A Phase II Study of Cetuximab/Irinotecan in Patients with Heavily Pretreated Metastatic Colorectal Cancer: Predictive Value of Early Specific Toxicities

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Abstract

Background: This study was designed to evaluate the predictive value of early specific toxicities on efficacy of weekly irinotecan/cetuximab administered as salvage therapy in patients with metastatic colorectal cancer (CRC) refractory to oxaliplatin and irinotecan. **Patients and Methods:** Seventy patients received a regimen composed of weekly irinotecan 125 mg/m^2 as a 1-hour intravenous infusion and cetuximab 400 mg/m^2 infused over 2 hours as the initial dose and 250 mg/m^2 infused over 1 hour for subsequent administrations. A single treatment cycle was composed of 4 weekly irinotecan infusions followed by 2 weeks of rest. The predictive value of adverse events (AEs) attributable to cetuximab (rash) and major toxicities attributable to irinotecan (gastrointestinal [GI] and hematologic) were observed after the first cycle of treatment and, therefore, correlated to activity and efficacy of cetuximab and weekly irinotecan. **Results:** Sixty-six of 70 patients received ≥ 1 cycle of chemotherapy and were therefore evaluable for response. Overall, toxicity observed was generally mild and manageable. According to an intent-to-treat analysis, a partial response was exhibited in 15.7% of patients, with a median progression-free survival (PFS) and median overall survival time of 4 months and 9 months, respectively. As expected, PFS (P = .01) and median survival (P = .04) correlated strongly with the presence and severity of the rash. Surprisingly, the presence of at least moderate hematologic and GI toxicity was associated with improved PFS (P = .03). **Conclusion:** Our data suggest that irinotecan-induced AEs might predict a better outcome in advanced CRC. This finding would identify a different subset of patients—those likely to benefit from a renewed sensitivity to irinotecan induced by cetuximab.

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Introduction

Advanced-stage colorectal cancer (CRC) is the third leading cause of cancer-related death in Western countries.[1] Fluoropyrimidine-based associations with irinotecan or oxaliplatin currently represent a standard of care in first- or second-line treatment, with a substantial increase in median overall survival (OS) from 12 months to approximately 21-22 months when all of the 3 available chemotherapeutic agents have been administered.[2,3] Moreover, the addition of the anti–vascular endothelial growth factor (VEGF) antibody bevacizumab to irinotecan-based first-line chemotherapy is associated with an improved time to tumor progression (TTP) and OS.[4] However, before the introduction of cetuximab, no cytotoxic drug with proven efficacy

Table 1 Patient Characteristics

Characteristic	N (%)
ECOG PS	
0	34 (48.6)
1	28 (40)
2	8 (11.4)
Sex	
Male	40 (57.1)
Female	30 (42.9)
Primary Site of Disease	
Colon	51 (72.9)
Rectum	19 (27.1)
Previous Adjuvant Therapy	26 (37.1)
EGFR IHC Score	
0	0
+1	6 (8.6)
+2	47 (67.1)
+3	17 (24.3)
Number of Disease Sites	
1	33 (47.1)
2	34 (48.6)
≥ 3	3 (4.3)
Previous Chemotherapy Lines	
1	41 (58.6)
2	12 (17.1)
≥ 3	17 (24.3)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry

Table 2 Early Toxicity Evaluated After 1 Treatment Cycle

Toxicity	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Leukopenia	12 (17.1)	6 (8.6)	6 (8.6)
Neutropenia	12 (17.1)	6 (8.6)	7 (10)
Anemia	10 (14.3)	5 (7.1)	1 (1.4)
Thrombocytopenia	7 (10)	2 (2.9)	–
Diarrhea	24 (34.3)	12 (17.1)	3 (4.3)
Mucositis	21 (30)	9 (12.9)	–
Nausea and Vomiting	17 (24.3)	5 (7.1)	–
Rash	23 (32.9)	26 (37.1)	4 (5.7)
Paronychial	21 (30)	3 (4.3)	–
Fatigue	31 (44.3)	23 (32.9)	1 (1.4)

was available for patients with progressive disease or those refractory to the aforementioned agents.[5]

Cetuximab is a chimeric immunoglobulin G1 monoclonal antibody (MoAb) that binds to epidermal growth factor receptor (EGFR) with high specificity and affinity, thus blocking ligand-induced phosphorylation of EGFR and blocking its downstream signaling. This effect results in inhibition of cell proliferation, angiogenesis, metastasis, and promotion of apoptosis and antibody-dependent cell-mediated cytotoxicity.[6,7]

Cetuximab was shown to have a 9% response rate (RR) when used as a single agent in patients in whom irinotecan failed.[8] However, the most impressive activity of cetuximab was observed in an initial clinical trial in which it was shown to have a 23% RR when combined with irinotecan in the same population.[9] Both of these findings were confirmed thereafter in the BOND (Bowel Oncology with Cetuximab Antibody) trial, a large, randomized, phase II study of cetuximab/irinotecan versus cetuximab alone in irinotecan-refractory CRC.[10] The trial found 23% and 10.8% RRs for irinotecan/cetuximab and cetuximab alone, respectively. The increased RR of the combination arm related to a statistically significant improve-

Figure 1 Kaplan-Meier Estimates of Progression-Free Survival

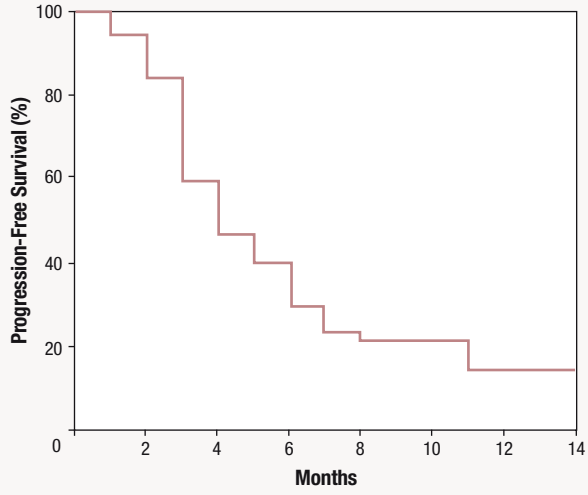


Figure 2 Kaplan-Meier Estimates of Overall Survival

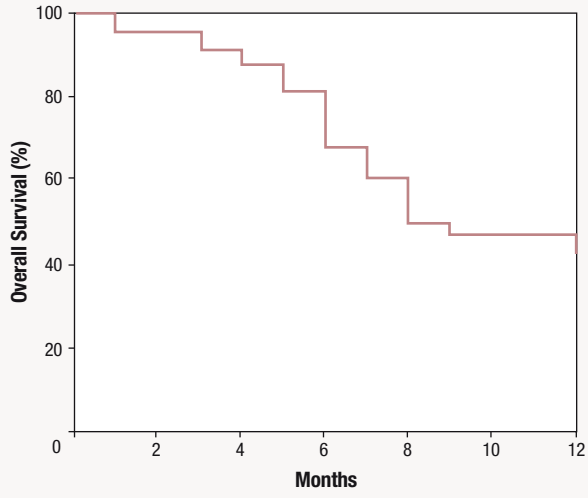


Figure 3 Kaplan-Meier Estimates of PFS by Skin Toxicity

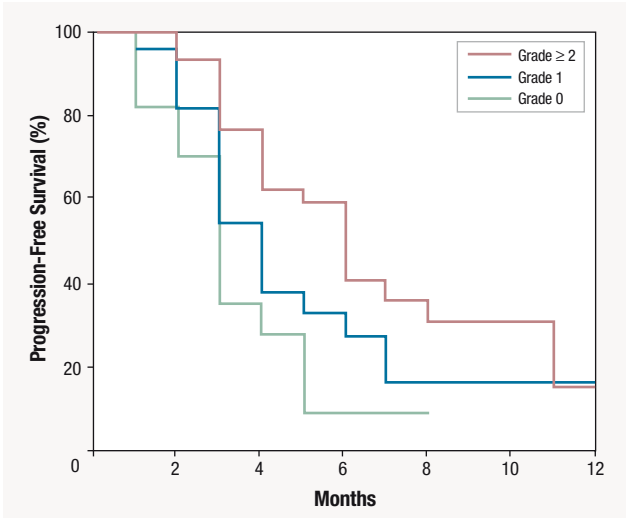
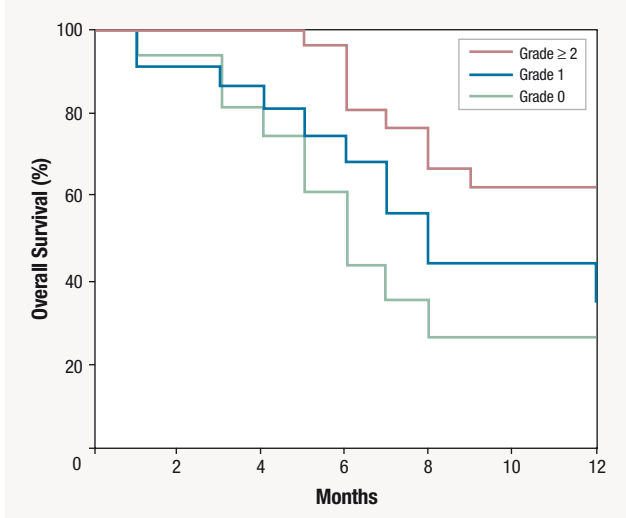


Figure 4 Kaplan-Meier Estimates of OS by Skin Toxicity

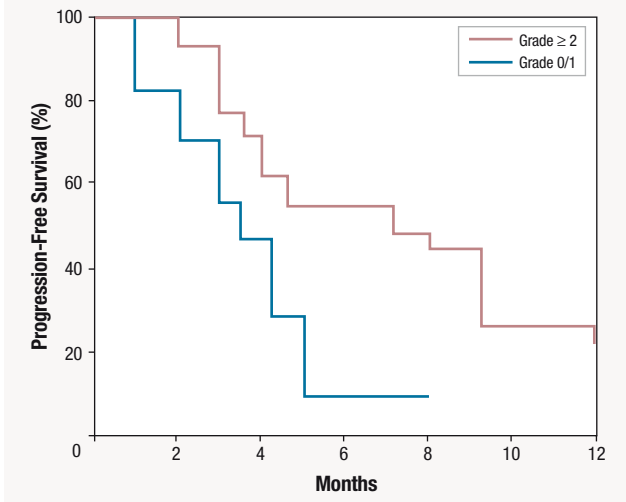


ment of the median TTP. Further analysis of the BOND data showed a clear association between higher grades of skin reaction and both RR and median TTP. This was true also for OS, the median value rising from 3 months in patients with no rash to 14 months in those with grade 3 rash. To date, the intensity of skin reaction is the only proven predictive factor for cetuximab efficacy; nonetheless, this evidence has not made the basis for any decision by regulatory authorities to restrict continued dosing of cetuximab to patients with a rash. Moreover, the evidence that up to 25% of patients would benefit from this treatment and the worldwide need to limit the expense for salvage treatment in oncology clearly addresses the research of clinical and/or molecular determinants for a better selection of patients. In a recent trial by Lenz et al, cetuximab alone produced an expected 9% RR in 57 patients with irinotecan-refractory CRC.[11] The severity of rash was related to efficacy, but neither EGFR kinase domain mutations nor EGFR gene amplification appear to be essential for response to cetuximab in this setting.

The impressive activity of cetuximab/irinotecan in patients with irinotecan-refractory CRC could be explained by their well-known preclinical synergistic interaction.[12] This synergy might depend on the believed potential of cetuximab to restore irinotecan sensitivity. Because recent data suggest a correlation between irinotecan-induced toxicity after the first treatment cycle and tumor shrinkage potential,[13] it has never been investigated whether irinotecan-induced toxicity would have an effect on efficacy of the combination.

The primary objective of this study was to investigate the predictive value of AEs attributable to cetuximab (rash) and major toxicities attributable to irinotecan (gastrointestinal [GI] and hematologic) on activity and efficacy of cetuximab and weekly irinotecan in patients with metastatic CRC refractory to irinotecan and oxaliplatin. Because cetuximab-induced rash appears after 4 weekly administrations in the vast majority of patients, we considered the predictive value of the aforementioned toxicities observed after the first cycle of treatment.

Figure 5 Kaplan-Meier Estimates of PFS by Any Other Toxicity



Patients and Methods

Patient Eligibility

Patients with pathologically confirmed CRC and any positive degree of EGFR immunostaining were eligible. All patients must have been documented with disease progression during or within 3 months after ≥ 2 chemotherapy lines for metastatic disease or adjuvant therapy plus ≥ 1 line for metastatic disease, including irinotecan-, oxaliplatin-, and fluoropyrimidine-based regimens. Eligibility criteria also included the following: age > 18 years; Eastern Cooperative Oncology Group performance status (PS) of 0-2; life expectancy of ≥ 3 months; no major surgery, radiation, chemotherapy, or investigational agent within 4 weeks; normal hematopoietic,

Table 3 Analysis of Prognostic Factors for Progression-Free Survival

Prognostic Factor	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Sex				
Male	1.285 (0.735-2.248)	.38	–	–
Female				
Age (Years)				
≤ 65	1.057 (0.608-1.838)	.844	–	–
> 65				
Adjuvant CT				
No	1.041 (0.593-1.828)	.888	–	–
Yes				
Site of Metastases				
Visceral	1.179 (0.636-2.184)	.601	–	–
Not visceral				
Number of Metastases				
> 1	1.482 (0.853-2.578)	.162	–	–
1				
Previous CT Lines				
3	1.705 (0.933-3.116)	.043	2.362 (1.165-4.79)	.017
≥ 3				
Response				
No	4.878 (1.511-5.752)	.008	3.942 (1.201-12.937)	.024
Yes				
PS				
1 vs. 0	1.365 (0.753-2.473)	.305	–	–
2 vs. 0	2.583 (1.149-5.805)	.022	3.51 (1.412-8.727)	.007
1 vs. 2	0.528 (0.232-1.202)	.028	0.319 (0.125-0.813)	.017
Rash Grade				
1 vs. 0	0.608 (0.296-1.249)	.176	–	–
1 vs. ≥ 2	1.51 (0.794-2.872)	.209	–	–
≥ 2 vs. 0	0.403 (0.2-0.813)	.011	0.408 (0.19-0.877)	.022
Other Toxicities (Grade)				
1 vs. 0	0.579 (0.279-1.202)	.143	–	–
1 vs. ≥ 2	1.375 (0.72-2.627)	.334	–	–
≥ 2 vs. 0	0.421 (0.21-0.844)	.015	0.426 (0.2-0.911)	.028

Other toxicities included hematologic and/or GI AEs.
Abbreviations: CT = chemotherapy; HR = hazard ratio

hepatic, and renal function; measurable disease; no coexisting medical problem of sufficient severity to limit study compliance; and no previous treatment with EGFR-targeting agents. Patients gave written informed consent before treatment.

Dosage and Drug Administration

Cetuximab was administered as a 120-minute intravenous (I.V.) infusion at 400 mg/m^2 followed by continuous weekly 60-minute infusions of 250 mg/m^2 and 60-minute irinotecan 125 mg/m^2 for 4 of 6 weeks. Diphenhydramine 50 mg I.V. was administered before the first treatment and then before subsequent doses at the discretion of the investigator.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Cetuximab dose modifications were indicated for hypersensitivity reactions and severe skin toxicity. For grade 1 hypersensitivity reaction, the infusion rate was reduced by 50%. For grade ≥ 2 hypersensitivity reaction, cetuximab was discontinued. For grade 3 skin toxicity, cetuximab was discontinued until the toxicity resolved to grade ≤ 2, at which time it was resumed. If the toxicity did not resolve to grade ≥ 2 within 4 weeks or grade 3 toxicity recurred ≥ 4 times, cetuximab was discontinued. A second or third recurrence of grade 3 toxicity required dose reductions to 200 mg/m^2 and 150 mg/m^2. Irinotecan dose modifications were indicated for diarrhea and hematologic toxicities. For grade 2 diarrhea, the infusion rate was reduced by 25%. For grade 3 diarrhea, irinotecan was discontinued until the toxicity resolved to grade ≤ 2, at which time it was resumed with 50% reduction, whereas it was discontinued in case of grade 4 diarrhea. Any grade 1 hematologic toxicity prompted 25% irinotecan dose reduction. In case of grade 2/3 hematologic toxicity, irinotecan was discontinued until recovery to grade ≤ 2, at which time it was resumed with 33% reduction, whereas it was definitively discontinued in case of grade 4 severity.

Pretreatment and Follow-up Studies

Histories, physical examinations, and safety assessments were performed pretreatment and weekly thereafter. Complete blood count with differential was performed weekly; complete serum chemistry, clotting studies, and urinalysis were monitored pretreatment, every 6 weeks, and at the end of treatment.

The Response Evaluation Criteria in Solid Tumors were used to assess tumor responses.[14] All objective responses were required to be confirmed by a follow-up computed tomography scan ≥ 4 weeks after documentation of the response and an independent review committee confirmed all responses. Irinotecan therapy was continued for a maximum of 6 cycles, whereas cetuximab treatment was continued in the absence of intolerable toxicity or progressive disease, defined as a ≥ 33% increase in ≥ 1 target lesion, unequivocal growth of existing nontarget lesions, the appearance of ≥ 1 new lesion, or reappearance of old lesions.

Statistical Methods

The correlation between predictive categoric variables was tested by the Pearson χ^2 test or Fisher's exact test. Overall survival and progression-free survival (PFS) were calculated by the Kaplan-Meier method from the date of the first day of treatment until progression of disease or death.[15] If a patient was not dead, survival was censored at the time of the last visit. Progression-free survival was calculated from the date of first treatment to the date of progression or death. If a patient had not progressed, TTP was censored at the time of the last visit. The log-rank test was used to assess differences between subgroups. A multivariate Cox proportional hazard model was also developed using stepwise regression with predictive variables, which were significant in the univariate analyses. Enter limit and remove limit were $P = .1$ and $P = .15$, respectively. Univariate and multivariate analysis was planned for PFS and OS outcome. The SPSS (11.0) statistical program was used for analysis.

Patient Characteristics

Seventy patients meeting the inclusion criteria were entered into the trial. Median age was 66 years (range, 31-79 years). Most patients were men, had colon as the primary site of disease, had PS ≤ 1 at diagnosis, and had metastasis at first diagnosis. More than half of the patients received cetuximab as third-line chemotherapy. Patient characteristics are shown in Table 1.

Results

Toxicity

Overall, toxicity observed was generally mild and manageable. Severe hematologic toxicity, mainly neutropenia, was observed in 10% of patients. Gastrointestinal AEs were represented by mild to moderate diarrhea and stomatitis. As expected, cutaneous toxicity has a high incidence, with 80% of patients reporting grade ≥ 1 rash. Fatigue was also frequent. Analysis of early AEs is shown in Table 2.

Table 4 Analysis of Prognostic Factors for Overall Survival

Prognostic Factor	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Sex				
Male	1.118 (0.538-2.323)	.764	–	–
Female				
Age (Years)				
≤ 65	1.346 (0.655-2.764)	.419	–	–
> 65				
Adjuvant CT				
No	1.734 (0.802-3.749)	.162	–	–
Yes				
Site of Metastases				
Visceral	1.148 (0.522-2.2)	.73	–	–
Not visceral				
Number of Metastases				
> 1	0.934 (0.454-1.918)	.851	–	–
1				
Previous CT Lines				
3	1.164 (0.543-2.493)	.696	–	–
≥ 3				
Response				
No	1.457 (0.437-4.862)	.54	–	–
Yes				
PS				
1 vs. 0	1.464 (0.645-3.325)	.362	–	–
2 vs. 0	3.244 (1.264-8.322)	.014	4.026 (1.494-10.851)	.006
1 vs. 2	0.514 (0.173-1.176)	.0104	0.256 (0.089-0.754)	.013
Rash Grade				
1 vs. 0	0.636 (0.268-1.51)	.305	–	–
1 vs. ≥ 2	2.198 (0.907-5.326)	.081	–	–
≥ 2 vs. 0	0.289 (0.116-0.719)	.008	0.214 (0.079-0.582)	.002
Other Toxicities (Grade)				
1 vs. 0	0.639 (0.269-1.517)	.31	–	–
1 vs. ≥ 2	2.212 (0.913-5.36)	.079	–	–
≥ 2 vs. 0	0.289 (0.116-0.717)	.007	0.214 (0.079-0.581)	.002

Other toxicities included hematologic and/or GI AEs.
Abbreviations: CT = chemotherapy; HR = hazard ratio

Activity and Efficacy

Sixty-six of 70 patients received ≥ 1 cycle of chemotherapy and were, therefore, evaluable for response. On the basis of an intent-to-treat analysis, a partial response was observed in 15.7% (95% CI, 7.2%-24.2%) of patients and stable disease in 28.6% of cases, even as 35 patients progressed.

After a median follow-up of 10 months (range, 1-15 months) from the start of cetuximab/irinotecan treatment, the median PFS for the entire cohort was 4 months (95% CI, 3-5 months), with 14.3% of patients progression free at 1 year (Figure 1). The median OS was 9 months (95% CI, 5-13 months), with 42.8% of patients surviving at 1 year (Figure 2).

Predictive Value of Adverse Events

Only patients developing grade ≥ 1 skin toxicity had a response. The presence of some grade skin toxicity was associated with an RR of 36.6%. The difference observed versus those patients without skin toxicity was statistically

significant (P = .02). With regard to the predictive value of any other nonhematologic toxicity and hematologic toxicity, we did not reveal any significant difference. We also observed a statistically significant higher RR for the subset of patients receiving cetuximab after 3 previous chemotherapy lines with respect to those administered with cetuximab as second- or third-line treatment (P = .01).

As expected, the PFS correlated strongly with the presence and severity of the rash, with median PFS times of 2.2 months (95% CI, 1.2-2.6 months) for patients without rash, 4.5 months (95% CI, 3.6-6.6 months) and 9.1 months (95% CI, 8.1-11 months) for those with grade 1 and grade ≥ 2 rash, respectively (P = .01; Figure 3). Similarly, median survival was better for those developing skin rash, with 26% of patients surviving at 1 year without rash, whereas 35% and 63% were the same figures in case of grade 1 and grade ≥ 2 rash, respectively (P = .04; Figure 4). The median survival time was not reached for those with severe rash. Surprisingly, and perhaps even more strikingly, the presence of grade ≥ 2 hematologic and GI toxicity was associated with improved PFS, with a median PFS of 3.7 months (95% CI, 2-4.4 months) and 7.2 months (95% CI, 6.4-8.7 months) for patients with grade ≤ 1 and grade ≥ 2 toxicities, respectively (P = .03; Figure 5). A trend toward improved median survival was observed for exerting patients with grade ≥ 2 toxicities, which, however, did not reach statistically significant difference.

The multivariate analysis of the predictive factors showed the development of grade ≥ 2 rash, grade ≥ 2 toxicity other than skin toxicity, and good PS to be independent factors for OS. In addition to these factors, response to treatment and > 3 previous treatment lines were found to be independent predictors for PFS. The results of univariate and multivariate analysis for PFS and OS are reported in Tables 3 and 4, respectively.

Discussion

The efficacy of cetuximab in patients with irinotecan-refractory disease is compelling. The clinical data currently support the use of cetuximab in patients with disease refractory to irinotecan-based chemotherapy in combination with irinotecan or alone in patients who are not able to tolerate reintroduction of irinotecan. The demonstration of efficacy in pretreated patients of bevacizumab added to FOLFOX (5-fluorouracil [5-FU]/leucovorin/oxaliplatin),[16] single-agent panitumumab,[17] and cetuximab/irinotecan/bevacizumab[18] would suggest a number of treatment options after failure of first- and second-line chemotherapy in advanced CRC. So far, distinct incremental benefits are noted for new targeted agents in patients with advanced CRC, with more prominent effects on disease progression than on death.[19] The last consideration is raising some concerns about the real effect of wide use of MoAb on OS prolongation and these agents' final cost-utility.[20,21]

We believe that new targeted agents will improve survival outcome even after failure of standard chemotherapy options; nevertheless, this improvement is clearly limited to a small subset of patients. In this setting, the need for treatment selection criteria is striking. With respect to the cetuximab case, none of molecular analyses of its target EGFR, eg, gene expression, gene amplification, or selected exons sequencing,[11] related to treatment efficacy. Recent data from a retrospective analysis showed molecular determinants, such as circulating VEGF level[22] or nuclear factor–κB expression,[23] might play a crucial role in predicting the efficacy of cetuximab/irinotecan. However, these findings deserve a validation in larger prospective studies and are, therefore, unlikely to find a current clinical application.

Conclusion

To date, cetuximab-induced cutaneous toxicity is the only proven parameter associated with response and survival, especially if we consider at least moderate rash (eg, grade ≥ 2). Our study, which primarily focused on the predictive value of early toxicities, confirms that patients with heavily pretreated CRC experienced progression after oxaliplatin- and irinotecan-based chemotherapy regimens. It is interesting to note that even at least moderate toxicities other than rash resulted in higher RRs and longer PFS. To our knowledge, this is the first evidence that irinotecan-induced AEs might predict a better outcome in advanced CRC. This could suggest that, in addition to those likely to benefit from cetuximab on the basis of cutaneous toxicity, a different subset might be identified, and patients could be likely to benefit from a renewed sensitivity to irinotecan induced by cetuximab. Although these results were confirmed at multivariate analysis, the limited number of patients entered onto our study does not allow any definitive conclusion on the predictive role of early specific toxicities. Moreover, every AE can be observed obviously only after ≥ 1 cycle of therapy and are then of no use as a pretreatment selection criterion. Nevertheless, looking forward to the availability of a robust molecular marker predicting tumor sensitivity to anti-EGFR therapy, clinical decision can be taken on the basis of early evaluation of cetuximab- and irinotecan-induced toxicities. A prospective study has therefore been planned to compare, in the same population, early withdrawal of cetuximab-weekly irinotecan and switch to capecitabine or protracted 5-FU in case of no grade ≥ 2 toxicity after the first cycle of chemotherapy while maintaining cetuximab/irinotecan in case of any grade ≥ 2 toxicity.

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