JBUON 2014; 19(1): 83-90
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Clinical benefit of cetuximab and prognostic value of cetuximab-related skin toxicity in metastatic colorectal cancer: a single institution analysis

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Summary

Purpose: *To evaluate the clinical benefits of cetuximab (CTX) and the prognostic value of CTX-related skin toxicity in metastatic colorectal cancer (mCRC) patients.*

Methods: *Sixty patients were tested for KRAS mutation at the Department of Oncology, Clinical Centre Nis. We assessed 34 wild-type KRAS mCRC patients treated with CTX. All of them were refractory to prior fluoropyrimidine, oxaliplatin and irinotecan-based regimens. The maximum grade skin toxicity according to treatment cycle was analyzed. Skin toxicity was grouped into clinically non-relevant skin toxicity (grade 0 -1: Group 1) and clinically relevant skin toxicity (grade 2-4: Group 2).*

Results: *Ten out of 33 patients (30.30%) achieved partial response (PR). Eight additional patients (24.24%) showed stable disease (SD), whereas 15 (45.45%) had disease progression (PD). No patient achieved complete response (CR). Overall response rate (ORR) was 30.30%, whereas the disease control rate (DCR) was 54.54%.The median progression free survival (PFS) was 14 weeks. Some degree of skin toxicity was observed in 79.41% (27/34) of the patients. Clinically non-relevant skin toxicity was observed in 50% (17/34), and clinically relevant in 50 % (17/34) of the patients. Grade 4 skin toxicity was documented in 1 patient. The mean PFS in Group 1 was 12.65±5.59 weeks and in Group 2 22.82±12.16 ($p<0.05$). The results showed that grade 2-4 skin toxicity was associated with significantly better response to treatment than skin toxicity grade 0-1, with regard to ORR (80.00 vs 20.00%; $p<0.05$) and DCR (66.66 vs 33.33%; $p<0.05$).*

Conclusion: *Cetuximab has clinical benefit when given alone or in combination with irinotecan in patients with irinotecan-refractory CRC. Skin toxicity was one of the predictors of response and it was in line with what was expected.*

Key words: *cetuximab, clinical benefit, metastatic colorectal cancer, skin toxicity*

Introduction

mCRC is still far from being a curable disease, except in cases of organ-confined (lung or liver) resectable metastatic disease. The aim of treatment in mCRC patients is to prolong overall survival (OS) and to decrease tumor-related symptoms without affecting the quality of life. The introduction of cetuximab and panitumumab, the new biologically active targeted agents, has been one of the most promising developments in cancer treatment in the past 5 years and has dramatically improved ORR, PFS and OS [1].

Epidermal growth factor receptor (EGFR), a member of an ErbB family of receptors, is relevant to colorectal cancer because the EGFR expression or up-regulation occurs in 60-80% of the cases, and the expression of the gene is associated with poor survival [2,3].

CTX is a chimeric immunoglobulin G1 monoclonal antibody which binds EGFR with high affinity and competitively inhibits ligand binding, induces receptor internalization and causes direct

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Received: 18/06/2013; Accepted: 30/06/2013

inhibition of the receptor tyrosine kinase activity. This blocks the downstream signal transduction via PI3K/Akt and RASRAF/MAPK pathways, inducing pro-apoptotic mechanisms and inhibiting cellular proliferation, angiogenesis and metastasis [4,5].

Ras constitutes a family of protoongenes with 3 different members known as Harvey- Ras (HRAS), Kirsten-Ras (KRAS) and N-Ras. KRAS mutations occur in approximately 35-43% of sporadic colorectal cancers. Up to 90% of the mutations can be detected in either codon 12 and 13, or, less frequently, in codons 61 and 63 [5-7]. Retrospective analyses of phase II and III studies have demonstrated that KRAS mutations are predictors of resistance to anti-EGFR therapy. Patients with mCRC with mutant (MT) KRAS tumor status do not derive clinical benefit [4, 8-10].

EGFR inhibitors are generally well tolerated and do not have the severe systemic side-effects usually seen with cytotoxic drugs. They often cause signs of skin toxicity, most often an acneiform eruption [3,11,12]. Response and survival of CTX-treated patients strongly correlates with the severity of the acneiform skin rash. The association of treatment efficacy with CTX-induced skin toxicity has already been described in several reports. Skin toxicity is an early event in the CTX treatment and it usually occurs within the first 21 days [3,5,13-15]. Skin rash is mostly mild-to-moderate in severity and requires therapeutic intervention in about one third of the patients. Although the skin rash is self-limiting and usually resolves without scarring upon discontinuation of anti-EGFR therapy, the condition can negatively affect the treatment compliance and quality of life [15,16].

Methods

Treatment

A total of 60 patients were tested for KRAS mutation at the Department of Oncology, Clinical Centre Nis, from January 2009 to August 2012. KRAS mutation was found in 26 (43.33%) patients.

We assessed 34 wild-type KRAS mCRC patients treated with CTX. All of them had histologically confirmed mCRC (adenocarcinomas), had undergone surgical resection of the primary tumor, and were refractory to prior fluoropyrimidine, oxaliplatin and irinotecan regimens.

Twenty patients received cetuximab combined with irinotecan plus 5-fluorouracil and folinic acid (FOLFIRI or IFL regimens), 8 received CTX combined with irinotecan, and 6 received CTX monotherapy. CTX as monotherapy or before chemotherapy (IFL and irinotecan) was administered at 400mg/m^2 as initial dose and 250 mg/m^2 weekly as i.v. infusion over 120 min. CTX in combination with FOLFIRI was given every two weeks at 500mg/m^2 as i.v. infusion over 120 min. Chemotherapy was given 60 min after CTX stopped. The histamine-receptor antagonist (chloropyramine chloride 40 mg i.v.) was used as premedication.

Treatment evaluation

Tumor response was evaluated by computerized tomography scans according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and classified as CR, PR, SD and PD. Complete and partial responders were then categorised as responding patients, while patients with SD or PD were categorised as non-responding patients.

Their performance status (PS) was evaluated in accordance with the Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS).

Evaluation of skin toxicity

Skin toxicity was evaluated using the NCI-CTCAE (National Cancer Institute Common Toxicity Criteria of Adverse Events) version 3.0, regardless of the chemotherapy cycle the patients were receiving. The results were classified as follows: grade 1: macular or papular eruption or erythema without associated symptoms; grade 2: macular or papular eruption or erythema with pruritis or other associated symptoms and localized desquamation or other lesion covering <50% of body surface area; grade 3: severe generalized erythroderma or macular, popular or vesicular eruption or desquamation covering ≥50% of body surface area; grade 4: generalized exfoliative, ulcerative or bullous dermatitis.

We analysed the maximum grade skin toxicity according to treatment cycle and its predictive value with regard to treatment efficacy. Furthermore, skin toxicity was grouped into clinically non-relevant skin toxicity (grade 0 -1) and clinically relevant skin toxicity (grade 2-4).

DNA extraction and mutation analyses

DNA was extracted from formalin-fixed paraffin-embedded tissue using Therascreen KRAS PCR kit (Qiagen, Germany) according to the manufac-

Table 1. Patient and disease characteristics

Characteristics	*N*	*%*	*Mean±SD*	*Median, range*
No. of patients	60	100.0		
KRAS wild	34	56.67		
KRAS mutant	26	43.33		
Sex (male/female)	25/9	(73.53/26.47)**		
Age (years)			64.74±9.26	64.50, 42-80
Primary site				
Colon	7	20.59		
Rectum	9	26.47		
Sigmoid	13	38.24*[a]		
Rectosigmoid	5	14.71		
Number of metastatic site				
1	11	32.35		
2	17	50.00**[b]		
3	6	17.65		
Metastatic organs				
Liver	28	82.35**[c],***		
Lymph nodes	11	32.35		
Peritoneum	1	2.94		
Spleen	2	5.88		
Vertebrae	1	2.94		
Lung	15	44.12		
Adrenals	3	8.82		
Sternum	1	2.94		
Ovary	2	5.88		
ECOG PS				
0	5	14.71		
1	25	73.53***[de]		
2	4	11.76		

* p<0.05, ** p<0.01, *** p<0.001, [a] vs rectosigmoid, [b] vs 3 metastatic organs, [c] vs lung, [d] vs ECOG=0, [e] vs ECOG=2. ECOG PS: Eastern Cooperative Oncology Group Performance Status, SD: standard deviation

turer`s instruction. The presence of KRAS mutation was determined by an allelic discrimination assay on Rotor-Gene Q Real time PCR system (Qiagen, Germany). All mutations were confirmed by direct sequencing. KRAS mutation analysis was performed in a Serbian reference laboratory for KRAS analysis (Institute of Oncology and Radiology, Belgrade).

Statistics

All analyses were performed using the Statistical Package for Social Sciences v.15.0 (SPSS 15.0) software. Descriptive parameters were expressed as percentages and frequencies, continuous variables were expressed as mean, standard deviation (SD), median (Me), and range.

Chi-square test was used for the analysis of some descriptive data frequency. The Shapiro-Wilk test was used for normality analysis of the continuous data. The Mann-Whitney U test was used for testing statistical differences of variables between two groups.

PFS was calculated from the start of CTX to either PD or death from any cause. A p-value of <0.05 was considered as statistically significant.

Results

Patients

Of the patients 73.53% were men and 26.47% women, with median age 64.5 years (Table 1). Half of the patients (17;50%) had two metastatic sites and the most common metastatic site (82.35%) was the liver.

Table 2. Therapies

	N	%	*Mean±SD*	*Median, range*
Regimen				
Mono CTX	6	17.65		
IFL plus CTX	7	20.59		
FOLFIRI plus CTX	13	38.24		
Irinotecan plus CTX	8	23.53		
Number of cycles			5.59±3.17	4.00, 2-12
Previous adjuvant therapy	19	55.88		
Prior 1st line therapy				
FOLFOX	18	52.94*[f]		
OXFL	14	41.18*[f]		
FL	2	5.88		
Prior 2nd line therapy				
FOLFIRI	20	58.82		
IFL	14	41.18		
Time between primary diagnosis and start of CTX (months)			28.03±17.29	21.50, 9-69
<12	4	11.76		
12-24	14	41.18*[g]		
>24	16	47.06*[g]		

*p<0.001, [f] vs FL, [g] vs 12 months, CTX: cetuximab

Table 3. Efficacy and skin toxicity

	N	%	*mean±SD*	*Median, range*
Response to therapy				
PR	10	30.30		
SD	8	24.25		
PD	15	45.45		
ORR	10	30.30		
DCR	18	54.55		
PFS (weeks)			17.74±10.65	14.00, 7-42
Skin toxicity (grade)				
0	7	20.59		
1	10	29.41		
2	12	35.29*[h],**[i]		
3	4	11.76		
4	1	2.94		
Clinically non-relevant skin toxicity (grade 0-1: group 1)	17	50.00		
Clinically relevant skin toxicity (grade 2-4: group 2)	17	50.00		

*p<0.05, *p<0.01, [h] vs grade 3, [i] vs grade 4. PR: partial response, SD: stable disease, PD: progressive disease, ORR: overall response rate, DCR: disease control rate

The median number of received cycles with CTX was 4 (range 2-14). ECOG PS ranged from 0 to 2.

Oxaliplatin was chosen as first-line therapy in 32 (94.12%) patients and all of the patients received irinotecan-based therapy (FOLFIRI or IFL) as second line. The median time between primary diagnosis and the administration of CTX was 21 months (Table 2).

Treatment efficacy

Treatment efficacy is shown in Table 3.

Table 4. Predictive value of skin toxicity

	N	%	*Mean±SD*	*Median, range*
PFS (weeks)				
Group 1 (skin toxicity grade 0-1)			12.65±5.59	10.00, 8-26
Group 2 (skin toxicity grade 2-4)			22.83±12.16*	24.00, 7-42
Skin toxicity (grade)				
PR			1.90±0.57*[j]	2.00, 1-3
SD			1.38±1.30	1.50, 0-3
PD			1.07±0.88	1.00, 0-3
Skin toxicity – group 1/ group 2				
PR	2/8	20.00/80.00*		
SD	4/4	50.00/50.00		
PD	11/4	73.33/26.77*		
ORR	2/8	20.00/80.00		
DCR	6/12	33.33/66.66		

*p<0.05, [j] vs PD. PR: partial response, SD: stable disease, PD:progressive disease, ORR: overall response rate, DCR: disease control rate, SD: standard deviation

One patient developed a strong reaction to CTX (dyspnea and grade 4 skin toxicity in the second cycle of therapy) and therapy was discontinued.

Ten out of 33 patients (30.30%) obtained PR. Eight additional patients (24.24%) showed SD, whereas 15 (45.45%) had PD. No patient achieved CR. ORR was 30.30%, whereas DCR was 54.54%.

The median PFS was 14 weeks (range 7-42).

Some degree of skin toxicity was observed in 79.41% (27/34) of the patients. Clinically non-relevant skin toxicity (grade 0-1: Group 1) was observed in 50% (17/34), and clinically relevant skin toxicity (grade 2-4: Group 2) in the remaining 50%. Grade 4 skin toxicity was documented in 1 patient.

Predictive value of skin toxicity for response and progression free survival

Table 4 shows that the mean PFS increased with increasing grade of skin toxicity. The mean PFS in Group 1 was 12.65±5.59 weeks and in Group 2 it was 22.82±12.16 ($p<0.05$).

Clinically relevant grade 2-4 skin toxicity was assosiated with significantly better response to treatment than grade 0-1 skin toxicity, with regard to ORR (80.00 vs 20.00%; $p<0.05$) and DCR (66.66 vs 33.33%; $p<0.05$).

Discussion

CTX has proven to be active in patients with mCRC refractory to irinotecan, oxaliplatin and fluoropyrimidines in phase II clinical trials [3,12,13,17]. However, even if CTX is active in irinotecan-resistant patients, the response rate with the combination of CTX and irinotecan is only 23% and PFS is 4.1 months [3].

We tested a series of 60 patients, in whom irinotecan therapy had failed, for KRAS mutation status and found 24 (43.33.%) cases with mutation. Knowing the predictive value of tumor KRAS mutation status in relation to the efficacy of CTX [4,17- 20], we treated only a group of 34 wild-type KRAS mCRC patients with CTX.

Treatment with CTX following a previously unsuccessful chemotherapy was associated with an almost doubled median OS and PFS in CRC patients with wild type KRAS. Several studies have shown an association between KRAS mutation status and the responsiveness of CRC to CTX [4,17,19,21,22]. Wild type KRAS is a strong predictor of significant increase in PFS and OS in these patients [4].

It is important to highlight that, in our series, the proportion of CR/PR, SD and PD patients was 30.30, 24.25 and 45.45% respectively, which is similar to the distribution reported in the randomized CTX trial [3]. Our data showed an ORR and DCR amounting to 54.54%. The median PFS was 14 weeks (~3.5 months) and KRAS mutation status was 43.33%. All these results are comparable to the results of the previous, second and third line studies, which estimated the value of adding CTX to irinotecan in irinotecan-resistant mCRC [3,4, 19,20,22,23].

The CECOG trial showed KRAS mutation fre-

quency of 47%, PFS interval 8.4 months longer than ours, and ORR amounting to 50% [23]. Lievre et al. presented a group of 89 mCRC patients and found ORR to be 40% in the group with wild type KRAS. The PFS interval in this group was 7.9 months [20]. Bienvenuti et al. reported KRAS mutation status in 33% of their cases, with ORR in wild type KRAS of 31% and PFS of 17 weeks [24]. Frattini et al. investigated tumors in 27 patients, and found KRAS mutation status in 37% and ORR in 53% of them [22].

One of the largest analyses was performed by De Rook et al. They evaluated 113 irinotecan-refractory mCRC patients treated with CTX-based therapy. Mutations of the KRAS gene were observed in 40.7% of the cases. ORR was 41% in the wild type KRAS vs 0% in mutant KRAS patients, whereas PFS was 6 months in the wild type group [4]. Cunningham et al. compared CTX monotherapy with CTX plus irinotecan in irinotecan-refractory mCRC and found RR of 22.9% in the combination therapy group vs 10.8% in the monotherapy group. PFS was significantly longer in the combination therapy group (4.1 vs 1.5 months, p<0.001) [3]. De Fiore et al. studied 59 patients and reported KRAS mutation rate of 37%. The ORR was 28% in the patient group with wild type KRAS and the PFS was 5.5 months [19].

The COIN study showed KRAS mutations in 43% of the patients and reported no benefit from adding CTX to oxaliplatin-based first line combination chemotherapy in the treatment of advanced colorectal cancer [25].

While the rash was disturbing from an esthetic standpoint, it was rarely severe and seldom resulted in the termination of treatment. Consistent with other reports of both EGFR-targeting antibodies and receptor TK inhibitors, the severity of the rash related strongly to both response and survival [26-29].

Skin toxicity, a well-known predictor of response, was one of the predictors in our study and it was in line with what was expected. When all 34 CTX-treated patients were analysed, clinically relevant skin toxicity (grade 2-4) proved to be associated with significantly higher response to treatment than grade 0-1 skin toxicity, with regard to ORR (80.00 vs 20%), DCR (66.66 vs 33.33%) and PFS (22.82 vs 12.65 weeks).

In 5 phase II studies, patients who developed acne-like rash were shown to have longer OS, suggesting that skin toxicity may be a relevant marker of CTX clinical response. Responses have been shown to correlate with the severity of the rash in phase II studies [3,4,13,26,30-32].

The BOND trial reported higher response rates in patients with skin rash compared with patients without skin rash (25.8 vs 6.3% respectively, p=0.005) [3]. Lenz et al. investigated 346 mCRC patients refractory to standard chemotherapy, who received CTX in a multicenter phase II trial. The median RR in the whole group was 12.4%. Patients with grade 1, 2 and 3 skin toxicity had a RR of 7.2, 17 and 20%, respectively [13]. Similarly, Saltz et al. showed longer survival in patients with severe skin toxicity [12]. In contrast, the results from the EVEREST study demonstrated no association between KRAS and skin toxicity [33].Also, Lievre et al. recorded a strong correlation between KRAS mutation and PFS and OS, whereas the skin rash was associated only with OS [17].

In conclusion, CTX has clinical benefit when given alone or in combination with irinotecan in patients with irinotecan-refractory mCRC. These results should prompt further studies with larger numbers of mCRC patients with the aim of establishing with certainty the clinical benefits of KRAS mutation status in anti EGFR antibodies-based chemo-targeted therapy. A major criticism directed to all studies of biomarkers predictive of clinical response to CTX and other anti EGFR antibodies in mCRC is that the clinical benefit is evaluated on the metastatic disease, whereas the presence of the marker is assessed from the primary tumor. Considering the genetic evolution of metastases compared to primary tumors, we think that determining the presence of alterations by screening metastases directly will be essential to predicting either sensitivity or resistance to these targeted therapies.

There were also patients with wild type KRAS tumors who did not respond to CTX and in whom the tumor progressed rapidly. Additional reliable and easily measured biomarkers are clearly needed to improve the identification of patients who can benefit from the treatment with CTX. The treatment, which is rather expensive, would be most cost-effective if given to patients with the highest chance of benefiting from it [21]. It is necessary to clearly define the subpopulation of patients who can truly benefit from CTX, because failure to do so means an increase in treatment costs, frequent trips to hospital and toxicity [34].

At present, the most urgent issue is that of identifying the mechanisms of secondary resistance to anti EGFR antibody therapies in mCRC. Even the best responses obtained in wild type KRAS tumors are transient and do not last longer than 12-18 months. In most cases the tumors rapidly begin to regrow after the massive initial reduction, and become refractory to further anti EGFR treatment [3].

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