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Clinical efficacy and safety of nimotuzumab plus chemotherapy in patients with advanced colorectal cancer: a retrospective analysis

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Abstract

Objective: To compare the clinical efficacy and safety of nimotuzumab combined with chemotherapy versus chemotherapy alone as first-line treatment for advanced colorectal cancer (ACRC).

Method: We retrospectively enrolled patients with ACRC treated with nimotuzumab plus chemotherapy (n = 40) or chemotherapy alone (n = 44). Responses were evaluated according to the Response Evaluation Criteria in Solid Tumors and adverse events according to the Common Terminology Criteria for Adverse Events 3.0.

Results: The objective overall response rate and disease control rate were higher in the combined-treatment group (55.0% vs 36.4% and 85.0% vs 75.0%, respectively), but the differences were not significant. There was no significant difference in median progression-free survival or median survival time between the combined-treatment and chemotherapy-alone groups (9.89 vs 7.86 months and 22.32 vs 18.10 months, respectively). There was no significant difference in adverse events between the two groups.

Conclusion: Nimotuzumab combined with chemotherapy had similar efficacy and safety to chemotherapy alone in patients with ACRC. The efficacy and safety of the combined treatment

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should be further studied in a randomized multicenter trial with a larger number of patients with ACRC.

Keywords
Advanced colorectal cancer, nimotuzumab, chemotherapy, combined treatment, adverse events, survival

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Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide, with serious effects on patient's lives.[1] CRC also has the second highest mortality rate of all types of cancer, with more than 50% of patients having distant metastases at the time of diagnosis. However, the development of combined chemotherapy protocols has improved the curative effect in patients with advanced CRC (ACRC) and extended the median survival time to 20 months.[2]

Fluoropyrimidine chemotherapy (parenteral 5-fluorouracil/leucovorin or oral capecitabine) in combination with oxaliplatin (FOLFOX or XELOX) or irinotecan (FOLFIRI), or capecitabine combined with oxaliplatin (CapeOx) are currently the first-line therapies for ACRC.[3] The clinical application of targeted drugs has further improved the efficiency and safety of ACRC chemotherapy.[4–7] The monoclonal antibodies cetuximab and panitumumab targeting the epidermal growth factor receptor (EGFR) have been approved for the treatment of refractory metastatic CRC in patients with wild-type *KRAS*.[8–10] However, the high costs of cetuximab and panitumumab mean that they are not reimbursed through medical insurance in China. Nimotuzumab is a humanized IgG1 monoclonal antibody targeting the extracellular domain of EGFR. It blocks the binding of EGF and transforming growth factor-alpha to EGFR and thus inhibits tumor cell growth, angiogenesis, and apoptosis.[11–14] In contrast to other approved anti-vascular endothelial growth factor agents including cetuximab and panitumumab, nimotuzumab needs bivalent binding for stable attachment to the cellular surface, leading to higher clinical efficiency and better safety.[15–21] Nimotuzumab has therefore been approved for the treatment of advanced head and neck cancer, nasopharyngeal cancer (NPC), glioma, and esophageal cancer in 30 countries.[22–28] In China, nimotuzumab was approved as a drug in combination with radiotherapy for the treatment of NPC in 2008 and was recommended by the Chinese edition of the National Comprehensive Cancer Network (NCCN) guidelines as a targeted therapy for NPC in 2009.[11]

Nimotuzumab is cheaper than cetuximab or panitumumab, and a series of clinical trials has reinforced its safety and efficacy for treating NPC within the Chinese population.[29–31] Owing to its promising efficacy and relatively low price, the China Food and Drug Administration has approved several clinical trials in patients with different tumors of epithelial origin. However, information on the combination of first-line treatment with nimotuzumab and chemotherapy drugs for ACRC is currently lacking. We therefore

compared the clinical efficacy and safety of nimotuzumab combined with chemotherapy and chemotherapy alone in Chinese patients with ACRC.

Materials and methods

Patients

We retrospectively enrolled patients treated in the Department of Abdominal Oncology of the Tumor Hospital Affiliated to Guizhou Medical University between January 2014 and June 2017. The patients' clinical data were recorded retrospectively. The study was approved by the Institutional Ethics Committee of Tumor Hospital Affiliated to Guizhou Medical University and signed informed consent was obtained from each participant.

The inclusion criteria were as follows: 1) age 18 to 75 years with basically normal cardiopulmonary function; 2) diagnosis of rectal or colon adenocarcinoma; 3) first treatment for ACRC without radical surgery, ACRC with recurrence and metastasis after radical resection, postoperative adjuvant chemotherapy for metastatic colorectal cancer; 4) at least one double-diameter-measurable lesion; 5) good physical condition with an Eastern Cooperative Oncology Group score of 0 to 1 or Karnofsky Performance Scale (KPS) score of 70 to 100; 6) routine blood and biochemical examinations met certain criteria (hemoglobin $\geq$90 g/L, absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, alanine aminotransferase [ALT] and aspartate aminotransferase [AST] $\leq$2.5 times upper limit of normal [ALT and AST $\leq$5 times upper limit of normal for patients with hepatic metastases], alkaline phosphatase [ALP] $\leq$2.5 times upper limit [ALP $\leq$5 times upper limit of normal for patients with hepatic or bone metastases], serum total bilirubin $<$1.5 times upper limit of normal, serum creatinine $<$1.5 times upper limit of normal, serum albumin $\geq$30 g/L); 7) non-active chronic hepatitis B; 8) received nimotuzumab plus FOLFOX/FOLFIRI chemotherapy or FOLFOX/FOLFIRI chemotherapy alone, and completed at least two cycles of chemotherapy and eight consecutive nimotuzumab treatments; 9) no previous treatment with EGFR monoclonal antibodies; and 10) wild-type *RAS* genes detected in pathological samples of primary tumor or metastasis. DNA was isolated using a TIANamp Genomic DNA Kit (Tiangen Co., Ltd., Beijing, China) and *KRAS* mutation status was detected by real-time polymerase chain reaction. *KRAS* mutation was accepted if the Ct value was $<$38 and the Ct difference between *KRAS* and RNaseP (i.e., the internal positive control) was $<$8, otherwise no *KRAS* mutation was detected.

Patients who met the following criteria were excluded: 1) malignancies other than CRC in the past 5 years; 2) *RAS* mutations or no *RAS* gene detection performed; 3) fewer than two chemotherapy cycles or eight nimotuzumab treatments; and 4) concomitant use of other anticancer drugs.

Treatment schedule

Nimotuzumab (Tai Xin Sheng®, Baitai Biological Pharmaceutical Co., Ltd., Beijing, China) was administered before the day of chemotherapy with the first dose administered as an intravenous infusion of 400 mg for 2 hours. Subsequent doses were administered by intravenous drip once a week over a period of $>$1 hour, for a total of eight treatments. No pretreatment was administered before nimotuzumab and no other drugs were given within 1 hour after infusion, except for normal saline.

Patients with primary metastatic CRC or recurrence and metastasis following radical surgery for ACRC (no adjuvant chemotherapy was performed) were administered

FOLFOX and patients with metastatic CRC after radical surgery with adjuvant chemotherapy received FOLFIRI.

All patients received serotonin receptor antagonists to prevent nausea and vomiting. Patients receiving chemotherapy containing irinotecan also received atropine 0.25 mg injected subcutaneously 30 minutes before chemotherapy. Routine blood, liver, and kidney function tests were performed once a week during chemotherapy. Granulocyte colony-stimulating factor was given in the event of grade 2 leukopenia and neutropenia. Treatments to protect the gastric mucosa and improve liver and kidney function were administered if necessary.

Evaluation of treatment response

Treatment efficacy was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST). Complete response (CR) was defined as disappearance of all target lesions and short diameter of all pathological lymph nodes (including target nodes and non-target nodes) reduced to <10 mm. Partial response (PR) was defined as total diameter of the target lesion decreased by at least 30% compared with baseline. Progressive disease (PD) was defined as the minimum value of the sum of the diameters of all target lesions measured during the whole research process, with a relative increase of at least 20%; if the baseline measurement value was the minimum, the baseline value was taken as the reference. In addition, the absolute diameter must be increased by at least 5 mm, and the presence of one or more new lesions was also considered as PD. Stable disease (SD) was defined as reduction of the target lesion less than PR but an increase less than the PD criteria. The objective overall response rate (ORR) was determined as CR + PR and the disease control rate (DCR) was CR+PR+ SD. Progression-free survival (PFS) was defined as the time from the beginning of treatment to the onset of tumor progression or death, and overall survival (OS) was defined as the interval between the start of treatment and death or last follow-up. Patients were followed-up at the end of treatment and then every 3 months.

Evaluation of adverse events

Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) 3.0. Adverse reactions were evaluated after each cycle of chemotherapy. Routine blood, liver, and kidney functions and electrolytes were reviewed before, during, and after each chemotherapy cycle. In the event of grade 4 myelosuppression or grade 3 diarrhea, oxaliplatin, irinotecan, and fluorouracil were reduced by 25% to 30% in the next cycle of treatment. If any grade 3 or worse adverse reactions remained after two dose reductions, the chemotherapy was stopped immediately.

Statistical analysis

All data were analyzed using SPSS for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). Comparisons were carried out using χ^2 or Fisher's exact tests. Survival probabilities were constructed using Kaplan–Meier survival estimates and compared by the log-rank test.

Results

Patient characteristics

Eighty-four well-documented patients with ACRC were included in this study, including 40 in the combined-treatment group and 44 in the chemotherapy-alone group. The patient characteristics are shown in Table 1. There were no significant differences between the combined-treatment

Table 1. General clinical features of patients with advanced colorectal cancer

	Combined-treatment group (n=40)	%	Chemotherapy-alone group (n=44)	%	*P* value
Sex					0.749
Male	25	62.5	26	59.1	
Female	15	37.5	18	40.9	
Age, years					0.677
≤55	20	50	24	54.5	
>55	20	50	20	45.5	
Initial KPS score before treatment					0.666
70 points	11	27.5	14	31.8	
≥80 points	29	72.5	30	68.2	
Primary tumor site					0.807
Rectum	23	57.5	28	63.6	
Colon	13	32.5	11	25.0	
Multiple primary colorectal	4	10.0	5	11.4	
Pathologic pattern					0.811
Adenocarcinoma (unknown)	13	32.5	17	38.6	
High- or medium-differentiated adenocarcinoma	16	40.0	15	34.1	
Poorly differentiated adenocarcinoma	11	27.5	12	27.3	
Metastatic site					0.998
Liver	19	47.5	22	50.0	
Lung	17	42.5	18	40.9	
Peritoneum	7	17.5	8	18.2	
Other	30	75.0	34	77.3	
Number of metastatic organs					0.565
Single	17	42.5	16	36.4	
≥2	23	57.5	28	63.6	
Chemotherapy regimen					0.806
FOLFOX4	13	32.5	16	38.6	
mFOLFOX6	6	15.0	8	15.9	
FOLFIRI	21	52.5	20	45.5	
Previous surgery					0.280
Yes	29	72.5	27	61.4	
No	11	27.5	17	38.6	
Chemotherapy cycles					0.641
2–3	10	25.0	13	29.5	
4–6	30	75.0	31	70.5	

KPS, Karnofsky Performance Scale

and chemotherapy-alone groups with regard to age, sex, initial KPS before treatment, primary tumor site, pathologic pattern, metastatic site, chemotherapy regimen, previous surgery, and chemotherapy cycles (Table 1).

Condition of treatment completion

All patients completed the follow-up and treatment. All 40 patients in the combined-treatment group received eight doses of nimotuzumab, including 10 who

Table 2. Treatment completion in patients treated with nimotuzumab plus chemotherapy or chemotherapy alone

	2–3 Cycles			4–6 Cycles		
Group	FOLFIRI	FOLFOX4	mFOLFOX6	FOLFIRI	FOLFOX4	mFOLFOX6
Combined treatment (n=40)	4	4	2	17	9	4
Chemotherapy alone (n=44)	6	3	4	14	13	4
P value			0.756			0.828

Table 3. Curative effects of nimotuzumab plus chemotherapy and chemotherapy alone

Group	Number of cases	CR	PR	SD	PD	RR	DCR
Combined treatment	40	0	22	12	6	55.0%	85.0%
Chemotherapy alone	44	0	16	17	11	36.4%	75.0%
P value			0.293	0.561	0.352	0.087	0.255

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective overall response rate; DCR, disease control rate

received two to three cycles of treatment and 30 who received four to six cycles of treatment. Among the 44 patients in the chemotherapy-alone group, 13 received two to three cycles and 31 received four to six cycles of treatment. There was no significant difference in treatment completion between the two groups (Table 2).

Treatment response evaluations

No patient in either group achieved CR. However, 22 patients in the combined-treatment group and 16 in the chemotherapy-alone group achieved PR. Compared with the combined-treatment group, a greater number of patients in the chemotherapy-alone group tended to have SD and PD; however, these differences were not statistically significant. There were no significant differences in ORR or DCR between the two groups (Table 3).

Survival analysis

The final follow-up was on 31 December 2017. All 84 patients (100%) fulfilled the follow-up criteria, and 71 patients (84.5%) died during the follow-up period. The median PFS rates were 9.89 months (95% confidence interval (CI): 5.733–14.407) and 7.86 months (95% CI: 3.446–12.274) in the combined-treatment and chemotherapy-alone groups, respectively. However, the difference between the groups was not significant (Figure 1).

The 1-, 2-, and 3-year survival rates were 80.0%, 39.1%, and 19.9% in the combined-treatment group and 72.7%, 27.5%, and 12.2% in the chemotherapy-alone group, respectively. The median OS was 22.32 months (95% CI: 18.363–26.257) in the combined-treatment group and 18.10 months (95% CI: 13.322–22.878) in the chemotherapy-alone group. There was no significant difference in OS between the groups (Figure 1).

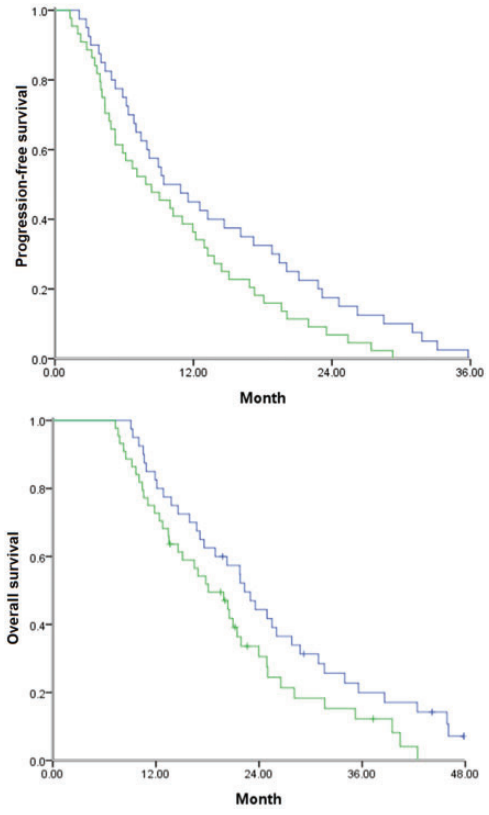

Figure 1. Kaplan–Meier curves of progression-free and overall survival in patients treated with combined treatment (blue) and chemotherapy alone (green)

Adverse events

The adverse events in this study included hematological and non-hematological toxicities (Table 4). The most common hematological toxicities included neutropenia and leukopenia. The incidence rates of grades 1 and 2 hematological toxicity in the combined-treatment and chemotherapy-alone groups were 65% and 70.5%, respectively, and the rates of grades 3 and 4 hematological toxicity were 27.5% and 31.8%, respectively. Two patients had grades 3 and 4 nausea and vomiting; the non-hematological toxicities (i.e., nausea, vomiting, diarrhea, abnormal liver function, abnormal renal function, peripheral neurotoxicity, and hand-foot syndrome) observed in all other patients were grades 1 and 2 adverse reactions. There were no significant differences between the two groups in terms of non-hematological toxicities. The main adverse reactions related to nimotuzumab were fever in one case and scattered skin rashes in three cases. The fever resolved and the skin rashes disappeared after symptomatic treatment.

Discussion

The EGFR signaling pathway has become an important target for drug therapy in patients with CRC. Drugs targeting the EGFR pathway currently include cetuximab and panitumumab, and studies of first-, second-, and third-line treatment (CRYSTAL,[32] EPIC,[33] CO.17[34]) have shown that cetuximab can effectively improve treatment efficiency and PFS in patients with ACRC. A similar conclusion was obtained in the PRIME study using panitumumab.[35] Only cetuximab is currently listed in China. However, acne-like rash and diarrhea have been reported to occur in 80% to 90% of patients taking cetuximab.[36–38] The toxic side effects are caused by the high affinity of cetuximab for EGFR leading to EGFR antagonism. Allergic reactions are also common adverse effects of monoclonal antibody targeted drugs, with an overall incidence of 19% to 23% for cetuximab, but only 2% to 3% for grade 3 to 4 allergic reactions.[39] However, given that cetuximab is not covered by medical insurance in China, its high price makes it inaccessible to most patients with ACRC in China.

Nimotuzumab is a novel EGFR monoclonal antibody. Numerous clinical studies have confirmed that nimotuzumab combined with chemotherapy significantly improves the disease control rate and survival benefit in patients with solid

Table 4. Toxic effects of nimotuzumab plus chemotherapy and chemotherapy alone

	Grade 1–2			Grade 3–4		
Toxic side effect	Combined treatment n (%)	Chemotherapy alone n (%)	*P* value	Combined treatment n (%)	Chemotherapy alone n (%)	*P* value
Hematological toxicity						
Leukocyte decrease	24 (242.0)	28 (282.6)	0.732	7 (72.5)	10 (102.7)	0.551
Granulocytopenia	21 (212.5)	22 (222.0)	0.819	3 (32.5)	5 (52.4)	0.818
Decreased hemoglobin	17 (172.5)	18 (182.9)	0.883	6 (62.0)	4 (42.0)	0.619
Thrombocytopenia	16 (162.0)	16 (162.4)	0.732	3 (32.5)	4 (42.0)	0.808
Non-hematological toxicity						
Nausea/vomiting	31 (312.5)	33 (332)	0.788	1 (12.5)	1 (12.3)	0.947
Diarrhea	6 (62)	7 (72.9)	0.908	0 (02)	0 (02)	–
Liver dysfunction	24 (242.0)	28 (282.6)	0.732	0 (02)	0 (02)	–
Kidney dysfunction	4 (42.0)	5 (52.4)	0.856	0 (02)	0 (02)	–
Peripheral neurotoxicity	1 (12.5)	2 (22.5)	0.626	0 (02)	0 (02)	–
Hand-foot syndrome	1 (12.5)	1 (12.3)	0.947	0 (02)	0 (02)	–

tumors.[22,28,40] Nimotuzumab has significantly lower affinity for the EGFR than panitumumab and cetuximab (dissociation constants: 10^{-9}, 3.9×10^{-10}, and 5×10^{-11} mol/L for nicodoxidane, cetuximab, and panidane, respectively), meaning that it binds monovalently to tissues with normal EGFR expression and thus dissociates easily, compared with molecules that bind covalently to tumor tissues with high EGFR expression and are thus more difficult to dissociate. Nimotuzumab may thus have similar anti-tumor efficacy to cetuximab, but milder side effects in clinical practice.[41] Preliminary studies have shown that radiotherapy combined with 200 mg nimotuzumab was safe and effective for the treatment of head and neck squamous cell carcinoma and pancreatic cancer. The recommended dose for subsequent studies of nimotuzumab is 200 to 400 mg. However, related clinical research in the context of CRC is currently lacking. In this study, we therefore retrospectively analyzed the efficacy and safety of nimotuzumab combined with chemotherapy in patients with ACRC.

All patients enrolled in the current study had ACRC with wild-type *KRAS*, because EGFR monoclonal antibodies are only used in patients with ACRC who have wild-type *KRAS* and *NRAS* alleles. Patients were treated with 400 mg nimotuzumab, which was the maximum dose in a phase I clinical trial.[31] We found no significant differences in ORR, DCR, PFS, and median survival between the two groups, suggesting similar efficacies of chemotherapy plus nimotuzumab and chemotherapy alone for ACRC. Regarding the safety profiles, there were no significant differences between the two groups and no new adverse reactions. In the future, larger sample sizes are needed to confirm our findings.

In conclusion, the current study suggested that the addition of nimotuzumab had no additional effect on the efficacy and safety of chemotherapy in patients with ACRC. Further studies with larger sample sizes are needed to confirm the efficacy and safety of combined treatment for ACRC.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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