence in young people can neither be explained on hereditary basis nor can it be attributed to bilharziasis The disease usually presents at an advanced stage and predisposing adenomas are rare Similarity of the data from different centers suggests that this is the picture of colorectal cancer typical of Egypt **(7)**.

Alcohol, Diabetes, diets high in fat and cholesterol, Ethnicity, Race, and Social Status, family medical history, genetics e.g. mutations leading to

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FAP (familial adenomatous polyposis) and HNPCC (hereditary nonpolyposis colorectal cancer), Inflammatory Bowel Disease (IBD), lack of exercise, obesity, personal medical history that includes polyps, bowel inflammation, or certain cancers, smoking [8].

So, there are many biological, genetic, molecular, and tissue- derived prognostic factors for CRCs. A study evaluated prognostic factors in patients who were metastatic at diagnosis or progressed to metastatic disease during follow-up Among the patients with metastatic CRC, those who benefited from first-line therapy, had history of metastasectomy, were K-RAS wild type and had low CA 19-9 levels before the first-line therapy, showed better prognosis independent of other factors [8]. standard chemotherapy The for patients with colon cancer for the last two decades consisted of 5-fluorouracil in combination with adjuncts such as levamisole and leucovorin This approach has been tested in several large randomized trials and has been shown to reduce individual 5-year risk of cancer recurrence and death by about 30% [9].

As regard metastatic disease, combination regimens of chemotherapy and targeted therapy provide improved efficacy and prolonged progression-free survival (PFS) [9].

Combination regimens provide improved efficacy and prolonged progression-free survival (PFS) in patients with metastatic colon cancer. The advent of new classes of active drugs and biologies for colorectal cancer has pushed the expected survival for patients with metastatic disease from 12 months two decades ago to about 22 months currently [10].

In a **phase III multicenter trial** in patients with advanced colorectal carcinoma refractory to fluorouracil, overall survival did not significantly differ between patients treated with fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) (n=246) compared with irinotecan (n=245); however, FOLFOX 4 improved response rate (RR) and time to progression (TTP) compared with irinotecan (P=0 0009 for each RR and TTP) FOLFOX4 was associated with more neutropenia and paresthesias [11].

Biologic agents used in the treatment of colon cancer include monoclonal antibodies against vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR), as well as a kinase inhibitor and a decoy receptor for VEGF [12].

Such agents include the following:

- Bevacizumab (Avastin)
- Cetuximab (Erbitux)
- Panitumumab (Vectibix)
- Regorafenib (Stivarga)
- Ziv-aflibercept (Zaltrap)

Cetuximab is a chimeric monoclonal antibody against EGFR that is approved for treatment of KRAS mutation-negative (wild-type), EGFR- expressing, metastatic colorectal cancer Cetuximab may be used as monotherapy or in combination with irinotecan (Camptosar) in patients with metastatic colorectal cancer refractory to fluoropyrimidine and oxaliplatin therapy Additionally, cetuximab is approved as combination therapy with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin). [12]

- KRAS mutations, which are present in about 40% of colon adenocarcinomas, affect sensitivity to anti-EGFR treatment The addition of anti-EGFR antibody treatment to standard chemotherapy regimens for patients with advanced colorectal cancer improves progression-free survival for those with wild-type KRAS status, but not those with mutant KRAS.

The CRYSTAL trial, a large international trial exploring the benefit of adding cetuximab to first-line chemotherapy with FOLFIRI, documented that only patients with wild-type KRAS derived clinical benefit from cetuximab In patients with mutant KRAS, adding cetuximab to chemotherapy provided no clinical benefit and resulted only in unnecessary toxicity. [12]

The aim of the current work was to study the efficacy of treatment of metastatic cancer colon (KRAS wild type) with chemotherapy plus anti-EGFR (Erbitux) and chemotherapy alone. The Efficacy is evaluated as regard, response rate, time to disease progression and toxicity. Inclusive data will be statistically analyzed for assessment of treatment results and survival. Primary end point: OS, Secondary end points: PFS, RR.

PATIENTS AND METHODS

This randomized phase II prospective study included a total of 37 patients of metastatic cancer colon (KRAS wild type) treated with chemotherapy plus anti-EGFR (Erbitux) and chemotherapy alone for (KRAS wild type) attending at Police Hospital. Approval of the ethical committee and a written informed consent from all the subjects were obtained. This study was conducted between September 2016 and August 2018.

Inclusion criteria

- Patients who were medically fit with life expectancy more than 6 months.
- Patients with pathologically proved colorectal cancer carcinoma and irresectable metastatic site.
- Age below 75 years.
- CBC neutrophil count >1,500\mm3, platelet count >100000\mm^3, hemoglobin > 9 g\dl liver function tests total bilirubin<1,5times the upper limit of normal aspartate aminotransferase andalanine aminotransferase < 2,5 times the upper limit of normal serum creatinine < 1.5 times the upper limit
- Performance status 0-2.

Exclusion criteria

Patients who are medically fit with life expectancy less than 6 months, who underwent best supportive care.

Patients with no pathological proof for diagnosis Patients having history of cancers other than colorectal cancer.

All patients were evaluated for:

Age, gender, weight, performance status, presenting symptoms, site of the disease, metastatic site, methods of diagnosis (Physical examination, CBC, LFTs, KFTs, CEA, CA19 9, C T, Colonoscopy), histopathological grade, KRAS mutations, tumor staging, response in the first assessment after 3 cycle by (ct) response in the second assessment after 6 cycle by (-CT), follow up until 8-2016

37 patients will be randomly assigned to receive either chemotherapy plus cetuximab (18 patients, arm a) and chemotherapy alone (19 patients, arm b).

In the follow up group, additional analysis for treatment was carried out include

- For systemic therapy: number of cycles, response, toxicity
- Picture of toxicity: skin rash, diarrhea, anemia neutropenia, neuritis.

The systemic therapy for the first group is in the form of: FOLFIRI plus cetuximab (only for KRAS wild-type tumors):

Cetuximab 400 mg/m loading dose over 2 h on day 1, thencetuximab 250 mg/m ^{2} over 1 h weekly plusjrinotecan 180 mg/m ^{2} IV over 30-90 min on day 1 plusleucovorin 400 mg/m ^{2}IV infusion to match duration of irinotecan infusion on day 1 plus5-FU 400 mg/m ^{2} IV bolus on day 1, then 1200 mg/m ^{2}/day for 2-d (total 2400 mg/m ^{2} over 46-48 h) continuous infusion; repeat every 2 weeks.

mFOLFOX6 plus cetuximab (only for KRAS wild-type tumors): Cetuximab 400 mg/m ^{2} loading dose on day 1, thencetuximab 250 mg/m weekly plusoxaliplatin 85 mg/m IV over 2 h on day 1 plusleucovorin 400 mg/m ^{2}**IV** over 2 h on day 1 plus5-FU 400 mg/m ^{2}**IV** bolus on day **1, then** 1200 mg/m ^{2}/day for 2-d continuous infusion; repeat every 2 wk for four to six cycles

Systemic therapy for the second group

mFOLFOX6: Oxaliplatin 85 mg/m ^{2} IV over 2 h on day 1plusleucovorin 400 mg/m ^{2} IV over 2 h on day 1 **plus5-FU** 400 mg/m^2 IV bolus on day 1, **then** 1200 mg/m ^{2}/day for 2-d continuous infusion; repeat every 2 wk. **or FOLFIRI: Irinotecan 180** mg/m ^{2} IV over **30-90** min on day **1** plus leucovorin **400** mg/m ^{2} IV infusion to match duration of irinotecan infusion on day 1 **plus5-FU 400** mg/m IV bolus on day 1, **thenl200** mg/m ^{2}/day for 2-d (total **2400** mg/m ^{2} over **46-48h)** continuous infusion; repeat every 2 wk.

Response rate was categorized according to WHO criteria:

- **Complete response (CR):** complete disappearance of all detectable disease and reversion of all radiological examinations to normal, by two observations not less than 4 weeks apart
- **Partial response (PR):** 50% or more decrease in tumor size (multiplication of longest diameter by the greater perpendicular diameter), determined by two observations not less than 4 weeks apart
- **Stationary disease (SD):** A 50% decrease in total tumor size cannot be established, nor has a 25% increase in size has been demonstrated
- **Progressive disease (PD):** 25% or more increase in size of the lesion or appearance of new lesions

Performance Status was categorized according to WHO:

1. Normal activity
2. Imbed more than 50% of time
3. Symptoms but ambulatory
4. 100% bedridden

In bed less than 50% of time [13]

Statistical methods

Statistical analysis was done using IBM SPSS® Statistics version 22 (IBM® Corp, Armonk, NY, USA) Numerical data were expressed as mean and standard deviation or median and range as appropriate Qualitative data were expressed as frequency and percentage Pearson's Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test All tests were two-tailed A p-value < 0 05 was considered significant

RESULTS

Table 1: Relation overall survival (OS) to different prognostic factors

	N	No of death	Cum. survival at 24 Months (95%)	Median survival	P-value
Mets colon	37	25	30.0 %	(18.9-23.07)	
Type of treatment					0.001
Chemotherapy alone	19	18	5.9 %	17.0%	
Chemotherapy +cetuximab	18	7	59.0 %	24.0%	
Age					
<50	14	10	0.402	20.0	.721
>50	23	15	0.220	21.9	
Sex					
Male	22	14	o.196	21.02	0.556
Female	15	11	0.220	20.98	
Site of cancer					
RT	16	13	0.164	17.99	0.160
LT	21	12	0.421	22.99	
F.H					
-ve	29	20	0.304	21.97	0.476
+ve	8	5	0.333	16.97	
PS					
0	12	7	0.292	22.0	0.644
1-2	25	18	0.292	20.9	
Smoking					
-ve	24	15	0.399	21.0	0.292
+ve	13	10	0.123	20.0	
Anemia					
No	11	7	0.218	20.0	0.605
Yes	26	18	0.325	21.0	
Neytropenia					
No	10	5	0.600	24.0	0.033
Yes	27	20	0.190	20.0	
Neurotoxicity					
No	25	15	0.364	21,0	0.395
Yes	12	10	0,200	7.99	
H.F.syndrome					
No	30	19	0.376	21.0	0.433
Yes	7	6	0.000	20.0	
Anorexia					
No	27	16	0.416	21.9	0.076
Yes	10	9	0.150	16.9	

Rt=right, Lt =left, PS= performance status, FH= family history, H Fsyndroms =hand and foot syndroms
The majority of patients in two groups recived et least 6 cycle of treatment (table 1).

Table 2: Difference in response between two groups according to different prognostic factors

	CR	RD	SD	PD	P-value
Site					
RT	1	9(56.3)	1(6.5)	5(25.0)	0..342
LT	1(4.8)	11(5.24)	5(23.9)	4(19.5)	
No of metastases					
1	2(13.3)	15(68.2)	4(13.7)	3(13.6)	0.281
2-3	0(4.0)	5(33.3)	3(20.0)	5(33.3)	
Type of treatment					
Chemotherapy	0	7(36.8)	5.(26.3)	7(31.6)	0..018
Chemotherapy+ Cetuximab	2(11.1)	13(72.2)	1(5.6)	2(11.1)	

Table 3: Difference in toxicity between two groups

Toxicity	Chemotherapy (n=18)	Chemotherapy + Cetuximab (n=19)	P-value
Neuro			
No	12	13	0.556
Yes	7	5	
H.F.syndrome			
No	14	16	0.405
Yes	5	2	
Nausea			
No	10	12	0.042
Yes	8	6	
Diarrhea			
No	15	14	0.741
Yes	4	4	
Anorexia			
No	10	15	0.040
Yes	9	3	
Anemia			
No	6	5	0.800
Yes	13	13	
Neutropenia			
No	9	10	0.020
Yes	10	8	

Factors affecting the response according to WHO regarding site of tumor there was no significant difference between RT and LT colon (P=0 342) but LT site with better response regarding type of treatment group with target therapy had significant difference in response (P= 0 018) and regarding number of metastatic sites did not alter response in the two groups (table 2,3).

Table 4: Relation of progression free survival (PFS) to different prognostic factors

	Number Of cases	No of events	Cum. Survival at 12 months	Median survival	P-value
Age					
<50	14	14	0.357	9.9	0.608
>50	23	23	0.304	10.0	
Sex					
Male	12	12	0.318	10	0.962
Female	15	15	0.333	10	
Type of treatment					
Chemotherapy	19	18	0.105	8.9	<0.01
Chemotherapy+ cetuximab	18	18	0.556	12.0	
Site of metastases					
RT	16	16	.313	10	0.312
LT	21	21	.343	12	
Previous of ttt					
Yes	17	17	0.353	6.9	0.351
No	20	20	0.300	10	
PS					
0	12	12	0.500	11	0.140
1-2	25	25	0.240	9	
F.H					
-ve	29	29	0.345	10	0.381
+ve	8	8	0.250	8.9	
No of metastases					
1	22	22	0.318	10	0.538
2-3	15	15	0.231	9	
Smoking					
-ve	24	24	0.333	9.9	0.916
+ve	13	13	0.308	10	
Neurotoxic					
Yes	25	25	0.321	10	0.281
No	12	12	0.333	9	
H.F. syndrome					
No	30	30	0.367	10	0.333
Yes	7	7	0.143	10	
Anorexia					
No	27	27	0.407	10.9	0.050
Yes	10	10	0.100	8.9	
Anemia					
No	11	11	0.615	10	0.050
Yes	26	26	0.091	8.9	

Median progression-free survival (PFS) of the whole studied sample (n =37) was 10.0 months (range 3.0 - 21.0). Median survival was significant higher in the chemotherapy and cetuxumab group (P= less than 0.001). using cox regression analysis group with cetuximab associated with better survival (P=0.047) with protective hazard ratio of 0.974. In this table cumulative PFS proportion is presented at 12 months. PFS was significant higher without anorexia and anemia. There was other factors alter PFS at 12 months.

DISCUSSION

Colorectal cancer is the third most common cancer worldwide and the fourth most common cause of death In Egypt, colorectal cancer usually present at an advanced stage and predisposing adenoma are rare **(14).**

As regard to age the mean age of the studied group was founded to be 48.1 + 14.2 years This is similar to the mean age in the united state in which the colorectal cancer is one of 10 most commonly diagnosed cancers among men and women aged 20 to 49 years **(14).**

CRC incidence and mortality rates have been declined in recent years, largely because of screening and surveillance programs that promote colonoscopy and shoot testing in this population **(15).**

As regard sex distribution, male to female ratio in the present study was (59 % vs 40 %) this is comparable to that found by the Austenian Society for gastroenterology and hepatology reported in JAMA, where men have higher rates of advanced tumors than women in all age groups, so males should start having screening colonoscopies at younger age than females [16].

This is also comparable to the records by the American cancer society who states that the lifetime risk of developing colorectal cancer is about 1 in 21 (4.7 %) for men and 1in 23 (4.4 %) for women this risk is slightly lower in women than in men [17].

Colorectal cancer is characterized by diarrhea, constipation, melena and pain Among the present study, pain was the most common symptoms in the two groups of patient with metastatic colorectal cancer These results were comparable to that founded by Smith and his colleagues, who recorded that abdominal pain and change in bowel habits were more common in patient with advanced disease [15].

The goal of treatment in metastatic cancer colon is twofold: palliation of symptoms and extension quality of life Symptomatic disease is likely to benefit from therapy with high response rates (RR) that promptly decreases tumor burden In contrast, some patients will be asymptomatic and extension of this state is the goal In these cases RR may be irrelevant, and well-tolerated regimens with overall survival (OS) benefit are preferred The potential for cure is thus contingent on response and combination cytotoxic regimens with high RR in selected patients [18].

As regard the site of metastases in our study, the liver was the most common site especially in the younger age group. These results were comparable to that recorded by Vander Geets and his colleges. He stated that of all patients with metastatic cancer, the most common sites of metastases were liver (70% in colon cancer, 70 % in rectal cancer) and the thorax (32%-47%) In colon, the third most common site was the peritoneum (21%) and was in bone (12%) [14].

In our study, we study the value of adding target therapy in the metastatic colon cancer patients some of them received chemotherapy with cetuximab as target therapy versus patients received chemotherapy alone.

Published data from other studies have observed that cetuximab was beneficial as part of down staging programs. The addition of cetuximab to chemotherapy regimens in patients with KRAS wild type colon cancer has been shown to increase the response rates and the number of patients being down –staged and offered potentially curative resection [19].

Similar to our study, The OPUS and CRYSTAL trials observed good response rates following the addition of cetuximab but low resection rates The CELIM and POCHER studies reported higher resection rates due to better patient selection and study design However, the majority of published studies tend it report minimal surgical data and lake short and long term outcomes However, the use of cetuximab with chemotherapy was improve the efficacy of down-staging programs [20].

Similar to our study, A retrospective analysis of the CRYSTAL and FIRE-3 confirmed the following data, primary tumor location was predictive of improved survival in RAS wild-type LCC (HR for OS in LCC 0.69; P-value <0.0001) and not in RCC (HR for OS 0.96: P-value 0.802) when chemotherapy plus anti –EGFR and chemotherapy only were compared as first –line treatment Moreover, LCC patients had greater benefit from chemotherapy plus anti –EGFR versus chemotherapy than RCC [2]

Cunningham et al showed an improved survival in patients with metastatic colorectal cancer following the addition of cetuximab [21].

Similar to our study, In the BOND trial, the authors showed that metastatic colorectal cancer patients receiving the combination therapy of cetuximab with irrinotecan had a significantly higher response rates and reduced tumour progression compared to patients treated with cetuximab alone [17].

In randomized trial consisting of 1298 patients with metastatic colorectal cancer refractory tofluoropyrimidine and oxaliplatin treatment, Sobrereo et al observed that cetuximab and irinotecan significantly increased both the response rates and progression-free survival compared to irinotecan alone. Nevertheless, the overall survival in both the above studies did not significantly improve with the addition of cetuximab [22].

Similar to our study, In the CRYSTAL study, ***Van Cutsem et al*** investigated the efficacy of first-line cetuximab with FOLFIRI alone in patients with unresectable metastatic colorectal cancer tumor responses were seen in 281.(46.9%) patients receiving cetuximab and FOLFIRI and in 232.(38.7%) patients receiving FOLFIRI alone in the ceuximab – FOLFIRI group, (7 %) of patients had surgery with curative intent for metastases compared with (3.7 %) in the FOLFIRI only group the rate of R0 resection was also higher in the cetuximab-FOLFIRI group (4.8%) compared to the FOLFIRI only group (1.7%) However, no details with respect to surgery for metastatic disease and pattern of recurrence were reported The median progression free and overall survival was 8.9 and 8,0months and 19.9 months and 18 6 months respectively in the cetuximab- FOLFIRI group and FOLFIRI only group This similarity in survival between treatment group was likely to be secondary to post-trial therapy (25.4 of patients in the FOLFIRI group and 6.2 % in the cetuximab-FOLFIRI group received EGFR antibody therapy post-study) [23].

Similar to our study, Raoul and co-investigators showed an overall response rate of 48% and median duration of response of 9.9 months following treatment with cetuximab combined with FOLFIRI This study also showed that the cetuximab

combination therapy successfully down-staged 14 (27%) patients that were deemed to have in operable disease prior to therapy, of which most had liver metastases, 2% for lung and 4% for metastases at other sites These patients underwent surgery with curative intent and the R0 resection rate was 71% (n=10) of cases the median overall survival was 22.4 months in the whole cohort no further details with regard to post–operative morbidity and survival were reported.[24].

Folprech and co-workers conducted a multi-centere randomized (CELIM) study to assess the efficacy of cetuximab in different chemotherapy regimens (FOLFOX-6 VERSUS FOLFIRI) in treatment of 106 patients with technically non-resectable or five or more CRLM atotal of 45.(42.4%).patients underwent liver resection of which 22.(41.5%).patients were from the cetuximab-FOLFOX-6 group and 23.(43.4%).patients were from the cetuxmab-FOLFIRI group the overall R0 resection rate was 34 % (n=36) [cetuximab-FOLFOX-6=20 (38%) and cetuximab-FOLFIRI =16 (30%)] Although this study reported significantly better dowen-etaging of CRLM with the addition of cetuximab to conventional chemotherapy, detail of resection, post-surgical outcomes and survival data were not reported [25].

The above published studies confirm that the response rates in patients with metastatic colorectal cancer that were refractory to irinotecan and /or oxaliplatin-based regimens improved following the addition of cetuximab, suggesting that resistance to previous chemotherapy regimens are not a negative predictor for response Nevertheless, the increase in response rates following combination thereby of cetuximab and chemotherapy regimens is not translated into a significant improvement in overall survival, even in patient with KRAS wild type metastatic colorectal cancer and its use in palliative setting cannot be recommended [26].

The OPUS study demonstrated that addition of cetuximab to 5 (FOLFOX4) significantly improved objective response and progression-free survival in the first line treatment of patients with KRAS wild- type metastatic colorectal cancer result in the extended analysis of RAS wild-type tumor (n=87),objective response was significantly improved by addition of cetuximab to FOLFOX4 (58% versus 29%:odds ratio 3.33 {95% confidence interval 1.36-8 17}, p=0.0084) although limited by population size there also appeared to be trends favoring the cetuximab arm in terms of PFS and overall survival in the ras wild- type group [8]

The phase III CRYSTAL study demonstrated that addition of cetuximab to FOLFIRI significantly improved overall survival, progression-free survival, and objective response in the first-line treatment of patients with KRAS codon 12/13 (exon2) wild-type metastatic colorectal cancer A clear and significant benefit associated with the addition of cetuximab to FOLFIRI was apparent in relation to OS, OFS, and objective response in patients with RAS wild-type tumor (n=367 out n=666 the HR for OS time and OR for objective response rate were more favorable toward FOLFIRI plus cetuximab in the RAS wild type population [23].

In summary, cetuximab was beneficial in down-staging programs and significantly improve progression-free survival and response rates for patients with metastatic colorectal cancer.

In the current our study, Median progression-free survival (PFS) of the whole studied sample (n =37) was 10.0 months (range 3.0.-.21.0) median survival was significant higher in the chemotherapy and cetuxumab group (P= less than 0.001) Using cox regression analysis group with cetuximab associated with better survival (P=0.047) with protective hazard ratio of 0.974. The cumulative PFS proportion is presented at 12 months.

Median.overall.survival.of.whole.studied.samples.(n=37).was.21.0.months.(range.18-23.months).and.there.were.25.cases.dead.and.all.cases.progressed..Median.OS.was.higher.in.chemotherapy.with.cetuximab.group.and.was.a.significant.difference.(P=0.001)..There.were.others.factors.studied.their.relation.to.OS.like.age.but.no.significant.difference.bit.older.patient.had.better.OS.by.(34.8.%.vs.28.6.%),.also.PS.no.significant.difference.but.patient.with.PS.=0.had.better.OS.by.(41.7%.vs.28%)..according.to.RT.and.LT.colon.there.was.LCC.with.better.OS.than.RCC.but.no.significant.difference.but.LT.site.of.colon.had.better.survival.by.(42.9.%vs.18..8%).

Factors affecting the response according to WHO regarding site of tumor there was no significant difference between RT and LT colon (P=0.342) but LT site with better response Regarding type of treatment group with target therapy had significant difference in response (P= 0.018) and regarding number of metastatic sites did not alter response in the two groups.

The most frequent toxicity related to treatment was neurotoxicity (33.4%), vomiting (35%) and anemia (26%) metastases were mostly in single site around 24 patients mainly metastasis to liver 62% difference in toxicity was significant only in anorexia, nausea and neutropenia.

The above published studies confirm that the response rates in patients with metastatic colon cancer that were refractory to irinote can and/or oxaliplatin-based regimens improved following the addition fcetuximab, suggesting that resistance to previous chemotherapy regimens are not a negative predictor for response to cetuximab.

Nevertheless, the increase in response rates following combination therapy of cetuximab and chemotherapy regimens is not translated in to a significant improvement in overall survival, even in patients with *KRAS* wild-type metastatic colon cancer, and hence its use in the palliative setting cannot be recommended [26].

CONCLUSION

Cetuximab was beneficial in down-staging programs and significantly improve progression-free survival and response rates and overall survival for patients with metastatic colorectal cancer.

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