ORIGINAL ARTICLE

Clinical predictors of response to cetuximab-chemotherapy in metastatic colorectal cancer

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Objective To identify clinical markers to predict which patients with advanced colorectal cancers are likely to benefit from cetuximab-chemotherapy.

Design Retrospective review.

Setting Oncology unit in a university teaching hospital in Hong Kong.

Patients A total of 102 patients with metastatic colorectal cancer treated with cetuximab-chemotherapy.

Main outcome measures Correlation of multiple potential clinical predictive factors with tumour response to cetuximab-chemotherapy.

Results The objective response rates to cetuximab plus chemotherapy were 53% in patients receiving first-line treatment and 17% in previously treated patients. The univariate analysis indicated that fewer prior lines of chemotherapy (odds ratio=0.36; 95% confidence interval, 0.21-0.63; P<0.01) and development of cetuximab-related grade 3 rash (5.52; 1.62-18.76; P<0.01) were associated with significantly higher response rates. Multivariate analysis confirmed the independent predictive value of the number of prior chemotherapy regimens (odds ratio=0.37; 95% confidence interval, 0.20-0.69; P<0.01) and grade 3 rash (4.65; 1.21-19.29; P=0.03).

Conclusions In this cohort of Chinese patients with advanced colorectal cancer, the presence of grade 3 rash and the number of prior chemotherapy regimens were independent predictors of response to cetuximab-chemotherapy. The utility of these clinical markers in clinical practice should be further evaluated together with established biomarkers.

Introduction

Colorectal cancer is a major cause of morbidity and mortality worldwide. In the past decade, the median overall survival of patients with metastatic colorectal cancer has increased from 12 months to approximately 20 months, mainly owing to the development of new combinations of standard chemotherapy, including: 5-fluorouracil, leucovorin, and either irinotecan or oxaliplatin.[1,2] The introduction of cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR), has further improved survival among patients with advanced colorectal cancer.[3] Although anti-EGFR therapies are effective in some patients, in many the disease is refractory. It is important to identify potential clinical and molecular determinants of responsiveness to anti-EGFR agents, so as to improve patient selection for such therapy.

Although early studies involving EGFR monoclonal antibodies required the detection of EGFR overexpression by immunohistochemistry before enrolment, subsequent analyses showed no apparent correlation between the extent of EGFR expression and the response of tumours to cetuximab therapy.[3,4] Among the explored clinical factors, drug-related acneform rash is the only recognised predictor of cetuximab efficacy. A strong correlation between the intensity and severity of the skin rash and drug response has been observed in all of the clinical studies using cetuximab in colorectal cancer.[3-5] In the subset analysis of patients who received cetuximab alone in the BOND trial, a significantly better response rate of 13% was observed in patients with skin rash, compared with a zero response rate in patients without skin rash.[3] Interestingly, patients with grade 3 skin rash had even higher response rates than those having lesser degrees of skin rash.

The mutation status of *KRAS*, the human homologue of the Kirsten rat sarcoma-2

Key words
Antibodies, monoclonal; Colorectal neoplasms; Exanthema; Neoplasm metastasis; Receptor, epidermal growth factor

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西妥昔單抗聯合化療治療轉移性直腸癌的臨床反應預測因子

目的 找出能夠辨認哪一類末期直腸癌患者對西妥昔單抗聯合化療有理想效果的預測因子。

設計 回顧研究。

安排 香港一所大學教學醫院的腫瘤部。

患者 患上轉移性直腸癌並接受西妥昔單抗聯合化療的102位病人。

主要結果測量 多個潛在的臨床反應預測因子與西妥昔單抗聯合化療的腫瘤反應。

結果 對西妥昔單抗聯合化療的反應率方面，首次接受化療的病人佔53%，以往曾接受化療的病人則有17%。單元分析顯示以下兩項因素與高反應率有關：以往接受較少化療（比數比=0.36；95%置信區間：0.21-0.63；P<0.01）及出現與西妥昔單抗聯合化療有關的第3級皮疹（比數比=5.52；95%置信區間：1.62-18.76；P<0.01）。多元分析證實這兩項因素的獨立預測值：以往化療次數（比數比=0.37；95%置信區間：0.20-0.69；P<0.01）及出現第3級皮疹（比數比=4.65；95%置信區間：1.21-19.29；P=0.03）。

結論 根據本研究中接受西妥昔單抗聯合化療的末期直腸癌患者的治療效果，出現第3級皮疹和以往化療次數是評估化療反應的獨立預測因子。使用這些臨床指標時必須進一步參考已知的生物指標。

virus oncogene that is involved in the downstream signalling cascade of the activated HER pathway, has recently emerged as an important biomarker of response to EGFR monoclonal antibodies. Lièvre et al[6] showed that the *KRAS* mutation was present in 43% of colorectal tumours and was significantly associated with clinical resistance to cetuximab.[6] The updated data from two first-line clinical trials (CRYSTAL and OPUS) confirmed that patients with wild-type KRAS tumours had significant improvements in response and survival when treated with cetuximab and either irinotecan-based (CRYSTAL study) or oxaliplatin-based (OPUS study) chemotherapy.[7,8] However, not all patients with KRAS tumours that are wild-type respond to cetuximab-based therapy. Therefore, the purpose of our study was to identify potential clinical markers to predict which patients with advanced colorectal cancers would respond best to cetuximab therapy.

Methods

Patient selection

All patients with histologically confirmed, recurrent, or metastatic colorectal cancer, who were treated with cetuximab in combination with chemotherapy at the Department of Clinical Oncology at the Prince of Wales Hospital between July 2004 and June 2008, were identified from the pharmacy record. Their hospital records were reviewed. They included patients who were previously untreated and those who had had prior chemotherapy for recurrent or metastatic diseases.

Treatment

Cetuximab was administered as a 2-hour intravenous (IV) infusion at 400 mg/m^2 followed by weekly 1-hour infusions of 250 mg/m^2. An alternative schedule of cetuximab at a dose of 500 mg/m^2 biweekly was also given; this schedule having been previously shown to be just as effective as the weekly schedule.[9] Patients received cetuximab in combination with any one of the following regimens: (i) irinotecan alone: IV irinotecan 180 mg/m^2 infused over 2 hours, every 2 weeks; (ii) modified FOLFIRI: IV irinotecan 180 mg/m^2 infused over 2 hours on day 1, followed by IV leucovorin 200 mg/m^2 as a bolus, IV 5-fluorouracil 400 mg/m^2 as a bolus then an infusion at 600 mg/m^2 over 22 hours on days 1 and 2, repeated every 2 weeks; (iii) FOLFOX4: IV oxaliplatin 85 mg/m^2 infused over 2 hours on day 1, followed by IV leucovorin 200 mg/m^2 as a bolus, IV 5-fluorouracil 400 mg/m^2 as a bolus then an infusion of 600 mg/m^2 over 22 hours on days 1 and 2, repeated every 2 weeks; (iv) XELOX: IV oxaliplatin 130 mg/m^2 infusion over 2 hours and oral capecitabine at 1000 mg/m^2 twice daily for 14 days, repeated every 3 weeks. Treatment was continued until disease progression, unacceptable toxicity, or refusal by the patient. In the event of adverse effects, cetuximab and chemotherapy dosages were adjusted at the discretion of the attending physician.

Evaluation of potential predictive factors

We assessed the following potential clinical predictive factors of response to cetuximab-chemotherapy: patient demographics (including age and gender); disease-specific data (including primary tumour site, primary tumour resection, previous adjuvant chemotherapy) and the number of prior lines of chemotherapy (ie the number of prior chemotherapy regimens received); baseline laboratory markers (including carcinoembryonic antigen [CEA], lactate dehydrogenase [LDH], alkaline phosphatase [ALP], bilirubin, and albumin levels); and a treatment-related factor (namely the severity of cetuximab-therapy–related acneform rash). Skin rash was graded using the National Cancer Institute Common Toxicity Criteria (version 2.0).

Evaluation of tumour response

The objective tumour response to cetuximab-

TABLE 1. Patient characteristics (n=102)

Characteristic	Data*
Age (years)	55 (33-83)
Sex	
Male	58 (57)
Female	44 (43)
Primary tumour site	
Colon	69 (68)
Rectum	33 (32)
Metastatic site	
Local recurrence	3 (3)
Liver	18 (18)
Lung	5 (5)
>1 Metastatic sites	76 (75)
Primary tumour resected	86 (84)
Previous adjuvant therapy	
Chemotherapy	24 (24)
Radiotherapy	9 (9)
Prior No. of chemotherapy sessions for metastatic disease	
0	30 (29)
1	25 (25)
2	42 (41)
3	3 (3)
>3	2 (2)
Pretreatment biochemistry†	
CEA level (μg/L)	53 (1-11 530)
LDH level (μmol/L)	263 (109-1273)
ALP level (IU/L)	106 (40-776)
Bilirubin level (μmol/L)	9 (3-45)
Albumin level (g/L)	41 (21-48)

* Data are shown as No. (%) or median (range)
† CEA denotes carcinoembryonic antigen, LDH lactate dehydrogenase, and ALP alkaline phosphatase

TABLE 2. Cetuximab treatment regimens and outcomes (n=102)

Characteristic	Data*
Cetuximab regimen	
With oxaliplatin-based chemotherapy	29 (28)
As first-line treatment	22 (76)
With irinotecan-based chemotherapy	73 (72)
As first-line treatment	8 (11)
No. of cycles of cetuximab	6 (1-24)
Reason for stopping treatment (n=94)†	
Progression	54 (57)
Cetuximab toxicity	3 (3)
Chemotherapy toxicity	12 (13)
Others	25 (27)
Adverse events	
Rash, grade 3	13 (13)
Infusion-related reaction, grade 3	1 (1)
Best response	
Complete response	8 (8)
Partial response	20 (20)
Stable disease	37 (36)
Progressive disease	37 (36)
Overall response rate‡	28 (28)
First-line treatment (n=30)	16 (53)
≥Second-line treatment (n=72)	12 (17)

* Data are shown as No. (%) or median (range)
† Eight patients were still on cetuximab treatment at the time of data analysis
‡ The overall response rate is the sum of the rate of complete response and the rate of partial response

chemotherapy was assessed by computed tomographic (CT) imaging pre- and post-treatment, and graded retrospectively by a blinded investigator, according to the Response Evaluation Criteria in Solid Tumors. Total-body positron emission tomography was also used to complement CT in the evaluation of complete responders. The best overall response was recorded for each patient.

Statistical analysis

Responders were defined as patients with a complete or partial response; non-responders were defined as having stable or progressive disease. Both univariate and multivariate analyses using logistic regression were performed to evaluate the relationship between various clinical parameters with the response rate to cetuximab-chemotherapy. Age, CEA, LDH, ALP, bilirubin and albumin levels, and the number of lines of prior chemotherapy were tested as continuous variables. Other features were tested as dichotomous variables: male versus female, primary tumour in colon versus rectum, primary tumour resection versus no resection, previous adjuvant chemotherapy versus no such chemotherapy, and grade 3 versus grades 0-2 rash. Data were analysed using SAS software (version 8.02; SAS Institute Inc, Cary [NC], US). All tests were two-sided and a P value of 0.05 or less was considered statistically significant.

Results

Patient characteristics

One hundred and two consecutive patients with recurrent and metastatic colorectal adenocarcinoma treated with cetuximab in combination with chemotherapy were selected. Patient characteristics are shown in Table 1. In most instances (84%), primary tumours were resected during the initial admission

TABLE 3. Possible predictors of response to cetuximab-chemotherapy used in the univariate analysis*

Variable	Odds ratio	95% Confidence interval	P value
Age	0.99	0.96-1.03	0.72
Sex	0.68	0.28-1.63	0.39
Primary tumour site	1.08	0.45-2.59	0.86
Primary tumour resected	0.57	0.19-1.76	0.33
Previous adjuvant chemotherapy	0.85	0.30-2.42	0.76
No. of prior chemotherapy regimens	0.36	0.21-0.63	<0.01
CEA	1.08	0.88-1.32	0.49
LDH	0.98	0.88-1.10	0.75
ALP	1.08	0.98-1.19	0.11
Bilirubin	0.98	0.91-1.06	0.62
Albumin	0.96	0.87-1.05	0.37
Grade 3 rash	5.52	1.62-18.76	<0.01

* CEA denotes carcinoembryonic antigen, LDH lactate dehydrogenase, and ALP alkaline phosphatase

TABLE 4. Predictors of response to cetuximab-chemotherapy in multivariate analysis

Variable	Odds ratio	95% Confidence interval	P value
No. of prior chemotherapy regimens	0.37	0.20-0.69	<0.01
Grade 3 rash	4.65	1.21-19.29	0.03

(when colorectal cancer was diagnosed). Adjuvant chemotherapy was given to 24 patients and adjuvant pelvic radiotherapy to nine. The majority of patients (66%) were treated with a cetuximab-based regimen as second- or third-line therapy, while 29% received this therapy as first-line, and 5% as fourth or a higher line of therapy.

Treatment characteristics and outcomes

The combination chemotherapy regimens with cetuximab used in these patients, reasons for stopping treatment, adverse events, and best response to treatment are summarised in Table 2. One cycle of cetuximab was defined as one dose of cetuximab given biweekly or two doses of cetuximab given weekly. Over half of the patients stopped cetuximab therapy due to progression; 3% because of unacceptable cetuximab-related toxicity and 13% due to chemotherapy-related toxicity. Other reasons for stopping treatment (27%) included financial constraints, tumours became adequately downstaged for subsequent surgery, or patient's choice. Of the 102 study patients, 13 endured a grade 3 skin rash with cetuximab for which subsequent dosing was omitted or reduced. A grade 3 infusion-related reaction (fever, dyspnoea, chest pain presenting during the infusion of the monoclonal antibody and attributed to cytokine release and unrelated to skin rash) developed in one patient for whom the treatment was discontinued. Notably, the overall response rate to cetuximab plus chemotherapy was 53% in patients receiving cetuximab as first-line treatment and 17% in previously treated patients.

Predictors of response

The univariate analysis indicated that having received fewer prior chemotherapy regimens (odds ratio [OR]=0.36; 95% confidence interval [CI], 0.21-0.63; P<0.01) and the presence of grade 3 rash (5.52; 1.62-18.76; P<0.01) were associated with a significantly higher tumour response rate to cetuximab-chemotherapy (Table 3). Response to cetuximab-chemotherapy was evident in 22% of patients without a reported grade 3 rash versus 61% in those developing such a rash. The response rate was 53% in patients who received cetuximab-chemotherapy as first-line treatment, and 17% in those who had had prior chemotherapy. The other evaluated variables were not significantly associated with the response rate (Table 3).

Multivariate analysis indicated that the number of prior chemotherapy regimens (OR=0.37; 95% CI, 0.20-0.69; P<0.01) and a cetuximab-chemotherapy–related grade 3 rash (4.65; 1.21-19.29; P=0.03) were independent predictors of tumour response (Table 4).

Discussion

Our results in Chinese patients with recurrent or metastatic colorectal cancer indicate that the presence of cetuximab-chemotherapy–related grade 3 rash and the number of prior chemotherapy regimens significantly predicted the response to treatment, using both univariate and multivariate analyses. Survival analysis was not performed due to the heterogeneous nature of our population in terms of tumour sites, recurrent disease, and types of salvage treatment offered.

Grade 3 skin rash was reported in 13% of our study patients, which was comparable to rates of 5 to 13% reported in previous studies describing cetuximab use as monotherapy or in combination with other agents.[3-5] The acneform rash usually manifests on the face, upper chest, and back, typically appears in the first 3 weeks of therapy and is reversible upon discontinuation of treatment. Grade 1 or 2 skin rash was not analysed separately because of bias from the under-reporting of milder rashes by physicians. In our study, patients with grade 3 rash achieved a response rate of 61% compared with 22% in those without such a rash (P<0.01). This concurs with the BOND trial, where corresponding response rates of 55% versus 18% were observed in patients developing grade 3 versus grades 0-2 skin reactions

after using cetuximab plus irinotecan (P<0.001).[3] Similarly, a later trial by Vincenzi et al[10] also entailing cetuximab and irinotecan treatment demonstrated a more favourable response rate in patients with a grade 3 skin rash as opposed to those without such a rash (63% vs 10%, P=0.006). It must be noted that in our study, skin toxicity was not consistently recorded in the medical records by the attending physicians. Although skin rash has been consistently proven to be strongly associated with response to cetuximab, not all responders experienced a grade 3 rash and hence this cannot be entirely relied upon for opting to continue cetuximab-based therapy. Nevertheless, as suggested in the EVEREST trial in which patients tolerating higher-than-standard doses of cetuximab enjoyed higher response rates, targeting doses to achieve a desired level of cutaneous toxicity may further increase the efficacy of such therapy.[11]

As expected, having received fewer prior number of chemotherapy regimens is associated with a better response rate to cetuximab therapy, since responsiveness to chemotherapy usually declines after repeated lines of treatment. After the publication of several positive studies on the addition of cetuximab to irinotecan- or oxaliplatin-based chemotherapy as first-line treatment of metastatic colorectal cancer, there has been a gradual shift towards offering such treatment for this disease, especially with respect to downstaging previously inoperable liver metastasis.[12-14] In our cohort, discontinuation of treatment due to cetuximab-related toxicity was uncommon (3%). Furthermore, we did not investigate skin rash per se as a prognostic marker because such patients had usually been treated with several cycles of cetuximab and therefore inherently they had survived longer. Although the monitoring of CEA and LDH levels are widely utilised in the management of colorectal cancer, in our study both tumour markers failed to predict response to cetuximab-based therapy. An elevated CEA level is a poor prognostic sign and correlates with reduced overall survival after surgical resection of colorectal carcinoma.[15] For patients with metastatic disease undergoing palliative chemotherapy, serial CEA determinations may identify responders before changes are evident by imaging.[16] In addition, pre-treatment levels of both CEA and LDH have been identified as independent prognostic factors in patients with liver metastases.[17] Perhaps future studies should test for any correlation between the response to cetuximab therapy and changes in CEA and/or LDH levels, rather than focusing on them merely as baseline markers.

Hebbar et al[18] published a retrospective study assessing the predictive value of baseline clinical factors in 311 patients with irinotecan-refractory metastatic colorectal cancer. A multivariate analysis identified prior response to irinotecan, number of metastatic sites, and disease duration as independent predictors of response. In contrast, our study was based on a series of unselected patients from the community, including those who were chemonaïve receiving cetuximab in combination with oxaliplatin- or irinotecan-based chemotherapy. Thus, the data may be more reflective of day-to-day practice in the community.

Our study was retrospective and so had certain inherent limitations. There may have been variations in the clinical evaluation and the assessment of certain predictors, especially the inter-observer differences due to subjective grading of skin toxicity. Information on certain variables was not available for all patients, which might have underestimated their predictive role. Furthermore, radiological reassessments were performed at different time-points for different individuals, which may also have affected our results. Clearly our patient population was heterogeneous in terms of previous combination chemotherapy received and lines of chemotherapy associated with cetuximab use. Such heterogeneity is nevertheless quite representative of common practice in Hong Kong. Finally, our results were based on experience at a single institution.

In conclusion, we have shown that the response to cetuximab-chemotherapy in metastatic colorectal cancer is associated positively with grade 3 skin rash, and negatively with the number of prior chemotherapy regimens. Our clinical findings support previous data in showing the strong association between the severity of the rash and drug response. A future prospective trial is needed to validate these clinical predictors. Additional reliable and easily measured clinical markers and biomarkers are clearly needed to improve the identification of patients who will benefit from cetuximab treatment.

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