Erlotinib and chemoradiation in patients with surgically resected locally advanced squamous cell carcinoma of the head and neck: a GICOR phase I trial

F. Arias de la Vega1*, J. Contreras2, M. de las Heras3, A. de la Torre4, V. Arrazubi5, I. Herruzo2, I. Prieto6, J. A. García-Saenz7, J. Romero4 & F. A. Calvo6; Members of the GICOR (Grupo de Investigación Clínica en Oncología Radioterápica) group

1Department of Radiation Oncology, Hospital de Navarra, Pamplona; 2Department of Radiation Oncology, Hospital Regional Universitario Carlos Haya, Málaga; 3Department of Radiation Oncology, Hospital Clínico San Carlos, Madrid; 4Department of Radiation Oncology, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid; 5Department of Medical Oncology, Hospital da Navara, Pamplona; 6Department of Radiation Oncology, Hospital General Universitario Gregorio Marañón, Madrid; 7Department of Medical Oncology, Hospital Clínico San Carlos, Madrid Spain

Received 25 August 2010; revised 3 February 2011 & revised 26 March 2011; accepted 4 May 2011

Background: Standard treatment of advanced squamous cell carcinoma of the head and neck (SCCHN) is concurrent chemoradiation. Erlotinib is an oral tyrosine kinase inhibitor of epidermal growth factor receptor, which has shown activity in SCCHN. Phase I study aims to determine the maximum tolerated dose and dose-limiting toxicity (DLT) of adding erlotinib to chemoradiation therapy in patients with surgically resected locally advanced SCCHN.

Patients and methods: Inclusion criteria—SCCHN patients with T3 or T4 primary lesion (except T3N0 with negative resection margins); pathologic N2–N3 disease; poor prognostic findings; age 18–70 years; Eastern Cooperative Oncology Group performance status of zero to one; no evidence of metastasis; adequate organic function and written informed consent. Study design—dose-escalating phase I study with three cohorts of three to six patients each that received increasing doses of erlotinib (100–150 mg/day p.o.) and cisplatin (30–40 mg/m² i.v., day 1) for 7 weeks.

Radiotherapy—standard regimen of 1.8 Gy daily (5 fractions/week) to a maximum total dose of 63 Gy in 7 weeks.

Results: Thirteen male (median age: 57 years) were enrolled. Overall, the regimen was well tolerated. Two of three patients treated at dose level III (erlotinib: 150 mg/day; cisplatin: 30–40 mg/m² i.v., day 1) developed DLT consisting of grade 3 infection and grade 3 mucositis. Other toxic effects included diarrhea, asthenia, and rash. Recommended dose for additional studies: erlotinib 150 mg/day p.o.; cisplatin 30 mg/m²/week i.v.
Conclusion: Erlotinib can be safely combined with chemoradiation without requiring dose reduction of chemo- or radiotherapy in this postsurgical population.

Key words: chemoradiation, erlotinib, phase I, SCCHN

introduction

Current management of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) consists of concomitant chemoradiation treatment. Such combined modality treatments have resulted in improved local control, overall survival and organ preservation as compared with radiation therapy or surgery alone [1–5]. In patients with resectable disease, up-front surgical resection followed by concurrent chemoradiation in high-risk patients is an accepted standard [6]. With conventional external beam radiotherapy and cisplatin-based chemotherapy, the long-term local control is ~70%–80%, potentially improving disease-free survival.

Recent studies have focused on strategies to improve the outcome of these patients while not compromising toxic effects. These include dose-escalated intense chemotherapy regimens, neoadjuvant chemotherapy, more sophisticated radiation therapy techniques and the introduction of novel targeted agents with both intrinsic antitumor efficacy and potent radiosensitizing/-modulating properties [7–9]. Despite innovative strategies, the prognosis for patients with locally advanced disease remains poor and 60%–70% of patients treated with curative intent will eventually recur.

One proven valuable strategy is targeting the epidermal growth factor receptor (EGFR), which is a transmembrane receptor involved in cell growth, invasion, metastasis and protection from apoptotic stimuli. SCCHN commonly overexpresses the EGFR (up to 90% of the tumors), which has been extensively studied as a strategic target in this disease with both small-molecule inhibitors of the intracellular tyrosine kinase domain of the EGFR as well as mAbs directed against the extracellular domain of the receptor [10, 11]. In SCCHN, the anti-EGFR mAb cetuximab is approved and recommended in combination with radiation therapy for the treatment of patients with locally advanced disease as well as in combination with chemotherapy for the treatment of patients with advanced cancer [10, 12]. Tyrosine kinase inhibitors (TKIs) of the EGFR have been also explored in this disease as single agents and in combination with chemotherapy in patients with metastatic disease [13–17]. Erlotinib, a specific and reversible TKI of the EGFR, has shown clinical activity as well as modulation of biomarkers related to EGFR inhibition properties in patients with SCCHN [17, 18].

The molecular characteristics of SCCHN, as well as the clinical and biological effects of erlotinib in SCCHN, provide the rationale to explore the activity and toxicity of this molecule in combination with definitive chemoradiation in a postsurgical patient population with high-risk prognostic features. The primary aim of this study was to determine the maximum tolerated dose (MTD) of erlotinib in combination with cisplatin and radiation therapy in a specific cohort of patients with post-resected locally advanced SCCHN. The secondary aim was to quantify the main toxic effects of the combination.

patients and methods

patient selection

Patients with histological or cytological diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx who had been treated with surgical resection with curative intent were eligible. Patients were required to have at least one of the following criteria: pT3–4 tumor stage (except T3N0 of the larynx with negative margins); pN2–3 nodal stage; or unfavorable pathological findings such as extranodal extension, positive resection margins, and perineural and/or vascular involvement. Other eligibility criteria included the following: age 18–70 years old; life expectancy ≥ 12 months; Eastern Cooperative Oncology Group (ECOG) performance status of zero to one; adequate bone marrow (absolute neutrophil count > 1.5 × 109/l, platelets > 100 × 109/l and hemoglobin > 9 g/dl), liver (bilirubin < 1.5 x upper limit of normal (ULN), alkaline phosphatase, aspartate transaminase and alanine transaminase < 3.0 × ULN], and renal function (calculated creatinine clearance > 60 ml/min or serum creatinine < 1.5 × ULN). Women of childbearing potential were required to have a negative pregnancy test within 48 h of study enrollment. In addition, fertile male and female patients were required to use appropriate contraceptive methods. Patients needed to be able to swallow pills or have a functioning gastrostomy tube. Patients with gastrointestinal disorders that could interfere with drug absorption were excluded. Patients with prior chemotherapy, radiation therapy, or treatment with inhibitors of the EGFR were excluded as well as patients with incomplete surgical resection. Other exclusion criteria included prior history of cancer (except nonmelanoma skin cancer or resected cervical cancer), pregnancy or lactation, active infection or any other concomitant disease that in the investigators’ criteria could negatively interfere with study treatment, increase the toxicity of study agents or limit treatment administration. Patients with significant ophthalmologic problems such as dry eye, queratoconjunctivitis sicca and Sjo¨gren’s syndrome or other disorders that could increase the risk of corneal damage were excluded.

Patients were required to give written informed consent before inclusion in the study. The trial protocol was approved by the institutional review board of involved institutions and the studies were conducted in accordance with the principles of the Declaration of Helsinki.

treatment administration

radiotherapy treatment. Patients were treated with conventional external beam radiation. Three-dimensional computerized tomography was used for radiotherapy treatment planning. Intensity-modulated radiation therapy was not allowed. Radiation therapy was administered in conventional 1.8 Gy/day fractions 5 days/week to a total dose of 63 Gy to the surgical bed and regional lymph node areas. At investigator’s discretion, the total dose could be increased to 66.6 Gy in patients with positive margins or extracapsular involvement.

cisplatin. Cisplatin was administered i.v. at a dose of 30–40 mg/m2 at day 1 of each week, for seven consecutive weeks.

erlotinib. Erlotinib was administered orally once a day at doses of 100 or 150 mg for seven consecutive weeks. Erlotinib was administered in the morning on an empty stomach with 200 ml of water.
dose escalation, MTD and dose-limiting toxicity definitions, and dose modifications related to treatment toxicity

dose escalation. This phase I trial explored three dose levels of cisplatin–erlotinib in combination with uniform and escalated dose of radiation therapy. Table 1 summarizes the dose of the chemotherapy and radiotherapy administered in each level as well as the number of patients treated at each dose level. Three patients were treated at dose level I consisting of erlotinib 100 mg and cisplatin 30 mg/m². If no patient developed dose-limiting toxic effects (DLTs), the next three patients were entered at dose level II of erlotinib 150 mg and cisplatin 30 mg/m². Subsequently, if no DLT was observed, the next group of three patients was treated with erlotinib 150 mg and cisplatin 40 mg/m². If one patient developed DLT at any dose level, an additional group of three patients were enrolled at that dose level. Dose escalation proceeded when all three patients at a given dose level had completed treatment. Only patients that did not receive a minimum of 1 week of treatment were replaced.

maximum tolerated dose. The MTD was defined at the dose level at which two of three or six patients developed a DLT. The immediate dose level below the MTD was considered the recommended phase II dose.

dose-limiting toxicity. DLT was defined as any grade 3–4 hematological or non-hematological clinically severe toxicity including the following: grade 3–4 diarrhea; grade 4 mucositis resulting in ≥2 weeks interruption of radiation therapy or that occurred in the first 3 weeks of treatment; grade 3–4 mucositis complicated with decrease in performance status (ECOG ≥ 2 or >40% decrement in Karnofsky scale, pain ≥ 7 in visual analog scale, weight loss ≥ 20% or needing parenteral nutrition); grade 3–4 or clinically unacceptable (cosmetically unacceptable to the patient) grade 2 skin rash; or any clinically relevant toxicity that results in discontinuation of treatment for ≥2 weeks.

dose modifications related to treatment toxicity. Radiotherapy. In case of treatment interruptions due to toxicity, no dose adjustment was carried out. Patients requiring interruption of radiation therapy for ≥7 consecutive days or 10 cumulative days were removed from the study.

cisplatin. Cisplatin was interrupted in patients who developed grade 2–4 toxicity until recovery to grade 0–1. Patients who did not recover from toxicity in 2 weeks were removed from the study. A patient was considered assessable if at least five doses of cisplatin were administered.

erlotinib. Patients who developed grade 1–2 diarrhea were instructed to continue erlotinib and to use loperamide. Drug was discontinued for patients with grade 3–4 diarrhea. Patients with grade 3 diarrhea who recovered to grade 0–1 within 2 weeks of treatment interruption could be retreated at a reduced dose level of 50 or 25 mg for patients treated with 100 mg or 100 or 50 mg for patients treated with 150 mg. Patients who developed grade 4 diarrhea, grade 3 diarrhea that did not recover in 2 weeks or who required more than two dose reductions were removed from the study. Similarly, the patients who developed grade 1–2 rash secondary to erlotinib were allowed to continue treatment at the same dose level and to receive either topical or oral treatment with tetracyclines, prednisone, or H1blockers. Patients who developed grade 4 toxicity were removed from the study. As described previously with intense diarrhea, patients who developed grade 3 toxicity had their treatment interrupted and reinitiated at a reduced dose level upon recovery. Once dose treatment was reduced due to toxicity, dose reescalation was not allowed.

study design and statistical considerations

This study is a phase I, multicenter, open label dose-escalation trial. A conventional 3 + 3 design was used with a fixed dose escalation of study drugs in three dose levels. The maximum total number of patients was 18. Toxicity was evaluated and reported using the National Cancer Institute—Common Toxicity Criteria v.3.0. Descriptive statistics were used to summarize patient demographics and toxicity events.

results

patient characteristics

A total of 13 patients, whose demographic characteristics are summarized in Table 2, were enrolled in this trial. All patients were male and the majority of them had an ECOG of zero. Ten patients presented with stage IV disease and only one patient had an oropharynx cancer.

treatment characteristics

The median dose intensity of study agents and DLTs are listed in Table 3. At dose level I, one patient developed grade 2 non-hematological toxicity (increase in serum creatinine secondary to cisplatin administration) and was replaced. Three patients completed treatment at this level. At dose level II, two patients developed DLT consisting of a grade 4 mucositis in week 3 and a grade 3 folliculitis in week 2 that required treatment discontinuation. A total of six patients were treated at this dose level. At dose level III, two patients developed DLT including a patient who presented with a grade 3 respiratory infection possibly related to study medication and a patient who developed a grade 3 mucositis with declining performance status. Therefore, the recommended phase II dose of this regimen is erlotinib 150 mg daily in combination with cisplatin 30 mg/m² weekly and concurrent 63 Gy of external beam radiotherapy.

toxicity

The most frequent adverse hematological events as a function of the dose level are listed in Table 4. In general, hematological toxicity was mild with only one patient at dose level I that developed a grade 3 anemia that was considered of minor clinical relevance according to the physician responsible. Table 5 lists the most relevant non-hematological events. The most severe event was mucositis (n = 7). Two of these episodes were considered DLTs including one patient treated at dose level II that developed a grade 4 mucositis and one patient treated at dose level III that presented with a grade 3 mucositis. An additional episode that was considered DLT was the development of grade 3 folliculitis at dose level II (n = 1; DLTs are included in Table 3). Other grade 3/4 toxic effects included two patients who developed grade 3 asthenia, one patient that developed a grade 3 skin toxicity at dose level III and one patient who developed a grade 4 skin toxicity at dose level II.

discussion

The EGFR is a superb target opportunity in SCCHN. Preclinical as well as clinical studies support the activity of anti-EGFR agents

Table 1. Treatment cohorts

<table>
<thead>
<tr>
<th>Cohorts (n)</th>
<th>Erlotinib (mg/day)</th>
<th>Cisplatin (mg/m²/week)</th>
<th>Radiotherapy (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I (4)</td>
<td>100</td>
<td>30</td>
<td>63</td>
</tr>
<tr>
<td>Level II (6)</td>
<td>150</td>
<td>30</td>
<td>63</td>
</tr>
<tr>
<td>Level III (3)</td>
<td>150</td>
<td>40</td>
<td>63</td>
</tr>
</tbody>
</table>
in this setting. In a rational step forward in clinical research, this study aimed to incorporate erlotinib in a commonly used chemoradiation regimen in post-resected patients with locally advanced SCCHN. The rationale for targeting the EGFR in SCCHN is well established. mAb compounds have been developed more intensively in clinical research. Thus, the results from preclinical and early phase II studies suggest that TKIs of the EGFR are active. Single-agent erlotinib in patients with locally advanced nonmetastatic SCCHN administered before surgical resection results in a 29% objective response rate and inhibits the activated EGFR and Erk [19].

The result of the present study demonstrates that full-dose erlotinib can be safely incorporated in a multimodality chemoradiation treatment regimen in the post-resected scenario. The principal toxic effects observed were mainly mucositis and skin rash, well within the expected range of toxic effects in this setting. Most patients were able to complete treatment as designed and recovered from treatment-induced toxic effects. It is becoming apparent that the efficacy of erlotinib may be dose related. SCCHN studies with this agent as in this setting. In a rational step forward in clinical research, this study aimed to incorporate erlotinib in a commonly used chemoradiation regimen in post-resected patients with locally advanced SCCHN. The rationale for targeting the EGFR in SCCHN is well established. mAb compounds have been developed more intensively in clinical research. Thus, the results from preclinical and early phase II studies suggest that TKIs of the EGFR are active. Single-agent erlotinib in patients with locally advanced nonmetastatic SCCHN administered before surgical resection results in a 29% objective response rate and inhibits the activated EGFR and Erk [19].

The result of the present study demonstrates that full-dose erlotinib can be safely incorporated in a multimodality chemoradiation treatment regimen in the post-resected scenario. The principal toxic effects observed were mainly mucositis and skin rash, well within the expected range of toxic effects in this setting. Most patients were able to complete treatment as designed and recovered from treatment-induced toxic effects. It is becoming apparent that the efficacy of erlotinib may be dose related. SCCHN studies with this agent as

Table 2. Patients’ characteristics

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Cisplatin dose intensity [median (range), mg/m²]</th>
<th>Erlotinib dose intensity [median (range), mg]</th>
<th>Accumulated dose of radiotherapy [median (range), Gy]</th>
<th>DLT (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>26.5 (17.5–30)</td>
<td>95.9 (84.8–100)</td>
<td>63 (63–63)</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>30 (17.5–31.2)</td>
<td>150 (144.1–150)</td>
<td>63 (14.4–66.6)</td>
<td>Grade 4 mucositis in week 3 (1); grade 3 folliculitis in week 2 (1)</td>
</tr>
<tr>
<td>III</td>
<td>33.9 (30–40)</td>
<td>146.7 (125–150)</td>
<td>63 (46.8–66.6)</td>
<td>Grade 3 respiratory infection (1); grade 3 mucositis (1)</td>
</tr>
</tbody>
</table>

DLT, dose-limiting toxicity.

Table 3. Dose intensity and DLTs

Table 4. Number of patients with hematological toxicity

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Anemia, grade 3–4</th>
<th>Neutropenia, grade 3–4</th>
<th>Leukopenia, grade 3–4</th>
<th>Thrombocytopenia, grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5. Number of patients with non-hematological toxicity

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Vomiting, grade 3–4</th>
<th>Nausea, grade 3–4</th>
<th>Mucositis, grade 3–4</th>
<th>Asthenia, grade 3–4</th>
<th>Skin toxicity, grade 3–4</th>
<th>Diarrhea, grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
well as similar EGFR inhibitors show that there is a relationship between the occurrence of skin rash, the principal toxicity of the drugs, and outcome [11]. In SCCHN, while gefitinib was effective at doses of 500 mg/day, the agent was essentially ineffective at 250-mg doses. Thus, administering full-dose erlotinib as requested and carried out in this study is of particular interest.

Recently, several studies attempting to combine inhibitors of the EGFR with chemoradiation treatments in SCCHN have been reported. Most of these studies show that the dominant toxic effects, as expected, are mucositis and skin rash. Studies that incorporated biomarker analysis show modulation of EGFR-related pathways in post-treatment biopsies. Interestingly, these studies demonstrate significant antitumor activity in patients with nonresected cancer with response rates in the range of 80%–100% [20–22]. The present trial was conducted in patients with resected disease and, therefore, response rate could not be determined but the high response rate observed in previous trials suggests that activity is high and will potentially result in excellent long-term cancer outcome.

In summary, full-dose erlotinib can be safely administered in combination with simultaneous cisplatin chemotherapy and radiotherapy in postsurgical patients with SCCHN. As toxicity and treatment compliance was acceptable, this schema will potentially result in excellent long-term cancer outcome.

The authors declare no conflict of interest.

acknowledgements

This work was presented in part at the American Society for Clinical Oncology Meeting in 2008.

funding

Roche Farma S.A., Spain.

disclosure

The authors declare no conflict of interest.

references