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ORIGINAL ARTICLE

Clinical study of cetuximab combined with radical radiotherapy in the treatment of locally advanced sinonasal squamous cell carcinoma

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Summary

Purpose: *To observe the efficacy and side effects of cetuximab combined with radical radiotherapy in the treatment of sinonasal squamous cell carcinoma (SCC), and to investigate the underlying mechanism of cetuximab.*

Methods: *62 patients with locally advanced sinonasal SCC diagnosed in our hospital from January 2013 to January 2014 were enrolled. Cetuximab and radical radiotherapy were simultaneously given to patients in the combination group, while only radical radiotherapy was given to patients in the radiotherapy group. Cetuximab was administered weekly until the end of radiotherapy. Patients intolerant to cetuximab or withdrawn the informed consent were excluded. On first administration, cetuximab was given i.v. at a dose of 400 mg/m^2 for more than 120 min, with maximum drop rate of 5 mL/min. Afterwards, cetuximab was given i.v. per week at a dose of 250 mg/m^2 for more than 60 min.*

Results: *(1) The objective response rate (ORR) and disease control rate (DCR) in the combination group was 77.42% and 93.54%, respectively, while the ORR and DCR in the radiotherapy group were only 45.61% and 70.97%, respectively ($p<0.05$). (2) The progression free survival (PFS) and the median overall survival (OS) in the combination group were 19.5 and 26.6 months, respectively, while in the radiotherapy group were only 13.8 and 18.9 months, respectively ($p<0.05$). (3) The incidence of rash in the combination group was significantly higher than that of the radiotherapy group ($p<0.05$). However, there were no significant differences in other adverse reactions between the two groups.*

Conclusions: *Combination of cetuximab with radical radiotherapy is safe and effective for advanced local sinonasal SCC and improves the survival rate and the prognosis of patients with sinonasal SCC.*

Key words: *cetuximab, chemotherapy, radiotherapy, sinonasal squamous cell carcinoma*

Introduction

Sinonasal malignancies (SNM) are relatively rare diseases, accounting for only 11.9% of head and neck neoplasms. Among them, SCC is frequently found in the maxillary sinus, which is the most common type of SNM that accounts for 70-80%, followed by sinus carcinoma and nasal carcinoma [1,2]. Early symptoms of SNM are difficult to be observed, which is an obstacle in the early disease diagnosis and treatment. As the nasal cavity and paranasal sinuses are adjacent to the oral cavity, orbit and skull base, multiple important organs and tissues may be involved with tumor expansion. So far, single therapy cannot efficiently achieve curative effect of SNM [3-5]. Therefore, it is of great significance to explore combination treatments of SNM.

In recent years, the role of molecular targeted therapies in various cancers has gradually been recognized. The advantages of target therapy, such as high effectiveness, low toxicity and selective targeting drugs, have brought encouraging survival

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benefits to patients with malignant tumors. Studies have suggested that epidermal growth factor receptor (EGFR) is one of the most studied targets. EGFR, a member of the family of growth factor receptors with tyrosine kinase activity, can inhibit cell apoptosis, promote cell proliferation and angiogenesis. Upregulated EGFR has been proved to be related to poor prognosis of cancers. More than 90% of patients with head and neck SCC express positive EGFR [6-8].

Cetuximab was initially applied in the treatment of advanced colorectal cancer with good results. Extensive clinical studies of cetuximab in head and neck carcinomas have been carried out. In addition, cetuximab was also demonstrated to exert effectiveness in non-small cell lung cancer, pancreatic cancer, gastric cancer, breast cancer, skin cancer, glioma and other malignant tumors [9-11]. Robert et al. [12] evaluated the efficacy of radiotherapy combined with cetuximab in 16 patients with advanced head and neck SCC. All evaluable patients achieved complete remission (CR) or partial remission (PR), of which 13 cases were in CR and 2 in PR. Cetuximab was first approved by EMEA in April 2006 for the treatment of advanced local head and neck SCC combined with radiotherapy, which was the well-known Bonner trial [13]. These results showed that cetuximab could significantly prolong the survival of patients with locally advanced head and neck cancer. Meanwhile, cetuximab improved the larynx preservation rate without any influence on the completion time of radiotherapy.

In this paper, 62 patients with head and neck SCC treated in our hospital from January 2013 to January 2014 were studied. Moreover, evaluated and analyzed were the short-term efficacy, PFS and OS of cetuximab combined with radiotherapy for patients with advanced local sinonasal SCC. Our study provided a basis for further exploring the clinical value of cetuximab in the treatment of advanced local sinonasal SCC.

Methods

Research subjects

Sixty-two patients with locally advanced sinonasal SCC diagnosed in our hospital from January 2013 to January 2014 were enrolled. All patients were pathologically confirmed as SCC. Before treatment, general physical examination, including nasopharynx, head and neck MRI, chest X-ray, abdominal B-ultrasound, whole body bone emission computed tomography (ECT) and chest and abdominal CT examination were performed to confirm the diagnosis and staging of sinonasal SCC. The disease stage of the enrolled patients was III or IV, and their life expectancy was at least 12 months. Before the following experiments, we performed general blood/pathological examinations on patients. The results indicated that patient Karnofsky Performance Scores (KPS) was over 70, neutrophils count was over 1.5×10^9/L, platelet count was over 100×10^9/L and hemoglobin was over 90 g/L. All patients had no evidence of distant metastasis. Sixty-two patients were then randomly assigned into either the combination group or radiotherapy group, with 31 cases in each group. There were 24 males and 7 females in the combination group, with an average age of 45.64±4.57 years. Among patients in the combination group, there were 19 cases of stage III and 12 cases of stage IV. In the radiotherapy group, there were 21 males

Table 1. Comparison of patient general characteristics in the two groups

Characteristics	*Combination group*	*Radiotherapy group*	*p value*
Age (years)			0.554
>60	6	9	
≤60	25	22	
Gender			0.570
Male	24	21	
Female	7	10	
KPS score			0.731
70/80	6	4	
90	25	27	
Tumor type			1.000
Maxillary sinus carcinoma	19	18	
Ethmoid carcinoma	12	13	
Stage			0.185
III	19	22	
IV	12	9	

and 10 females, with an average age of 46.95±5.67 years. Among patients in the radiotherapy group, there were 22 cases of stage III and 9 cases of stage IV. No significant differences in gender and age were observed between the two groups (p>0.05). Results of routine blood tests, liver and kidney function of all patients were normal so that the therapeutic effects could be evaluated. The specific situations are shown in Table 1.

Cetuximab treatment

Patients in the combination group were treated weekly with cetuximab until the end of radiotherapy. Patients who were intolerant to cetuximab or withdrawn the informed consent were excluded. Cetuximab dose was calculated according to the body surface area of the subjects. The first administration dose of cetuximab was 400 mg/m^2 infusion for more than 120 min, with a maximum drop rate of 5 mL/min. Afterwards, cetuximab was infused weekly at a dose of 250 mg/m^2 for more than 60 min. All cardiac signs were monitored by electrocardiograph during the cetuximab administration. Antihistamines and corticosteroids were used before cetuximab treatment to reduce the risk of anaphylaxis. On the first stage of combination treatment, cetuximab infusion was carried out in the morning, while radiotherapy was delivered in the afternoon. For the second stage, cetuximab infusion was performed 1 hr after the completion of radiotherapy in the morning.

Radiotherapy

Simultaneous intensity-modulated radiotherapy (IMRT) was carried out 1 week after the initial treatment of cetuximab. All patients received the same radiotherapy schedule with two stages. For the first stage, radiation with 1.8 Gy/day was delivered to the face-neck field and the lower neck field 5 times a week. The first stage of radiation lasted for 3.6 weeks, with an overall radiation dose of 32.4 Gy. For the second stage, radiation with 1.8 Gy was delivered in the lower neck field in the morning twice a day. Radiation in the lower neck field was carried out 5 times a week and lasted for a total of 2.4 weeks. Simultaneous IMRT was also carried out in the second stage in the primary lesion and positive lymph nodes at a dose of 1.5 Gy. The total irradiation of IMRT was 18 Gy.

Assessment criteria

Imaging review was performed immediately after the last treatment. Three months later, the imaging examination was performed again to evaluate the treatment efficacy. Response Evaluation Criteria in Solid Tumors (RECIST) were used to objectively evaluate the efficacy of the radiotherapy alone or the combination treatment, including complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). During treatment, the blood routine tests were performed weekly. Liver and kidney function, blood electrolyte and electrocardiogram were performed every 2 weeks. Weight loss, skin and mucosa condition and other side effects were recorded in detail. The toxicity was assessed using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC version 3.0).

Follow-up

All patients were followed up every 3 months for 2 years after the end of treatment, and then every half year for another 2 years. Relevant examinations were performed in the follow-ups, including physical examination, liver and kidney function examination, chest CT, upper and lower abdominal CT, head and neck CT or MRI, bone ECT, etc. The PFS and 3-year OS survival rates were analyzed.

Statistics

SPSS17.0 software package (Chicago, IL, USA) was used to analyze the data. All quantitative measurement data were expressed as mean ± standard deviation. The t-test was used for comparison between groups, and chi-square test was used to compare the percent data. Multivariate analysis was performed using multiple linear regression and binomial logistic regression and a p<0.05 was considered as statistically significant.

Results

Comparison of short-term efficacy between the two groups

All patients in the combination group were treated with cetuximab for 7 weeks. After combination treatment, 8 cases achieved CR and 16 PR. The ORR and DCR in the combination group was 77.42% and 93.54%, respectively, while 4 cases achieved CR and 10 PR in the radiotherapy group. The ORR and DCR was 45.61% and 70.97%, respectively. The ORR and DCR in the combination group were significantly higher than those in the radiotherapy group, and the differences were statistically significant (p<0.05; Table 2).

Table 2. Comparison of short-term efficacy between the two groups

Group	*CR*	*PR*	*SD*	*PD*	*ORR (%)*	*DCR (%)*
Combination group	8	16	5	2	77.42	93.54
Radiotherapy group	4	10	8	9	45.16	70.97
p value					0.018	0.043

For abbreviations see text

Comparison of the prognosis of the two groups of patients

Patients in the combination group and the radiotherapy group were followed up for 1.74±1.29 years and 1.45±1.35 years, respectively. The differences in the follow-up time and survival rate between the two groups were statistically significant ($p<0.05$). The PFS and the median OS in the combination group were 19.5 months (95% CI, 17.5-20.5) and 26.6 months (95% CI, 21.4-28.6), respectively, while in the radiotherapy group, the PFS and the median OS were 13.8 months (95% CI, 11.2-14.8) and 18.9 months (95% CI, 16.2-19.19), respectively. The differences in the PFS and OS between the two groups were highly significant ($x^2=20.832$, $p=0.000$, $x^2=11.137$, $p=0.001$). The 3-year OS rate in the combination group and the radiotherapy group was 35.48 and 9.68%, respectively ($p<0.05$; Figure 1).

Correlation between the primary tumor site and the efficacy of cetuximab combined with radiotherapy

Among the 31 patients in the combination group, there were 19 cases of maxillary sinus SCC and 12 cases of ethmoid sinus SCC. The ORR of the two groups was 78.94 and 75.00%, respectively, and the DCR of the two groups was 94.73 and 91.67%, respectively. No significant differences in ORR and DCR between the two groups were observed ($x^2=0.66$, $p=0.395$ and $x^2=0.115$, $p=0.705$; Table 3). The median PFS in the two groups was 20 months (95% CI, 16.1-21.9) and 18.9 months (95% CI, 15.8-20.2), and the median OS was 26 months (95% CI, 21.1-26.9) and 27.8 months (95% CI, 20.5-33.5), respectively. No significant differences between the median PFS and OS in the two groups were observed ($x^2=2.002$, $p=0.157$ and $x^2=0.022$, $p=0.882$; Figure 2).

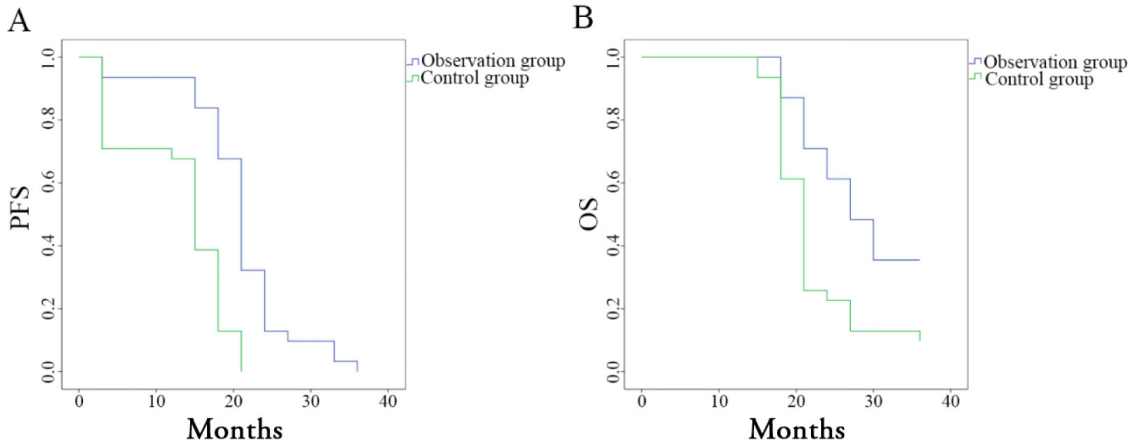

Figure 1. Progression-free survival (PFS) and overal survival (OS) for patients with sinonasal SCC treated with cetuximab combined with radical radiotherapy. **A:** PFS of the two groups; the difference was statistically significant (p=0.000). **B**: OS of the two groups; the difference was statistically significant (p=0.001).

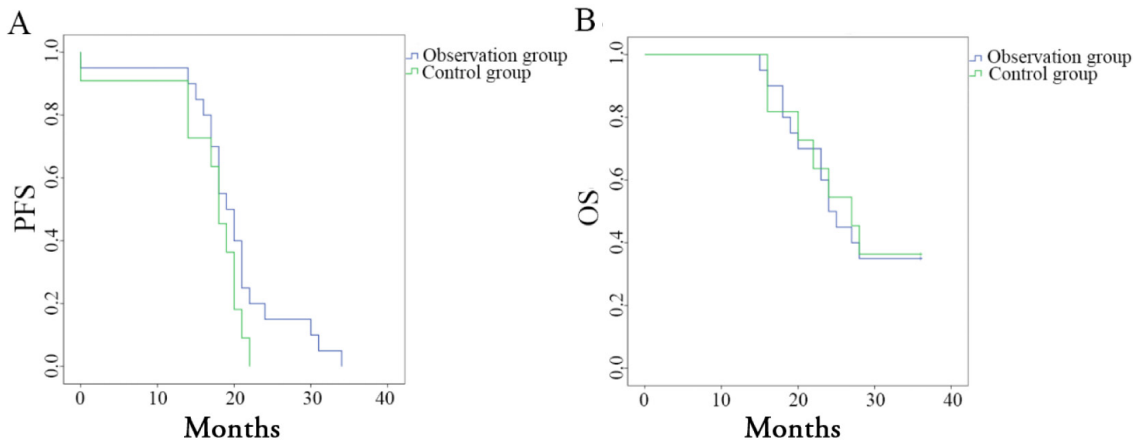

Figure 2. Progression-free (PFS) survival and overall survival (OS) for patients with maxillary sinus SCC and ethmoid sinus SCC treated with cetuximab combined with radical radiotherapy. **A:** PFS of patients with maxillary sinus SCC and ethmoid sinus cancer; the difference was not statistically significant (p=0.157). **B:** OS of maxillary sinus SCC and ethmoid sinus SCC; the difference was not statistically significant (p=0.882).

Table 3. Comparison of the short-term efficacy of cetuximab in the treatment of maxillary sinus SCC and ethmoid sinus SCC

Tumor type	*n*	*CR*	*PR*	*SD*	*PD*	*ORR (%)*	*DCR (%)*
Maxillary sinus carcinoma	19	4	11	3	1	78.94	94.73
Ethmoid carcinoma	12	4	5	2	1	75.00	91.67
p value						1.000	1.000

For abbreviations see text

Table 4. Adverse reactions in both groups

Group	*Leukemia n (%)*	*Erythra n (%)*	*Gastrointestinal reactions n (%)*	*Neurotoxicity n (%)*	*Liver/kidney function injury n (%)*
Combination group	8 (25.81)	17 (54.84)	10 (32.26)	5 (16.13)	4 (12.90)
Radiotherapy group	6 (19.35)	3 (9.68)	8 (25.81)	6 (19.35)	3 (9.68)
p value	0.762	0.000	0.780	1.000	1.000

Adverse reactions

As shown in Table 4, the main adverse reactions in the combination group and radiotherapy group were leukopenia (25.81 and 19.35%, respectively), skin rash (54.84 and 9.68%), liver and kidney dysfunction (12.9% and 9.68%), gastrointestinal reactions (32.26 and 25.81%) and neurotoxicity (16.13 and 19.35%). The incidence of rash increased significantly in the combination group compared with that of the radiotherapy group. However, there were no statistical differences in the incidences of other adverse reactions. The results showed that the combination of cetuximab and radiotherapy can increase significantly the incidence of rash, without any influence on other adverse reactions.

Discussion

EGFR is overexpressed in many malignant tumors. The expression rate of EGFR in the head and neck SCC is up to 90%. Upregulation and activation of EGFR are related with decreased disease-free survival (DFS) and OS rate, which is predictor of poor prognosis in the head and neck SCC [14-16]. EGFR activation is divided into three steps. The first step is the homodimers and heterodimers formed by the binding of EGFR with its corresponding ligand. The second step is the phosphorylation of 6 specific receptors facilitated by the formation of EGFR dimers. The phosphorylation then transfers various external signals into cells via the Ras-Raf-MAPK pathway and PI3K-PKC-IKK pathway. Finally, the transcription level of the genes in the nucleus is increased to promote the cell proliferation, thus increasing the expression level of EGFR [17,18].

Cetuximab is a relatively novel recombinant human/mouse chimeric IgG1 monoclonal antibody. As the first target drug approved for treating head and neck SCC, cetuximab is targeted against chimeric EGFR monoclonal antibodies by specifically binding with its extracellular domain to inhibit the EGFR signaling pathway. Cetuximab exerts its antitumor activity by inhibiting the proliferation of tumor cells, promoting apoptosis of tumor cells and blocking tumor angiogenesis, thus enhancing the therapeutic effect of chemoradiotherapy [19-23]. Cetuximab can also reduce the release of metalloproteinases and vascular endothelial growth factor (VEGF), thus activating the body's immune function by inhibiting tumor angiogenesis and metastasis [24,25]. Meanwhile, cetuximab exerts a synergistic antitumor effect through the reversal of tumor cell resistance and blockage of DNA repair [26]. It can further kill tumor cells by inducing antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [27].

Huang et al. [28] have shown that cetuximab can enhance the sensitivity of the head and neck SCC to radiotherapy. In their study, they found that after the establishment of human head and neck SCC xenografts in a nude mice model, the combination treatment of cetuximab with radiotherapy could completely clear the tumor tissues in a volume of 20 mm^3 and 100 mm^3 within 55-100 days. The effect of the combination treatment was significantly better than that of single radiotherapy. Curran et al. [29] also showed that in patients with advanced head and neck SCC, the tumor control

rate and OS rate of patients treated with cetuximab and radiotherapy were significantly better than those of the single radiotherapy ($p<0.05$).

In this study, the short-term efficacy after the combination treatment was evaluated. Eight cases achieved CR and 16 PR in the combination group. The ORR and DCR in the combination group were 77.42 and 93.54%, respectively, which were significantly higher than those of the radiotherapy group. The PFS and the median OS in the combination group was 19.5 months (95% CI, 17.5-20.5) and 26.6 months (95% CI, 21.4-28.6), respectively, which were also significantly higher than those of the radiotherapy group. It was further demonstrated that cetuximab combined with radiotherapy could improve the prognosis of patients with sinonasal SCC. Our study also revealed a great efficacy of cetuximab for different primary sites of the sinonasal SCC.

In this study, the main adverse reactions of patients with sinonasal SCC were rash, gastrointestinal reactions, leukopenia and neurotoxicity. No obvious hypersensitivity was seen. A previous study showed that the severity of rash is positively related to the efficacy of cetuximab [30]. In our study, the skin rash was found in 54.84% of the patients in the combination group, which was distributed in the facial parts, trunk and limbs. There were no significant differences in other adverse reactions, suggesting that the combination treatment does not exacerbate the adverse reactions of radiotherapy.

Conclusions

The combination of cetuximab with radical radiotherapy is safe and effective in patients with locally advanced sinonasal SCC, offering improved survival and prognosis.

Conflict of interests

The authors declare no conflict of interests.

References

1. Harvey RJ, Dalgorf DM. Sinonasal malignancies. Am J Rhinol Allergy 2013;27 (Suppl 1):S35-S8.
2. Dutta R, Dubal PM, Svider PF, Liu JK, Baredes S, Eloy JA. Sinonasal malignancies: A population-based analysis of site-specific incidence and survival. Laryngoscope 2015;125:2491-7.
3. Mahalingappa YB, Khalil HS. Sinonasal malignancy: Presentation and outcomes. J Laryngol Otol 2014;128:654-7.
4. Rahman M, Siddique MA, Ali MI, Rahman T, Choudhury AA, Khan JA. Study of commonest variety of sinonasal malignancy and its sex wise distribution. Mymensingh Med J 2015;24:832-7.
5. Chu Y, Liu HG, Yu ZK. Patterns and incidence of sinonasal malignancy with orbital invasion. Chin Med J (Engl) 2012;125:1638-42.
6. Cohen RB. Current challenges and clinical investigations of epidermal growth factor receptor (EGFR)- and ErbB family-targeted agents in the treatment of head and neck squamous cell carcinoma (HNSCC). Cancer Treat Rev 2014;40:567-77.
7. Numico G, Russi EG, Colantonio I et al. EGFR status and prognosis of patients with locally advanced head and neck cancer treated with chemoradiotherapy. Anticancer Res 2010;30:671-6.
8. Salomon DS, Brandt R, Ciardiello F, Normanno N. Epidermal growth factor-related peptides and their receptors in human malignancies. Crit Rev Oncol Hematol 1995;19:183-232.
9. Wollina U. Update of cetuximab for non-melanoma skin cancer. Expert Opin Biol Ther 2014;14:271-6.
10. Ji L, Gu D, Tan X, Sun H, Chen J. A meta-analysis of clinical trials over regimens with or without cetuximab for advanced gastric cancer patients. JBUON 2017;22:900-4.
11. Heigener DF, Pereira JR, Felip E et al. Weekly and every 2 weeks cetuximab maintenance therapy after platinum-based chemotherapy plus cetuximab as first-line treatment for non-small cell lung cancer: Randomized non-comparative phase IIIb NEXT trial. Target Oncol 2015;10:255-65.
12. Robert F, Ezekiel MP, Spencer SA et al. Phase I study of anti-epidermal growth factor receptor antibody cetuximab in combination with radiation therapy in patients with advanced head and neck cancer. J Clin Oncol 2001;19:3234-43.
13. 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.
14. Carballeira A, Ginarte M, Diniz-Freitas M et al. Immunohistochemical evaluation of EGFR expression in lip squamous cell carcinoma. Correlation with clinicopathological characteristics. Histol Histopathol 2014;29:641-8.
15. Grobe A, Eichhorn W, Fraederich M et al. Immunohistochemical and FISH analysis of EGFR and its prognostic value in patients with oral squamous cell carcinoma. J Oral Pathol Med 2014;43:205-10.
16. Li JC, Zhao YH, Wang XY et al. Clinical significance of the expression of EGFR signaling pathway-related proteins in esophageal squamous cell carcinoma. Tumour Biol 2014;35:651-7.

17. Raben D, Bianco C, Milas L, Ang KK. Targeted therapies and radiation for the treatment of head and neck cancer: Are we making progress? Semin Radiat Oncol 2004;14:139-52.
18. Trussoni CE, Tabibian JH, Splinter PL, O'Hara SP. Lipopolysaccharide (LPS)-Induced biliary epithelial cell NRas activation requires epidermal growth factor receptor (EGFR). PLoS One 2015;10:e125793.
19. Khelwatty SA, Essapen S, Seddon AM, Modjtahedi H. Prognostic significance and targeting of HER family in colorectal cancer. Front Biosci (Landmark Ed) 2013;18:394-421.
20. Huether A, Hopfner M, Baradari V, Schuppan D, Scherubl H. EGFR blockade by cetuximab alone or as combination therapy for growth control of hepatocellular cancer. Biochem Pharmacol 2005;70:1568-78.
21. 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.
22. Wong SF. Cetuximab: An epidermal growth factor receptor monoclonal antibody for the treatment of colorectal cancer. Clin Ther 2005;27:684-94.
23. Milas L, Fan Z, Andratschke NH, Ang KK. Epidermal growth factor receptor and tumor response to radiation: In vivo preclinical studies. Int J Radiat Oncol Biol Phys 2004;58:966-71.
24. Vincenzi B, Zoccoli A, Pantano F, Venditti O, Galluzzo S. Cetuximab: From bench to bedside. Curr Cancer Drug Targets 2010;10:80-95.
25. Troiani T, Zappavigna S, Martinelli E et al. Optimizing treatment of metastatic colorectal cancer patients with anti-EGFR antibodies: Overcoming the mechanisms of cancer cell resistance. Expert Opin Biol Ther 2013;13:241-55.
26. Chibaudel B, Tournigand C, Andre T, de Gramont A. Therapeutic strategy in unresectable metastatic colorectal cancer. Ther Adv Med Oncol 2012;4:75-89.
27. Rivera F, Vega-Villegas ME, Lopez-Brea MF. Cetuximab, its clinical use and future perspectives. Anticancer Drugs 2008;19:99-113.
28. Huang SM, Harari PM. Modulation of radiation response after epidermal growth factor receptor blockade in squamous cell carcinomas: Inhibition of damage repair, cell cycle kinetics, and tumor angiogenesis. Clin Cancer Res 2000;6:2166-74.
29. Curran D, Giralt J, Harari PM et al. Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. J Clin Oncol 2007;25:2191-7.
30. 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.