Review

Advanced Squamous Cell Carcinoma of the Head and Neck: The Current Role of Cetuximab

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Abstract
We review clinical trials of squamous cell carcinoma of the head and neck (SCCHN) to address the current and potential uses of cetuximab (CTX). PubMed was reviewed to identify papers published between 2010 and 2016. The search terms used were "cetuximab" and "head and neck cancer." A total of 634 articles were identified. Phase II or III studies with CTX in patients with advanced SCCHN without treatment or with recurrent/metastatic tumors were selected. Forty-six registries were obtained. Information was critically reviewed and relevant information presented. As definitive treatment of advanced squamous cells carcinomas and as palliative treatment of recurrent/metastatic disease, CTX alone or associated with chemotherapy and/or radiotherapy is an alternative to chemoradiotherapy because of its distinct and favorable toxicity profile.

Introduction

Surgery and radiotherapy (RT) used to be the treatment of choice for advanced squamous cell carcinoma of the head and neck (SCCHN), but combinations of chemotherapy (CT) were added with the aim of improving results. In 1976, we reported the use of induction with bleomycin and concomitant RT in advanced SCCHN. Twenty patients received the combination, 5 reaching excellent response and 9 good response [1]. Since that time several papers, but espe-
cially after 1990 large series, showed some advantages of combined therapeutic approaches, including organ conservation.

In 2009 however, Pignon et al. [2] performed a meta-analysis which included trials conducted between 1965 and 2000 comparing locoregional treatment to locoregional treatment plus CT in SCCHN patients. With a total of 87 trials and 16,485 patients, the hazard ratio of death was 0.88 ($p < 0.0001$), with an absolute benefit for CT of 4.5% at 5 years, and a significant interaction ($p < 0.0001$) between CT timing (adjuvant, induction, or concomitant) and treatment. Both direct (6 trials) and indirect comparisons showed a more pronounced benefit of concomitant CT as compared to induction CT. For the 50 concomitant trials, the hazard ratio was 0.81 ($p < 0.0001$), and an absolute benefit 6.5% at 5 years. The benefit of concomitant CT was confirmed and was greater than the benefit of induction CT. Then, Blanchard et al. [3] evaluated the magnitude of benefit according to tumor site, and they showed that the benefit of the addition of CT to locoregional treatment is consistent in all tumor locations of SCCHN.

Later studies showed that concomitant chemoradiotherapy (CRT) produced better results than RT alone, improving the survival of patients with advanced unresectable carcinomas. CRT became the standard adjuvant treatment of high-risk patients after surgery and the nonsurgical treatment of choice for advanced laryngeal and hypopharyngeal squamous cell carcinoma (SCC). However, toxicity was a limiting factor in these fragile patients with serious comorbidities.

The discovery of signaling pathways involved in SCCHN led to the development of anti-epidermal growth factor receptor monoclonal antibodies. Cetuximab (CTX) has been assayed and has demonstrated remarkable activity with a favorable toxicity profile; it has been approved by the Food and Drug Administration (FDA) in 2006 in combination with RT for the treatment of locoregionally advanced SCCHN, and in 2011 in combination with platinum and 5-fluorouracil (5-FU) as first-line treatment of recurrent and/or metastatic SCCHN. We review the clinical trials of CTX in SCCHN in order to address its current and potential clinical uses.

### Materials and Methods

The PubMed database was searched for studies published from January 2010 to September 2016 containing the terms “cetuximab” and “head and neck cancer.” The literature search was limited to articles in English about human head and neck cancers treated with RT or CT. Potentially relevant abstracts presented at annual meetings of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) as well as American Society for Radiation Oncology (ASTRO) papers were also examined. Study selection included the following: (a) observational and prospective studies about radiodermatitis assessment and treatment; (b) randomized, double-blind, placebo-controlled, or uncontrolled studies; (c) retrospective and uncontrolled studies; (d) systematic reviews and meta-analyses; and (e) consensus guidelines. Furthermore, the electronic search results were supplemented by manual examination of reference lists from selected articles and were periodically updated until September 2016. Based on the literature review, we identified phase II and III trials in advanced head and neck cancer in 2 different categories – advanced nonmetastatic carcinomas (CTX associated with induction CT, RT, and CRT), and recurrent/metastatic carcinomas (CTX associated with CT and RT) – which were used to structure this review.

### Results

A total of 634 articles were identified. Phase II or III studies with CTX in patients with advanced SCCHN without treatment or with recurrent/metastatic tumors were selected. Forty-six registries were obtained. The information was critically reviewed and relevant information presented.
Advanced Nonmetastatic SCC without Previous Treatment: CTX Associated with Induction CT

Advanced SCCHN has a poor prognosis, although some patients achieve permanent locoregional control (LRC) with aggressive treatment, but fragile patients with comorbidities may not tolerate treatment. CTX-based bioradiotherapy (BRT) can be an alternative to CRT due to its activity and toxicity profile. The following phase II studies explored the efficacy and toxicity of induction BRT.

Kies et al. [4], in SCC with advanced nodal disease, used 6 weekly doses of paclitaxel (135 mg/m²), carboplatin (AUC = 2), and CTX (400 mg/m² initially and 250 mg/m² for weekly maintenance). Then patients received risk-based locoregional therapy (RT, CRT, or surgery). After induction, 9 of 47 patients (19%) achieved complete response (CR) and 36 (77%) partial response (PR). After a mean follow-up of 33 months, 3-year progression-free survival (PFS) and overall survival (OS) were 87 and 91%, respectively. The most common grade 3 or 4 toxicities were skin reactions (45%) and nonfebrile neutropenia (21%).

Adkins et al. [5] explored induction with CTX (250 mg/m² weekly), nab-paclitaxel (100 mg/m² weekly), cisplatin (75 mg/m² on day 1), and 5-FU (750 mg/m²/day on days 1 and 3, every 21 days) for 3 cycles, followed by CRT with cisplatin (100 mg/m² on days 1, 22, and 43). After 2 induction cycles, CR was obtained in 53%. Two-year OS and PFS were 84 and 65%. Treatment was well tolerated; 96% of the patients completed 3 planned induction cycles, and 90% completed the RT protocol.

Charalambakis et al. [6] explored docetaxel, cisplatin, 5-FU, and CTX, followed by CTX concomitant with RT. Among 22 patients, 8 developed grade 3–4 toxicity during induction, 6 of them mucositis; 18 completed 3 induction cycles; 3 obtained CR and 15 PR. After 19 months, 13 patients were alive, but 9 had died, 7 because of persistence or relapse and 2 due to unrelated causes.

Wanebo et al. [7] evaluated paclitaxel and carboplatin with CTX in 74 resectable patients followed by CRT with same drugs. At week 14, patients with a negative biopsy completed CRT (68–72 Gy), and the remaining patients received surgery. At 1 year, 70% avoided surgery without progression or death, and 90% completed CRT. Three-year OS and PFS were 78 and 55%, respectively. Progression occurred in 37% (local 16%, regional 8%, locoregional 3%, and metastatic 8%). Toxicity included hematological alterations.

Argiris et al. [8] explored in 39 patients CTX plus docetaxel (75 mg/m² day 1) and cisplatin (75 mg/m² day 1) every 21 days for 3 cycles, followed by concomitant RT with cisplatin (30 mg/m²) and weekly CTX for 6 months. After a mean follow-up of 36 months, OS and PFS were 74 and 70%, respectively. Toxicity included neutropenic fever (10%) and grade 3 or 4 mucositis (54%) during induction, and hypomagnesaemia (39%) during CRT.

Advanced Nonmetastatic SCC without Previous Treatment: CTX in Association with RT

Bonner et al. [9] conducted a phase III trial to evaluate CTX with RT. Poor surgical candidates with locally advanced SCC of the oropharynx, hypopharynx, and larynx were randomly assigned to RT and concomitant weekly CTX (n = 211) versus RT alone (n = 213). LRC was 24.4 vs. 1.9 months with and without CTX, respectively (p = 0.005). After a median follow-up of 54 months, OS was 49.0 and 29.3 months with and without CTX, respectively (p = 0.03). PFS was 17.1 and 12.4 months with and without CTX, respectively. CTX diminished risk of progression (p = 0.006) and death by 26%. With the exception of acneiform rash and infusion reactions, the rate of severe adverse events did not differ between groups. Ninety percent of patients received all planned treatments. The study showed that concomitant treatment with CTX improved LRC and decreased mortality versus RT alone, without increasing common adverse events. It was crucial for the approval of CTX with RT for the treatment of locoregionally advanced SCCHN by the FDA and European Agency for the Evaluation of Medicinal
Products (EMEA). However, at the time of publication, concomitant CRT was indeed the standard for unresectable SCCHN. Four years later [10], 5-year OS was 45.6 and 36.4% with and without CTX, respectively. Notably, OS was better in patients with grade 2 or higher acneiform rash ($p = 0.002$). Curran et al. [11] evaluated the quality of life (QoL) of the same patients employing the EORTC criteria as well as the QLQ-C30 and QLQ-C35 questionnaires at initiation and 1, 4, 8, and 12 months after treatment. BRT did not decrease QoL.

Dattatreya and Goswami [12] observed an overall response rate (ORR) of 68.42% and a 2-year OS of 84% in 19 unresectable patients treated with BRT, as in Bonner et al.’s trial [9]. At 2 years, 13 patients remained without progression.

Okano et al. [13] evaluated 22 patients treated with CTX for 7 weeks with RT: 1.8 Gy once a day for 3.6 weeks, followed by 1.8 Gy in the morning and 1.5 Gy in the evening for 2.4 weeks. All patients completed at least 70% of the planned treatment. At 8 weeks, the ORR was 82%. Grade 3 or 4 adverse events included mucositis (73%), dermatitis (27%), and infection. The study concluded that BRT with concomitant boost is a well-tolerated treatment.

Lefebvre et al. [14] explored induction CT followed by CRT or BRT for laryngeal preservation. Stage III or IV patients with SCC of the larynx/hypopharynx received 3 cycles of induction CT with 75 mg/m² of docetaxel and cisplatin on day 1, and 750 mg/m² of 5-FU on days 1–5. Patients with worse than PR underwent laryngectomy. Patients with better response were randomly assigned to RT (70 Gy) and cisplatin (100 mg/m²) on days 1, 22, and 43 of RT (group A), or RT with CTX (group B). Three months later, organ preservation was evaluated, and 18 months afterward laryngeal function and OS. Of the initial 153 cases, 116 were analyzed; there were not significant differences between groups regarding preservation of laryngeal function (87 vs. 82%) and OS (92 vs. 89%). However, CTX/RT was better tolerated, and rescue surgery was feasible only among those submitted to CTX/RT. Acute toxicity of CRT produced more adjustments than toxicity of CTX/RT. In CRT, 22.4% of patients developed renal toxicity. Regarding adherence, 42% of patients received 3 planned cycles of cisplatin, but 71% received the planned cycles of CTX. The study corroborated the favorable toxicity profile of CTX with better adherence rates. Remarkable, it failed to demonstrate any superiority of CRT to BRT in the consolidation phase.

Similarly, Keil et al. [15] evaluated 49 patients after 3 cycles of induction CT: docetaxel (75 mg/m²), cisplatin (75 mg/m²) on day 1, and 5-FU (750 mg/m²/day) on days 1–5, followed by RT, and weekly CTX. Forty-four patients received BRT. Two years later, 25 patients maintained CR. Two-year PFS and OS were 59 and 63%, respectively. Adverse events included radiodermatitis (30%), mucositis (27%), and nonfebrile neutropenia (17%). Rampino et al. [16] also assessed 2 cycles of docetaxel, cisplatin, and 5-FU followed by BRT. In 36 stage III and IV patients, CR and PR were 60.6 and 33.3%, respectively. Toxicities included febrile neutropenia (6%) and dermatitis (48%) during induction, and mucositis (33%) and dysphagia (12%) during BRT.

Mesía et al. [17] selected 91 stage III–IV patients with oropharyngeal SCC assigned to RT with accelerated concomitant boost (69.9 Gy) plus CTX, or the same treatment with 12 consecutive weeks of CTX maintenance. One-year LRC was greater among those treated with maintenance CTX (59 vs. 47%), but was similar at 2 years. The patients treated with CTX maintenance recovered faster from adverse events.

León et al. [18] analyzed the response to and the surgical complications of rescue surgery after CRT ($n = 154$) or BRT ($n = 33$). BRT patients were older and had more comorbidities. In their sample, 37.2% of patients with CRT and 61.5% of those with BRT were submitted to rescue surgery. Multivariable analysis showed that the most important factor associated with successful rescue surgery was BRT. Postoperative complications were higher with CRT (62.5 vs. 12.5%). Five-year OS after rescue surgery was 26.0% for CRT and 70.0% for CTX/RT, showing that patients after CTX/RT remained better candidates for rescue surgery. Patients with CTX/RT developed fewer postoperative complications and had better survival.
Remarkably, after induction CT, direct comparison of CRT and BRT in SCC of the larynx showed no different oncological results; however, the rate of successful rescue surgery after BRT is higher and associated with better survival.

**Advanced Nonmetastatic SCC without Previous Treatment: CTX with CRT**

CTX with RT or CT has demonstrated positive results and favorable toxicity profiles. Thus, addition of CTX to CRT could intensify its benefit. Ang et al. [19] examined CTX added to accelerated RT with cisplatin. Stage III or IV patients received RT and cisplatin without (group A) and with CTX (group B). Of 891 patients, 630 were alive at the time of analysis (3.8 years of follow-up), but there were not differences in 30-day mortality, 3-year PFS, 3-year OS, locoregional failure, or metastasis.

Egloff et al. [20] evaluated the addition of CTX to CRT in unresectable patients. Seventy patients received CTX, cisplatin (75 mg/m² every 3 weeks) for 3 cycles, and concomitant RT. In the absence of unacceptable toxicity or disease progression, patients continued monotherapy with CTX for 6–12 months. A total of 71.6% received 3 cycles of cisplatin, and 74.6% maintained therapy with CTX. Mean PFS was 19.4 months, 2-year OS 66, and ORR 66.7%. Toxicity included mucositis (55%), dysphagia (46%), and neutropenia (26%).

Harari et al. [21] randomly assigned 238 patients to RT (60 Gy), CTX, and cisplatin 30 mg/m² or docetaxel 15 mg/m² once weekly. Two-year OS was 69% for the CTX plus cisplatin group and 79% for the CTX plus docetaxel group; the PFS rate was 57 and 66%, respectively. Grade 3 or 4 myelosuppression was observed in 28% (with cisplatin) and in 14% (with docetaxel). PFS was compared with that of those who received CT in the RTOG-9501 study, with a better 2-year PFS of 11.1% compared to 2.5%.

Likewise, Suntharalingam et al. [22] examined CTX, paclitaxel, and carboplatin weekly, concomitantly with RT. The doses were conventional for CTX, 40 mg/m² for paclitaxel, and AUC = 2 for carboplatin. RT consisted of 1.8 Gy/day until completing 70.2 Gy. Forty-three patients completed RT, 74% without interruption. Six patients experienced local relapse and 10 distant failure. CR was 84%, and the 3-year LRC rate was 72%. Three-year OS and PFS were 59 and 58%, respectively. Grade 3 toxicity included mucositis (79%), leukopenia (19%), neutropenia (19%), radiodermatitis (16%), and rash (9%).

Merlano et al. [23] coordinated a study with 45 stage III–IV patients who received 3 cycles of cisplatin (20 mg/m²/day) and 5-FU (200 mg/m²/day) during 5 days, alternating with 3 divided courses and RT up to 70 Gy concomitantly with CTX at conventional weekly doses. CR was 71%, and median PFS and OS were 21 and 32.6 months, respectively. Acute grade 3 or 4 toxicity was as expected; however, radiodermatitis was observed in 33 patients.

Matuschek et al. [24] evaluated the feasibility of CRT plus CTX followed by CTX during 6 months in patients with close margins (<5 mm) or extracapsular spread. Intensity-modulated RT (IMRT) consisted of 61.6 Gy (1.8/2.0/2.2 Gy, days 1–36) concomitant with cisplatin at 20 mg/m² and 5-FU at 600 mg/m², on days 1–5 and 29–33. CTX was given at conventional weekly doses. CTX adjuvant monotherapy started after CRT at 500 mg/m² every 2 weeks for 6 months. Fifty-five patients concluded CRT. Grade 3 or 4 adverse events included mucositis (46%), RT-associated dermatitis (28%), and skin reactions not associated with RT (14%). Of all patients, 80% remained with monotherapy at 3 months and 63% at 5 months. Concurrent treatment and maintenance was administered in 48% of patients. Maintenance was viable and toxicity according as expected.

Granados Garcia et al. [25] explored CTX, gemcitabine, and RT in 20 patients. Weekly CTX was administered at conventional doses, gemcitabine at 50 mg/m² for 7 weekly cycles, and classic RT until 70 Gy. CR and ORR were 82.4 and 100%, respectively; median OS was 53 months. Common adverse events included nausea, neutropenia, lymphopenia, and mucositis, the two latter in 88.2% of patients, but were manageable; grade 3 radioepithelitis occurred in 23.1%.
Kao et al. [26] evaluated CTX, 5-FU, and hydroxyurea with simultaneous integrated boost IMRT (SIB-IMRT) in stage IVA and IVB or high-risk stage III patients. Thirty-three patients received SIB-IMRT at low-risk (43.2–48 Gy) and high-risk (54–63 Gy) doses. The mean radiation dose was 72 Gy in 1.5-Gy fractions twice daily during weeks 1, 3, 5, 7, and 9. Simultaneous treatment consisted of 5-FU (600 mg/m²), hydroxyurea (500 mg twice a day), and CTX. The rates of LRC, distant control, and 2-year PFS and OS were 83, 79, 69, and 86%, respectively. Grade 3 toxicity was mucositis (33%), radiodermatitis (15%), anemia (18%), leukopenia (18%), neutropenia (12%), and thrombocytopenia (3%). Most of the patients (64%) tolerated treatment without grade 4 acute or late events.

Recurrence/Metastatic Head and Neck Carcinoma: CTX in Association with CT

Recurrence disease is often unresectable and treatment becomes palliative, in which case QoL takes precedence. Thus, an effective and less toxic treatment is desirable.

CTX has been assayed in combination with various CT agents. In a phase II trial, Burtness et al. [27] evaluated 117 patients randomly assigned to cisplatin every 4 weeks plus CTX (group A) or placebo (group B). PFS and OS were 4.2 and 9.2 months, respectively in group A and 2.7 and 8.0 months, respectively in group B. ORR was 26% in group A versus 10% in group B (p = 0.03). Baselga et al. [28] explored the same combination in 96 refractory recurrent/metastatic patients. Patients received CTX in weekly doses, followed by cisplatin at the same doses registered for each patient prior to study admission when disease progressed. ORR was 10%, with a disease control rate of 53%. Time of progression and OS were 85 and 183 days, respectively. The most common adverse event was acneiform rash.

Likewise, Herbst et al. [29] evaluated CTX with cisplatin in refractory metastatic disease; 132 patients received 2 cycles of cisplatin/paclitaxel or cisplatin/5-FU. Patients with CR or PR (n = 30) continued standard treatment. A total of 76 patients with stable disease (SD) (n = 51) or progressive disease (PD/1) (n = 25) received CTX in weekly doses and cisplatin (75 or 100 mg/m² on day 1 every 3 weeks). The protocol was amended to recruit patients during the 90 days after cisplatin-based therapy (PD/2) (n = 54). CR was observed in 20% of patients with PD/1, 6% with PD/2, and 18% with SD. Time of progression was 4.2, 4.1, and 7.4 months for groups PD/1, PD/2, and SD, respectively, while OS was 6.1, 4.3, and 11.7 months, respectively. The most common adverse events were anemia, rash, leukopenia, fatigue, nausea, and vomiting. Seven patients developed grade 3 or 4 hypersensitivity to CTX.

These studies support the addition of CTX to cisplatin-based CT to produce better results than CT alone in recurrent metastatic patients, even in those with platinum-refractory disease. The ESMO and National Comprehensive Cancer Network (NCCN) guidelines support the use of CTX as first-line treatment in recurrent/metastatic, persistent disease.

Vermorken et al. coordinated a pivotal study. As published in 2007 [30], they evaluated the feasibility and safety of monotherapy with CTX for 6 weeks in patients with PD under platinum-based therapy (2–6 cycles). Fifty-three of 103 patients received CTX with or without platinum. Under monotherapy, ORR was 13%, disease control 46%, and time to progression 70 days. In combined therapy, ORR was 0%, disease control 26%, and time of progression 50 days. OS reached 178 days. The experimental treatment was well tolerated; 49% of patients experienced grade 1 or 2 rash with monotherapy. This study demonstrated that CTX as a monodrug is active and well tolerated in patients with recurrent metastatic disease.

In 2008, Vermorken et al. [31] published the phase III EXTREME trial. The study enrolled 422 patients with recurrent/metastatic SCC; one-half received cisplatin (100 mg/m²) on day 1 or carboplatin (AUC = 5) plus 5-FU (1,000 mg/m² daily) during 4 days, every 3 weeks, for 6 cycles. The remaining patients received the same CT plus CTX at conventional doses for 6 cycles, but patients with SD who received CT plus CTX continued with CTX until progression or unacceptable toxicity. The study demonstrated that addition of CTX to CT improved
Addition of CTX prolonged OS from 7.4 to 10.1 months ($p = 0.04$), PFS from 3.3 to 5.6 months ($p < 0.001$), and ORR from 20 to 36% ($p < 0.001$). In addition, CTX diminished the risk of death by 20%. The incidence of grade 3 or 4 adverse events between groups was similar, except for skin reactions (9 vs. 1%), sepsis (4 vs. 1%), and hypomagnesaemia (5 vs. 1%), with greater effects associated with CTX. The treatment duration with CTX as monotherapy was 18 weeks. The relative dose intensity of CTX was >80% in 84 and 82% of patients in the first therapy phase and under maintenance, respectively. This was the first randomized assay that demonstrated the benefit of adding a novel drug to CT, i.e., CTX improves OS as first-line treatment in patients with recurrent/metastatic SCCHN. Later, Mesía et al. [32] examined the QoL of these patients according to the EORTC criteria as well as the QLQ-C30 and QLQ-C35 questionnaires. Of the 442 randomly assigned patients, 291 completed the questionnaires. The study concluded that the addition of CTX to platinum- and 5-FU-based CT did not deteriorate QoL. In fact, it showed a better global status of QoL/health ($p = 0.041$) without a difference in the social functioning scale and with better control of deglutition problems.

Yoshino et al. [33] evaluated CTX, cisplatin at 100 mg/m$^2$ on day 1, and 5-FU at 1,000 mg/m$^2$/day on days 1–4 for 6 cycles as first-line treatment in metastatic SCC. ORR was 36%, disease control rate 88%, and PFS and OS were 4.1 and 14.1 months, respectively. With the same protocol, Guo et al. [34] studied the combination in 68 Asian patients. The ORR was 55.9%, including 2 CR. OS and PFS were 12.6 and 6.6 months, respectively. Grade 3 and 4 adverse events occurred in 60.3%.

De Mello et al. [35] retrospectively evaluated 121 patients who received cisplatin plus 5-FU and CTX every 3 weeks for 6 cycles. Patients with SD additionally received CTX until progression or unacceptable toxicity. Addition of CTX led to OS and PFS of 11 and 8 months, respectively. Control rate was 48.9% and ORR was 23.91%. Most common adverse events were grade 3 or 4 febrile neutropenia (5.7%), skin rash (3.8%), or mucositis (3.8%). Bossi et al. [36] evaluated cisplatin, 5-FU, and CTX as first-line treatment followed by CTX maintenance every other week. While maintenance patients developed skin rash (grade 3, 16%; grade 2, 23%), fatigue (grade 3, 3%; grade 2, 16%), diarrhea (grade 3, 7%; grade 2, 13%), hypomagnesaemia (grade 4, 3%; grade 3, 3%; grade 2, 19%), and mucositis (grade 3, 3%; grade 2, 23%), the study showed that CTX maintenance was well tolerated.

In non-candidates for cisplatin due to progression with the same or cisplatin contraindication, 3 studies evaluated the combination of CTX with paclitaxel. Hitt et al. [37] examined 46 patients who received paclitaxel (80 mg/m$^2$) and CTX as first-line treatment until progression or unacceptable toxicity. ORR was 54%, with a CR of 22% and a disease control rate of 80%. PFS and OS were 4.2 and 8.1 months, respectively. Grade 3 adverse events presented as skin rash (24%), asthenia (17%), and neutropenia (13%). Péron et al. [38] evaluated paclitaxel and CTX after failure of cisplatin-based CT; 42 patients were treated with weekly CTX and paclitaxel at 60–80 mg/m$^2$ weekly until progression or unacceptable toxicity. OR was 38% and disease control rate 74%, while PFS and OS were 3.9 and 7.6 months, respectively. The most frequent grade 3 or 4 adverse events were neurotoxicity and skin rash in 17 and 12% of patients, respectively. Similarly, Jiménez et al. [39] evaluated paclitaxel with weekly CTX in previously treated patients. Twenty-two patients received paclitaxel (80 mg/m$^2$) and CTX until progression or unacceptable toxicity. ORR was 55%; 1 patient developed CR and 9 PR. OS and PFS were 9.1 and 5.4 months, respectively. Seventy percent presented rash; there was a positive association between rash severity and OR (grade 0–1 with an OR of 33% versus grade 2–3 with an OR of 64%) ($p = 0.03$).

Knoedler et al. [40] evaluated 84 patients treated with docetaxel at 35 mg/m$^2$ weekly for 6 cycles with CTX at conventional doses, until progression or unacceptable toxicity. Eleven percent achieved PR and 40% SD, for a disease control rate of 51%. ORR was 49% in patients with platinum-sensitive disease and 50% in patients with platinum-resistant disease. PFS
and OS were 3.1 and 6.7 months, respectively. The most common grade 3 or 4 adverse events were mucositis (8%), pneumonia (8%), fatigue (8%), and skin reactions (14%).

Guigay et al. [41] studied the efficacy and safety of 4 cycles of docetaxel (75 mg/m²), cisplatin (75 mg/m²) on day 1, and CTX at common weekly doses, every 21 days for 4 cycles, plus maintenance with CTX (500 mg/m² every 2 weeks) until disease progression or toxicity. Among 54 patients, after 4 cycles OR, OS, and PFS were 44.4%, 14 months, and 6.2 months, respectively. The most common grade 3 or higher adverse events were rash (16.6%) and nonfebrile neutropenia (20.4%). The authors concluded that this schema is viable, convenient and active, with a manageable toxicity.

**Recurrent/Metastatic Head and Neck Carcinoma: CTX in Association with RT**

Since satisfactory results of concomitant RT with CTX in locally advanced SCCHN were missing, Jensen et al. [42] evaluated 73 elderly and multimorbid patients with primary/recurrent SCC (22 patients with reirradiation). ORR, PFS, and OS were 59.4%, 15 months, and 18 months, respectively. Seven patients discontinued CTX, 4 due to grade 3 allergic reactions and 3 because of skin reactions. Balermpas et al. [43] similarly evaluated reirradiation with CTX in 18 unresectable and recurrent patients after simultaneous or sequential RT with cisplatin-based CT. ORR, OS, and PFS were 47%, 8.38 months, and 7.33 months, respectively. One-year OS and local control rate were 44 and 33%, respectively. Acute toxicity included 5 patients with grade 3 acneiform rash. Later, 5 patients developed grade 3 trismus and 1 a grade 3 noninfectious sialadenitis.

Relapse has a poor prognosis. High toxicity was observed when surgery, RT, and CT were combined. Although reirradiation could produce better results compared to CT alone, toxicity is a limiting factor leading to suboptimal results. Stereotactic RT offers more exact and less toxic irradiation. Due to this, Laritgau et al. [44] treated recurrent or unresectable disease or new primary tumors in a previously irradiated field with reirradiation doses of 36 Gy in 6 fractions and 5 doses of concomitant CTX. Sixty patients had been previously treated with RT, 85% with surgery, and 48% with CT. The mean time between first RT and stereotactic irradiation was 38 months. At 3 months, ORR was 58.4% and disease control 91.7%. One-year OS was 47.5%. Skin toxicity occurred in 41 patients. The authors concluded that this schema offers a rescue treatment with acceptable response in patients with poor prognosis.

Heron et al. [45] retrospectively compared stereotactic RT alone and concomitant with CTX. In 70 unresectable recurrent patients, those who received concomitant treatment showed an advantage in OS versus RT alone (24.5 vs. 14.8 months, respectively), without a significant increase of grade 3 or 4 toxicity. Even more, the advantage was also observed in patients who received CTX as first-line treatment.

Vargo et al. [46] reported the first prospective QoL evaluation after reirradiation with stereotactic RT with and without CTX. A total of 150 patients who had previously received <40 Gy were treated with stereotactic RT at 40–50 Gy in 5 fractions with or without concomitant CTX. The University of Washington Quality of Life Questionnaire Revised (UW-QOL-R) was applied. Analysis showed better deglutition (p = 0.025), conversation (p = 0.017), salivation (p = 0.041), activity (p = 0.032), and recreation scores (p = 0.039) with CTX.

Vargo et al. [47] evaluated the efficacy of stereotactic radiation in previously irradiated patients with locally recurrent SCCHN. RT consisted of 40–44 Gy in 5 fractions on alternate days during 1–2 weeks, with CTX at usual doses. One-year PFS was 33%, local relapse-free survival 60%, locoregional relapse-free survival 37%, and distant metastases relapse-free survival 71%. Mean survival was 10 months and 1-year OS was 40%. After 18 months of follow-up, 69% of the patients had died of disease, 4% had died with disease (15% of them without progression), 10% remained alive without progression, and 2% remained alive with progression. Grade 3 toxicity was observed in 6% of the patients.
After rescue surgery in previously irradiated patients, locoregional relapse constitutes the main pattern of failure. Some studies suggest the use of conventional irradiation and adjuvant CT, but with severe toxicity. Vargo et al. [48] examined stereotactic RT and CTX after rescue surgery to improve tumor control and diminish toxicity. Twenty-eight patients with high risk of relapse (positive surgical borders or capsular rupture) were treated with stereotactic RT (40–44 Gy in 5 fractions between 1 and 2 weeks) with concomitant CTX at usual doses. All patients had prior RT (70 Gy; range, 54–99 Gy), and the irradiation interval was 25 months. After 14 months, LRC, distant control, PFS, and 1-year OS were 51, 90, 49, and 64%, respectively. Severe acute (≥ grade 3) and severe chronic toxicity rates were 0 and 8%, respectively. At 6 months, 56% of patients reported a stable and/or superior QoL.

Due to the favorable effects of the association of CTX and RT, it seems logical to search for the benefit in recurrent patients, with the possibility of irradiation thanks to technological advances. The evidence shows that these patients could benefit from locoregional treatment with BRT, improving activity with respect to RT alone, without deterioration of QoL.

Discussion

Selective inhibition of epidermal growth factor receptor with CTX has contributed to the development of several approaches for the treatment of SCCHN under different clinical circumstances and with different objectives. Selective pathway inhibition has been used as initial treatment of patients with locoregionally advanced disease and as palliative treatment of patients with unresectable or metastatic recurrent disease, both with very favorable toxicity profiles as well as better tolerability and adherence, factors which usually limit the use of other forms of treatment.

Since the first reports of its use in SCCHN, CTX has acquired considerable importance in the management of advanced neoplasms because of its activity and favorable toxicity profile (Table 1). Mature results of direct comparisons between CRT and BRT do not exist, but indirect comparisons suggest a similar activity and a better toxicity profile of CTX. Thus, CTX is a viable option for patients with advanced tumors who cannot receive CRT due to advanced age or comorbidities.

CTX has been tested in patients with very advanced nonmetastatic SCC. When associated with induction CT, several phase II studies have shown it to produce active schedules with a favorable toxicity profile. Similarly, in patients with advanced SCCHN without previous treatment submitted to concomitant CRT plus CTX, very active schemas are produced too; however, toxicity does not increase significantly in comparison with concomitant CRT. These phase II studies suggest that both schemas should be tested in further phases of investigation to clarify its true value.

In patients with recurrent or metastatic SCCHN, the addition of CTX to palliative CT with taxanes or platinum produces active schemas associated with improved survival, acceptable toxicity, and good QoL, leading to the conclusion that CTX is a valuable agent for palliative purposes.

CTX also demonstrated significant activity in recurrent tumors with resistance to platinum-based schemas (Table 2). Another important observation is that patients submitted to BRT who require complementary or rescue surgery with greater frequency are apt to tolerate surgery compared to those having failed CRT.

Concerning toxicity, regardless of p16 status, associated with HPV infection and response to treatment, addition of CTX to RT did not alter the incidence, time to onset, severity, or duration of mucositis and dysphagia and did not increase the frequency of feeding tube use [49]. The observation, in relation with a better OS in patients with grade 2 or higher acneiform
rash, has been corroborated by Bar-Ad et al. [50]. Their analysis included 602 patients who received a loading dose and ≥1 CTX dose concurrent with definitive CRT (70 Gy + cisplatin) or postoperative CRT (60–66 Gy + docetaxel or cisplatin). Grade 2–4 CTX rash was associated with better survival. The authors theorized that this was due to reduction of distant metas-

#### Table 1. Cetuximab in advanced locoregional squamous cell carcinoma of head and neck

<table>
<thead>
<tr>
<th>n</th>
<th>Treatment</th>
<th>Clinical indicators</th>
<th>Reference (first author)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ORR</td>
<td>CR</td>
</tr>
<tr>
<td>47</td>
<td>CTX+P+Ca RT, CRT,</td>
<td>19%</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>or surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>CTX+P+C+5-FU RT+C</td>
<td>53%</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>CTX+D+C+5-FU RT+CTX</td>
<td>3/18</td>
<td>15/18</td>
</tr>
<tr>
<td>74</td>
<td>CTX+P+Ca RT+CTX+P+Ca</td>
<td>78%</td>
<td>3 y</td>
</tr>
<tr>
<td>39</td>
<td>CTX+D+C RT+CTX+C CTX</td>
<td>74%</td>
<td>3 y</td>
</tr>
<tr>
<td>211</td>
<td>RT+CTX</td>
<td>49 m</td>
<td>17.1 m</td>
</tr>
<tr>
<td>19</td>
<td>RT+CTX</td>
<td>68.4%</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>RT+CTX</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>116</td>
<td>TPF RT+CTX</td>
<td>89%</td>
<td>18 m</td>
</tr>
<tr>
<td>49</td>
<td>TPF RT+CTX</td>
<td>33/44</td>
<td>63%</td>
</tr>
<tr>
<td>36</td>
<td>TPF RT+CTX</td>
<td>60.6%</td>
<td>33.3%</td>
</tr>
<tr>
<td>91</td>
<td>RT+CTX</td>
<td>59%</td>
<td>1 y</td>
</tr>
<tr>
<td>20</td>
<td>RT+CTX+G</td>
<td>100%</td>
<td>61.5%</td>
</tr>
<tr>
<td>60</td>
<td>RT+CTX+C CTX</td>
<td>66.7%</td>
<td>39%</td>
</tr>
<tr>
<td>238</td>
<td>RT+CTX+C RT+CTX+D</td>
<td>69%</td>
<td>2 y</td>
</tr>
<tr>
<td>45</td>
<td>RT+CTX+C +5-FU</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>RT+CTX+P +Ca</td>
<td>84%</td>
<td>59%</td>
</tr>
<tr>
<td>33</td>
<td>RT+CTX+5-FU+H</td>
<td>86%</td>
<td>2 y</td>
</tr>
</tbody>
</table>

5-FU, 5-fluorouracil; C, cisplatin; Ca, carboplatin; CR, complete response; CRT, chemoradiotherapy; CTX, cetuximab; D, docetaxel; G, gemcitabine; H, hydroxyurea; LRC, locoregional control; m, month(s); n, number of patients; ORR, overall response rate; OS, overall survival; P, paclitaxel; PFS, progression-free survival; PR, partial response; RT, radiotherapy; TPF, taxane, platinum, and fluorouracil; y, year(s).
This observation was noted mainly in p16-negative patients. Nevertheless, rare grade 2–4 acute in-field radiation dermatitis was associated with a higher rate of late grade 2–4 skin fibrosis.

In Bonner et al.’s phase III study [49], 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 RT alone and RT plus CTX. Regardless of p16 status, the addition of CTX to RT did not alter the incidence, time to onset, severity, or duration of mucositis and dysphagia and did not impact the frequency of feeding tube use [51].

Recently, consensus reports have been published on the clinical definition and management of dermatitis in patients treated with RT with or without systemic therapies in order to improve skin toxicity management; those papers offer statements about the management of dermatitis and a review of the recent literature on these topics [52–55]. In patients with untreated recurrent or metastatic SCCHN, the most common grade 3 or 4 adverse events in the CT-alone and CTX groups were anemia (19 and 13%, respectively), neutropenia (23 and 22%, respectively), and thrombocytopenia (11% in both groups). Sepsis occurred in 9 patients in the CTX group and in 1 patient in the CT-alone group (p = 0.02). Of 219 patients receiving

### Table 2. Cetuximab in recurrent/metastatic squamous cell carcinoma of the head and neck

<table>
<thead>
<tr>
<th>n</th>
<th>Treatment</th>
<th>Clinical indicators</th>
<th>Reference (first author)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR</td>
<td>CR</td>
<td>PR</td>
</tr>
<tr>
<td>117</td>
<td>C+CTX</td>
<td>26%</td>
<td>9.2 m</td>
</tr>
<tr>
<td>96</td>
<td>C+CTX</td>
<td>10%</td>
<td>6.1 m</td>
</tr>
<tr>
<td>222</td>
<td>C or Ca+ 5-FU+CTX</td>
<td>36%</td>
<td>10.1 m</td>
</tr>
<tr>
<td>121</td>
<td>C+5-FU+CTX</td>
<td>24%</td>
<td>11.0 m</td>
</tr>
<tr>
<td>33</td>
<td>C+5-FU+CTX</td>
<td>36%</td>
<td>14.1 m</td>
</tr>
<tr>
<td>68</td>
<td>C+5-FU+CTX</td>
<td>56%</td>
<td>12.6 m</td>
</tr>
<tr>
<td>46</td>
<td>P+CTX</td>
<td>54%</td>
<td>22%</td>
</tr>
<tr>
<td>22</td>
<td>P+CTX</td>
<td>55%</td>
<td>9.1 m</td>
</tr>
<tr>
<td>42</td>
<td>P+CTX</td>
<td>38%</td>
<td>7.6 m</td>
</tr>
<tr>
<td>84</td>
<td>CTX+D</td>
<td>11%</td>
<td>6.7 m</td>
</tr>
<tr>
<td>54</td>
<td>C+D+CTX</td>
<td>44%</td>
<td>14 m</td>
</tr>
<tr>
<td>73</td>
<td>RT+CTX</td>
<td>59.4%</td>
<td>18 m</td>
</tr>
<tr>
<td>18</td>
<td>RT+CTX</td>
<td>47%</td>
<td>8.3 m</td>
</tr>
<tr>
<td>70</td>
<td>RT+CTX</td>
<td>24.5 m</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>RT+CTX</td>
<td>58.4%</td>
<td>47.5%</td>
</tr>
<tr>
<td>50</td>
<td>RT+CTX</td>
<td>10 m</td>
<td>40% 1 y</td>
</tr>
<tr>
<td>28</td>
<td>RT+CTX</td>
<td>64% 1 y</td>
<td>49% 1 y</td>
</tr>
</tbody>
</table>

5-FU, 5-fluorouracil; C, cisplatin; Ca, carboplatin; CR, complete response; CTX, cetuximab; D, docetaxel; LRC, locoregional control; m, month(s); n, number of patients; ORR, overall response rate; OS, overall survival; P, paclitaxel; PFS, progression-free survival; PR, partial response; RT, radiotherapy; y, year(s).
CTX, 9% had grade 3 skin reactions and 3% had grade 3 or 4 infusion-related reactions. There were no CTX-related deaths [31].

In conclusion, addition of CTX to CT and RT produces several active treatment schedules with a favorable toxicity profile that are very useful in different settings, including curative intent and palliative purposes. It is of outmost importance that good responses associated with CTX in the palliative setting, which usually limit the appearance of symptomatology due to disease progression, be translated into a better QoL for patients suffering from this agonizing disease.

Disclosure Statement

The authors have no conflicts of interest to declare.

References


