·**Clinical Research**·

Efficacy of cetuximab combined with chemotherapy in 53 patients with advanced colorectal cancer

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【**Abstract**】**Background and Objective:** Cetuximab combined with chemotherapy has been a great achievements in the treatment of patients with advanced colorectal cancer in recent years, however, few reports based on large patient cohorts are available in China. This study analyzed the efficacy of cetuximab combined with chemotherapy in 53 patients with advanced colorectal cancer. **Methods:** Clinical data of 53 patients with advanced colorectal cancer, treated by cetuximab combined with chemotherapy at the Sun Yat-sen Cancer Center from March 2005 to April 2008 were analyzed for short-term efficacy and safety. The efficacies of the regimen used as first-line and non-first-line treatment were compared by a χ^2 test; its prognostic value was analyzed by a multivariate Cox proportional hazard model. **Results:** Of the 53 patients, 40 were men and 13 were women, with a median age of 55 years. All patients had colorectal adenocarcinoma. A total of 572 weeks (median 8 weeks) of cetuximab treatment were completed. The overall response rate of the regimen was 39.6% and the disease control rate was 66.0%. The disease control rates when the regimen was used as first-line and non-first-line treatment were similar (P=0.177). For these 53 patients, clinical stage was an independent prognostic factor (P=0.002, OR > 1). The most common adverse events (grades Ⅲ – Ⅳ) included acne-like rash (7.5%), neutropenia (18.9%), and diarrhea (5.6%). No hypersensitive reactions or treatment-related deaths were observed. Only one patient discontinued treatment because of grade IV diarrhea and neutropenia. **Conclusions:** Cetuximab combined with chemotherapy can achieve relatively high rates of disease control for patients with advanced colorectal cancer, with fewer adverse events. Whether cetuximab as a first-line treatment has a better effect than as a non-first-line treatment needs further study.

Key words: centuximab, advanced colorectal cancer, short-term efficacy, prognosis, safety

Colorectal cancer is a common malignant tumor, and about 25% of colorectal cancer patients have already developed potential metastasis when they are diagnosed. During the entire course of the disease, around 50% of patients will develop metastasis. In advanced colorectal cancer, patients are mainly treated with a chemotherapy-based integrated strategy. Cytotoxic agents used in chemotherapy are generally nonspecific, and induce substantial toxicity and adverse reactions. New molecule-targeting agents are designed to overcome the shortcomings of cytotoxic agents and may reverse the resistance to cytotoxic agents in tumor cells. The combination of cytotoxic and targeting agents increases the efficacy in advanced colorectal cancer.[1,2] However, relevant studies to date have not included patients from Asia. Herein we studied 53 patients with advanced colorectal cancer who were treated with cetuximab at the Sun Yat-sen University Cancer Center from March 2005 to April 2008. In the hope of building clinical experience treating Asian patients with advanced colorectal cancer with cetuximab, we evaluated the short-term efficacy of cetuximab and the difference in efficacy of cetuximab as first-line and non-first-line treatment and its influence on prognosis, as well as summarizing the common toxicity and side effects of cetuximab.

Materials and Methods

Clinical data

From March 2005 to April 2008, the Sun Yat-sen University

Cancer Center treated 53 hospitalized patients with advanced colorectal cancer who had evaluable lesions, complete medical data, and completed ≥ 2 cycles of cetuximab treatment. Retrospective analysis was performed on these patients.

Among the 53 patients, 40 were men and 13 were women. They aged from 31 years to 82 years, with a median age of 55 years. Pathologically confirmed colon cancer was seen in 37 patients and rectal cancer in 16 patients. With the histology of adenocarcinoma, 9 patients had highly differentiated cancer, 34 had moderately differentiated cancer, and 10 had poorly differentiated cancer. Based on the TNM Classification by the International Union Against Cancer (UICC), the disease was rated as stage II in 5 patients, stage III in 16 patients, and stage IV in 28 patients when they were first diagnosed. Another 4 patients had already been surgically treated in other hospitals, and thus staging was not certain in these patients. Among all patients, 52.8% (28/53) had distant metastasis when first diagnosed. Of them, 82.1% (23/28) had liver metastasis, 17.9% (5/28) had lung metastasis, 14.3% (4/28) had abdominal or pelvic metastasis, 3.6% (1/28) had brain metastasis, and 3.6% (1/28) had cervical and mediastinal lymph node metastasis. Concomitant metastasis of liver and lung was seen in 3 patients, concomitant metastasis of liver, cervical, and mediastinal lymph nodes in 1 patient, concomitant metastasis of lung and brain in 1 patient, and concomitant metastasis of liver, abdominal, and pelvic cavity in 1 patient.

The clinical features in these patients when cetuximab treatment was given are as follows. The Eastern Cooperative Oncology Group (ECOG) score was ≤ 2 in all patients. Of them, 9.3% (5) had local recurrence and 90.6% (48) had distant metastasis. Among them, 70.8% (34) had liver metastasis, 45.8% (22) had lung metastasis, 8.3% (4) had abdominal or pelvic metastasis, 6.3% (3) had bone metastasis, 4.2% (2) had brain metastasis, 2.1% (1) had renal metastasis, and 2.1% (1) had cervical and mediastinal metastasis. Concomitant metastasis of liver and lung was seen in 12 patients, concomitant metastasis of lung and brain in 2 patients, concomitant metastasis of liver, cervical, and mediastinal lymph nodes in 1 patient, concomitant metastasis of liver, lung, and bone in 1 patient, concomitant metastasis of liver and bone in 1 patient, concomitant metastasis of lung and pelvic cavity in 1 patient, and concomitant metastasis of kidney and bone in 1 patient.

Evaluation criteria

Response Evaluation Criteria in Solid Tumors (RECIST) were used to evaluate the short-term efficacy of cetuximab. Response was rated as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Disease control was defined as "CR+PR+SD". In our study, efficacy evaluation was based on computed tomography (CT) images. Adverse reactions were evaluated as grades 0-IV according to the Common Toxicity Criteria by the US National Cancer Institute.

Treatment methods

In all patients, cetuximab combined with chemotherapy was given as palliative treatment. A total of 45 patients had an irinotecan-based chemotherapy regimen and 8 had an oxaliplatin-based chemotherapy regimen.

Cetuximab was used once a week until disease progression, intolerable side effects, or discontinuation due to financial issues. The first dosage of cetuximab was given via intravenous drip at 400 mg/m² for more than 2 h. Then cetuximab was used once a week at the dosage of 250 mg/m2 via intravenous drip for more than 1 h. The infusion rate started from 1 mL/min, and was increased if no allergic reactions were seen within 10 min, with the maximal rate of less than 5 mL/min. Pretreatment with intramuscularly injected diphenhydramine (40 mg) and intravenously injected cimetidine (400 mg) was given before each intravenous infusion of cetuximab.

Follow-up

In our study, the follow-up ended as of January 8, 2009. The patients were followed for 5–98.5 months, with a median of 34 months.

Statistical methods

Statistical analyses were conducted with SPSS16.0 software. A χ^2 test was used to compare the short-term efficacy of cetuximab plus chemotherapy as first-line and non-first-line treatment. Multivariate analysis was conducted with a Cox proportional hazard model to evaluate the influence of clinical and pathologic features and first-line cetuximab treatment plus chemotherapy on the prognosis of patients with advanced colorectal cancer.

Results

Treatment compliance efficacy

Treatment compliance and efficacy in 53 patients with advanced colorectal cancer are shown in Table 1. In the 53 patients, a total of 572 weeks of cetuximab treatment was completed. In particular, each patient completed 2–60 weeks of cetuximab treatment, with a median number of 8 cycles. In 86.8%

Table 1　Effect of cetuximab combined with chemotherapy on 53 patients with advanced colorectal cancer (ACRC)

Cetuximab	Number	Chemo therapy regimen (number)		Efficacy [number (%)]			
		OXA-based regimen	IRI-based regimen	PR	SD	PD	DC
First-line	15	8	7	8(53.3)	4(26.7)	3(20.0)	12(80.0)
Second-line	16	15	1	7(43.8)	4(25.0)	5(31.3)	11(68.8)
Third-line	14	14	0	4(28.6)	3(21.4)	7(50.0)	7(50.0)
Fourth-line	8	8	0	2(25.0)	3(37.5)	3(37.5)	5(62.5)
Total	53	45	8	21(39.6)	14(26.4)	18(34.0)	35(66.0)

OXA-based, oxaliplatin-based chemotherapy; IRI-based, irinotecan-based chemotherapy. PR, partial response; SD, stable disease; PD, progression disease; DC, disease control.

(46/53) of patients, the treatment lasted for ≥ 4 successive cycles.

Comparing efficacy of cetuximab as a first-line and a non-first-line treatment

The evaluation on the difference in the rate of disease control with cetuximab plus chemotherapy as first-line and non-first-line treatment suggested that the disease control rate was higher in the first-line setting compared to the non-first-line setting, but the difference was not statistically significant (Table 2).

Table 2 Effect of cetuximab in first-line and non-first-line treatments

Cetuximab	DC [number (%)]	PD [number (%)]	Total (number)	P
First-line	12(80.0)	3(20.0)	15	0.177
Non-first-line	23(60.5)	15(39.5)	38	
Total	35(66.0)	18(34.0)	53	

Footnotes as in Table 1.

Analysis of survival

As of the follow-up cutoff date, 39 patients died, 2 were lost to follow-up, and 12 survived. Of those who survived, performance score (PS) was ≤ 1 in 10 patients, 2 in one patient, and 3 in one patient. Total survival duration was 5.0–98.5 months, with a median of 34 months.

Clinical data of the 49 patients who had used cetuximab at any time during the entire treatment course (4 patients were not included due to uncertain staging after surgical treatment in other hospitals) are shown in Table 3. Factors that potentially influenced prognosis were introduced into the Cox model, including sex, age (patients were classified as high risk or non-high risk based on age), family history, primary site (colon/rectum), clinical staging (TNM) at diagnosis, differentiation level, first-line treatment regimen, whether cetuximab was used in first-line palliative treatment, and efficacy of the first-line palliative treatment. Since the pathology was adenocarcinoma in all patients on our study, pathology was excluded in the analysis of prognosis. The multivariate analysis showed that clinical stage was an independent prognostic factor (P<0.05), with poorer

Table 3 Clinical data of 49 patients with ACRC treated with cetuximab

Clinical factor	Item	Number(%)
Gender	Male	37(75.5)
	Female	12(24.5)
Age (years)	40–59(Risk group)	25(51.0)
	<40 or ≥60(Non-risk group)	24(49.0)
Family history	Yes	10(20.4)
	No	39(79.6)
Tumor site	Rectum	15(30.6)
	Colon	34(69.4)
Primary clinical stage	II	5(10.2)
	III	16(32.7)
	IV	28(57.1)
Histological differentiation	Well	6(12.3)
	Moderate	33(67.3)
	Poor	10(20.4)
Primary treatment	Operation and chemotherapy	42(85.7)
	Others	7(14.3)
First-line chemotherapy	Chemotherapy and cetuximab	37(75.5)
	Chemotherapy	12(25.5)
Chemotherapy results	PR	24(48.9)
	SD	9(18.4)
	PD	16(32.7)

All patients were ACRC with local relapse or metastasis when they accepted centuximab, though some of them were Stage II at initial visit. Other footnotes as in Table 1.

prognosis for later stages; primary site might be an independent prognostic factor (0.05<P<0.10), with poorer prognosis for rectal cancer than for colon cancer; in patients with advanced colorectal cancer who had used cetuximab during palliative treatment, whether cetuximab was used as first-line treatment was not an independent prognostic factor (Table 4).

Safety and side effects

The most common side effects of cetuximab were acneiform eruption or rash (81.1%; grades III–IV in 7.5%), neutropenia (67.9%; grades III–IV in 18.9%), and diarrhea (20.8%; grades

Table 4 Multivariate survival analysis of 49 patients with ACRC treated with cetuximab

Variate	B	SE	Wald	P	OR	95% CI for Exp(B)
Gender	−0.171	0.496	0.118	0.731	0.843	0.319–2.230
Age	−0.119	0.408	0.086	0.770	0.888	0.399–1.973
Family history	0.470	0.455	1.069	0.301	1.600	0.657–3.900
Tumor site(rectum /colon)	0.753	0.448	2.820	0.093	2.123	0.882–5.111
Clinical stage	1.057	0.346	9.355	0.002	2.878	1.462–5.667
Histological differentiation	0.307	0.334	0.843	0.358	1.359	0.706–2.618
Primary treatment	0.454	0.787	0.333	0.564	1.574	0.337–7.360
First-line chemotherapy with or without cetuximab	−0.038	0.510	0.006	0.940	0.962	0.354–2.616
Efficacy of first-line treatment	0.278	0.258	1.159	0.282	1.321	0.796–2.192

SE, standard error; OR, odds ratio; CI, confidence interval.

Ⅲ – Ⅳ in 5.6%). These side effects were mostly mild and reversible. No hypersensitive reaction or treatment-related death was recorded. Among the 53 patients, only one patient discontinued treatment due to severe diarrhea and grade Ⅳ myelosuppression. No intolerable side effects were reported in the rest of the patients.

Discussion

In 1983, Mendelsohn *et al.*[3] suggested that the epidermal growth factor receptor (EGFR) was a target for antitumor treatment. Not only was EGFR seen on the epithelium, it was also expressed in malignant tumor cells.[4] Between 75% –89% of colorectal cancers express EGFR, which is correlated to poor prognosis, including low survival rate, frequent metastasis, and insensitivity and resistance to chemotherapy.[5] Cetuximab exerted its antitumor activity by acting on EGFR on the surface of tumor cells, and its cytocidal effect in tumor cells by activating the immune system.[6]

In 2004, cetuximab was approved by US Food and Drug Administration (FDA) as a treatment for patients with colorectal cancer who had positive EGFR expression as detected by the EGFR pharmDx™ kit.[7] At that time, a number of clinical studies found that sensitivity to cetuximab was predicted as long as immunohistochemical detection revealed EGFR expression in tumor cells, regardless of its expression level, the percentage of stained cells, and staining intensity.[8-10] Recent studies have found that the efficacy of cetuximab is irrelevant to EGFR level in immunohistochemical detection, and that some patients with negative EGFR might also be sensitive to cetuximab.[11,12] Recently, a literature review suggested that antibodies used in detection were unable to predict the sensitivity of tumors to cetuximab, together with the diversity of EGFR receptors in tumors, had made immunohistochemistry an unreliable approach for screening patients.[13]

Cetuximab improved the efficacy of chemotherapy

Cetuximab could enhance the cytotoxicity of chemotherapy by interfering with the growth and proliferation pathways activated by EGFR, and increase the sensitivity to chemotherapy in tumor cells when used in combination.[14,15] In patients with colorectal cancer who were resistant to irinotecan, oxaliplatin, and fluorouracil, response rates with cetuximab alone were 11.6% –12.4% , the rate of disease control was 46% , and progression-free survival (PFS) and survival duration were 1.4 months and 6.6 months, respectively.[8,11] The renowned BOND study suggested that in patients with colorectal cancer that underwent multiple chemotherapy treatments and with resistance to irinotecan, the combination of cetuximab and irinotecan could produce a response rate and disease control rate of 22.9% and 55.5%, respectively, better than those seen with cetuximab alone (10.8% and 32.4% , respectively). PFS and survival in the combination group were 4.1 months and 8.6 months, respectively, which were also better than those treated with cetuximab alone (1.5 months and 6.9 months, respectively). For patients who had disease recurrence after treatment with cetuximab or irinotecan, the disease control rate was 39.3%

when they switched to the combination of cetuximab and irinotecan.[1,9] The recent MABEL study, which included 1147 patients with EGFR-positive metastatic colorectal cancer that underwent multiple previous chemotherapy treatments who experienced recent treatment failure with an irinotecan-based chemotherapy, suggested that the 12-week PFS rate was 61% , the median survival was 9.2 months, and the 1-year survival rate 38% in patients treated with the combination of cetuximab and irinotecan.[2]

These were the clinical studies with cetuximab as second-line treatment or above. In recent years, there were also multicenter studies with cetuximab as first-line treatment. In 2006, the American Society of Clinical Oncology (ASCO) reported the phase III clinical trial of the Cancer and Leukemia Group B (CALGB 80203),[16] which assigned patients to FOLFOX ± cetuximab or FOLFIRI ± cetuximab treatment regimens. The results showed that the response rate was higher in the combination group compared to chemotherapy alone (52% vs 38% ; P=0.029). At ASCO 2007, Van Cutsem *et al.*[17] presented CRYSTAL, a phase Ⅲ clinical trial using cetuximab combined with FOLFIRI as a first-line treatment for patients with metastatic colorectal cancer. Both response rate and PFS were improved in those treated with cetuximab plus chemotherapy compared to those treated with chemotherapy alone (46.9% vs. 38.7%, P= 0.05; 8.9 months vs. 8.0 months, P=0.036). In addition, the relative risk for disease progression decreased by 15% with cetuximab. Based on these results, European countries approved cetuximab in combination with FOLFIRI as a first-line treatment for patients with colorectal cancer without K-ras mutation.[17] A recent report suggested that with cetuximab combined with irinotecan and capecitabine as first-line treatment for patients with advanced and metastatic colorectal cancer, CR, PR, SD, and PD rates were 5.7%, 37.7%, 43.4%, and 13.2%, respectively, with a disease control rate of 86.8% and median PFS of 7 months.[18]

When comparing these large-scale clinical studies, rates of response and disease control were significantly improved with cetuximab plus chemotherapy as a first-line treatment than as a second-line treatment or above. PFS was also prolonged, but whether the difference was significant should be further confirmed by more clinical studies. We conducted a direct comparison of the short-term efficacy of cetuximab combined with chemotherapy as first-line and non-first-line treatment, and revealed that the rates of response and disease control of cetuximab plus chemotherapy were 39.6% and 66.0%, respectively. When it was used as first-line treatment, the response rate and disease-control rate were 53.3% and 80.0%, respectively, while the response rate and disease-control rate in the non-first-line setting were 43.4% and 60.5% , respectively. Our results were generally consistent with those reported by the clinical studies mentioned above, which indicated that disease-control rate in the first-line setting was higher than that in the non-first-line setting. However, our statistical analysis suggested an insignificant difference. Since the sample size of our study was small, and the number of patients with cetuximab as first-line treatment was small as well, future studies with larger sample sizes are needed.

The multivariate analysis of our study suggested that for

patients who used cetuximab during palliative treatment, clinical stage was an independent prognostic factor, while whether cetuximab was used as first-line treatment was not an independent prognostic factor. The clinical studies mentioned above reported the influence of cetuximab treatment combined with chemotherapy on PFS and survival duration, but had not compared the influence of cetuximab plus chemotherapy as first-line and non-first-line treatment on prognosis. In our study, we analyzed survival by introducing relevant factors into a multivariate model. Unfortunately, due to the short marketing time and high price of cetuximab in our country, the number of patients participating in our study was small. More robust results could be obtained by analyzing more patients in the future.

Influential factors in the efficacy of cetuximab

The statistical analysis in the MABEL study[1] revealed that some clinical features in patients could influence PFS with cetuximab. The Karnofsky Performance Status (KPS) ($\leqslant$ 80 vs. > 80), efficacy with recent irinotecan treatment (non-CR/PR vs. CR/PR), and metastatic lesions ($\geqslant$2 vs. 1) were negative factors, while lines of previous chemotherapy ($\geqslant$3 vs. 1), nationality (Britain vs. Italy), and body surface area (BSA) (> 1.8 m^2 vs. 1.6 –1.8 m^2) were positive factors. However, the BOND study suggested that response rate was not related to the type and number of previous chemotherapy agents, the number of chemotherapy cycles, or the lines of chemotherapy.[1,9]

On the molecular level, patients with the K-ras mutation in tumor tissue are primarily resistant to cetuximab. CRYSTAL and OPUS trials[17,19] revealed that patients with the K-ras mutation treated with chemotherapy plus cetuximab had poorer efficacy than those treated with chemotherapy alone, while those with wild-type K-ras who were treated with the combination had higher response rates and longer median survival times than those treated with chemotherapy alone. The idea that K-ras mutation detection should be performed before the clinical use of cetuximab and those with the mutation should not be treated with cetuximab was reported in the February issue of the *Journal of Clinical Oncology* (JCO) this year as a special contribution from ASCO, and as well as the 2009 National Comprehensive Cancer Network (NCCN) guidelines for colorectal cancer.[20,21] Since cetuximab is expensive, there are great implications to finding an accurate, practical, and economical predictor for its precise clinical application while avoiding wasting medical resources.

Safety of cetuximab

Clinical practice has proven that cetuximab is safe, and that most toxicity and side effects are tolerable. The MABLE study analyzed 1147 patients, and the most common treatment-related toxicity and side effects (grades Ⅰ–Ⅳ; grades Ⅲ–Ⅳ) were acneiform eruption (76%, 13%), diarrhea (67%, 19%), neutropenia (23%, 10%), dyspnea (23%, 6%), and infusion reaction (16%, 2%).[2] For patients in our study, common side effects were generally consistent with those in the studies mentioned above: acneiform eruption (81.1%; grades Ⅲ–Ⅳ in 7.5%), neutropenia (67.9%; grades Ⅲ–Ⅳ in 18.9%), and diarrhea (20.8%; grades Ⅲ–Ⅳ in 5.6%). Most these side effects were mild and reversible. No dyspnea or infusion reaction was seen.

Acneiform eruption was a common side effect in EGFR-targeting agents, and response rate and survival duration were positively correlated to the severity of the rash. The incidence of acneiform eruption was 80%–86% with cetuximab, while the incidence of grades Ⅲ–Ⅳ eruption in cetuximab alone and cetuximab plus chemotherapy were 5% and 15%, respectively. In patients treated with cetuximab plus chemotherapy, the response rate in those with a rash was higher than those without a rash (25.8% vs. 6.3%). In patients with a rash of grade Ⅲ or above, the response rate was 20%–34% and the median survival duration was 9.4–10.8 months. The 15-week PFS rate was higher in patients with the acne-like rash than in those without the rash (56% vs. 40%), and higher in those with a grades Ⅲ–Ⅳ rash than those with a grades Ⅰ–Ⅱ rash (77% vs. 55%).[1,2,6,9,11,22] In the EVEREST study reported at ASCO 2006,[23] patients who did not develop a rash at the standard dosage were either assigned to the increased dosage group (the dosage was increased until the rash developed) or continued in the standard dosage group. The results showed response rates in these two groups were 30% and 13%, respectively, indicating that increased dosage in patients who did not have a rash at the standard dosage could improve efficacy. In our study, 81.1% of patients showed an acne-like rash to varying extents, but no patient discontinued treatment due to such an effect. In the published literature, the treatment for the rash was mainly glucocorticoid and lotion. In our clinical practice, rose attar or a flos lonicerae (honeysuckle) extract solution produced rapid response and were effective, even when used repeatedly, without inducing side effects.

Infusion reaction was another side effect of cetuximab, with an incidence of 16% and a lower incidence of grades III-IV reaction (around 1%–2%). Pretreatment with antihistamines and glucocorticoids could reduce the incidence.[10,18] In our study, patients were treated with diphenhydramine (40 mg) and cimetidine (400 mg) before the cetuximab treatment, and no infusion reaction was seen. But in our clinical experience, some patients developed mild infusion reactions even with pretreatment. Mild (grades Ⅰ–Ⅱ) infusion reactions were seen as cutaneous pruritus, eruption, rigor, pyrexia, sweating, headache, or even chest tightness and dyspnea. Severe (grades Ⅲ–Ⅳ) reactions often presented as the rapid development of an airway obstruction (bronchial spasm, wheezing, and hoarseness), urticaria, and hemodynamic changes. Once an infusion reaction is seen, the infusion should be discontinued and dexamethasone given right away, and vital signs should be monitored. For those with mild to moderate reactions, the infusion could be restarted at a lower infusion rate under intensive monitoring of clinical symptoms and vital signs, when the infusion-related symptoms are relieved. If these infusion reactions are not seen again, the patient could continue treatment, but at a lower infusion rate in subsequent sessions. For those with severe infusion reactions, effective and timely management should be given, including oxygen inhalation, glucocorticoids, antihistamines, and cardiovascular drugs, and treatment with cetuximab should be terminated for good. It was reported that in patients who developed severe infusion reactions to the human-mouse chimeric monoclonal EGFR antibody cetuximab, the infusion

reaction was not seen again when they switched to human-derived monoclonal EGFR antibody panitumumab.[24,25] In our clinical experience, we have also seen one patient who was allergic to cetuximab that did not show allergic reactions when switched to panitumumab. Currently, individual case reports with regard to this are rare, not to mention large-scale case reports.

Cetuximab brings new hope for patients with advanced colorectal cancer by improving the efficacy of chemotherapy for colorectal cancer when used in combination. Except for infusion reactions and acneiform eruptions, the side effect profile is not significantly different from that of chemotherapy alone. In the 2009 NCCN guidelines, cetuximab had been classified as a first-line treatment for colorectal cancer. But whether both response rate and total survival duration are improved by using cetuximab as first-line treatment as compared to non-first-line treatment has yet to be confirmed. Individuals with mutated K-ras are resistant to cetuximab, while only those with wild-type K-ras are sensitive to cetuximab. However, only 40% –53% of those with wild-type K-ras (translating into about 20% –30% of all patients with colorectal cancer) benefited from cetuximab,[21] whereas the rest of them may never benefit from this expensive agent. Further exploration on a reliable and practical predictor for a precisely tailored treatment in clinical practice is thus of great significance.

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