ORIGINAL ARTICLE

Gefitinib with concurrent chemoradiation in locally advanced head neck cancer

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Abstract

Background: *Chemoradiation is standard treatment in locally advanced oropharyngeal and hypopharyngeal cancer but only few surviving for long term. Novel therapeutic agents targeting EGFR receptors demonstrated survival benefit in palliative setting and radiosensitization in preclinical studies. We compared cisplatin based concurrent chemoradiation with cisplatin and gefitinib based chemoradiation in patients with locoregionally advanced oro-hypo pharyngeal cancer.* **Methods:** *Patients of oro-hypo pharyngeal squamous cell carcinoma with age between 18 and 70 and with locally advanced (stage III and IV, M0) were randomly assigned to receive either radiation with cisplatin 100 mg^2 on d1, 23 and 43 or radiation with cisplatin in same dose plus gefitinib 250 mg daily started two week before commencing radiotherapy till the end of radiation treatment. Primary and secondary end points were progression free and overall survival, respectively.* **Results:** *Out of total 67 patients randomized, 32 received cisplatin with radiation (arm I) and 35 received cisplatin plus gefitinib with radiation (arm II). Overall response rates (complete and partial) were 62% and 71.42% in arm I and arm II, respectively, with no statistically significant difference (P = 0.605). The median progression free survival was 24 months for arm I while it was 35 months for arm II (P = 0.2877, hazard ratio [HR] = 0.688, 95% CI 0.3346–1.4150). The median overall survival was 31 months for arm I and 37 months for arm II (P = 0.4344, hazard ratio [HR] = 0.7542 95% CI 0.3661–1.5539). Proliferative disease showed trend towards significance in terms of response but could not reach the level of significance (P = 0.086). No statistically significant difference was found in toxicity profile of two arms.* **Conclusion:** *Gefitinib and cisplatin combination is well tolerated concurrently with radiation but does not have impressive effect on response rate, progression free survival and overall survival, but encouraging result was seen in response rate in proliferative morphology.*

Keywords: *Chemoradiation; Gefitinib; Locally advanced head neck cancer*

Gefitinib concurrente con quimiorradiación en el cáncer de cabeza y cuello localmente avanzado

Resumen

Antecedentes: *La quimiorradiación es el tratamiento estándar para el cáncer orofaríngeo e hipofaríngeo localmente avanzado, aunque con una baja supervivencia a largo plazo. Los agentes terapéuticos noveles que focalizan los receptores EGFR han demostrado un beneficio de supervivencia en términos paliativos y de radiosensibilización en estudios preclínicos. Comparamos la quimiorradiación concurrente con cisplatino y la quimiorradiación con cisplatino y gefitinib en pacientes con cáncer hipofaríngeo locorregionalmente avanzado.* **Métodos:** *Se seleccionó aleatoriamente a pacientes con carcinoma oro-hipo-faríngeo de células escamosas y localmente avanzado (estadios iii y iv, M0), con edades de 18 a 70 años, para*

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tratamiento de radiación con cisplatino 100 mg² a d1, 23 y 43, o de radiación con cisplatino en las mismas dosis más administración diaria de gefitinib 250 mg, iniciada 2 semanas antes del comienzo de la radioterapia y hasta el final del tratamiento de radiación. Los criterios de valoración primario y secundario fueron la ausencia de progresión y la supervivencia general, respectivamente. **Resultados:** *De los 67 pacientes aleatorizados, a 32 se les administró cisplatino con radiación (brazo 1) y a 35 cisplatino más gefitinib con radiación (brazo 2). Los índices de respuesta general (completa y parcial) fueron del 62 y el 71,42% en el brazo i y el brazo ii, respectivamente, sin diferencia estadísticamente significativa (p = 0.605). La supervivencia media libre de progresión fue de 24 meses para el brazo i y de 35 meses para el brazo ii (p = 0.2877, cociente de riesgo instantáneo [HR] = 0.688, IC del 95%, 0.3346-1.4150). La supervivencia general media fue de 31 meses para el brazo i y de 37 meses para el brazo ii (p = 0.4344, cociente de riesgo instantáneo [HR] = 0.7542, IC del 95%, 0.3661-1.5539). La patología proliferativa reflejó una tendencia hacia la significación en términos de repuesta, aunque no pudo alcanzar el nivel de significación (p = 0.086). No se observó diferencia estadísticamente significativa en cuanto al perfil de toxicidad de los 2 brazos.* **Conclusión:** *La combinación de gefitinib y cisplatino es bien tolerada en concurrencia con la radiación, aunque no tiene un efecto sorprendente sobre el índice de respuesta, la supervivencia libre de progresión y la supervivencia general, pero se han observado resultados esperanzadores en cuanto al índice de respuesta en la morfología proliferativa.*

Palabras clave: *Quimiorradiación; Gefitinib; Cáncer localmente avanzado de cabeza y cuello*

Introduction

Head and neck cancer constitute 5% of all the cancers worldwide and is sixth most common malignancy.[1] It is the most common malignancy in Indian males comprising 23% of all cancers.[2] Head and neck cancer also comprises 6% of all cancers in female. The disproportionately higher prevalence of head and neck cancer in relation to other malignancies in India is due to the use of tobacco in various forms, consumption of alcohol and low socioeconomic conditions.

Chemoradiation is the standard treatment in locally advanced oropharyngeal and hypopharyngeal cancer with 5 year relative survival of 36.5% and 26.8% (SEER data). Approximately 50–60% of patients have local disease recurrence within 2 years, and 20–30% of patients develop metastatic disease.[3,4] In advanced disease patients, survival has not significantly improved in last 25 years despite advances in surgical and radiation techniques, and chemotherapy. Research in molecular biology and monoclonal antibodies, leading to development of novel therapeutic agents that interact with selective biologic pathways in the cancer cell, has generated considerable attention recently after those are successfully used in the treatment of chronic myeloid leukemia (CML). Studies in clinics have focused on epidermal growth factor receptor (EGFR) antagonists and revealed that EGFR activation promotes a multitude of important signalling pathways associated with cancer development and progression, and importantly, resistance to radiation.[5–7] Since radiation therapy plays an integral role in managing head and neck squamous cell cancer, inhibiting the EGFR pathway might improve efforts in cancer cure. The question now to understand is when the application of these EGFR inhibitors are relevant to an individual patient and how and when these drugs should be combined with radiation and chemotherapy. The prognostic-predictive value of EGFR expression in head neck squamous cell carcinoma has been shown in several studies including a correlative analysis of patients enrolled into a phase III trial conducted by the Radiation Therapy Oncology Group.[8] In theory, the blockade of EGFR receptor should result in the inhibition of tumour growth and radiation sensitization. Work in this paper is an effort to collect data on combining gefitinib with cisplatin and radiation in oropharyngeal and hypopharyngeal cancer and to find whether these novel agent can be incorporated with standard treatment.

Methods

Patients

This randomized study was conducted at J K Cancer Institute which is largest centre in state of Uttarpradesh in India. Eligibility criteria were age more than 18 years up to 70 years and had squamous-cell carcinoma of the oropharynx and hypopharynx, confirmed by histologic or cytologic analysis. All patients had previously untreated and locoregionally advanced disease (stage of III or IV without distant metastases), an Eastern Co-operative Oncology Group (ECOG) performance status of 1 or less, and adequate hematologic, renal, and hepatic function. Patients should be medically suitable for concurrent chemoradiation. Patients who granted consent to participate in study and data publication were included only. Initial evaluations included history

taking, physical examination, dental evaluation, hematologic and biochemical analysis, electrocardiography, magnetic resonance imaging or computed tomography (CT) of the head and neck, and chest radiography. Other investigations were performed where indicated and required. Study was approved by GSVM Medical College, Kanpur ethics committee.

Study design

Patients were randomly assigned to study groups after verification of eligibility to receive either radiation with concurrent cisplatin 100 mg/m^2 on day 1, 22 and 43 or radiation with concurrent cisplatin and daily gefitinib 250 mg per oral started two week before starting of RT and given daily till completion of RT. Radiotherapy was given in conventional 2 Gy per fraction, 5 days in a week to a total of 70 Gy to primary and gross nodal disease. Elective nodal irradiation was done using 50–60 Gy according to risk. During chemoradiation, patients were monitored clinically and when needed, with laboratory tests and imaging.

The primary end point, progression-free survival (PFS), was defined as the time from randomization to progression, relapse, or death, whichever occurred first. If progression, relapse, or death did not occur before the cutoff date, data were censored at the time of the last valid assessment before the cutoff date. Secondary end points overall survival (OS) and toxic effects. All patients received adequate antiemetic and supportive medications during chemotherapy.

Response evaluation was done after 4–6 weeks of completion chemoradiotherapy and thereafter followed up every 1–3 months interval. Suspicious residual or recurrent lesions were confirmed by needle or tissue biopsy. Evaluation was according to RECIST (Response Evaluation Criteria In Solid Tumors) criteria as having complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Patients with residual or recurrent disease were offered salvage chemotherapy or possible surgical intervention or palliative treatment. Patients were evaluated for toxicity weekly during radiation and thereafter in each follow-up and graded according to the Radiation Therapy Oncology Group (RTOG) Acute and Chronic Radiation Morbidity Criteria. Toxicities appearing after 6 months were regarded as late toxicities and if occurred during treatment or up to 6 months following treatment were regarded as acute toxicities.

Statistical analysis

For categorical variables, Chi-Square and Fisher Exact tests were used, while for continuous variables, the mean and standard deviation (SD) were compared using independent samples *t* test with 95% confidence interval (CI). A two-sided level of significance of 0.05 was applied to all tests. Time-to-event data were described with the use of Kaplan–Meier curves. Confidence intervals were calculated for median progression-free survival and overall survival. Time-to-event intervals were compared between groups with the logrank test.

Results

The median age for arm I was 54 years, while it was 50 years for arm II. The majority of patients were males comprising 30 patients out of 32 in arm I and 34 patient out of 35 in arm II. Six patients (18.75%) were non-smokers in arm I while in arm II nine patients (25.71%) were non smoker. Twenty one patients (65.62%) had ECOG performance status of 0 in arm I and twenty five patients (71.43%) in arm II. Ratio of oropharyx to hypopharyx in arm I and II were 1.28 and 1.19, respectively. Majority of patients in both groups had stage IV disease, constituting 22 patients (68.75%) in arm I and 23 patients (65.71%) in arm II. All the patients' parameters including tumour and nodal status were comparable and statistically not different in both arms (Table 1).

Overall response rates (complete and partial) were 62% and 71.42% in arm I and arm II, respectively, with no statistically significant difference (0.605). Same is true with partial and complete responses compared separately. Proliferative disease showed trend towards significance but could not reach the level of significance (Table 2). For surviving patients in arm I, the median duration of follow-up was 22 months (range 13–42 months) while it was 23 months (range 12–45 months) in arm II. The median progression free survival was 24 months for arm I while it was 35 months for arm II (P = 0.2877, hazard ratio [HR] 0.688, 95% CI 0.3346–1.4150). The 1 and 2 year PFS were 61.4% and 44.3% for arm I while 72.4% and 54.3% respectively in arm II with no significant statistical difference ($P > 0.05$) (Fig. 1). The median overall survival was 31 months for arm I and 37 months for arm II (P = 0.3130, hazard ratio [HR] 0.6952 95% CI 0.3358–1.4390). The 1 and 2-year OS was 75.6% and 62.7% for arm I and 85.4% and 68.8% for group II with no statistically significants difference ($P > 0.05$) (Fig. 1). There was a trend towards separation of two overall survival curve up to around

Table 1. Baseline characteristics of study population.

	Arm I (32)	Arm II (35)	p value
0,1-4]Age (Yrs) Median (Range) 0,1-4]	54 (37–67)	50 (38–65)	0.356
Sex Male Female 0,1-4]	30 2	34 1	0.603
Smoking Yes No 0,1-4]	26 6	26 9	0.566
ECOG 0 1 0,1-4]	21 11	25 10	0.798
Site oro hypo 0,1-4]	18 14	19 16	1.00
Stage III IV 0,1-4]	10 22	12 23	1.00
Tumour status T1 T2 T3 T4 0,1-4]	0 6 13 13	1 7 12 15	1.00
Nodal status N0 N1 N2 N3	3 9 13 7	4 7 16 8	1.00

Table 2. Response to treatment and survival.

	Arm I	Arm II	P value
0,1-4]Response Overall Complete Partial	20 (62%) 10 (31%) 10 (31%)	25 (71.42%) 15 (42.86%) 10 (28.57%)	0.605* 0.466* 0.978*
0,1-4] Proliferative disease Overall response	21 (65.62%) 14	24 (68.57%) 22	0.997* 0.086$^{\alpha}$
0,1-4] Progression free survival (Median) Overall survival (Median)	24 31	35 37	0.2877$^{\beta}$ 0.5375$^{\beta}$

* The P value was calculated with the use of fisher test.
αThe P value was calculated with the use of Chi-square test.
βThe P value was calculated with the use of log-rank test.

Table 3. Adverse Events of chemoradiotherapy (acute and chronic).

Reaction	Arm I	Arm II	P value
	Grade 0/I/II + III/IV	Grade 0/I/II + III/IV	
Mucositis	22 + 10	23 + 12	^{2}0]NS$^{\alpha}$
Rad Derm	26 + 08	25 + 10	
Lary oedema	20 + 12	22 + 13	
Dysphagia	18 + 14	21 + 14	^{4}0]SS$^{\alpha}$
Xerostomia	25 + 07	27 + 08	
Subcut fibrosis	19 + 13	24 + 11	
Skin Rashes	0 + 0	12 + 2	
Diarrhoea	31 + 1	32 + 3	

$^{\alpha}$The *P* value was calculated with the use of Chi-square test.

25 months but it was lost afterward. It may signify effect of palliative treatment.

Acute toxicities were considered tolerable in both groups and except specific toxicities of gefitinib (diarrhoea and skin rashes), no significance difference found in two groups (Table 3). The most common acute adverse reactions encountered were, mucositis, radiation dermatitis, and dysphagia. Most of them were grade 1 and 2 and were treated on an out patient basis. Late toxic effects recorded were xerostomia, subcutaneous fibrosis and laryngeal oedema.

Discussion

Combined treatment approaches have become standard for patients with locally advanced squamous cell carcinoma of head and neck (LA-SCCHN). Several randomized phase III trials and metaanalysis documented a survival and/or organ preservation benefit from the addition of chemotherapy to RT as primary therapy. Multiple chemotherapeutic agents had been investigated; of which cisplatin was the most extensively used and was considered as the standard of care for patients with LA-SCCHN. Newer targeted therapy against EGFR receptor has shown response and benefit in palliative setting. This study was done to see any advantage in response and survival, adding newer agent gefitinib with the most extensively used cisplatin as a chemoradiotherapy schedule. Advantages of concurrent chemoradiation over radiation alone for both definitive and post operative settings in head neck cancer, using cisplatin as the

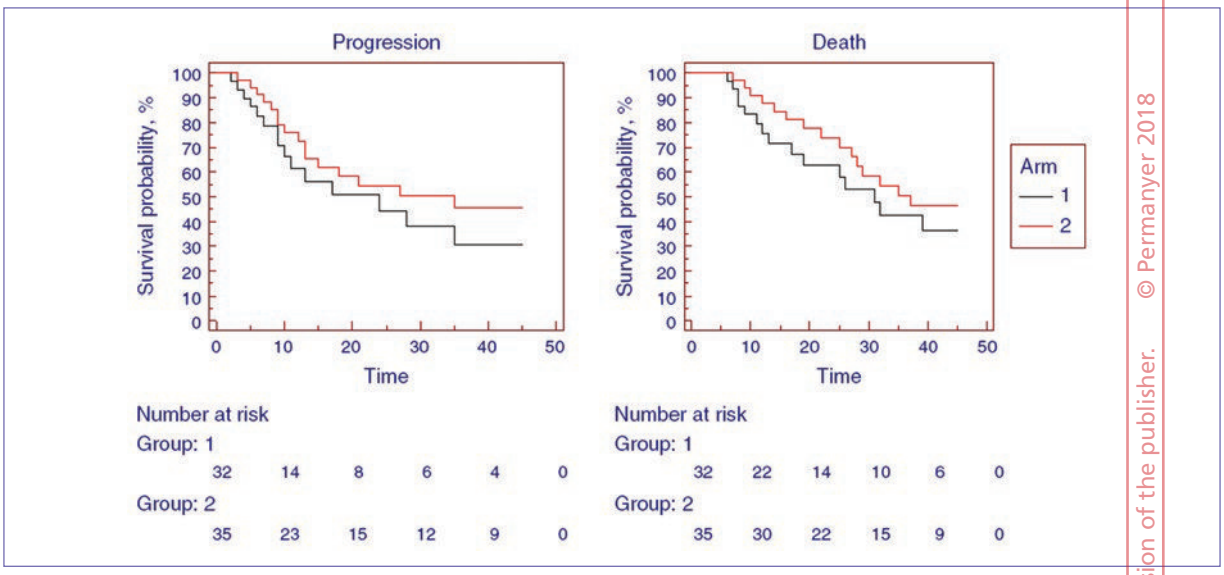

Figure 1. Progression free and overall survival. Estimated with Kaplan–Meier method.

mainstay chemotherapy have proven in many large randomized studies and metanalyses.[9–11] Meta-Analysis of chemotherapy in Head and Neck Cancer study (MACHNC), involving 63 randomized trials and nearly 11,000 individual patients data to assess the impact on survival of adding chemotherapy to locoregional disease showed that adding chemotherapy to radiotherapy in locally advanced disease improved OS by 8% at 5 years.[12] Recent updated analysis with addition of randomized clinical trials between 1994 and 2000 conformed consistent results.[13] Newer targeted agents, working on specific molecular target responsible for malignant growth, arising hope in improving survival were tried in recurrent and palliative setting. Cituximab, gefitinib and erlotinib were used in most of the studies. The role of these EGFR inhibitors in first-line, combined modality therapy for patients with head neck cancer remains undefined.[14] Bonner et al.[15,16] demonstrated that the combination of cetuximab and radiation was superior to radiation alone in patients with stage III/IV oropharyngeal, hypopharyngeal, or laryngeal SCCHN, with clinically and statistically significant improvements in the duration of locoregional control and overall survival. Rao et al.[17] shared their experience with gefitinib in the treatment of recurrent SCCHN with symptomatic improvement in about 63% of patient population. Phase II studies published in 2003, evaluating role of oral gefitinib as first-or second-line monotherapy in patients with recurrent or metastatic head neck cancer.[18,19] These two studies by Cohen et al. showed disease control rate of 53% and 36%, respectively. Preclinical studies strongly suggested that the combination of gefitinib and radiation completely inhibited the downstream signalling of EGFR and had a strong inhibitory effect on DNA-PKc pathways after.[20] A study from University of Colorado, USA by Chen et al.[21] revealed that gefitinib was well tolerated with concomitant boost RT or concurrent chemoradiotherapy with weekly cisplatin and protracted administration of gefitinib for up to 2 years at 250 mg daily was also tolerated well. Whether addition of gefitinib can improve survival outcome in locally advanced SCCHN, considering encouraging response rates and minimal side effects in previous studies, this prospective study was designed. The two groups were comparable in terms of age and sex distribution, smoking habit, performance status, stage, and primary site. Overall response (complete and partial) was achieved in 62% patients in the arm I that is control group, which was comparable with other studies. In the study arm (arm II), a greater proportion of patients achieved overall response (71.42%) but could not reach to a statistically significant level (P = 0.605). Thirty one percent patients achieved CR in the control arm while 42.86% patients achieved CR in the study arm. However, this encouraging result could not be validated with a statistical significance. Addition of gefitinib to cisplatin based chemoradiotherapy regimen was well tolerated and toxicities in two treatment arms were comparable. Mucositis, radiation dermatitis, xerostomia, laryngeal oedema and dysphagia were most common radiation related grade III and IV reactions in both groups but no statistical

significant difference in incidences (Table 3). None of the patients interrupted treatment due to radiation reaction and managed conservatively. No significant increase in late toxicities was noted as well. Exceptions to these findings were diarrhoea, and skin rashes which occurred significantly more in the gefitinib containing arm. However, both diarrhoea and skin rashes could be adequately managed conservatively and did not contribute to treatment delay. Disease free survival (DFS) and overall survival analysis demonstrate difference in progression free survival and overall survival but it could not validate statistically. This is may be because of the underpowered study and small study population. Progression free survival as well as overall survival are comparable to other studies.[10-15,22,23] It is known that most of the SCCHN over-express EGFR but mutational status is not predictive biomarkers,[24] so EGFR expression study was not asked due to considerable involved cost.

As of now, we can comment that addition of gefitinib to classical cisplatin based chemoradiation is well-tolerated with encouraging results in terms of complete response in a subgroup of patients with proliferative morphology. This study could not find statistically significant benefits in progression free survival and overall survival with addition of gefitinib. A larger and statistically powered study may find difference in survival.

Conflict of interest

The authors have no conflicts of interest to declare.

References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CACancer J Clin. 2011;61:69.
2. Mishra A, Meherotra R. Head and neck cancer: global bur-den and regional trends in India. Asian Pac J Cancer Prev.2014;15:537-50.
3. Murar S, Forastiere AA. Head and neck cancer: chang-ing epidemiology, diagnosis, and treatment. Mayo Clin Proc.2008;83:489-501.
4. Colevas AD. Chemotherapy options for patients with metastaticor recurrent squamous cell carcinoma of the head and neck. JClin Oncol. 2006;24:2644-52.
5. Gupta AK, McKenna WG, Weber CN, et al. Local recurrence inhead and neck cancer: relationship to radiation resistance andsignal transduction. Clin Cancer Res. 2002;8:885-92.
6. Baumann M, Krause M. Targeting the epidermal growth fac-tor receptor in radiotherapy: radiobiological mechanisms,preclinical and clinical results. Radiother Oncol. 2004;72:257-66.
7. Santini J, Formento J, Francoual M, et al. Characterization,quantification, and potential clinical value of the epidermalgrowth factor receptor in head and neck squamous cell car-cinomas. Head Neck. 1991;13:132-9.
8. Ang K, Berkey B, Tu X, et al. Impact of epidermal growth fac-tor receptor expression on survival and pattern of relapse inpatients with advanced head and neck carcinoma. Cancer Res.2002;62:7350-6.
9. Browman GP, Hodson DI, Mackenzie RJ, Bestic N, Zuraw L, Can-cer Care Ontario Practice Guideline Initiative Head and NeckCancer Disease Site Group. Choosing a concomitant chemother-apy and radiotherapy regimen for squamous cell head and neckcancer: a systematic review of the published literature withsubgroup analysis. Head Neck. 2001;23:579-89.
10. El-Sayed S, Nelson N. Adjuvant and adjunctive chemotherapy inthe management of squamous cell carcinoma of the head andneck region. A meta-analysis of prospective and randomizedtrials. J Clin Oncol. 1996;14:838-47.
11. Munro AJ. An overview of randomised controlled trials of adju-vant chemotherapy in head and neck cancer. Br J Cancer.1995;71:83-91.
12. Pignon JP, Bourhis J, Domenge C, Designé L, MACH-NC Col-laborative Group: Meta-Analysis of chemotherapy on head andneck cancer. Chemotherapy added to locoregional treatment forhead and neck squamous-cell carcinoma: Three meta-analysesof updated individual data. Lancet. 2000;355:949-55.
13. Pignon J-P, le Maître A, Maillard E, et al. Meta-analysis ofchemotherapy in head and neck cancer (MACH-NC): an updateon 93 randomised trials and 17,346 patients. Radiother Oncol.2009;92:4-14.
14. Hainsworth JD, Spigel DR, Burris HA 3rd, et al. Neoadjuvantchemotherapy/gefitinib followed by concurrent chemother-apy/radiation therapy/gefitinib for patients with locallyadvanced squamous carcinoma of the head and neck. Cancer.2009;115:2138-46.
15. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetux-imab for locoregionally advanced head and neck cancer: 5-yearsurvival data from a phase 3 randomised trial, and relationbetween cetuximab-induced rash and survival. Lancet Oncol.2010;11:21-8.
16. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetux-imab for squamous-cell carcinoma of the head and neck. N EnglJ Med. 2006;354:567-78.
17. Rao R, Anil K, Bansal L, et al. Survival benefit and efficacy ofgefitinib in recurrent metastatic head and neck cancer. IndianJ Med Paediatr Oncol. 2007;28:5-10.
18. Cohen EE, Rosen F, Stadler WM, et al. Phase II trial of ZD1839 inrecurrent or metastatic squamous cell carcinoma of the headand neck. J Clin Oncol. 2003;21:1980-7.
19. Cohen EE, Kane MA, List MA, et al. A phase II study of 250 mg gefitinib (ZD1839) monotherapy in recurrent or metastatic squa-mous cell carcinoma of the head and neck. Proc Am Soc ClinOncol. 2003;22:502.
20. Shintani S, Li C, Mihara M, et al. Enhancement of tumor radiore-sponse by combined treatment with gefitinib (Iressa, ZD1839),an epidermal growth factor receptor tyrosine kinase inhibitor,is accompanied by inhibition of DNA damage repair and cellgrowth in oral cancer. Int J Cancer. 2003;107:1030-7.21. Chen C, Kane M, Song J, et al. Phase I trial of gefi tinib in combi-nation with radiation or chemoradiation for patients with locallyadvanced squamous cell head and neck cancer. J Clin Oncol.2007;25:4880-6.
22. Saarilahti K, Bono P, Kajanti M, et al. Phase II prospective trialof gefitinib given concurrently with cisplatin and radiotherapyin patients with locally advanced head and neck cancer. J Oto-laryngol Head Neck Surg. 2010;39:269-76.
23. Cripps C, Winquist E, Devries MC, et al. Epidermal growth factorreceptor targeted therapy in stages III and IV head and neckcancer. Curr Oncol. 2010;17:37-48.
24. Tan EH, Goh C, Lim WT, et al. Gefitinib, cisplatin, and concur-rent radiotherapy for locally advanced head and neck cancer:EGFR FISH, protein expression, and mutational status are notpredictive biomarkers. Ann Oncol. 2012;23:1010-6.