Cetuximab in squamous cell head and neck carcinomas

V. Gebbia1,2*, F. Giuliani3, V. M. Valori4, R. Agueli1, G. Colucci3 & E. Maiello4

1Medical Oncology Unit, La Maddalena Hospital, Palermo; 2Department of Experimental Oncology and Clinical Applications, University of Palermo, Palermo; 3Medical Oncology Unit, National Cancer Institute, Bari; 4Medical Oncology Unit, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy

The epidermal growth factor receptor (EGFR) antagonist, cetuximab, has recently been shown to enhance the effects of radiotherapy, and reports to date indicate that this effect occurs without any change in the pattern and severity of toxicity usually associated with head and neck radiation and/or chemotherapy (CT) administration. Moreover, several studies have reported that the expression of EGFR is strongly linked to poor outcome in patients undergoing therapy. Therefore, the presence of the EGFR in almost all cases of head and neck carcinoma offers a new therapeutic opportunity to most patients. In this paper, we report a review of the major studies dealing with the use of cetuximab in advanced head and neck cancer.

**Key words:** cetuximab, head and neck cancer, EGFR, patient outcome, chemotherapy, toxicity

**rationale**

The rationale for the use of cetuximab in patients with squamous cell head/neck carcinomas (SCHNC) is soundly based on both preclinical and translational investigations. Human SCHNC frequently display high epidermal growth factor receptor (EGFR) gene copy number as determined by FISH analysis. EGFR polysomy and/or gene amplification is in turn associated with poor prognosis showing for FISH-positive patients a worst progression-free survival (PFS) and overall survival (OS) when compared with FISH-negative ones [1, 2]. However, there was no correlation between EGFR expression and T stage, N stage, stage grouping, and recursive partitioning analysis classes. Therefore, EGFR expression, which vary considerably among patients, is a strong independent prognostic factor survival parameters and a robust predictor for local recurrence but not for distant metastasis.

Cetuximab is able to modulate apoptosis and proliferation, blocking cell cycle at G1 phase and—most important—to enhance the effects of radiation (radiotherapy, RT) against SCHNC cells in cell culture [3] and in athymic mice xenograft assays [4, 5]. These data prompted studies aimed to the selection of patients for aggressive treatments targeting EGFR pathway [6, 7].

The safety, pharmacokinetics, and efficacy of cetuximab in combination with RT were studied in a phase I trial on 16 patients with advanced SCHNC [8]. A standard dose escalation procedure with five dose levels of cetuximab (100–500 mg/m²) plus conventional RT (70 Gy, 2 Gy/day). Cetuximab was delivered as a loading dose of 100–500 mg/m², followed by weekly infusions of 100–250 mg/m² for 7–8 weeks. Most patients experienced grade 1–2 fever, asthenia, nausea, liver, and skin toxic effects. Skin toxicity outside of the RT field was not strictly dose dependent; however, grade 2 or higher events were observed in patients treated with higher dose regimens. Grade 4 allergic reactions occurred in one case. No antibodies against cetuximab were detected. All patients achieved an objective response (13 complete and two partial remissions). These data indicated that cetuximab can be safely administered with RT being the recommended dose the same as that employed for colorectal carcinoma.

**locally advanced SCHNC**

The treatment of locally advanced, unresectable SCHNC is multidisciplinary and involves the use of RT and CT which can be delivered concomitantly or sequentially or omitted [9, 10]. In selected patients, surgery may be reconsidered after RT and/or CT. The benefit of adding CT to locoregional therapy for nonmetastatic disease was confirmed by the results of a meta-analysis of 87 trials including >16 000 patients [9]. Therefore, cetuximab has been explored in combination with RT alone, concomitant chemo-RT, and induction CT.

**cetuximab plus RT**

The radiosensitizing effects of cetuximab represented the basis for the clinical development of cetuximab in combination with RT in patients with locally advanced/recurrent SCHNC [11]. In 2006, Bonner et al. [12] reported a large multinational, randomized study carried out to evaluate the impact of cetuximab on patients treated with RT for locally advanced SCHNC. More than 400 patients were randomized to receive RT alone or RT plus weekly cetuximab at an initial dose of 400 mg/m², followed by 250 mg/m² for the whole length of RT. The addition of cetuximab significantly improved median duration of locoregional control (24.4 versus 14.9 months; hazard ratio (HR) 0.89; P = 0.005), median PFS (HR 0.70;
P = 0.006), and median OS (49 versus 29.3 months; HR 0.74; 
P = 0.03). With the exception of acneiform rash and infusion reactions, the incidence of grade 3 or greater toxic effects, including mucositis, did not differ significantly between the two groups.

cetuximab plus concomitant chemo-RT

Pfister et al. [13] investigated the use of cetuximab in combination with CT and RT in patients with stage III–IV M0 SCCHN. Twenty-one patients received concomitant boost RT (1.8 Gy/day weeks 1–6; boost: 1.6 Gy 4–6 h later weeks 5–6; 70 Gy total to gross disease), cisplatin (100 mg/m^2 i.v. weeks 1 and 4), and cetuximab (400 mg/m^2 i.v. week 1, followed by 250 mg/m^2 weeks 2–10). Despite the fact that the study was closed for significant adverse events (two deaths, one myocardial infarction, one bacteremia, and one atrial fibrillation), however antitumor efficacy was impressive. With a median follow-up of 52 months, the 3-year OS rate is 76%, the 3-year PFS rate is 56%, and the 3-year locoregional control rate is 71%. The authors stated that this regimen is not currently recommended outside of the clinical trial setting, but further research is warranted.

cetuximab and induction CT

Kies et al. [14] carried out a phase II trial aimed to explore the impact of the addition of standard dose cetuximab on induction CT with six weekly cycles of paclitaxel (Taxol) 135 mg/m^2 and carboplatin area under the curve 2 in a series of 41 assessable patients. Choice of surgery ± postoperative RT, definitive primary RT, or concomitant chemo-RT was based upon tumor stage and site at diagnosis. All patients had a major objective response: 17% a partial response and 83% a complete response. Overall, 24% of patients were disease free after CT. Toxicity was generally acceptable with grade 3–4 leukopenia in 34% of cases, grade 3 folliculitis in 47%, and serious hypersensitivity reactions in 4%. These results indicate that although inclusion of cetuximab in induction CT is feasible and very effective, however, further confirmatory trials are needed to optimize schedule.

metastatic/recurrent SCHNC

Patients with recurrent and/or metastatic SCHNC may be amenable for reirradiation, rescue surgery, CT, or simply best supportive care largely depending on their clinical characteristics and performance status at relapse. However, in all above-mentioned clinical settings their prognosis is poor even if palliative CT has demonstrated survival advantages over best supportive care [15]. Most regimens include cisplatin or carboplatin in combination with infusional 5-fluorouracil (5-FU), taxanes or new drugs and are able to induce a major objective response in ~30% of patients whose survival is generally in the range of 6–9 months [15, 16]. A series of studies have shown the activity of cetuximab in the treatment of recurrent/metastatic disease both as first-line therapy and following platinum failure [17]. Three phase I studies of cetuximab plus CT were reported by Baselga et al. [18] which showed that cetuximab has a dose-dependent nonlinear pharmacokinetics and its clearance is not changed by the coadministration of cisplatin. In over 13 patients treated with cisplatin and cetuximab, most completed the planned treatment and two partial responses were recorded.

second-line CT

The prognosis for patients progressing after cisplatin-based CT is particularly poor. In these patients, the alternative therapeutic options are discouraging and the response rates are generally <5%. For these reasons, a possible role of cetuximab alone or in combination with a platinum compound has been explored in few phase II trials.

Trigo et al. [19] tested the activity of standard dose single-agent cetuximab in a phase II trial in a series of 103 SCHNC patients who progressed after platinum-based CT. Preliminary data reported a 17% overall response rate with a 53% tumor growth control rate. The median time to progression (TtP) was 85 days and the median OS was 175 days. These results show that cetuximab is active as a single agent in this group of patients whose prognosis is particularly dismal.

Baselga et al. [20] reported a multicenter phase II study aimed to the evaluation of the efficacy and safety of cetuximab in combination with platinum-based CT in a series of 96 patients with platinum-refractory recurrent/metastatic SCHNC. Patients progressing after receiving platinum-based regimen received cetuximab at standard dose. The response rate according to an intent-to-treat analysis was 10%, with a tumor growth control rate of 53%. The median TtP and OS were 85 and 183 days, respectively, without severe toxicity. As expected, the most common cetuximab-related adverse events were skin reactions, particularly an acne-like rash.

Herbst et al. [21] treated 132 patients with refractory metastatic or recurrent SCHNC with two cycles of cisplatin/paclitaxel or cisplatin/5-FU every 3 weeks. Thirty patients who had a complete or partial response continued standard CT. Seventy-six patients with stabilization (group 1) or progressive disease (group 2) received combination therapy with cetuximab and cisplatin at 75–100 mg/m^2 i.v. every 3 weeks. The study was amended to enroll patients who had developed progressive disease within 90 days after any platinum-based therapy (group 3). An objective response was achieved in nine patients with previous stabilization (19%) with a median duration of 4.2 months, in three patients (6%) progressing after CT with a median duration of 4.1 months, and in nine patients (18%) with stable disease (less than a 50% reduction and less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and the appearance of no new lesions) with 11.7 months.

The authors concluded that the combination of cetuximab and platinum-based CT is an active and well-tolerated approach to the treatment of this poor prognosis patients for whom there are no recommended standard therapeutic options. Cetuximab did not exacerbate cisplatin toxicity but was associated with skin rash in a majority of patients and occasional serious allergic reactions.

first-line CT

The Eastern Cooperative Oncology Group carried out a phase III trial where 117 patients with recurrent/metastatic SCHNC...
were randomly assigned to receive cisplatin 100 mg/m$^2$ every 4 weeks, with weekly cetuximab or placebo with PFS as primary end point [22]. Median PFS was 2.7 months for the cetuximab arm and 4.2 months for the placebo one with an HR of 0.78. Median OS was 8.0 and 9.2 months, respectively, for the cetuximab arm and the placebo one ($P = 0.21$). Although the differences in PFS and OS were not statistically significant, however, objective response rate in patients treated with cetuximab was statistically superior than in the placebo group (26% versus 10%; $P = 0.03$). Correlation analysis between clinical end points and skin toxicity showed a survival advantage for the development of rash with an HR for survival by skin toxicity in cetuximab-treated patients of 0.42 (95% confidence interval 0.21–0.86).

**conclusions**

The availability of cetuximab determined a major positive impact on the management of advanced SCHNC especially when combined with primary RT in locoregionally advanced disease [23]. When the presence of EGFR in almost all cases of SCHNC makes possible the use of such agent on a large scale. Further studies are, however, needed to elucidate the molecular markers of response and resistance and the possible role of this antibody in the treatment of recurrent/metastatic cases.

**references**