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ORIGINAL ARTICLE

Cetuximab in third-line therapy of patients with metastatic colorectal cancer: A single institution experience

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Summary

Purpose: *Cetuximab, an IgG1 chimeric monoclonal antibody (MAB) against epidermal growth factor receptor (EGFR) has activity against metastatic colorectal cancers (mCRC) that express EGFR. The purpose of this study was to demonstrate the efficacy and safety of cetuximab administered to patients with EGFR-positive mCRC.*

Methods: *72 patients with wild-type KRAS mCRC were enrolled. All of them had previously been treated with a fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy. Patients received cetuximab as monotherapy or in combination with irinotecan-based chemotherapy. All patients were to be treated until the occurrence of disease progression or unacceptable toxicity.*

Results: *All patients were evaluated for progression free survival (PFS), overall survival (OS) and safety. The median PFS was 4.77 months (95% CI: 4.08–5.45), with an actuarial 47.22% without progression at 3 months and 16.67% at 6 months. The median OS was 11.35 months (95% CI: 9.64–13.06), with 79.17% of the patients being alive at 6 months and 30.56% at 12 months. PFS was significantly higher in patients with skin toxicity as compared to those without skin toxicity (5.31 vs 2.61 months, p<0.001) and with smaller number of metastatic organs vs greater number of metastatic organs (p=0.05). OS was significantly higher in patients with good performance status (p=0.004), with skin toxicity (p=0.013) and with smaller number of metastatic organs (p<0.001). Superior survival rates with higher grades of skin toxicity were noticed. As for patient characteristics, there were no significant differences in age, gender, and primary site localization.*

Conclusion: *Cetuximab improved PFS, OS and preserved the quality of life in patients with mCRC whose previous treatments had failed.*

Key words: *cetuximab, metastatic colorectal cancer, skin toxicity, survival*

Introduction

CRC is currently the third most common cancer worldwide and fourth leading cause of cancer-related deaths. Moreover, its incidence is increasing [1]. Approximately 25% of CRC patients show overt metastases on presentation and an additional 25–35% of patients will develop metastases during the course of their disease [2].

Survival of mCRC patients has been more than doubled in the past 20 years. This significant improvement is mainly due to the development of new combinations of standard chemotherapy, and also to the introduction of new targeted therapies, such as monoclonal antibodies against epidermal growth factor receptor (EGFR) or monoclonal antibodies against vascular endothelial growth factor (VEGF).

5-fluorouracil (FU) and folinic acid (FA) induce tumor regression in 20% of the patients with advanced or mCRC, achieving an overall survival from 6 to 12 months. The combination of irinote-

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can and oxaliplatin, as first- and second-line therapy, improves the results. First-line combination chemotherapy raises response rates to almost 50% and PFS from 4–6 months to 6–8 months. Second-line therapy achieves response rates in the range of 5–20%, increases PFS to 4–6 months [3,4] and also adds to a prolonged OS.

The addition of targeted therapies to standard chemotherapy regimens results in an increase of toxicity and treatment costs [5] and therefore requires identification of decision-making tools for selecting patients who are likely to benefit from them.

EGFR is a member of ErbB family of receptors, and is relevant for CRC because the expression or upregulation of the EGFR gene occurs in the majority of studies at approximately 60–80% of the examined cases. Expression of the gene is associated with poor prognosis [6].

Cetuximab is a chimeric IgG1 MAB that binds to EGFR with high specificity and with 5– to 10–fold greater affinity than either epidermal growth factor or TGF*a*, thus blocking ligand-induced phosphorylation of EGFR. In addition, cetuximab enhances the effects of irinotecan [7].

The purpose of this study was to demonstrate the efficacy and safety of cetuximab administered either alone or in combination with irinotecan in patients with EGFR-positive mCRC who were refractory to irinotecan.

Methods

Cetuximab monotherapy or in combination with irinotecan was licensed in July 2008 by the European Medicines Agency and in September 2009 by the Food and Drug Administration for the treatment of advanced, EGFR-positive CRC patients after failure of 5-FU, oxaliplatin and irinotecan-based chemotherapy.

As for Serbia, cetuximab was registered in May 2009 for patients with KRAS wild-type mCRC who had progression on irinotecan. From June 2009 to May 2014, the Clinic of Oncology, Clinical Center Nis enrolled 72 patients for third-line therapy of histologically confirmed wild-type KRAS mCRC. All of them were refractory to prior chemotherapy with fluoropyrimidine, oxaliplatin and irinotecan. Patients had ECOG performance status (PS) 0-2 and adequate hematological parameters, liver and renal function.

EGFR expression was analyzed by means of Rotor-Gene Q Real time PCR system (Qiagen, Germany) at the Institute of Oncology and Radiology, Belgrade and iCycler IQ Real-Time PCR Detection System (Bio-Rad, USA) at the Clinic of Oncology, Clinical Center Nis.

Treatment

Patients received cetuximab as monotherapy or in combination with irinotecan-based chemotherapy: FOLFIRI (irinotecan 180 mg/m^2 as a 90-min infusion day 1; LV 400 mg/m^2 as a 2-h infusion immediately followed by 5-FU bolus 400 mg/m^2 and 46-h continuous infusion of 2400 mg/m^2, every 2 weeks), IFL (irinotecan 125 mg/m^2 as a 90-min infusion day 1; LV 20 mg/m^2 as a 2-h infusion immediately followed by 5-FU bolus 500 mg/m^2, in 4 consecutive weeks, and one week rest), and single-agent irinotecan (irinotecan 125 mg/m^2 as a 90-min infusion day 1, in 4 consecutive weeks, and one week rest).

In premedication, a histamine-receptor antagonist and atropine (0.25-0.50 mg) were given before each infusion. Moreover, dexamethasone was given at a flat dose of 12 mg. A standard antiemetic drug was always given in premedication and in the following days, all in accordance with the attending physician's opinion.

Cetuximab was given intravenously at an initial dose of 400 mg/m^2, administered over a period of 120 min, followed by a weekly maintenance infusion of 250 mg/m^2, administered over a period of 60 min. Antihistamine (chloropyramine chloride 40 mg i.v.) was given 30-60 min before each dose of cetuximab. Chemotherapy started 60 min after the completion of cetuximab infusion.

All patients were to be treated until the occurrence of disease progression or unacceptable toxicity.

Treatment evaluation

Tumor response was evaluated every 8 weeks by means of consistent imaging techniques (CT or MRI). Assessment was performed by a radiologist who used Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and classified them as CR, PR, SD and PD.

PFS was calculated as the period from the first infusion with cetuximab to the first observation of disease progression. OS was calculated as the period from the first infusion of cetuximab until death from any cause. Both PFS and OS were estimated by Kaplan-Meier method.

Safety evaluation

Toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0. Administration of cetuximab was delayed in cases of grade ≥3 skin toxicity. In case of 2nd occurrence of grade 3 or 4 NCI-CTC toxicity, cetuximab dosage was reduced to 200 mg/m^2 in the subsequent treatment cycles. In case of 3rd occurrence cetuximab dosage was reduced to 150 mg/m^2 in the subsequent treatment cycles. Cetuximab was stopped in case of 4th occurrence of grade ≥3 skin toxicity. Modifications of the dose of cetuximab were performed only in cases of toxic effects to the skin. Irinotecan was delayed in case of hematologic or non-hematologic toxic effects.

Table 1. Patient, disease and treatment characteristics

Characteristics	*N*	*%*
Patients	72	100.0
Age, years*		
< 65	37	51.39
65	35	48.61
Sex		
Male	53	73.61
Female	19	26.39
ECOG PS		
0	4	5.56
1	62	86.11
2	6	8.33
Primary site		
Colon	15	20.83
Sigmoid	20	27.78
Rectum	37	51.39
Site of progression		
Liver	56	77.78
Lung	29	40.28
Lymph nodes	10	13.89
Local recurrence	13	18.05
No. of progression sites		
1	30	41.67
2	33	45.83
3	9	12.50
1st line chemotherapy		
FOLFOX	41	56.94
OXFL	29	40.28
5-FU/LV	2	2.78
2nd line chemotherapy		
FOLFIRI	40	55.56
IFL	32	44.44
CEA (ng/ml)		
Median	63.03	
Range	39-82	

For abbreviations see text

Statistics

Statistical analyses were carried out by means of SPSS statistical package (version 17.0; SPSS Inc., Chicago, ILL). The x^2 test was used to calculate the p value for association between some descriptive data frequency. A p value <0.05 was considered as statistically significant for all analyses. Univariate and multivariate analysis estimated the relationship between survival and the other variables.

P value and hazard ratios (HR) with 95% confidence intervals (CI) were calculated from stratified Cox regression models. The significance of factors potentially associated with survival was determined by multivariate analysis using Mantel-Cox proportional hazard model. PFS and OS were summarized by means of Kaplan-Meier plots.

Results

Between June 2009 and May 2014, we enrolled 72 patients with wild-type KRAS mCRC at the Clinic of Oncology, Clinical Center Nis. All of them were previously treated with a fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy. The cut-off date was set on 31st May 2014 (including patients continuing treatment).

The main characteristics of our patients are listed in Table 1. Median age was 63 years (range 39–82), 53 (73.61%) patients were male, while the male/female ratio was 1: 0.4. The primary location of cancer was colon (35 patients), and rectum (37 patients). The most common metastatic site was liver (77.78%), and more than half of the patients (58.33%) had 2 or 3 metastatic sites. Most patients were in good ECOG PS, with 4 patients in PS=0 and 62 patients in PS=1.

Treatment

Almost all patients (97.22%) received oxaliplatin-based chemotherapy (FOLFOX 4, OXFL) in first-line therapy. Only 2 patients received 5-FU and folinic acid (5-FU/LV). In the second-line, all patients received irinotecan-based chemotherapy (FOLFIRI, IFL; Table 1).

The median number of administered courses was 12 (range 2-36). Ten patients received cetuximab monotherapy, 40 received cetuximab combined with irinotecan alone, and 22 received cetuximab combined with irinotecan plus 5-FU and folinic acid (FOLFIRI, IFL). All patients received pre-medication, and most of them (86.11%) were treated with antihistamines and corticosteroids (Table 2).

The number of courses by patient characteristics is shown in Table 3. The number of courses was significantly higher in patients with skin toxicity as compared to patients without skin toxicity (13.93 vs 5.72%, p<0.001), and higher, but not significantly, in patients with combination chemotherapy vs cetuximab monotherapy (12.24 vs 9.60%, p=0.417).

After treatment with cetuximab, patients received best supportive care (38 patients, 52.78%), chemotherapy (27 patients, 37.50%), surgery (1

Table 2. Previous treatment details

Details	*N*	*%*
No. of courses*		
< 4	12	16.67
4-15	36	50.00
16-31	23	31.94
≥ 32	1	1.39
Combination chemotherapy		
Yes	10	13.89
No	62	86.11
Irinotecan	40	55.55
FOLFIRI	12	16.67
IFL	10	13.89
Premedication		
Antihistamine	10	5.56
Antihistamine + corticosteroid	62	86.11

*median 11.87 (range 2-36)

Table 3. Number of courses by patient characteristics

Characteristics	*No. of patients*	*No. of courses Median (range)*	*p value**
	72	11.87 (2–36)	
Age (years)			0.622
< 65	37	11.54 (2–31)	
≥ 65	35	12.23 (2–36)	
Combination chemotherapy			0.417
Yes	10	9.60 (2–22)	
No	62	12.24 (2–36)	
Skin toxicity			0.001
Yes	18	5.72 (2–11)	
No	54	13.93 (2–36)	

*Mann-Whitney U test

patient, 1.39%), radiotherapy (2 patients, 2.78%) and other treatments (4 patients, 5.55%).

Survival

In the intention-to-treat analysis, 72 patients were evaluated for PFS and OS. As shown in Table 4. the median PFS was 4.77 months (95% CI: 4.08–5.46), with an actuarial 47.22% without progression at 3 months and 16.67% at 6 months. The median OS time was 11.35 months (95% CI: 9.64–13.07), with 79.17% of the patients being alive at 6 months and 30.56% at 12 months. Kaplan-Meier survival is shown in Figure 1.

Safety and toxicity

Skin disorders (acne-like skin rash, dry skin, paronychia) of any grade were most frequently observed as adverse drug reactions (ADRs). Skin toxicity was observed in 54 (75.0%) patients, with median time to the onset of 15 days. Grade 3 toxicity was observed in 20 patients (27.78%), and grade 4 in only 1 patient (1.39%). Supportive therapy of skin toxicity led to an improvement of symptoms in the majority of patients with topical and sometimes with systemic therapy. Infusion reactions (IRs) and electrolyte abnormalities including hypomagnesaemia were less common. Most IRs, especially those of grade 3, occurred at the first administration of cetuximab, within 60 min from the beginning of administration.

Hematologic and gastrointestinal toxicity were related only to the group of patients with chemotherapy.

Prognostic factors

The incidence of skin toxicity and response to therapy are shown in Table 4. PFS was significantly higher in patients with skin toxicity as compared to those without skin toxicity (5.31 vs 2.61 months; p<0.001). Additionally, OS was significantly higher in patients with skin toxicity as compared to those without skin toxicity (12.21 vs 7.92 months; p=0.013).

Univariate analysis of the relationship between survival outcome and patient characteristics showed that the presence of skin toxicity and smaller number of metastatic organs were significantly associated with better PFS (Figure 2) and OS. On the other hand, poor ECOG PS, greater number of metastatic organs and the absence of skin toxicity were significant negative prognostic factors for OS (Table 5) (Figure 3). There were superior survival rates with higher grades of skin toxicity. As for patient characteristics, no significant differences were noticed in age, gender, and primary site localization.

In multivariate analysis, the presence of skin toxicity was identified as an independent prognostic factor indicative for better PFS, with 73% reduction in the risk of progression (HR 0.27; 95% CI: 0.132–0.564). Poor ECOG PS, greater number of metastatic organs and the absence of skin toxicity were independent prognostic factors negative-

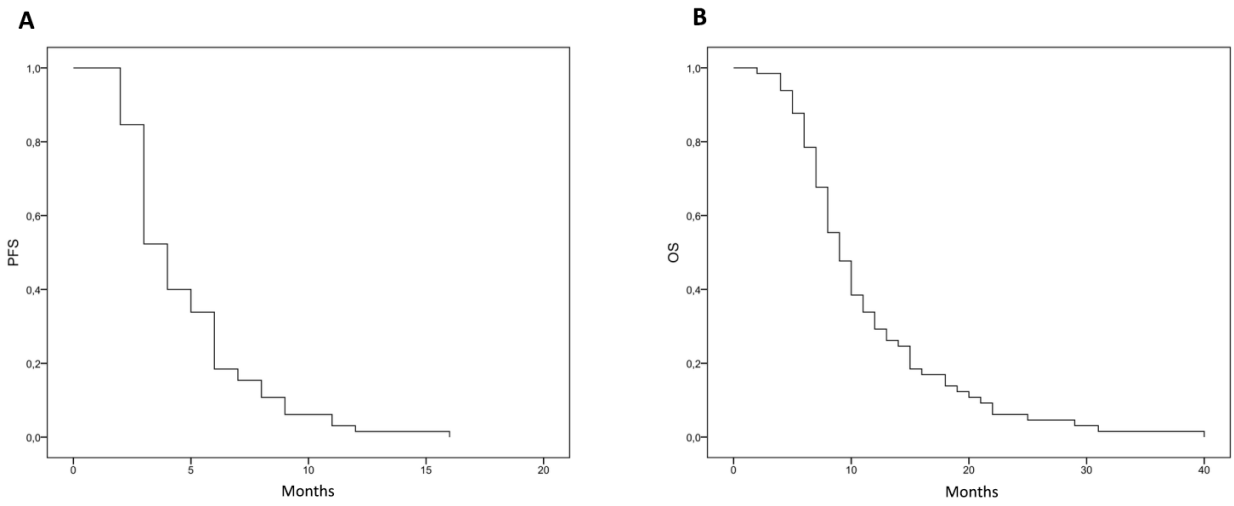

Figure 1. A: Progression free survival and **B:** Overall survival.

Table 4. Incidence of skin toxicity and survival

	N	%	*Median, range (months)*
Grade of skin toxicity			
0	18	25.00	
1	17	23.61	
2	16	22.22	
3	20	27.78	
4	1	1.39	
Low grade (0 – 1)	35	48.61	
High grade (2 – 4)	37	51.39	
PFS			4.77 (2 - 16)
Skin toxicity (-)			2.61 (2 - 4)
Skin toxicity (+)			5.31 (2 - 16)
OS			11.35 (4 - 40)
Skin toxicity (-)			7.92 (4 - 15)
Skin toxicity (+)			12.21 (4 - 40)

PFS: progression free survival, OS: overall survival

ly affecting the OS (Table 5; Figure 2).

Discussion

In patients with wild-type KRAS mCRC cetuximab is active in different lines of treatment as a single agent or in combination with chemotherapy [8-11]. Earlier studies, which combined cetuximab with irinotecan in the treatment of mCRC, showed improvements in response rates and PFS [12-15]. Later studies demonstrated that cetuximab was also active alone as third-line treatment vs best supportive care in the wild-type KRAS mCRC [6,10,16,17]. In third-line therapy, after progression on prior chemotherapy with fluoropyrimidine, oxaliplatin and irinotecan, the combination of cetuximab with irinotecan was more active than cetuximab alone [6].

The efficiency of cetuximab as monotherapy and cetuximab plus irinotecan in 329 patients

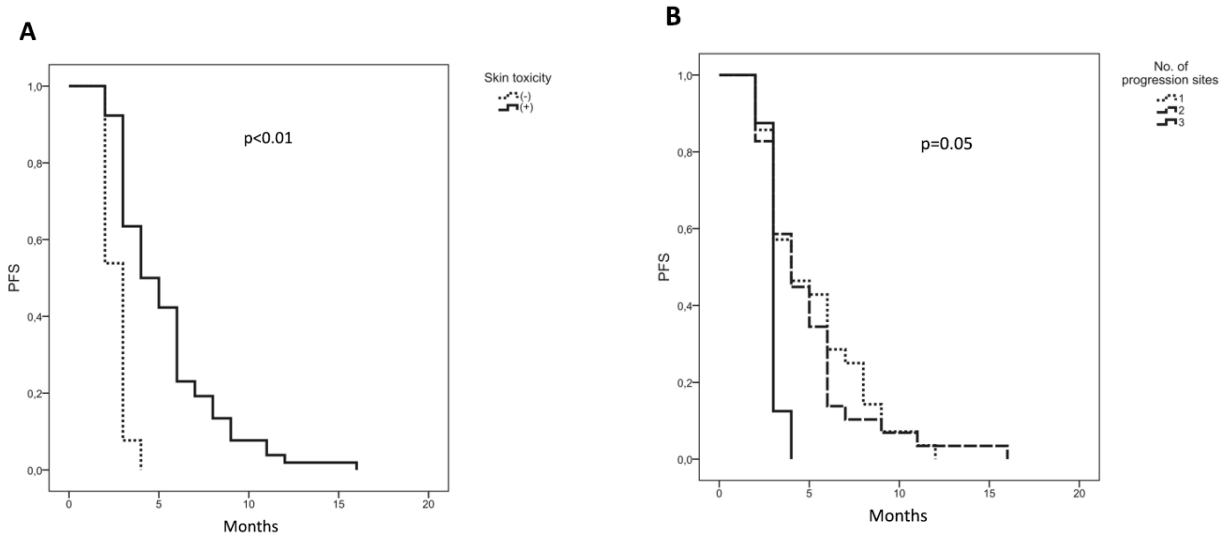

Figure 2. The impact of **A:** skin toxicity and **B**: number of progression sites on progression free survival.

Table 5. Univariate and multivariate analysis of factors potentially associated with survival

Factors	*Univariate*				*Multivariate*				*p value*
	PFS		*OS*		*PFS*		*OS*		
	Median (months)	*p*	*Median (months)*	*p*	*HR (95% CI)*	*p*	*HR (95% CI)*		
Age, years									
< 65	4.47	0.422	10.79	0.454	0.763 (0.460-1.266)	0.295	0.852 (0.512-1.417)		0.536
≥ 65	4.93		11.59						
Sex									
Male	4.79	0.891	11.52	0.847	1.116 (0.605-2.057)	0.725	1.214 (0.643-2.292)		0.550
Female	4.72		10.94						
ECOG PS									
0	7.00	0.219	21.67	0.004	1.183 (0.636-2.200)	0.595	2.256 (1.134-4.489)		0.020
1	4.78		11.30						
2	3.50		6.67						
Primary site									
C18.0	4.93	0.207	11.00	0.162	1.092 (0.799-1.492)	0.582	0.991 (0.718-1.368)		0.956
C18.7	4.31		9.58						
C20.0	4.74		12.19						
No. of progression sites									
1	5.18	0.050	12.64	<0.001	1.265 (0.807-1.984)	0.306	1.708 (1.066-2.738)		0.026
2	3.61		8.56						
3	3.00		6.25						
Skin toxicity									
(-)	2.61	<0.001	7.92	0.013	0.273 (0.132-0.564)	< 0.001	0.477 (0.244-0.934)		0.031
(+)	5.31		12.21						

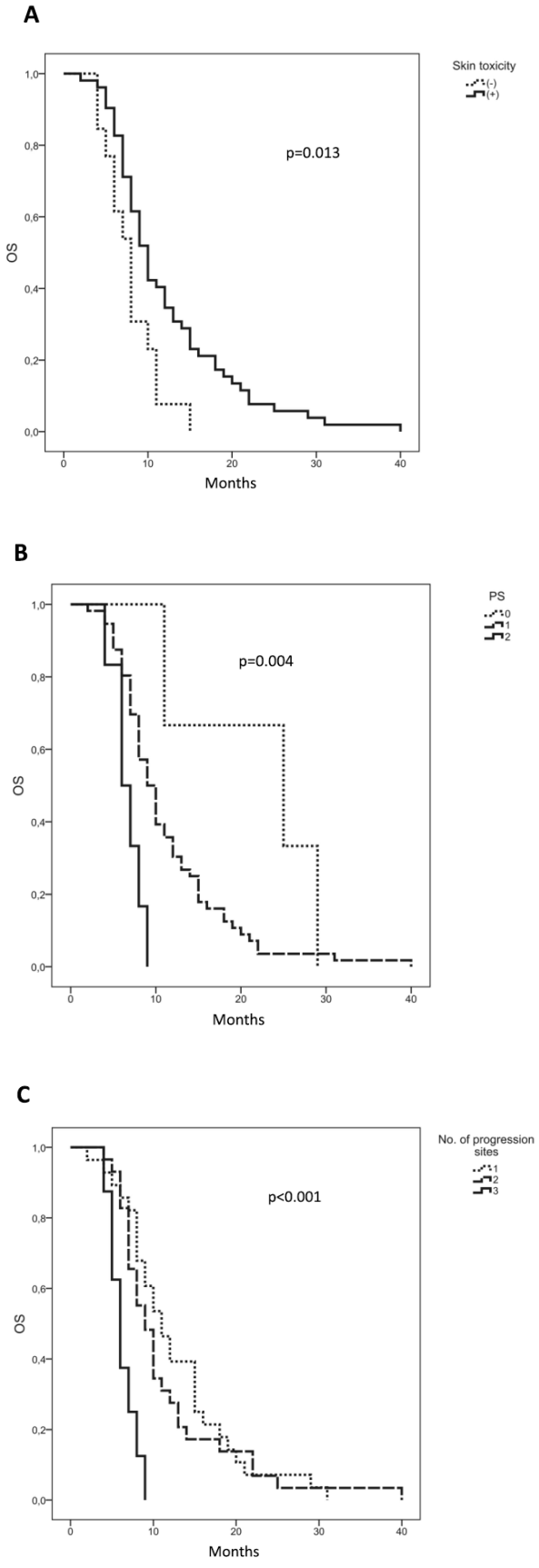

Figure 3. The impact of **A:** skin toxicity, **B:** performance status and **C:** number of progression sites on overall survival.

with EGFR-expressing mCRC who had failed an irinotecan-based regimen was initially demonstrated in BOND trial [6]. This study demonstrated that cetuximab monotherapy was active in heavily pretreated mCRC patients and that cetuximab in combination with irinotecan was able to overcome resistance to irinotecan. PFS was significantly longer in the combination therapy group (4.1 vs 1.5 months, p<0.001). The median OS was 8.6 months in the combination therapy group vs 6.9 months in the cetuximab monotherapy group (p=0.48). Patients with skin rash had better response rate than patients without skin rash (25.8 vs 6.3% respectively, p=0.005).

After progression on first and second-line therapy, all patients were tested on KRAS mutation status. Then, we enrolled 72 patients with wild-type KRAS mCRC. Our results were comparable with the results of BOND study. The median PFS was 4.77 months (range 2-16), and the median OS was 11.35 months (range 4-40). The median PFS was longer in the combination therapy group (4.93 vs 3.78 months). The median OS was 11.80 months in the combination therapy group vs 8.56 months in the cetuximab monotherapy group. This confirmed that pretreatment with oxaliplatin and irinotecan did not have a negative impact on the response to cetuximab plus irinotecan since all our patients had been previously treated with oxaliplatin and irinotecan in first and second-line chemotherapy.

One of the largest studies designed to confirm the findings of BOND study was MABEL study with 1147 treated patients [18]. The expected 50% PFS rate at 12 weeks was exceeded. PFS rate was 61%, with median OS of 9.2 months and 1-year survival rate of 38%. With a median OS of 11.35 months and 1-year survival rate of 30.56%, our results were comparable with this study.

Results of many trials showed a relationship between skin toxicity and OS in patients treated with cetuximab. In some studies, this relationship was independent of rash grade, but in other studies the advantage was appreciable only in grade 2 or 3 skin toxicity [6,10,16,17,19,20].

In BOND study, the authors demonstrated that patients with skin rash had better response rates than patients without skin rash (25.8 vs 6.3% respectively, p=0.005) [6]. Lenz et al. published the results of their study with 346 patients with CRC previously treated with a fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy. A partial response was 7% in grade 1 skin rash, 17% in grade 2 and 20% in grade 3 [16]. A study

carried out by Saltz et al. reported a longer survival in patients with higher grade skin toxicity [17,19]. Lievre et al. showed high correlation between KRAS mutation and PFS and OS, whereas skin rash was only associated with OS [9]. Results of EVEREST study demonstrated no correlation between KRAS and skin toxicity [21].

In a meta-analysis of 9 trials with 5333 patients, Balagula et al. demonstrated that the incidence of high grade skin toxicity was significantly higher in patients with cetuximab in combination with chemotherapy (12.8%, 95% CI: 9.1–17.7) as compared to cetuximab monotherapy (6.3%, 95% CI: 3.7–10.5) [22].

As for our study, we retrospectively analyzed 72 patients treated with cetuximab monotherapy or in combination with irinotecan-based chemotherapy. A significant correlation was observed between skin rash and survival (PFS and OS). The median number of treatment courses in patients without skin toxicity was 5.72, and in patients with skin toxicity 13.93 ($p<0.001$). Patients who developed skin toxicity had better PFS (5.31 vs 2.61 months, $p<0.001$), and better OS (12.21 vs 7.92 months, $p=0.013$). Patients without skin toxicity were two times more likely to develop tumor progression significantly earlier than patients with skin toxicity. In multivariate analysis, skin toxicity was demonstrated to be the only independent prognostic factor with regard to PFS (HR 0.27; 95% CI: 0.13–0.56). Good ECOG PS, smaller number of metastatic organs and the presence of skin toxicity were independent prognostic factors indicative for better OS.

Patients with mCRC refractory to chemotherapy without mutations in codon 12 or 13 of the KRAS gene responded in 13–17% of the cases [6]. Most patients with KRAS codon 12 and 13 wild-type tumors did not respond to anti-EGFR therapy [23].

In the CO.17 study, patients refractory to prior chemotherapy received cetuximab monotherapy. KRAS was shown not to be a strong prognostic factor in chemotherapy-refractory mCRC [11]. Mutations in other downstream effectors of the EGFR signaling pathway, such as BRAF, NRAS, and PIK3CA, also had a negative effect on response to anti-EGFR antibodies [24-26]. Evaluation of these mutations could result in improvements in response rates in KRAS, BRAF, NRAS, and PIK3CA exon 20 wild-type population.

After evaluating the role of genetic markers in chemo-refractory mCRC, the European Consortium concluded that if KRAS was of wild type, assessment of BRAF, NRAS, and PIK3CA mutational status would give additional predictive information for benefit to cetuximab therapy [27]. Response rate in wild-type KRAS patients was 36%. In patients with no mutations in KRAS, BRAF, NRAS, and PIK3CA response rate rose to 41%.

Traditional KRAS testing identified mutations in codons 12 and 13 of exon 2. In the FIRE 3 study, investigators compared the combination of cetuximab or bevacizumab with FOLFIRI as first-line treatment in 592 wild-type KRAS exon 2 mCRC patients. New mutations were found in 16% of KRAS exon 2 wild-type patients, including KRAS exons 3 and 4 and NRAS exons 2, 3, and 4. The frequency of BRAF mutation was 10%. PIK-3CA mutations in exons 9 and 20 mutations were found in 7.3%. The median OS was significantly higher with cetuximab (33.1 months) than with bevacizumab (25.6 months) in patients without RAS mutations. The authors concluded that RAS testing identified a population of mCRC with more benefit from cetuximab therapy [28].

In CRYSTAL and OPUS trials a pooled analysis showed that wild-type KRAS patients who had BRAF mutations had poor prognosis. BRAF-mutated patients had worse survival rate than wild-type BRAF patients with clearly demonstrated prognostic value. On the other hand, predictive value was still controversial [29-31]. Patients with wild-type KRAS and NRAS tumors had better PFS and better OS from anti-EGFR therapy in combination with chemotherapy [32].

After all multiple study results, today's KRAS testing is no longer sufficient and RAS testing (KRAS and NRAS) will become standard method for identifying suitable patients before starting anti-EGFR therapy. From 2014, KRAS and NRAS testing have been recommended by EMEA and NCCN.

Conclusions

In third-line treatment of mCRC patients, cetuximab was shown to be active and well tolerated. Cetuximab improved PFS and OS, and preserved the quality of life in patients with mCRC whose previous treatments had failed. The incidence of adverse drug reactions was not different from previously published results in other institutions. With RAS testing as standard method, we could make a more precise selection of patients suitable for EGFR-targeted therapy.

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