A phase I/II trial of gefitinib and radiotherapy in patients with locally advanced inoperable squamous cell carcinoma of the head and neck

Francesco Caponigro[a], Carmen Romano[c], Amalia Milano[a], Raffaele Solla[d], Giovanni Franchin[e], Vincenzo Adamo[f], Ettore Mari[g], Brunello Morrica[b] and Stefano Pepe[c]

Two different doses of gefitinib, administered along with standard radiation therapy, were tested in locally advanced inoperable head and neck cancer with the aim of finding the maximum tolerated dose and assessing the toxicity and activity of the combination. The standard '3 + 3' design was used for the phase I study. Radiation therapy was given according to conventional dose and schedule. Gefitinib dose escalation was stopped if more than one-third of patients of a given cohort had dose-limiting toxicity. Dose-limiting toxicity was observed in three of four patients treated at the dose of 500 mg, and included grade 3 stomatitis in three patients and grade 3 liver toxicities in one patient. The dose level of 250 mg was recommended for the phase II study. Six confirmed objective responses were observed among 16 patients. Our results do not support further trials with gefitinib and radiation therapy, according to our schedule, in this patient population. Integration of gefitinib within chemoradiotherapy regimens and combination with other biological therapies may represent the next challenge. *Anti-Cancer Drugs* 19:739–744 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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[a]Medical Oncology B, [b]Radiotherapy, National Tumor Institute of Naples "G. Pascale" Foundation, [c]Medical Oncology, [d]Radiotherapy, Federico II University, Naples, [e]Radiotherapy, Oncology Reference Center, Aviano, [f]Department of Human Pathology, Medical Oncology and Integrated Therapies, 'G. Martino' University, Messina and [g]Research and Development, AstraZeneca, Basiglio, Italy

Correspondence to Dr Francesco Caponigro, Medical Oncology B, National Tumor Institute of Naples 'Fondazione G. Pascale', Via M. Semmola, 80131 Naples, Italy
Tel: +39 081 590 3362; fax: +39 081 590 3822;
e-mail: caponigrof@libero.it

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Introduction

Head and neck cancer (HNC) is among the most common cancers worldwide and squamous cell carcinoma represents the most common histology. In most cases, HNC is diagnosed as unresectable locally advanced disease whose 5-year survival is less than 10% [1]. Combined chemoradiotherapy has represented the mainstay of treatment over the last decades, but, disappointingly, patient outcome has not substantially improved.

Epidermal growth factor receptor (EGFR) is a 170-kDa transmembrane glycoprotein receptor, which exerts multiple functions through an intrinsic tyrosine kinase activity, which is activated upon ligand binding. EGFR is overexpressed in approximately 90% of HNC and has been associated with worse prognosis, thereby providing a rationale for clinical investigation of EGFR-targeting drugs in HNC [2].

EGFR targeting can be considered as one of the most exploited approaches to a rational targeted therapy of cancer, and it can be basically achieved by either monoclonal antibodies directed against the extracellular domain of the receptor or by small molecules that act by inhibiting EGFR-specific tyrosine kinases [3]. Gefitinib was the first orally available EGFR–tyrosine kinase inhibitor (TKI) to undergo clinical evaluation in human cancer. A preclinical rationale for gefitinib use in HNC has been provided by Di Gennaro *et al.* [4]. In their studies, gefitinib induced growth arrest in HNC cell lines by inhibiting EGFR-mediated signaling; cell cycle kinetic analysis demonstrated that gefitinib induced a delay in cell cycle progression and a G_1 arrest together with a partial G_2/M block; this was associated with increased expression of both $p27^{KIP1}$ and $p21^{CIP1/WAF1}$. The first clinical trial of gefitinib (500 mg/day) in recurrent or metastatic squamous cell HNC was performed by Cohen *et al.* [5]; a 10.6% response rate and a 53% disease control rate were reported; median progression-free survival (PFS) was 3.4 months in this study, whereas median overall survival (OS) was 8.1 months. In another phase II clinical and molecular trial, gefitinib at the dose of 500 mg was tested in 32 patients with recurrent squamous cell HNC. In cohort A (no previous chemotherapy), three partial responses (PRs) and six stable diseases (SDs) were observed of 20 patients (clinical benefit = 45%). In

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cohort B (one previous chemotherapy), three of 12 patients achieved SD (clinical benefit = 25%). Median duration of response was 6 months in the overall patient population; median time to progression was 3 months, and median survival was 6 months. Importantly, no association between changes in c-myc or cyclin D1 gene expression and clinical benefit was observed [6]. The results of an expanded access program of gefitinib as palliative treatment in recurrent or metastatic HNC have been recently reported. Response rate was much lower than that in the Cohen study (8%), whereas disease control was achieved in 36% of patients. Median time to progression was 2.6 months, whereas median survival was 4.3 months [7]. The comparison of the two above studies indicated a substantially better outcome in the first, which can be partially explained by the different patient characteristics in the two studies. Further efforts in the use of gefitinib in patients with recurrent/metastatic HNC included the use of a lower gefitinib dose (250 mg daily) [8]; in keeping with earlier studies in nonsmall cell lung cancer (NSCLC) that showed similar efficacy for the 250 and 500 mg daily doses, but better tolerability for the lower dose [9,10]. Unfortunately, this study showed that 250 mg gefitinib had less activity than 500 mg, with only one PR (giving an objective response of 1.4%), 33% SD rate, median PFS of 1.8 months, and OS of 5.5 months [8]. Gefitinib monotherapy has undergone a phase III evaluation within a randomized trial of two different doses of gefitinib (250 and 500 mg/daily) and weekly methotrexate, given at the dose of 40 mg/m^2. Final data of this study, which was run in patients with recurrent or metastatic squamous cell HNC, have been recently presented, and no differences in OS, response rates, and toxicities were observed among the three treatment arms [11]. As for all biologic drugs, single agent studies have paved the way to combinations with other therapeutic modalities, among which is radiation therapy. After initial reports of enhanced radiation response with anti-EGFR therapies, the confirmation of improved local tumor control in animal model systems using median tissue culture dose experiments was reported [12]. Examples of specific mechanisms for enhancement of radiation response include the capacity of EGFR inhibitors to abrogate radiation-induced phosphorylation of EGFR, to enhance radiation-induced apoptosis, and to attenuate radiation-induced expression of DNA repair proteins [12].

Cetuximab, a chimeric monoclonal antibody targeting EGFR, has been the first EGFR-targeting agent to be used in combination with radiotherapy in HNC and positive results have been reported. [13].

In the present trial, two different doses of gefitinib (250 and 500 mg daily), administered along with standard radiation therapy, were tested in locally advanced inoperable squamous cell HNC with the main aim of finding the maximum tolerated dose (MTD) and assessing the activity of the combination by estimating the complete response (CR) rate, the PR rate, the duration of response, progression-free survival, and OS. The characterization of the safety profile of gefitinib alone and of the combination was a further endpoint of the study.

To the best of our knowledge, this is the first study of gefitinib and radiotherapy, used together without concomitant chemotherapy, to be carried out in locally advanced inoperable squamous cell HNC.

Patients and methods

Patient selection

Eligibility criteria for study entry included histologically confirmed, inoperable, and locally advanced squamous cell carcinoma of the head and neck (undifferentiated nasopharyngeal carcinoma was not allowed) with at least one bidimensionally measurable target lesion; age 18–75 years; WHO performance status (PS) 0 or 1; life expectancy of at least 3 months; and adequate baseline organ function defined as absolute neutrophil count $\geq 2000 \times 10^9$/l, platelets $\geq 100\,000 \times 10^9$/l, bilirubin ≤ 1.5 mg/dl, serum transaminases ≤ 2.5 times the upper limit of reference range (ULRR) in the absence of liver metastases or less than five times the ULRR in the presence of liver metastases, serum creatinine less than 1.25 times the ULRR. Previous surgery was not allowed. Patients were ineligible if they had received earlier radiotherapy or chemotherapy. Patients with a history of other coexisting malignancies or malignancies diagnosed within the last 5 years, with the exception of adequately treated cone-biopsed in-situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin, were also ineligible. Pregnancy, lactation, uncontrolled infections, unstable systemic diseases, any evidence of clinically active interstitial lung disease, and any unresolved grade 2 or higher Common Toxicity Criteria version 2.0 were also exclusion criteria. Concomitant use of phenytoin, carbamazepine, barbiturates, rifampicin, or St John's Wort was not allowed. The study was sponsored by AstraZeneca, Basiglio, Italy (study no. 1839IL/0070, Clinical Trials. gov Identifier: NCT00233636). The study was approved by the Ethics Committee of each participating center. Written informed consent was obtained from each patient before registration.

Treatment plan

This was a multicenter, open-label, noncomparative, two step phase I/II study, with a dose-finding period to determine the MTD of daily gefitinib administered in combination with a standard radiotherapy regimen, followed by a phase II study to evaluate the therapeutic activity of the combination of the selected dose of gefitinib with a standard radiotherapy regimen.

Gefitinib was administered once a day on a continuous basis. The treatment was administered for a maximum of 12 months or until disease progression, unacceptable toxicity or withdrawal of consent. The minimum amount of follow-up was 12 months. Radiotherapy was started concomitantly with gefitinib and was administered in daily fractions of 2.0 Gy according to the standard of each participating center.

Cohorts of three patients were treated with gefitinib at the first dose level (250 mg). If one or two patients in the initial cohort had dose-limiting toxicity (DLT), three other patients were enrolled at the same level. Dose escalation proceeded if no patients had DLT, which was defined as grade 3–4 hematologic, neurologic, cardiac, lung, renal, or hepatic toxicity; grade 3–4 weight loss with PS deterioration; and deterioration of visual acuity thought to be associated with gefitinib treatment, grade 3–4 skin or gastrointestinal toxicity, and grade 4 dysphagia. Dose escalation was stopped if more than one-third of patients of a given cohort had DLT. The dose of gefitinib could be interrupted for a maximum of 14 days in the presence of grade 3 or 4 toxicity. Once the adverse event (AE) decreased in severity to grade 1, the patient continued to take the assigned dose. If the AE resolved to grade 2, patients in the 500 mg cohort had their dose reduced to 250 mg, whereas patients in the 250 mg cohort were taken off study.

Patient evaluation

At enrollment, patients were evaluated by complete history and physical examination, PS recording, heart rate and blood pressure, complete blood cell (CBC) count, serum chemistries, urinalysis, ECG, chest radiograph, and total body computed tomography scan. Other exams were performed only in the presence of clinical indication. Patients were monitored throughout the treatment by clinical examination, toxicity assessment, CBC counts, biochemistry, concurrent illness, or therapy on day 1 of each week during radiotherapy. ECG and ophthalmic assessment were performed as clinically indicated.

During the treatment with single-agent gefitinib, the patients were monitored by clinical examination, toxicity assessment, CBC counts, biochemistry, concurrent illness or therapy, and tumor assessment 4 weeks after the end of radiotherapy and at every 8-week interval thereafter until trial closure. Response was assessed according to Response Evaluation Criteria in Solid Tumors. Responding or stable patients received additional treatment for maximum of 12 months or until progression or unacceptable toxicities. National Cancer Institute Common Toxicity Criteria version 2.0 were used to grade toxicity.

Statistical methods

The standard '3 + 3' design was used for the phase I study. O'Brien and Fleming's method [14] was used to calculate the number of patients required in the phase II part of the study. A sample size of 28 patients receiving the MTD was to give more than 80% probability of rejecting a baseline response rate of 70% with an exact 5% one-sided significance test when the true response was at clinically relevant rate of 90%. The hypothesis that the response rate was equal to or less than the baseline was rejected if 23 responses or more were observed of the 28 patients. Response rates were summarized by proportions together with a 95% confidence interval (CI). PFS was calculated from the time of study entry to the first evidence of disease progression; OS was calculated from the time of study entry to patient's death or last follow-up. The Kaplan–Meier analysis was used for evaluation of PFS and OS.

Results

Patient characteristics

Between July 2003 and March 2006, 16 patients were enrolled in this study. The planned sample size was not reached owing to the low accrual, which was likely because of the increased awareness that concomitant chemoradiotherapy was the best therapeutic option in this subset of patients. Twelve patients were males, four patients were females. Median age was 58.5 (range: 43–73) years. All patients had stage IV disease. PS was 1 in the majority of patients. Hypopharynx was the most frequent site of primary tumor. The characteristics of the eligible patients are summarized in Table 1.

Dose escalation results

Two dose levels were tested. No DLT occurred among the first three patients treated at 250 mg, so gefitinib dose was escalated to 500 mg. Two patients had DLT among the first three patients treated at 500 mg; an additional patient treated at 500 mg had DLT; therefore, the accrual at the higher dose was stopped and further patients were treated at 250 mg. In total, 12 and four patients were enrolled at dose level of 250 mg and 500 mg, respectively. DLT observed at the higher dose included grade 3 stomatitis in three patients and grade 3 liver toxicities in one patient.

The dose level of 250 mg was recommended for the phase II study. The occurrence of AEs represented the main cause of gefitinib interruption at both dose levels. Patient

Table 1 Characteristics of eligible patients (total $n=16$)

Median age (years) (range)	58.5 (43–73)
Sex (male/female)	12/4
Performance status 0	5
Performance status 1	11
Primary site	
Hypopharynx	7
Oral cavity	4
Oropharynx	3
Neck not otherwise specified	1
Parapharyngeal	1

decision (in two cases) and liver toxicity, lung toxicity, and low compliance (in one case each) were additional reasons for treatment interruption. The median duration of gefitinib treatment was 100 (range: 36–272) days, and it was 27.4 (range: 9.9–74.5%) of the maximum planned duration. The median total given dose of radiotherapy was 69 (range: 50–104) Gy. Radiotherapy was given for a median of 8 (range: 7–13) weeks, which was slightly more than expected, and mainly owing to the occurrence of toxicities.

Toxicity

Six patients died during the study as a result of AEs (three patients treated at 250 mg and three patients at 500 mg). In particular, two of these patients had a cardiovascular arrest and two other patients died of gastrointestinal toxicity (diarrhea and dysphagia, respectively). The fifth patient passed away after an overwhelming sepsis, whereas the last patient died of an intratumoral hemorrhage. None of these deaths was considered related to gefitinib by any single investigators, whereas dysphagia was considered likely to be related to radiation therapy.

Five serious AEs (SAEs) occurred in the subgroup of patients treated at 250 mg; three SAEs were observed in the group of patients treated at 500 mg. The overall incidence of treatment-induced SAEs was 9%. Sixty-eight AEs, which are detailed in Table 2, were considered linked to the combination of gefitinib and radiotherapy. Table 3 details grade 3 and 4 overall toxicities observed at the two dose levels.

Response

All sixteen patients were evaluable for response. The median duration of follow-up was 8.3 (range: 2–26) months. At the time of study closure, 11 patients had died and five were alive. Four patients had a complete response, which was confirmed in three cases; eight patients had a PR, which was not confirmed in six patients. SD and disease progression were observed in one and three patients, respectively. Median duration of response was 5.4 (range: 1–21) months. The observed SD lasted 7.4 months. The median PFS was 6.7 months (95% CI: 4.5–12.1) and the median OS was 8.5 months (95% CI: 4.6–not reached). The Kaplan–Meier plots for PFS and OS are shown in Figs 1 and 2, respectively.

Table 2 Number of adverse events related to the combination of gefitinib and radiotherapy

Toxicity	Number of AEs	CTC grade 1	CTC grade 2	CTC grade 3	CTC grade 4
Stomatitis–mucositis	14	6	4	4	0
Dysphagia	5	2	3	0	0
Diarrhoea	6	6	0	0	0
Vomiting	3	2	1	0	0
Anorexia	1	1	0	0	0
Fatigue	4	2	2	0	0
Anemia	1	0	0	0	1
Neutropenia	1	0	1	0	0
Fever	1	1	0	0	0
Cough	1	1	0	0	0
Skin toxicities	11	8	3	0	0
Edema	3	2	1	0	0
Worsening of general condition	1	0	0	1	0
Liver toxicities	7	3	0	4	0
Weight loss	4	0	4	0	0
Dysgeusia	1	0	1	0	0
Radiation dermatitis	2	2	0	0	0
Mouth dryness	1	1	0	0	0
Erythema	1	1	0	0	0

AEs, adverse events; CTC, Common Toxicity Criteria.

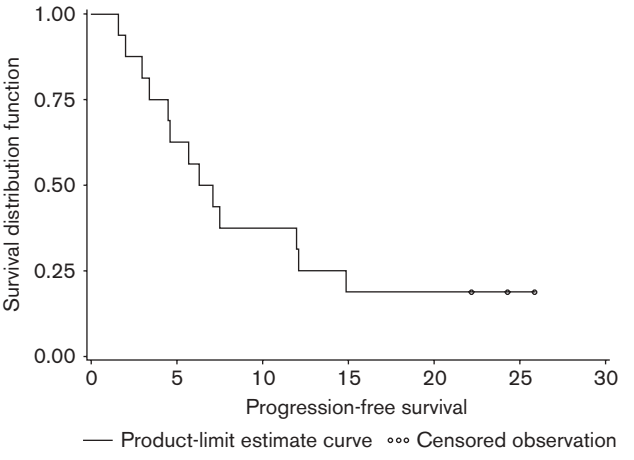
Discussion

The aim of this study was to clinically evaluate the combination of radiation therapy and an EGFR–TKI, such as gefitinib. The rationale for this study was sound and preclinical data strongly supported it [12]. The dose of 250 mg daily was selected for phase II. Grade 3 stomatitis was the main DLT of the combination in keeping with a possible worsening of radiotherapy toxic

Table 3 Grade 3–4 overall toxicities observed at the two gefitinib dose levels

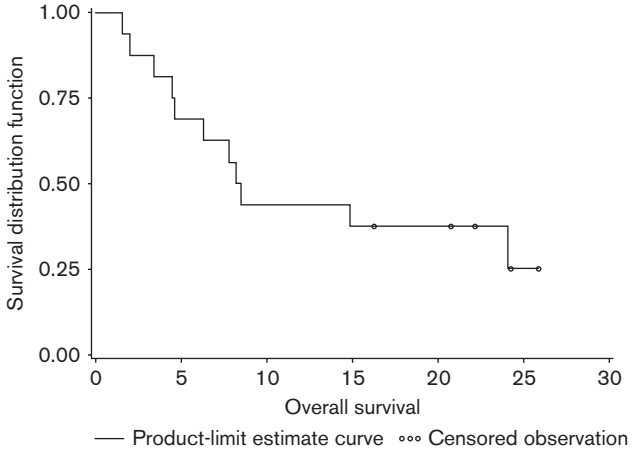
	Gefitinib dose level 250 mg	Gefitinib dose level 500 mg
Grade 3 toxicities		
Atherosclerosis	1	0
Mucositis	1	0
Hepatic toxicities	3	1
Stomatitis	0	3
Worsening of general conditions	0	1
Grade 4 toxicities		
Anemia	1	0
Hemorrhage	0	1
Infection	0	1
Cardiac arrest	1	1
Hypercalcemia	1	0

Fig. 1



The Kaplan–Meier plot of progression-free survival.

Fig. 2



The Kaplan–Meier plot of overall survival.

effect induced by gefitinib. Six patients died as a result of AEs and although none of these deaths was considered related to gefitinib, some concern is raised by this occurrence. Furthermore, response and survival data were disappointing. Although, to the best of our knowledge, no other trials of gefinitib and radiotherapy only have been carried out, gefitinib has been widely tested in combination with radiochemotherapy, chemotherapy, and biological therapy. Ahmed *et al.* [15] have undertaken a study of gefitinib with a concurrent chemoradiation regimen followed by gefitinib adjuvant therapy in locally advanced disease. A very encouraging 91% complete response rate was observed in the study; estimated OS was 83% at 2 years, 73% at 3 years whereas toxicity was consistent with chemoradiotherapy trials. Chen *et al.* [16] have recently published the data of a phase I trial of concurrent, daily gefitinib and radiation or chemoradiation for patients with locally advanced squamous cell HNC. Eligible patients were treated with daily gefitinib (250 or 500 mg) combined with either altered fraction radiation therapy alone or chemoradiotherapy in patients with intermediate or locally advanced stage disease, respectively. Once the safety profile of gefitinib and radiotherapy was established, additional patients were accrued combining gefitinib with weekly cisplatin and concurrent radiation therapy. The combination of gefitinib and radiotherapy was well tolerated at both gefitinib dose levels, with no significant increase in radiotherapy-induced toxicities. Increased toxicity was observed in patients also receiving chemotherapy, and DLT included one grade 4 diarrhea and one grade 4 neutropenic fever. Fifteen patients started maintenance gefitinib, and eight (53%) experienced grade 1–2 acne-like skin rash and diarrhea, but no grade 3 or 4 toxicity occurred. Among clinical studies of gefitinib and chemotherapy, the combination of gefitinib with docetaxel and cisplatin has been tested, and a median PFS of 5.1 months has been reported [17].

More recently, combination studies of other TKI, such as erlotinib and lapatinib, with radiation therapy have been started, but only very preliminary data are currently available. In particular, a phase I/II study of erlotinib with cisplatin and radiotherapy showed that the combination was safe and feasible [18], whereas results from an ongoing phase I study of lapatinib in combination with cisplatin and radiotherapy in locally advanced HNC demonstrated minor AEs and encouraging clinical activity [19].

Significantly different data have been observed with the combination of radiation therapy and cetuximab, a chimeric monoclonal antibody targeting EGFR. This combined approach has shown improved survival with respect to radiation therapy alone in a randomized phase III trial in patients with locally advanced disease, thus qualifying as a possible new standard in this subset of patients [13]. Other monoclonal antibodies, such as panitumumab, a fully human monoclonal antibody anti-EGFR, have shown activity and are now under evaluation.

A recent Asian study has analyzed EGFR in 41 HNC patients for the detection of somatic mutations by PCR-single-strand conformational polymorphism analysis. Three EGFR mutations (7.3%) were detected in exon 19. However, nonsignificant association with histologic or demographic variables was observed, thus suggesting a different etiology of EGFR mutations in HNC with respect to NSCLC [20]. The issue of the occurrence of EGFR mutations and sensitivity to TKI in HNC has also been investigated by Cohen *et al.* [21]. This study has shown the rarity of EGFR kinase mutation in unselected cases of HNC in American patients.

Cancer cells have an ability to harness diverse growth factors signaling pathways for cell survival. The existence of these escape mechanisms reinforces the need for combination of targeted therapies, among which are combination of anti-EGFR therapies and combination of therapies targeting EGFR and downstream effectors. Matar *et al.* [22] have studied the effect of the combination of gefitinib and cetuximab in a panel of human cancer cell lines and in an EGFR-dependent human tumor xenograft model (A431). The combined treatment with the two agents resulted in a synergistic effect on cell proliferation, a greater inhibition of EGFR-dependent signaling, and induction of apoptosis [22]. Clinical trials of combinations of EGFR-targeted drugs have recently started and the combination of gefitinib and cetuximab has proved feasible in HNC patients at the common dose of both agents, with hints of meaningful clinical activity [23]. Resistance to EGFR-targeted drugs may be related to abnormal activation of receptor downstream effectors, which may render tumors insensitive to EGFR blockade.

This concept may pave the way to clinical trials of combinations of EGFR-targeted drugs and downstream acting agents [24]. In particular, phase I studies of gefitinib and sorafenib [25] and of gefitinib and RAD-001 [26], respectively, have been run in NSCLC and are both showing preliminary hints of clinical activity.

We conclude that our study does not support further trials with gefitinib and radiation therapy according to the present schedule. Appropriate integration of gefitinib within chemoradiotherapy regimens and combination with other biological therapies may represent a rational way forward and strong efforts are worth pursuing in this setting.

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