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BRIEF REPORT

Safety and efficacy of cetuximab combined with chemotherapy in Chinese patients with advanced non-small cell lung cancer

Xiaoyan Si & Li Zhang

Department of Respiratory Diseases, Peking Union Medical College Hospital, Beijing, China

Keywords
cetuximab; chemotherapy; non-small cell lung cancer.

Correspondence
Li Zhang, Department of Respiratory Diseases, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, no. 1, Shuaifuyuan Wangfujing, Beijing100730, China.
Tel: +86 10 88068206
Fax: +86 10 65128635
Email: zhangli1026@sohu.com

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Abstract

Background: The aim of this study was to evaluate safety and efficacy of cetuximab combined with chemotherapy in Chinese patients with advanced non-small cell lung cancer (NSCLC).

Methods: A retrospective analysis of clinical data was conducted in patients who were given cetuximab combined with chemotherapy in the department of respiratory medicine, Peking Union Medical College Hospital between June 2008 and July 2011. All patients signed the informed consent, and consented to offer clinical information.

Results: Twenty-two patients were enrolled in this study. Nine patients were alive up to analysis, and the longest survival was 28.9 months. The objective response rate (ORR), disease control rate (DCR), median progression free survival (PFS), and estimated least median overall survival (OS) were 36.4%, 59.1%, 5.3 months and 10.1 months, respectively. Results for the 16 patients treated as first line setting were 50.0%, 62.5%, 6.0 months and 10.1 months, respectively. The common adverse events included skin toxicity (14, 63.6%), alanine aminotransferase elevation (7, 31.8%), hematological toxicity (5, 22.7%), allergy (1, 4.5%) and fever (5, 22.7%).

Conclusion: Cetuximab combined with chemotherapy for Chinese patients with advanced NSCLC had promising ORR, DCR, and PFS, especially in the first line subgroup. Serious adverse events had low incidence and were manageable.

Introduction

Epidermal growth factor receptor (EGFR), a transmembrane receptor, plays an important role in multiple processes involved in carcinogenesis. Most non-small cell lung cancer (NSCLC) tumors are found to express or overexpress the EGFR.[1–3] Cetuximab is a chimeric (human/mouse) IgG1 monoclonal antibody directed against EGFR. It suppresses EGFR-mediated cell signaling by blocking ligand binding to the receptor.[4] Cetuximab also kills tumor cells via antibody-dependent cellular cytotoxicity.[5] Robert and Thienelt *et al.* conducted studies of cetuximab combined with platinum-based chemotherapy as first line therapy in advanced NSCLC, which suggested that it had an acceptable safety profile.[6,7] Several phase II randomized controlled clinical trials indicated that cetuximab combined with cisplatin/vinorelbine or cisplatin/gemcitabine were superior to chemotherapy alone in objective response rate (ORR), progression-free survival (PFS) and overall survival (OS).[8,9] Two phase III trials, FLEX (First-line Erbitux in Lung Cancer) and BMS099 (Bristol-Myers Squibb 099) were designed to evaluate efficacy of cetuximab combined with a platinum-based doublet.[10,11] The FLEX trial, with 1125 patients enrolled, showed that cetuximab combined with chemotherapy significantly improved median OS (11.3 months vs. 10.1 months, P = 0.0441) and response rate (36% vs. 29%, P = 0.012) compared to chemotherapy alone, across all prespecified subgroups based on gender, age, the Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking status, histology, and tumor stage. However, PFS was identical at 4.8 months in each group. Cetuximab combined with chemotherapy did not improve median OS compared to chemotherapy alone in

Asian subgroup (n = 121, 17.6 vs. 20.4 months, P = not significant). However, the Asian subgroup that received cetuximab also received fewer EGFR tyrosine kinase inhibitors (50% vs. 73%), which may have had an effect on the outcomes. The BMS099 trial, with 676 patients enrolled, indicated that the addition of cetuximab to taxane/carboplatin (TC) did not significantly improve the primary end point; PFS assessed by independent radiologic review committee (IRRC). The difference in OS favored cetuximab but did not reach statistical significance. Only 16 Asian patients were enrolled in the BMS099 trial, and analysis of this subgroup was not conducted. So we need randomized, controlled clinical trials about Asian population alone to explore whether cetuximab combined with chemotherapy will improve efficacy. It is necessary to accumulate clinical information prior to conducting trials. This study summarized 22 advanced NSCLC Chinese patients treated with cetuximab combined with chemotherapy to evaluate safety and efficacy.

Patients and methods

Patients

This retrospective study was conducted through a review of medical records of patients with advanced NSCLC who received cetuximab combined with chemotherapy in the Department of Respiratory Medicine, Peking Union Medical College Hospital (PUMCH) during June 2008 to July 2011. Eligibility criteria included: (i) histological or cytological diagnosis; (ii) stage IIIb, IV, or unresectable stage IIIa; (iii) the presence of at least one measurable tumor lesion; and (iv) choice of cetuximab combined with chemotherapy at patients' own will. All patients signed informed consent of cetuximab combined with chemotherapy, and consented to offer clinical information. The characteristics of the study population are outlined in Table 1.

Table 1 Demographic and clinical data of the study population (n = 22)

Variable	n	%
Gender		
Male	16	72.7
Female	6	27.3
Age (36~82 years)		
<60 years	16	72.7
≥60 years	6	27.3
ECOG PS		
0	10	45.5
1	4	18.2
2	8	36.4
Tumor stage		
IIIA	1	4.5
IIIB	2	9.1
IV	19	86.4
Tumor differentiation		
Highly	2	9.1
Moderately-poorly	12	54.5
Unknown	8	36.4
Histology		
Adenocarcinoma	18	81.8
Squamous carcinoma	2	9.1
Adenosquamous carcinoma	1	4.5
Non-small cell lung cancer	1	4.5
Smoking history		
Yes	14	63.6
Never	8	36.4
Chemotherapy-naive		
No	6	27.3
Yes	16	72.7

Methods

Cetuximab was intravenously infused at a loading dose of 400 mg/m^2 on day one, and from day eight at a dose of 250 mg/m^2 per week. Premedication with an antihistamine drug was given before infusion. Platinum-based (carboplatin or cis-platinum) chemotherapy combined were variable (see Table 2). Chemotherapy was conducted until disease progression or unacceptable toxicity. Chemotherapy ended if no progression occurred at the end of 6 cycles. Only two patients who achieved PR and one patient who achieved SD could afford to keep on receiving cetuximab of 250 mg/m^2 per week.

EGFR expression

EGFR expression of tumor cells was measured by the technique of immunohistochemistry (IHC) in department of pathology, PUMCH. EGFR IHC score was a product of the percentage of cancer cells positive for EGFR protein on the cell surface, multiplied by the overall intensity of staining (ranging from 0 to 3+), producing a number from 0 to 300. Staining was graded by one pathologist.

Assessments

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) at intervals of six weeks after given cetuximab until disease progression, including complete response (CR), partial response (PR),

Table 2 Chemotherapy combined

Regimen	No. of patients
Pemetrexed 500 mg/m^2 d1	8
Docetaxel 75 mg/m^2 d1	6
Gemcitabine 800 mg/m^2 d1,d8	3
Paclitaxel 175 mg/m^2 d1	2
Irinotecan 100 mg/m^2 d1	2
Etoposide 60 mg/m^2 d1–5	1

All above regimens are 3-week cycle.

Table 3 Efficacy, median progression-free survival and overall survival of subgroups

Variable	No. of patients	Best overall response PR/SD/PD	ORR	P value	DCR	P value	Median PFS (months)	Median OS (months)
Total	22	8/5/9	36.4		59.1		5.3	10.1†
Gender								
Male	16	6/3/7	37.5	1.00	56.3	1.000	5.3	9.1†
Female	6	2/2/2	33.3	0	66.7		5.6	12.3
Age (years)								
<60	16	6/3/7	37.5	1.00	56.3	1.000	6.0	12.3†
≥60	6	2/2/2	33.3	0	66.7		5.0	8.9†
ECOG PS								
0–1	14	7/2/5	50.0	0.16	64.3	0.662	6.0	13.1†
2	8	1/3/4	12.5	7	50.0		5.3	8.9†
Histology								
Adenocarcinoma	18	7/5/6	38.9	1.00	66.7	0.264	5.6	12.3†
Non-adenocarcinoma	4	1/0/3	25.0	0	25.0		5.0	7.5†
Smoking history								
Yes	14	5/3/6	35.7	1.00	57.1	1.000	5.2	8.9†
Never	8	3/2/3	37.5	0	62.5		6.0	12.3
Chemotherapy-naive								
No	6	0/3/3	0.0	0.05	50.0	0.655	5.3	10.2†
Yes	16	8/2/6	50.0	1	62.5		6.0	10.1†
Skin toxicity								
No	8	2/2/4	25.0	0.64	50.0	0.662	5.6	10.2†
Yes	14	5/3/4	42.9	9	64.3		5.3	10.1†

†, estimated least median overall survival.

stable disease (SD) and progressive disease (PD). Complete blood counts and serum chemistry were done at baseline and every week during the treatment phase. Clinical adverse events and changes in the laboratory parameters were assessed according to the National Cancer Institute's common toxicity criteria (version 3). PFS was calculated at a month from the time cetuximab was given until radiological confirmed disease progression was first noted or death from any cause occurred (when death occurred within 42 days of the last tumor response assessment). OS time was calculated in the months from the time cetuximab was given until the date of death. Performance status was assessed according to the ECOG performance status scale at baseline and after six infusions of cetuximab.

Analysis

The collected data was analyzed using Statistical Package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL). We calculated object response rate (ORR (CR+PR)/(CR+PR+SD+PD)), disease control rate (DCR, (CR+ PR+SD)/(CR+PR+SD+PD)), median PFS and median OS of all patients and subgroups. Fisher's exact test was used to compare ORR and DCR between subgroups. A significance level of 0.05 was used throughout all statistical tests in this study.

Results

EGFR IHC score

EGFR IHC scores were analyzed in tissue sections from eight of 22 patients. Among these, six demonstrated an IHC score of 0–199, and two demonstrated an IHC score of 200–300.

Efficacy analysis

The median number of chemotherapy cycles given was four (range 1–6) and the median duration of cetuximab was 12 weeks (range 1–25). To the date of analysis, nine patients were alive, the longest survival being 28.9 months. Table 3 shows efficacy, median PFS and OS of subgroups. Table 4 shows the EGFR IHC scores of eight patients and respective efficacy.

Performance status analysis

Eighteen patients were given two or more cycles of chemotherapy. PS scores didn't elevate at the end of two cycles of chemotherapy compared to pre-therapy. Performance status scores improved in three patients, from 2 to 1, 2 to 0, and 1 to 0.

Table 4 Epidermal growth factor receptor immunohistochemistry scores and efficacy

No.	EGFR IHC score	Best overall response	PFS (months)	OS (months)
1	0	PD	0	5.8
2	0	PD	0	1.6
3	105	PR	16.0	17.0
4	120	SD	6.0	6.5†
5	140	PD	0	0.9
6	180‡	PD	0	22.5
7	235	PR	5.0	5.9
8	290‡	PR	9.8	14.9†

†, the time of given cetuximab to the last followup; ‡, EGFR mutation of L858R.

Adverse events

The major adverse event was skin toxicity (14/22, 63.6%). All occurred during the first 21 days of therapy, including acne-like rash and paronychia. Ten patients had grade 1, one patient (4.5%) had grade 2, and three patients (13.6%) had grade 3 (paronychia). Paronychia was relieved after drainage and antibiotic medication. Alanine aminotransferase elevated in seven patients (31.8%), grade 1 in six patients (27.2%), and grade 3 in one patient (4.5%). All recovered after receiving hepatoprotecants and continued to receive cetuximab. Five patients (22.7%) had hematological toxicity. Three patients with grade 2 leukopenia were relieved by granulocyte clony stimulating factor. The other two patients with grade 4 thrombocytopenia had received cetuximab combined with docetaxel and cis-platinum. Doses of docetaxel and cis-platinum were decreased, and cetuximab continued. Platelet counts then recovered. One patient (4.5%) had a grade 1 allergy, manifesting as flush, nausea, vomiting, and malaise, which was relieved by discontinuing cetuximab and receiving antihistamine, after which cetuximab dosing recommenced. Five patients (22.7%) had fever. Four patients (18.2%) had grade 1 fever and were relieved without any treatment. One patient had grade 4 fever and was relieved by ceasing cetuximab. Three patients had nausea and vomiting, relieved by antiemetic. The rate of Grade 3 or 4 adverse events was 31.8%. Table 5 shows the regimens combined with cetuximab and relevant grade 3 or 4 adverse events.

Discussion

We attempted to analyze the impacts of clinical factors on efficacy. As nine patients survived, we could not estimate the least median overall survival. It is necessary to follow up to compare median OS between subgroups.

ORR, DCR, and median PFS in patients with PS 0–1 were superior numerically to those of patients with PS 2. We, therefore, recommended cetuximab combined with chemotherapy applied in PS 0–1 patients in order to achieve better efficacy, although our study showed no statistical significance in ORR (P = 0.167) and DCR (P = 0.662) between subgroups.

It seemed that patients with adenocarcinoma had better efficacy numerically although there was no significant difference in ORR (P = 1.000) and DCR (P = 0.264). We considered cetuximab combined with chemotherapy was more suitable to adenocarcinoma patients.

Our study showed no significant difference in ORR (P = 1.000) and DCR (P = 1.000) between smoking and non-smoking subgroups.

Our study also showed that ORR, DCR and median PFS were 50.0%, 62.5% and 6.0 months in the subgroup of cetuximab combined with chemotherapy as first line therapy, respectively. The ORR had near statistical significance (P = 0.051) between the first and non-first line subgroups. Although our study had different characteristics of patients and different chemotherapy regimens combined, we still attempted to compare our data with other trials. ORR and median PFS in the BMS099 trial were 25.7%, 4.40 months, respectively.[11] Those in the FLEX trial were 36%, 4.8 months, respectively.[10] Xia *et al*. summarized eight trials concerning cetuximab combined with chemotherapy as first line therapy, and concluded that ORR, DCR, and median PFS were 33.2% (95% CI: 30.3%–36.1%), 65.2% (95% CI: 60.7%–69.7%), 5.0 months (95% CI: 4.7–5.3 months), respectively.[12] ORR in our study is higher than it was in the BMS099 and FLEX trials. We infer that it may be due to small sample size, different population and histology constitution. The proportions of Asian population were 2% (14/676) in the BMS099 trial, 11% (121/1125) in the FLEX trial, and 100% in our study. The proportion of adenocarcinoma

Table 5 The platinum-based regimen combined with cetuximab and grade 3 or 4 adverse events

Regimen	No. of patients	Skin toxicity	ALT	Hematological toxicity	Fever
Pemetrexed	8	3, 37.5%	1,12.5%	0	0
Docetaxel	6	0	0	2, 33.3%	0
Gemcitabine	3	0	0	0	1, 33.3%
Paclitaxel	2	0	0	0	0
Irinotecan	2	0	0	0	0
Etoposide	1	0	0	0	0

was 52% in the BMS099 trial, 48% in the FLEX trial, and 81.8% in our study. The combination of adenocarcinoma and Asian patients were good prognostic factors in FLEX trial.

The subgroup analysis of the FLEX trial showed that an acne-like rash was associated with an improved outcome for patients given cetuximab combined with chemotherapy (median OS: 15.0 vs. 8.8 months, $P < 0.0001$, RR: 44.8% vs. 32.0%, $P = 0.0039$, median PFS: 5.4 vs. 4.3 months, $P = 0.0031$).[13] In accordance with the FLEX trial, ORR ($P = 0.649$) in patients with skin toxicity in our study was superior numerically to that in patients without it. However, our study did not show that median PFS in patients with skin toxicity was superior numerically to that in patients without it.

We examined the EGFR IHC scores of tumor cells from only eight patients because of specimen condition. Both patients with IHC scores of 0 got PD. Both patients with IHC scores of more than 200 achieved PR. But we could not analyze the impact of EGFR IHC scores on efficacy because of the small sample.

Recently, quality of life has been a focus. As a retrospective study, we evaluated quality of life by ECOG performance status scores. After two cycles of chemotherapy combined with cetuximab, the PS score did not rise.

We observed adverse events of cetuximab combined with chemotherapies. Skin toxicity was common(63.6%), but did not cause discontinuation of treatment. The incidences of acne-like rash were 88.6% and 84% in studies by Robert and Thieneit, respectively. As cetuximab is a chimeric antibody, allergic reaction is a possibility. Only three patients (13.6%) discontinued cetuximab because of allergy, grade 3 ALT elevation and grade 4 fever. Except those patients with grade 4 fever, two other patients continued to receive cetuximab after remission. All grade 3 skin toxicities occurred in patients receiving pemetrexed/platinum combined with cetuximab. All grade 4 hematological toxicities occurred in patients receiving docetaxel/platinum combined with cetuximab. Because of the small sample and lack of a control group, we were not convinced that it was related with the regimens, but maintain that attention should be paid to respective adverse events when combining these regimens.

As cetuximab is too expensive for most Chinese patients, this is a small sample sized retrospective study. Our department will investigate more cases of Chinese patients receiving cetuximab combined with chemotherapy so that we can obtain more experience and data about safety and efficacy in future. The limitation of this study is the lack of a platinum-based chemotherapy only control group; therefore, we could not positively ensure that the efficacy is attributed to cetuximab.

Conclusion

Cetuximab combined with platinum-based chemotherapy for Chinese patients with advanced NSCLC had promising ORR, DCR, and PFS, especially in the first line subgroup. Serious adverse events had low incidence and were manageable.

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None.

Disclosure

No conflicts of interest by any author to be disclosed.

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