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ORIGINAL ARTICLE

Effect of cetuximab combined with IMRT and concurrent chemotherapy in treating locally advanced nasopharyngeal carcinoma

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Summary

Purpose: *To explore the efficacy and safety of cetuximab combined with intensity-modulated radiotherapy (IMRT) and concurrent cisplatin-based chemotherapy in the treatment of patients with locally advanced nasopharyngeal carcinoma.*

Methods: *The clinical information of 126 patients with locally advanced nasopharyngeal carcinoma, who were admitted to and treated in our department from September 2013 to May 2016, was collected, and they were randomly divided into two groups: cetuximab combined with IMRT and concurrent cisplatin-based chemotherapy group (Cetuximab group, n=63) and IMRT combined with concurrent cisplatin-based chemotherapy group (Control group, n=63). The clinical efficacy, changes in patients' quality of life and incidence of adverse reactions were observed and compared between the two groups, and the tumor progression and survival of the patients were followed up and recorded.*

Results: *The patients in Cetuximab group exhibited substantially higher objective remission rate (ORR) and disease control rate (DCR) [90.5% (57/63) and 100%] than those in Control group [71.4% (46/63) and 88.9% (56/63)] (p=0.011 and 0.007). After treatment, the physiological status, social and familial status and emotional status based on the FACT-H&N scale were not statistically significantly different between the two groups of patients, but the patients in Cetuximab group had notably superior functional status, additional items for the head and neck and total scale score to those in Control group (p=0.011, 0.021 and 0.038). Additionally, the main adverse reactions of patient after treatment included myelosuppression, fever, gastrointestinal reactions, acne-like rash, radiodermatitis, oral mucositis, and liver and kidney function impairment, most of which were in grade I-II (p>0.05), and the differences between the two groups were not statistically significant (p>0.05). According to the log-rank test, the differences in the OS and PFS of patients between the two groups were not statistically significant (p=0.411 and 0.114).*

Conclusions: *Cetuximab combined with IMRT and concurrent cisplatin-based chemotherapy has better clinical short-term efficacy in treating locally advanced nasopharyngeal carcinoma, and the patients treated have improved quality of life and can tolerate adverse reactions.*

Key words: *nasopharyngeal carcinoma, cetuximab, intensity-modulated radiotherapy, concurrent radiochemotherapy, efficacy*

Introduction

Nasopharyngeal carcinoma is a special type of head and neck cancer, and exhibits obvious regional and racial characteristics. It has a higher morbidity rate in Asia, especially in China and Southeastern Asia regions, and the cases of nasopharyngeal carcinoma in China account for 50-80% of the total in the world, with Southern China as an endemic region [1]. About 70% of patients are first diagnosed

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with locally advanced nasopharyngeal carcinoma, and the 5-year survival rate for them after conventional radiotherapy alone remains unsatisfactory [2]. In recent years, concurrent radiochemotherapy has become the standard treatment for the patients with locally advanced nasopharyngeal carcinoma, but there are still 20-30% of patients experiencing treatment failure, and some of them have difficulty tolerating high-intensity concurrent radiochemotherapy [3,4].

Targeted therapeutic agents have been the hotspot for the research on tumor treatment in recent years, and several clinical studies have demonstrated that epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab can improve the efficacy of radiotherapy and chemotherapy in patients with head and neck squamous carcinoma or nasopharyngeal carcinoma [5,6]. The combination of cetuximab and concurrent radiochemotherapy is promising for further raising the efficacy in nasopharyngeal carcinoma patients, and prolonging the survival of patients, without increasing common radiotherapy-related adverse reactions [7]. However, there is also a report that the addition of cetuximab leads to the increases in the cases of severe radiodermatitis and oral mucositis [8]. Therefore, this study retrospectively analyzed the clinical information of 126 patients with locally advanced nasopharyngeal carcinoma, who were admitted to and treated in our hospital from September 2013 to May 2016, and comparatively analyzed the efficacy and safety of cetuximab combined with intensity-modulated radiotherapy (IMRT) and concurrent cisplatin-based chemotherapy and IMRT combined with cisplatin-based chemotherapy in treating locally advanced nasopharyngeal carcinoma, hoping to provide a more scientific basis for the development of effective treatment regimens.

Methods

General information

The present study enrolled the patients who were definitely diagnosed with locally advanced nasopharyngeal carcinoma in our hospital from September 2013 to May 2016 and first treated. Inclusion criteria: patients aged >18 years, those definitely diagnosed with nasopharyngeal carcinoma through biopsy, those in stages III, IVA and IVB based on the 2010 7th edition of UICC/AJCC clinical staging system for nasopharyngeal carcinoma, those with measurable primary tumor foci, those with KPS score ≥70 points, those with predicted survival ≥6 months, those with blood routine examination results: WBC ≥4.0×10^9/L, Hb ≥100 g/L, and PLT ≥100×10^9/L, and those with liver function parameters ALT, AST and bilirubin < normal values by 1.5 folds. Exclusion criteria: patients who were proven to have distant metastases and received surgical treatment for primary tumor foci or lymph nodes, those receiving radiotherapy, EGFR targeted medication, chemotherapy or immunotherapy for primary foci or lymph nodes, those who developed other malignancies within 5 years, those with peripheral neuropathy >grade I, those who were known to be allergic to any treatment in this study, or those complicated with severe lung or heart disease. A total of 126 patients conforming to the criteria were included, and there were 99 males and 27 females, aged 34-69 years old and 45.5±10.7 years old on average, with the course of 2-12 months and mean of 3.9±2.6 months.

Table 1. Demographics and general clinical data of all studied patients

Parameters	*Cetuximab group (n=63) n (%)*	*Control group (n=63) n (%)*	*p value*
Gender (Male/Female)	46/17	53/10	0.192
Age (years), mean±SD	44.73±9.68	46.10±9.08	0.414
Course of the disease (months), mean±SD	4.3±2.7	3.6±3.1	0.179
Pathological type			0.316
II	43 (68.3)	49 (77.8)	
III	20 (31.7)	14 (22.2)	
UICC staging			0.765
III	35 (55.6)	39 (61.9)	
IVA	23 (36.5)	20 (31.7)	
IVB	5 (7.9)	4 (6.4)	
Karnofsky score			0.463
80-90	37 (58.7)	41 (65.1)	
70-80	26 (41.2)	22 (34.9)	

UICC: Union Internationale Contre le Cancer.

In terms of pathological type, the subjects consisted of 34 cases of non-keratinizing undifferentiated carcinoma [World Health Organization (WHO) type III] and 92 cases of non-keratinizing differentiated carcinoma (WHO type II), and based on the UICC clinical staging system, there were 74 cases in stage III, 43 cases in stage IVA and 9 cases in stage IVB. All subjects were randomly divided into two groups: cetuximab combined with IMRT and concurrent cisplatin-based chemotherapy group (Cetuximab group, n=63) and IMRT combined with concurrent cisplatin-based chemotherapy group (Control group, n=63). The clinical baseline information of the two groups of patients was comparable (Table 1). All the subjects were informed of this study according to the Declaration of Helsinki and signed the informed consent before study entry. This study was approved by the Ethics Committee of General Hospital of Ningxia Medical University.

Treatment methods

Radiotherapy: All patients received IMRT radical external irradiation, with the X-ray intensity as 6 MV and the number of irradiation field as 9. The volume of targets was delineated on each layer of computed tomography (CT) images on an IMRT workstation, based on the nasopharyngeal carcinoma and cervical lymph node metastases in patients shown in the magnetic resonance imaging (MRI) and CT findings at admission, the gross tumor volume of nasopharynx (GTVnx, nasopharyngeal carcinoma infiltration area and posterior pharyngeal lymph node area), gross target volume of nodes (GTVnd, cervical metastatic lymph nodes), clinical target volume 1 (CTV1, the whole nasopharynx, posterior pharyngeal lymphatic region, clivus, cranial base, lower part of sphenoid sinus, parapharyngeal space, 1/3 of posterior nasal cavity and maxillary sinus and lymph node area with metastatic lymph nodes), and CTV2 (cervical lymphatic drainage area without metastatic lymph nodes). Planning target volume (PTV) was generated by the IMRT planning system. The prescription dose was 66.0-75.9 Gy for GTVnx, 60-70 Gy for GTVnd, 60-64 Gy for CTV1 and 54-60 Gy for CTV2, once/d for 30-33 times and 5 d/week for 6-7 weeks in total.

Concurrent chemotherapy: Cisplatin was administered at 80 mg/m^2 on the first day once every 3 weeks, and its course depended on the actual duration of IMRT. If the duration of IMRT was extended into ≥6 weeks, the 3rd course of concurrent chemotherapy could be conducted. Before and after injection of cisplatin, antiemetic drugs were routinely given for relieving vomiting, combined with hydration therapy and alkalization of urine.

Cetuximab treatment: The patients were administered simultaneously with cetuximab (NDC S0242-05l-21, Germany) in combination with radiochemotherapy once a week. With the first dose based on 400 mg/m^2, cetuximab was dissolved in 250 mL of normal saline and slowly intravenously dripped for >120 min. From the 2nd week, the dose was reduced and calculated based on 250 mg/m^2, with the intravenous drip time >60 min. Prior to each intravenous drip, H1 receptor antagonist and dexamethasone were given for pretreatment, thereby reducing allergy and other infusion reactions. Once any severe hypersensitivity reaction occurred, cetuximab should be discontinued immediately and permanently.

Observation indicators

Before commencing treatment, MRI scans were performed, and the changes in tumor size were measured via indirect or electronic nasopharyngoscopy every week during treatment and immediately after treatment. At 3 months after treatment, the efficacy was confirmed based on MRI scans. The efficacy was evaluated with reference to the WHO Response Evaluation Criteria in Solid Tumors: complete remission (CR): after treatment, the patients exhibit complete tumor regression and improvement in clinical symptoms, partial remission (PR): after treatment, the product of the maximum diameter and maximum vertical diameter of solid tumors is reduced by more than 50%, with no enlargement of metastatic lymph nodes and others, which last for longer than 1 month, ineffective (stable disease, SD): after treatment, the product of the above two diameters is decreased by no more than 50%, with no more than 25% enlargement, which last for more than 1 month, and progressive disease (PD): after treatment, the product of the two diameters of solid tumors is increased by over 25%. Objective response rate (ORR) = (CR + PR)/the total ×100%, and disease control rate (DCR) = (CR + PR + SD)/the total ×100%.

Before treatment and at 3 months after treatment, the patients were subjected to assessment of quality of life using the Functional Assessment of Cancer Therapy-Head & Neck cancer (FACT-H&N) scale that comprises the general module of malignancies (FACT-G) (physical status, social and familial status, emotional status and functional status), and specific module of tumors, and those with higher scores have better quality of life.

Adverse reactions and safety were assessed using Common Terminology Criteria for Adverse Events v3.0, and acute radioactive reactions were evaluated based on the RTOG/EORTC.

The survival of patients was followed up and recorded. Progression-free survival (PFS) refers to the duration from the start of treatment to the disease progression or death, and overall survival (OS) is the duration from the start of treatment to death or the last follow-up day or the follow-up deadline in March 2019. The OS of the patients lost to follow-up was calculated until the last follow-up day.

Statistics

In the present study, SPSS 22.0 (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation and intergroup comparisons were made using pairwise t-test. Enumeration data were presented as ratio (%), and x^2 test was performed for intergroup comparisons. The survival curves were plotted using the Kaplan-Meier method, and the log-rank test was conducted to evaluate survival differences between two groups. $P<0.05$ suggested statistically significant differences.

Results

Clinical short-term efficacy

Cetuximab group had 32 cases of CR, 25 cases of PR, 6 cases of SD and 0 case of PD, with ORR of 90.5% (57/63), and DCR of 100%, while Control group consisted of 20 cases of CR, 26 cases of PR, 10 cases of SD and 7 cases of PD, with ORR of 71.4% (46/63) and DCR of 88.9% (56/63). ORR and DCR in Cetuximab group were notably higher than those in Control group, and the differences were statistically significant (p=0.011 and 0.007) (Table 2).

Comparison of quality of life between the two groups of patients before and after treatment

According to the comparison of the FACT-H&N scale score, there were no statistically significant differences in the physiological status, social and familial status, emotional status, functional status, addition items for the head and neck, and total scale score between the two groups of patients before treatment (p>0.05). After treatment, the physiological status, social and familial status and emotional status based on the FACT-H&N scale still exhibited no statistically significant differences between the two groups of patients, but the patients in Cetuximab group had notably superior functional status, additional items for the head and neck and total scale score to those in Control group (p=0.011, 0.021 and 0.038) (Table 3).

Table 2. Comparison of clinical efficacy of patients in the two groups

Parameters	*Cetuximab group (n=63)*	*Control group (n=63)*	*p value*
CR	32	20	
PR	25	26	
SD	6	10	
PD	0	7	
ORR, n (%)	57 (90.5)	46 (71.4)	0.011
DCR, n (%)	63 (100)	56 (88.9)	0.007

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

Incidence of adverse reactions

During treatment, the two groups of patients had different degrees of adverse reactions, and the most common side reaction was acne-like rash which occurred in 53 and 47 cases in the two groups, respectively, mainly in the face, followed by the neck, chest, back and limbs. The incidence rate of oral mucositis was 69.8% (44/63) and 54.0% (34/63) in the two groups, respectively. Other side reactions were nausea, vomiting, diarrhea, myelosuppression, fever and liver and kidney function impairment, most of which were in grade 1-2. During treatment, the skin of some patients with acne-like rash was scrubbed using honeysuckle water, and those suffering from oral mucositis were given intravenous nutrition support, combined with gargling with the prepared mouthwash fluid containing dexamethasone, gentamycin and lidocaine. Additionally, those with leukopenia and thrombocytopenia >grade 3 were promptly treated with granulocyte colony stimulating factor or interleukin-11. The incidence rate of adverse reactions in the two groups of patients was not statistically significantly different (p>0.05) (Table 4)

Table 3. Comparison of FACT-H&N scores of patients in the two studied groups

Parameters	*Cetuximab group (n=63)*	*Control group (n=63)*	*p value*
Pretreatment			
Physiological status	23.53±5.56	22.79±4.48	0.412
Social and family status	22.63±4.67	21.26±3.90	0.352
Emotional status	19.08±3.81	19.33±4.79	0.416
Functional status	14.85±5.47	15.24±5.69	0.696
Head and Neck additional items	26.33±5.88	25.52±5.70	0.434
Total scores	106.42±18.62	104.14±20.38	0.513
Posttreatment			
Physiological status	23.92±4.66	23.23±4.37	0.393
Social and family status	21.43±4.32	21.96±4.14	0.483
Emotional status	19.59±3.87	19.89±4.06	0.672
Functional status	19.93±4.63	17.86±4.37	0.011
Head and Neck additional items	23.78±5.15	21.53±4.60	0.021
Total scores	108.75±19.91	104.47±22.49	0.038

Table 4. Comparison of adverse reactions of patients in the two studied groups

	Cetuximab group (n=63) n (%)	*Control group (n=63) n (%)*	*p value*
Bone marrow suppression	32 (50.8)	24 (38.1)	0.498
Fever	22 (34.9)	17 (27.0)	0.335
Acne-like rash	53 (84.1)	47 (74.6)	0.187
Gastrointestinal reaction	25 (39.7)	31 (49.2)	0.282
Oral mucositis	44 (69.8)	34 (54.0)	0.067
Radiodermatitis	26 (41.3)	23 (36.5)	0.584
Hepatic dysfunction	30 (47.6)	33 (52.4)	0.593
Renal dysfunction	16 (25.4)	14 (22.2)	0.676

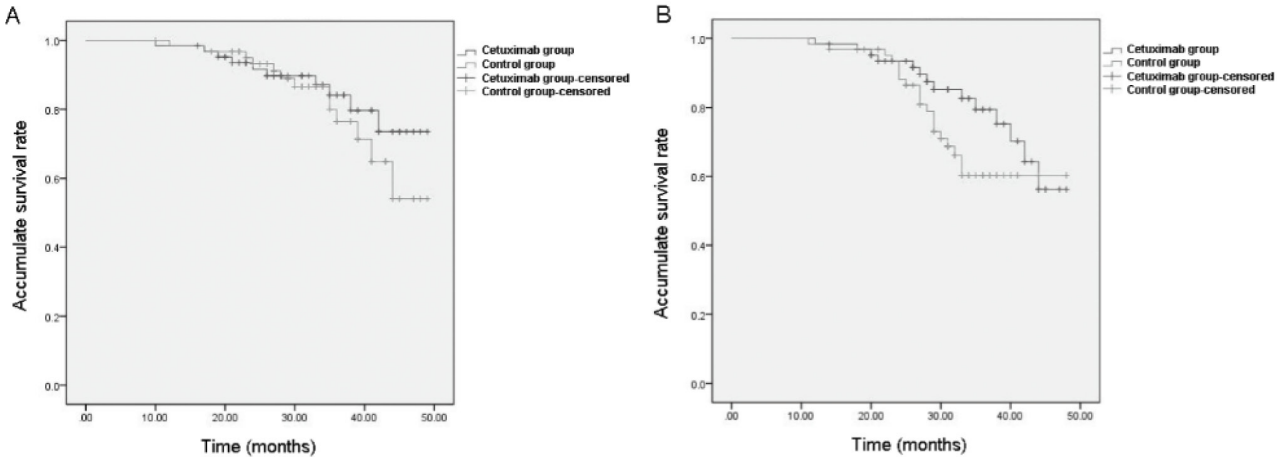

Figure 1. Kaplan-Meier survival curves of the studied patients. The difference of overall survival rate **(A)** and progression free survival rate **(B)** of patients in Cetuximab group and Control group had no statistical significance (p=0.411, p=0.114).

Survival follow-up results

All the patients were followed up for 10-50 months. In Cetuximab group, no patients had local recurrence, but 5 patients developed metastases at 9-37 months after treatment, of whom, there were 3 cases of lung metastasis, 1 case of complicated intracranial metastasis, 1 case of liver metastasis and 1 case of bone metastasis complicated with intracranial metastasis, with 10 deaths in total. Control group exhibited 4 cases of local nasopharyngeal recurrence at 24, 36, 40, and 41 months after treatment, respectively, and 1 case of local lymph node recurrence at 22 months after treatment. Besides, 9 patients had metastases, namely 5 cases of lung metastases, 1 case of complicated bone metastasis, 1 case of complicated liver metastasis and 2 cases of bone metastasis alone, and a total of 13 patients died. The 3-year OS and PFS rates were 92.1% (58/63) and 77.8% (49/63), respectively, in Cetuximab group and 81.0% (51/63) and 68.3% (43/63), respectively, in Control group. The Kaplan-Meier survival curves of patients are shown in Figure 1 and log-rank test showed no difference in the OS and PFS of patients between the two groups (p=0.411 and 0.114).

Discussion

EGFR gene, a proto-oncogene, is relatively highly expressed in the head and neck tumors. According to the study of Chua et al [9], high expression of EGFR gene lowers the disease-free survival (DFS) and OS rate of cancer patients, and Chuang et al [10] also found that EGFR gene amplification is closely associated with poor prognosis of head and neck squamous cell carcinoma, indicating that controlling the over-activated EGFR signaling pathway may affect the prognosis of this malignancy. As a humanized chimeric monoclonal antibody of immunoglobulin, cetuximab can competitively inhibit the binding of EGFR to its ligand, and block the phosphorylation of

receptor-related enzymes to further suppress cell growth, induce cell apoptosis and reduce the generation of matrix metalloproteinases and VEGF, thereby resisting tumors. Cetuximab can not only induce tumor cell apoptosis, but also arrest cells in phase G1 when they are relatively sensitive to radiotherapy, and reduce S-phase cells resistant to radiotherapy, thus enhancing the sensitivity to radiotherapy [11].

The study of Huang et al [12] argued that cetuximab can enhance cytotoxic drug activity and that its combination with standard chemotherapeutic agents can significantly improve the efficacy in treating nasopharyngeal carcinoma. Bonner et al [13] reported that cetuximab combined with radiotherapy exhibits favorable efficacy and tolerance of patients in the treatment of locally advanced head and neck cancer, with the median survival of 49 months and 5-year survival rate of 45.6%. In addition, Chan et al [14] adopted cetuximab combined with carboplatin for recurrent or metastatic nasopharyngeal carcinoma in case of failure in platinum-based chemotherapy and found that the DCR is 60% and median survival is 8 months. A multi-center randomized controlled phase III clinical study reported by Eze et al [15] compared the combination of cetuximab and chemotherapy with chemotherapy alone, and found that the median survival is 10.1 months and 7.4 months (p=0.036), respectively, suggesting that the addition of cetuximab to standard chemotherapy regimen can further effectively heighten the survival rate.

In this study, cetuximab combined with IMRT and concurrent cisplatin-based chemotherapy were employed as the first treatment for the patients with locally advanced nasopharyngeal carcinoma, and according to the review results at 3 months after treatment, the ORR and DCR were 90.5% and 100%, respectively, and the clinical short-term efficacy was significantly superior to that in Control group (p=0.011 and 0.007). In terms of long-term survival, the results of a phase II single-center study of locally advanced nasopharyngeal carcinoma conducted by Ma et al [16] revealed that the 2-year OS and PFS rates were 89.9% and 86.5%, respectively, in the patients receiving cetuximab combined with concurrent chemoradiotherapy, with the median follow-up time of 31.8 months. The results of this study showed that the 3-year OS and PFS rates of patients in Cetuximab group were higher than those in Control group [92.1% (58/63) *vs.* 81.0% (51/63), and 77.8% (49/63) *vs.* 68.3% (43/63)], which are basically consistent with the results of the above studies, but the differences in the OS and PFS between the two groups of patients were not statistically significant according to the log-rank test (p=0.411 and 0.114).

The results of clinical studies reported by Bonner et al [17] manifested that compared with radiotherapy alone, the addition of cetuximab does not raise the incidence rates of adverse reactions such as oral mucositis, radiodermatitis or difficulty swallowing or their severity. However, literature has reported severer oral mucositis and radiodermatitis in recent years, with the incidence rates of oral mucositis and radiodermatitis ≥ grade 3 as about 49-77% [8,18]. Walsh et al [8] compared the adverse reactions caused by radiotherapy combined with cisplatin-based chemotherapy with those caused by radiotherapy combined with cetuximab, and suggested that cetuximab can lead to severer grade 3 oral mucositis (p=0.14) and radiodermatitis (p=0.000) than concurrent cisplatin-based chemotherapy. In contrast, Koutcher et al [19] made similar comparisons and found that compared with concurrent cisplatin-based radiochemotherapy, cetuximab combined with radiotherapy does not increase the incidence rate of grade 3-4 adverse reactions or their severity. According to the findings in this study, Cetuximab group had higher incidence rates of oral mucositis, radiodermatitis and acne-like rash than Control group, but the differences were not statistically significant, implying that the combination of cetuximab does not elevate the incidence rate of adverse reactions.

The present study has quite a number of drawbacks, including small sample size, incomplete evaluation criteria and follow-up content, and failure to further research the possible mechanism of cetuximab treatment. The conclusion reached in this study needs to be further verified through large-sample multi-center randomized controlled trials in the future, so as to provide more potent bases for the options of regimens in treating patients with locally advanced nasopharyngeal carcinoma.

Conclusions

Cetuximab combined with IMRT and concurrent cisplatin-based chemotherapy has better clinical short-term efficacy in treating locally advanced nasopharyngeal carcinoma, and the patients have improved quality of life and can tolerate adverse reactions.

Conflict of interests

The authors declare no conflict of interests.

References

1. Chua M, Wee J, Hui EP, Chan A. Nasopharyngeal carcinoma. Lancet 2016;387:1012-24.
2. Ma YX, Zhang H, Li XH, Liu YH. MiR-30e-5p inhibits proliferation and metastasis of nasopharyngeal carcinoma cells by target-ing USP22. Eur Rev Med Pharmacol Sci 2018;22:6342-9.
3. Bian S, Wang Z, Chen Y, Li R. SPLUNC1 and MLL3 regulate cancer stem cells in nasopharyngeal carcinoma. J BUON 2019;24:1700-5.
4. Chen J, Lu F, Hu C. MicroRNA-299 targets VEGFA and inhibits the growth, chemosensitivity and invasion of human nasopharyngeal carcinoma cells. J BUON 2019;24:2049-55.
5. Xia WX, Liang H, Lv X et al. Combining cetuximab with chemoradiotherapy in patients with locally advanced nasopharyngeal carcinoma: A propensity score analysis. Oral Oncol 2017;67:167-74.
6. Xu T, Ou X, Shen C, Hu C. Cetuximab in combination with chemoradiotherapy in the treatment of recurrent and/or metastatic nasopharyngeal carcinoma. Anticancer Drugs 2016;27:66-70.
7. Li Y, Chen QY, Tang LQ et al. Concurrent chemoradiotherapy with or without cetuximab for stage II to IVb nasopharyngeal carcinoma: a case-control study. BMC Cancer 2017;17:567.
8. Walsh L, Gillham C, Dunne M et al. Toxicity of cetuximab versus cisplatin concurrent with radiotherapy in locally advanced head and neck squamous cell cancer (LAHNSCC). Radiother Oncol 2011;98:38-41.
9. Chua DT, Nicholls JM, Sham JS, Au GK. Prognostic value of epidermal growth factor receptor expression in patients with advanced stage nasopharyngeal carcinoma treated with induction chemotherapy and radiotherapy. Int J Radiat Oncol Biol Phys 2004;59: 11-20.
10. Chung CH, Ely K, McGavran L et al. Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas. J Clin Oncol 2006;24: 4170-6.
11. Sung FL, Poon TC, Hui EP et al. Antitumor effect and enhancement of cytotoxic drug activity by cetuximab in nasopharyngeal carcinoma cells. In Vivo 2005;19:237-45.
12. Huang SM, Bock JM, Harari PM. Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. Cancer Res 1999;59:1935-40.
13. Bonner JA, Harari PM, Giralt J et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21-8.
14. Chan AT, Hsu MM, Goh BC et al. Multicenter, phase II study of cetuximab in combination with carboplatin in patients with recurrent or metastatic nasopharyngeal carcinoma. J Clin Oncol 2005;23:3568-76.
15. Eze N, Lee JW, Yang DH et al. PTEN loss is associated with resistance to cetuximab in patients with head and neck squamous cell carcinoma. Oral Oncol 2019;91:69-78.
16. Ma BB, Kam MK, Leung SF et al. A phase II study of concurrent cetuximab-cisplatin and intensity-modulated radiotherapy in locoregionally advanced nasopharyngeal carcinoma. Ann Oncol 2012;23:1287-92.
17. Bonner JA, Harari PM, Giralt J et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567-78.
18. Budach W, Bolke E, Homey B. Severe cutaneous reaction during radiation therapy with concurrent cetuximab. N Engl J Med 2007;357:514-5.
19. Koutcher L, Sherman E, Fury M et al. Concurrent cisplatin and radiation versus cetuximab and radiation for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2011;81:915-22.