

Cetuximab: its unique place in head and neck cancer treatment

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Abstract: Head and neck cancer is the sixth most common cancer worldwide. At present, globally about 650,000 new cases of squamous cell carcinoma of the head and neck (SCCHN) are diagnosed each year. The epidermal growth factor receptor (EGFR) is almost invariably expressed in SCCHN. Overexpression of the EGFR is a strong and independent unfavorable prognostic factor in SCCHN. Cetuximab is a chimeric monoclonal antibody, which binds with high affinity to the extracellular domain of the human EGFR, blocking ligand binding, resulting in inhibition of the receptor function. It also targets cytotoxic immune effector cells towards EGFR-expressing tumor cells (antibody dependent cell-mediated cytotoxicity). The addition of cetuximab to radiotherapy (RT) improves locoregional control and survival when compared to RT alone. The addition of cetuximab to platinum-based chemoradiation (CRT) is feasible but does not lead to an improved outcome. Cetuximab plus RT has never been compared prospectively to CRT, which therefore remains the standard treatment for patients with locoregionally advanced SCCHN for whom surgery is not considered the optimal treatment, provided they can tolerate CRT. The addition of cetuximab to platinum-based chemotherapy prolongs survival in patients with recurrent or metastatic SCCHN. The combination of a platinum-based regimen and cetuximab should be considered as the standard first line regimen for patients who can tolerate this treatment.

Keywords: SCCHN, cetuximab, recurrent metastatic, locoregionally advanced, chemoradiation

Introduction to the management issues in the treatment of head and neck cancer

More than 90% of head and neck cancers are of squamous cell histology and originate in the lip, oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx.¹

Head and neck cancer is the sixth most common cancer worldwide. At present, globally about 650,000 new cases of squamous cell carcinoma of the head and neck (SCCHN) are diagnosed each year.² SCCHN is most commonly linked to tobacco use. Frequent and heavy consumption of alcohol also increases the risk of SCCHN, and this is particularly so when tobacco and alcohol are used together.³ Human papillomavirus is a causal factor in the development of oropharyngeal cancer, even in never-smokers and never-drinkers.^{4,5} Human papillomavirus related tumors have a better prognosis, regardless of which treatment is used.^{6,7} SCCHN is considered to be the final stage of a multistep process evolving from normal histology over hyperplasia, dysplasia, and carcinoma in situ to invasive carcinoma.⁸ The management of SCCHN is complex and requires a multidisciplinary approach.^{9,10} Single modality treatment with

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surgery or radiotherapy (RT) is generally recommended for the approximately 40% of patients who present with stage I or II disease.¹⁰ For patients who present with locoregionally advanced (LA) disease at diagnosis, combined modality therapy is generally recommended. For patients with unresectable disease and for patients with resectable disease in whom organ preservation is desired, the current standard treatment is concurrent cisplatin-based chemoradiation (CRT).¹⁰ Cisplatin in combination with RT is also indicated postoperatively in patients with high risk pathological findings at surgical resection.¹⁰ Despite such a combined approach, a significant majority of patients with LA-SCCHN at diagnosis will develop a (loco)regional recurrence or distant metastases. Patients with recurrent or metastatic (R/M) SCCHN have a poor prognosis with a median overall survival (OS) ranging between 6 and 9 months in most studies.¹¹

Expression of the epidermal growth factor receptor (EGFR) and its ligand transforming growth factor alpha occurs early in the carcinogenesis of SCCHN.¹² The EGFR is almost invariably expressed in SCCHN.^{12,13} Overexpression of EGFR is a strong and independent unfavorable prognostic factor in SCCHN.^{14,15}

Review of pharmacology, mode of action, and pharmacokinetics of cetuximab

Thus far, cetuximab (Erbix[®]; Merck KgaA, Darmstadt, Germany; Imclone Systems, Somerville, NJ, USA) is the only targeted agent which has been approved for the treatment of SCCHN by the regulatory agencies of the United States and Europe.^{16,17} Cetuximab is a chimeric monoclonal antibody of the immunoglobulin G1 class, which binds with high affinity to the extracellular domain of the human EGFR. As the affinity of cetuximab for EGFR is approximately 5 to 10 fold higher than that of the endogenous ligands, it blocks the binding of these ligands resulting in inhibition of the receptor function. Furthermore, cetuximab induces the internalization of EGFR, which can lead to downregulation of EGFR. It also targets cytotoxic immune effector cells towards EGFR expressing tumor cells (antibody dependent cell-mediated cytotoxicity).¹⁸ In vitro exposure of squamous cell carcinoma (SCC) cell lines derived from head and neck cancer patients to cetuximab inhibits proliferation in a time-dependent manner.¹⁹ Cells accumulate in G1 of the cell cycle. Radiosensitivity is enhanced and radiation-induced apoptosis is amplified both in single dose and fractionated radiation experiments.¹⁹

Cetuximab and cisplatin induced an (supra)additive effect when combined with irradiation in SCCHN cell lines.^{20,21} Cisplatin and cetuximab in combination resulted in substantial growth inhibition of well-established SCC xenografts when compared with both an untreated control group and animals treated with a single modality.²² The population pharmacokinetics of cetuximab have been characterized in 143 R/M-SCCHN patients.²³ Cetuximab pharmacokinetics were best described by a two-compartment model with Michaelis–Menten-type saturable elimination. Population estimates of the pharmacokinetic parameters were V_{max} (maximum elimination rate) 4.38 mg/hour (15.4%), K_m (the concentration with half-maximal elimination rate) 74 $\mu\text{g/mL}$, central compartment volume (V_1) 2.83 L (18.6%), peripheral compartment volume 2.43 L (56.4%), and intercompartmental clearance 0.103 L/hour (97.2%). Cetuximab pharmacokinetic parameters remained constant during prolonged therapy. Clinical dose adjustments beyond the approved body surface area-based dosing of cetuximab may be warranted in patients with extreme deviations of their actual body weight from ideal body weight.²³

Baselga et al²⁴ treated 52 patients in three successive Phase I clinical trials of cetuximab as a single dose ($n = 13$), weekly multiple dose ($n = 17$), and weekly multiple dose with cisplatin ($n = 22$). Cetuximab dose levels were 5, 20, 50, and 100 mg/m^2 . In the study combining cetuximab with cisplatin, cetuximab was further escalated to 200 and 400 mg/m^2 . Cisplatin was given at a dose of 60 mg/m^2 once every 4 weeks. Cetuximab displayed nonlinear pharmacokinetics, with complete saturation of systemic clearance with cetuximab doses in the range of 200–400 mg/m^2 . Cetuximab clearance did not change with repeated administration or with coadministration of cisplatin.

Shin et al²⁵ conducted a Phase Ib study with cetuximab in combination with cisplatin in patients with recurrent SCCHN. Twelve patients who had high levels of EGFR expression and tumors easily accessible for repeated biopsies (pre-therapy, 24 hours after first infusion, and 24 hours before third infusion) were entered at three different dose levels of cetuximab (100 mg/m^2 as a loading dose with maintenance doses at 100 mg/m^2 weekly; 500 mg/m^2 as a loading dose with maintenance doses at 250 mg/m^2 weekly; and 400 mg/m^2 as a loading dose with maintenance doses at 250 mg/m^2 weekly). The loading dose of 400 mg/m^2 followed by a maintenance dose of 250 mg/m^2 achieved a high percentage of saturation of EGFR in tumor tissue, and these doses were recommended for Phase II or III clinical trials. Combined cetuximab and cisplatin therapy did not appear to induce overlapping toxic effects in this Phase I study.

Robert et al²⁶ demonstrated that cetuximab at a loading dose of 400 or 500 mg/m² followed by a weekly maintenance dose of 250 mg/m² could be safely combined with conventionally fractionated RT (70 Gy in 2 Gy fractions) and hyperfractionated RT (76.8 Gy in 1.2 Gy fractions twice daily) in patients with LA-SCCHN.

Efficacy studies, including any comparative studies

The results of published or presented randomized Phase III trials with cetuximab in SCCHN are summarized in Table 1.

LA-SCCHN

Cetuximab in combination with RT

Bonner et al^{27,28} conducted a multinational, randomized study to compare RT alone with RT plus cetuximab, in the treatment of stage III or IV nonmetastatic, measurable SCC of the oropharynx, hypopharynx, or larynx. Patients were randomly assigned to treatment with RT alone (213 patients) or RT plus weekly cetuximab (211 patients) at the summary of product characteristics (SPC) recommended dose (initial loading dose of 400 mg/m² followed by weekly administration of 250 mg/m²).^{29,30} RT consisted of one of the following three regimens: once daily RT delivered at 2 Gy per day to a total dose of 70 Gy to gross disease; twice daily RT delivered as 1.2 Gy in two separate fractions each day (separated by ≥6 hours) to a total dose of 72.0–76.8 Gy; and concomitant boost RT delivered as 1.8 Gy per day for 30 fractions, with a second fraction of 1.5 Gy delivered more than 6 hours after the first fraction during the last 12 days of treatment for a total dose of 72 Gy. At least 50–54 Gy was to be delivered

to the uninvolved nodal areas of the neck. Grossly involved neck nodes could receive the reduced gross disease dose of 60 Gy if a neck dissection was planned after RT. The median duration of locoregional control (primary endpoint) was 24.4 months among patients treated with cetuximab plus RT and 14.9 months among those given RT alone (hazard ratio [HR] for locoregional progression or death: 0.68; $P = 0.005$). RT plus cetuximab significantly prolonged progression-free survival (PFS) (HR for disease progression or death: 0.70; $P = 0.006$). Median OS for patients treated with cetuximab and RT was 49.0 months (95% confidence interval [CI]: 32.8–69.5) versus 29.3 months (95% CI: 20.6–41.4) in the RT alone group (HR: 0.73; 95% CI: 0.56–0.95; $P = 0.018$). The 5-year OS rate was 45.6% in the cetuximab plus RT group and 36.4% in the RT alone group. For the patients treated with cetuximab, OS was significantly improved in those who experienced an acneiform rash of at least grade 2 severity compared with patients with no rash or grade 1 rash (HR: 0.49; 95% CI: 0.34–0.72; $P = 0.002$).^{27,28}

The efficacy results of an adequately sized Phase III trial comparing cetuximab plus RT with cisplatin-based CRT have not been reported thus far. Therefore cisplatin-based CRT is still widely accepted as the standard treatment for patients with LA-SCCHN, based on the solid results of a large meta-analysis including data on 17,346 patients which showed an absolute survival benefit at 5 years of 6.5% with the concomitant administration of chemotherapy and RT.³¹ In contrast, the benefit of cetuximab has only been demonstrated in one single randomized trial involving 424 patients.^{27,28}

Data from retrospective analyses at least do not support the substitution of cisplatin by cetuximab in association

Table 1 Randomized Phase III trials with cetuximab in SCCHN

Author	Treatment	N	LRC (months)	OS (months)	PFS (months)	ORR
Locoregionally advanced disease						
Bonner et al ^{27,28}	RT	213	14.9*	29.3		64%
	RT + cetuximab	211	24.4*	49		74%
	<i>P</i> -value		0.005	0.018	0.006	0.02
Ang et al ⁴⁵	CRT	448		79.7 [‡]	64.3 ^{*†}	
	CRT + cetuximab	447		82.6 [‡]	63.4 ^{*†}	
	<i>P</i> -value			0.17	0.67	
Recurrent/metastatic disease						
Vermorken et al ⁶⁸	Platinum/5-FU	220		7.4*	3.3	20%
	Platinum/5-FU + cetuximab	222		10.7*	5.6	36%
	<i>P</i> -value			0.04	<0.001	<0.001
Burtneß et al ⁶⁷	Cisplatin + placebo	60		8	2.7*	10%
	Cisplatin + cetuximab	57		9.2	4.2*	26%
	<i>P</i> -value			0.21	0.09	0.03

Notes: *Primary endpoint; [†]2-year PFS rate; [‡]2-year OS rate. Platinum/5-FU: cisplatin (100 mg/m²) or carboplatin (AUC 5) on day 1, followed by 5-FU 1000 mg/m²/day as a continuous infusion day 1–4.

Abbreviations: RT, radiotherapy; CRT, chemoradiation; N, number of patients; LRC, locoregional control; OS, overall survival; PFS, progression-free survival; ORR, overall response rate.

with RT in LA-SCCHN patients who can tolerate CRT. Koutcher et al³² retrospectively compared 174 consecutive, newly diagnosed LA-SCCHN patients treated from March 1, 2006 to April 1, 2008 with RT and either single-agent cisplatin ($n = 125$) or cetuximab ($n = 49$). Patients who received additional concurrent, induction, or adjuvant systemic therapy, weekly cisplatin, prior head and neck RT, or primary surgical resection were excluded. At a median follow-up of 22.5 months for living patients, the 2-year locoregional failure rate was 5.7% for RT with cisplatin and 39.9% for RT with cetuximab ($P < 0.0001$). The 2-year failure-free survival and OS rates were 87.4% versus 44.5% ($P < 0.0001$) and 92.8% versus 66.6% ($P = 0.0003$), respectively, in favor of cisplatin. The results were upheld on multivariate analysis. Late grade 3 or 4 toxicity and feeding tube dependency 9 months after completion of RT were similar in the two groups. Obviously, the results have to be interpreted cautiously because of the retrospective nature of the study and significant differences in patient characteristics; ie, the patients treated with cetuximab being older and having a lower creatinine clearance.

Walsh et al³³ retrospectively reviewed acute toxicity in 34 patients treated with cetuximab and RT at St Luke's Hospital in Dublin, Ireland, comparing it with a matched group of 33 patients treated with cisplatin and RT at the same institution. The cetuximab group experienced significantly more \geq grade 3 oral mucositis ($P = 0.014$) and skin dermatitis ($P = 0.0004$), more $\geq 10\%$ weight loss ($P = 0.03$), and required more enteral feeding ($P = 0.05$).

Chew et al³⁴ retrospectively analyzed 190 files of patients treated at the British Columbia Cancer Agency with RT and either cisplatin 100 mg/m² on day 1, 22, and 43, or weekly cetuximab. Cetuximab treated patients were significantly older (median 63.1 versus 56.5 years). Cisplatin treated patients required more dose reductions and dose delays. Weight loss was higher in cisplatin treated patients. There was a trend to more unexpected admissions and feeding tube insertions with cisplatin. However, there was a difference in locoregional relapse rate in favor of cisplatin (7.6% versus 20.8%; $P = 0.008$).

Shapiro et al³⁵ retrospectively reviewed the records of patients treated at Memorial Sloan Kettering Cancer Center with either concurrent cetuximab, concurrent 5-fluorouracil (FU)/carboplatin, or concurrent high dose cisplatin, and intensity-modulated RT (IMRT). Patients receiving cetuximab or 5-fluorouracil (5-FU)/carboplatin were significantly older, had a lower performance status, a higher Charlson score, a higher T stage, and a worse renal function. After adjusting for risk factors, there was no significant difference

in locoregional relapse-free survival or OS between patients treated with cisplatin or with 5-FU/carboplatin. Late toxicity was worst with the latter regimen. However, cetuximab and RT treatment resulted in a significantly inferior OS and locoregional relapse-free survival.

Pryor et al³⁶ reviewed acute toxicity data from 42 patients receiving cetuximab and RT and a matched cohort of 36 patients receiving CRT or altered fractionation RT. Cetuximab treated patients experienced higher rates of grade 3 or greater cheilitis (26% versus 6%, $P = 0.01$) and anterior stomatitis (38% versus 6%, $P = 0.002$). Overall, these retrospective data do not seem to be in favor of replacing cisplatin and RT by cetuximab and RT when patients are able to tolerate cisplatin and RT.

Cetuximab in combination with CRT

The addition of cetuximab to cisplatin-based CRT in patients with LA-SCCHN was demonstrated to be feasible.^{37–41} Efficacy data in Phase II trials were promising. Concurrent delivery of weekly carboplatin at an area under the curve of 2 mg per mL per minute, (AUC 2), paclitaxel 40 mg/m², cetuximab, and RT (1.8 Gy per day up to 70.2 Gy) was well-tolerated and resulted in encouraging local control and survival rates in a Phase II study enrolling 43 patients.⁴⁰

Merlano et al⁴² treated 45 patients with stage III–IV non-metastatic (M0) SCCHN with RT administered as a single daily fraction (days 1–5 in weeks 2–3, 5–6, and 8–10 up to a dose of 50 Gy/ 2 Gy per fraction) to the clinical target volume, including the tumor, the metastatic lymph nodes, and the draining clinical negative lymphatic pathways. A further boost up to 66–70 Gy was prescribed to the tumor and the metastatic lymph nodes. Chemotherapy consisted of cisplatin 20 mg/m²/day and 5-FU 200 mg/m²/day on days 1–5 of weeks 1, 4, and 7. Cetuximab was delivered weekly on day 1, from weeks 1 to 10. Acute grade 3–4 toxic effects were in the expected range, although grade 3 radiodermatitis occurred in 73% of the patients. The complete response rate (primary endpoint) was 71%.

Kao et al³⁷ treated 33 patients with stage IVa or IVb SCCHN with simultaneous integrated boost IMRT, 5-FU and hydroxyurea, and cetuximab. RT was administered at 1.5 Gy per fraction twice daily, on days 1 through 5 on an alternating week schedule. Macroscopic tumor volume received from 72–73.5 Gy, microscopic positive margins received 66 Gy, high risk microscopic disease received 54–63 Gy, and low risk microscopic disease received 43.2–48 Gy. Systemic treatment consisted of continuous-infusion 5-FU at a dose of 600 mg/m² daily for 120 hours, hydroxyurea 500 mg orally every 12 hours

on days 1 through 5, and cetuximab administered on day 1. No anticancer therapy was administered on days 6 through 14. After a median follow-up of 24 months, the 2-year rates of locoregional control, distant control, disease-free survival, and OS were 83%, 79%, 69%, and 86%, respectively. Grade 3 toxicity consisted of mucositis in 33% of patients, radiation dermatitis in 15% of patients, anemia in 18% of patients, leucopenia in 18% of patients, neutropenia in 12% of patients, and thrombocytopenia in 3% of patients.

Tong et al⁴¹ also conducted a Phase II trial evaluating the tolerability and efficacy of incorporating cetuximab and simultaneous integrated boost IMRT into the 5-FU and hydroxyurea CRT regimen in 65 patients with stage IVa or IVb or high risk stage III SCCHN. At a median follow-up of 28 months, 2-year locoregional control, distant control, PFS, event-free survival, and OS were 79%, 83%, 72%, 63%, and 80%, respectively. p16 expression was associated with a significantly better outcome. The most common grade 3–4 toxicities were mucositis (46%), leukopenia (18%), anemia (18%), and dermatitis (17%).

Seiwert et al³⁹ randomized 110 patients with LA-SCCHN, who had received two cycles of carboplatin, paclitaxel, and cetuximab as induction chemotherapy (ICT), between weekly cetuximab in combination with either 5-FU, hydroxyurea, and hyperfractionated week-on week-off RT (72–74 Gy) (CetuxFHX), or cisplatin accelerated RT with concomitant boost (72 Gy) (CetuxPX). After a median follow-up of 21 months, 2-year OS rates were 89.5% with CetuxFHX and 91.4% with CetuxPX. Two-year PFS rates were 82.3% and 89.7%, respectively ($P = 0.18$). Grade 3 or greater mucositis was present in 91.1% (CetuxFHX) and 94.3% (CetuxPX) of patients; grade 3 or greater dermatitis was present in 82.1% (CetuxFHX) and 50.9% (CetuxPX) of patients. Ninety-five percent of the patients completed therapy, demonstrating that cetuximab can be incorporated safely in both CRT platforms.

Conflicting data have been presented on the feasibility of the combination of RT, cetuximab, and pemetrexed.^{43,44}

Unfortunately, the addition of cetuximab to cisplatin-based CRT does not seem to further improve the outcome. In Radiation Therapy Oncology Group (RTOG) 0522,⁴⁵ 895 evaluable patients with stage III or IV nonmetastatic SCCHN were randomized to receive either CRT (72 Gy in 42 fractions over 6 weeks plus cisplatin 100 mg/m² on days 1 and 22) or the same regimen plus weekly cetuximab. At the time of the third interim analysis, after 337 events and after a median follow-up of 2.4 years for the surviving patients, the conditional power of the trial becoming positive

was below 10%, triggering early reporting. Over 90% of the patients received the planned two doses of cisplatin in both arms. The 2-year PFS (primary endpoint) was 64.3% with CRT and 63.4% with CRT plus cetuximab (HR: 1.05; 95% CI: 0.84–1.29; $P = 0.67$). The 2-year OS rates were 79.7% and 82.6%, respectively (HR: 0.87; 95% CI: 0.66–1.15; $P = 0.17$). The estimated 2-year locoregional relapse rate was 19.8% and 24.5%, respectively ($P = 0.92$). The 2-year distant metastasis rate was 12.0% and 7.6%, respectively ($P = 0.07$). Overall, there was no difference regarding acute grade 3 or 4 toxicities between both arms. However, grade 3 or 4 mucositis (33% in CRT versus 43% in CRT plus cetuximab) and in-field dermatitis (15% in CRT versus 25% in CRT plus cetuximab) was more common in the cetuximab containing arm. Grade 3 or 4 dermatitis outside the radiation field occurred in 19% of the patients treated with cetuximab.

Cetuximab administered adjuvantly

Mesia et al⁴⁶ randomly assigned 91 stage III–IV M0 oropharyngeal tumors to treatment with accelerated concomitant boost RT (69.9 Gy) with cetuximab or the same treatment with the addition of 12 consecutive weeks of cetuximab maintenance therapy. The locoregional control rate at 1 year (primary endpoint) was higher among patients in the experimental arm, treated with cetuximab maintenance (59% versus 47%), although the difference was not statistically significant ($P = 0.25$). Moreover, the increase in locoregional control was not maintained after 2 years of follow-up (44% in both arms), suggesting that an EGFR blockade of limited duration is not sufficient to eliminate minimal residual disease.

Cetuximab and ICT

The role of ICT in the treatment of LA-SCCHN remains controversial.^{47–50} The association of cetuximab and ICT was tested in several Phase II studies and found to be feasible in most.^{51–54} Efficacy data were promising and support further evaluation.

Argiris et al⁵¹ added weekly cetuximab to docetaxel 75 mg/m² on day 1, cisplatin 75 mg/m² on day 1 (TPE), repeated every 21 days for three cycles, followed by RT with concurrent cisplatin 30 mg/m² and cetuximab weekly (XPE), and maintenance cetuximab for 6 months. Of 39 enrolled patients, 36 had stage IV disease and 23 an oropharyngeal primary. Acute toxicities during TPE included neutropenic fever (10%); during XPE, acute toxicities included grade 3 or 4 oral mucositis (54%) and hypomagnesemia (39%). With a median follow-up of 36 months, 3-year PFS and OS rates were 70% and 74%, respectively.

Kies et al⁵² added cetuximab to ICT consisting of six weekly cycles of paclitaxel 135 mg/m² and carboplatin (AUC 2). The most common grade 3 or 4 toxicity was skin rash (45%), followed by neutropenia (21%) without fever. After ICT, 19% of the patients achieved a complete response and 77% achieved a partial response. After ICT, patients underwent risk-based local therapy, which consisted of either RT, CRT, or surgery, based on tumor stage and site at diagnosis. In Eastern Cooperative Oncology Group (ECOG) E2303,⁵³ 63 patients with resectable stage III or IV SCCHN were treated with 6-week cycles of paclitaxel, carboplatin (AUC 2), and cetuximab, followed by CRT (weekly paclitaxel 30 mg/m², carboplatin AUC 1, and cetuximab). If at week 14, after a radiation dose of 50 Gy, tumor was still present on biopsy, salvage surgery was performed. In case of a negative biopsy (9% of the patients), CRT was continued to a total dose of 68–72 Gy. Two-year PFS and OS rates were 82% and 66%, respectively. A local recurrence occurred in 17.5% of the patients.

Adkins et al⁵⁴ treated 30 patients with stage III or IV SCCHN with ICT consisting of nab-paclitaxel 100 mg/m² weekly on days 1, 8, and 15; weekly cetuximab at the SPC recommended dose; cisplatin 75 mg/m² on day 1; and 5-FU 750 mg/m²/day as a continuous infusion on days 1–3 (ACPF). Patients received three 3-week cycles prior to CRT consisting of IMRT 70 Gy in 35 fractions of 2 Gy over 7 weeks and cisplatin 100 mg/m² on days 1, 22, and 43. One patient died during ICT due to a neutropenia-related pneumonia. Three patients could not be treated with cisplatin according to protocol due to toxicity. The complete response rate at the primary tumor site after two cycles of ACPF was 53% and the overall response rate was 100%. Twenty-nine (96%) patients completed three cycles of ACPF, 26 (90%) completed definitive RT per protocol, and 22 of the 27 evaluable patients (81%) received at least two of the three planned doses of cisplatin with RT. The estimated 2-year OS and PFS rates were 84% and 65%, respectively.

The addition of cetuximab to full dose docetaxel/cisplatin/5-FU (TPF) appears to be toxic. The European Organisation for the Research and Treatment of Cancer (EORTC)⁵⁵ treated 47 patients with unresectable stage III or IV M0 SCCHN with four 3-week cycles of European TPF (docetaxel 75 mg/m² and cisplatin 75 mg/m² on day 1, followed by 5-FU 750 mg/m²/day on days 1–5) with prophylactic antibiotics. Cetuximab at the recommended dose was started on day 1 of the first cycle and was to be given weekly until the end of RT. If at least stable disease was observed after four cycles of TPF, patients were randomized to CRT either with weekly cisplatin 40 mg/m² or with weekly carboplatin

(AUC 1.5). Patients with progressive disease on ICT went off the study. The primary endpoint was the feasibility to reach at least 80% of per protocol dose intensity of RT, cisplatin, and cetuximab. The trial was stopped early because of safety concerns. Grade 3–5 events included cardiac events (one patient, grade 3), febrile neutropenia (four patients, one grade 4), infection (four patients, one grade 4), mucositis/stomatitis (four patients, one grade 4), bowel perforation (three patients, grade 4), upper gastrointestinal bleeding (one grade 4), and pulmonary events (four patients \geq grade 4). There were two deaths (one due to unknown cause at day 19 and one due to septic shock at 31 days after the start of treatment).⁵⁵

In a Phase I study⁵⁶ using the American TPF regimen, which consists of three 3-week cycles of docetaxel 75 mg/m² on day 1, cisplatin 100 mg/m² on day 1, and 5-FU 1000 mg/m²/day administered as a continuous infusion on days 1–4, the 5-FU dose had to be reduced to 850 mg/m²/day. The main toxicity was gastrointestinal (mucositis, diarrhea, and enteritis).

Jordan et al⁵⁷ treated 152 SCCHN patients with T3 or T4 tumors with three 3-week cycles of TPF (docetaxel 75 mg/m² on day 1, cisplatin 35 mg/m² on days 1 and 2, and 5-FU 750 mg/m²/day, as a continuous infusion on days 1–5, with pegfilgrastim support) followed by CRT (63 Gy in 35 fractions of 1.8 Gy over 7 weeks and weekly cisplatin, 40 mg/m²) plus weekly cetuximab. The complete response rate in the 142 patients who were evaluated after the completion of therapy was 57%. Grade 3 or 4 toxicities occurred in 34 of the 142 patients (24%). In 15 patients, CRT had to be interrupted due to dermatitis.

An attractive approach might be the sequential administration of ICT prior to RT with cetuximab. Ghi et al⁵⁸ randomized 420 patients to RT either with two cycles of cisplatin/5-FU during weeks 1 and 6 of radiotherapy, or with weekly cetuximab, or to the same treatment (RT either with two cycles of cisplatin/5-FU, or with weekly cetuximab) preceded by 3-weekly cycles of TPF (docetaxel 75 mg/m² and cisplatin 80 mg/m² on day 1, followed by 5-FU 800 mg/m²/day as continuous infusion for 96 hours), according to a 2 \times 2 factorial design. No advantage for cetuximab with RT over CRT was observed regarding grade 3–4 in-field toxicities and feasibility. Treatment compliance was superior with CRT.

In the TREMPIN Phase II trial,⁵⁹ 110 patients with SCC of the larynx or hypopharynx suitable for total laryngectomy were treated with three 3-week cycles of TPF (docetaxel 75 mg/m² and cisplatin 75 mg/m² on day 1, followed by 5-FU 750 mg/m²/day on days 1–5). Patients who obtained at least a partial response (82% of the patients) were randomized to receive RT (70 Gy in 35 fractions over 7 weeks) either with

cisplatin 100 mg/m² on days 1, 22, and 43, or with weekly cetuximab. Treatment compliance was better in the cetuximab arm with 71% of the patients receiving all planned cetuximab administrations versus 42% of the patients receiving the planned three cycles of cisplatin. There was no difference in grade 3 or 4 mucosal toxicity, but grade 3 or 4 in-field dermatitis was more frequently observed with cetuximab (57% versus 26%; $P < 0.001$). Grade 1 renal dysfunction at last evaluation was observed in 22.4% of the patients treated with cisplatin. The larynx preservation rate 3 months after treatment (primary endpoint) was 95% with cisplatin versus 93% with cetuximab. The locoregional failure rate after a median follow-up of 36 months was 11.7% with cisplatin and 21.4% with cetuximab. However, more salvage laryngectomies were performed in the cetuximab arm, resulting in a similar ultimate locoregional failure rate in the two arms (10% with cisplatin versus 8.9% with cetuximab). The 2-year laryngoesophageal dysfunction-free survival was 79% with cisplatin versus 71% with cetuximab ($P = 0.3$).⁵⁹

Keil et al⁶⁰ treated 49 LA-SCCHN patients with three 3-weekly cycles of TPF (docetaxel 75 mg/m² day and cisplatin 75 mg/m² day 1, and infusional 5-FU 750 mg/m²/day on days 1–5) followed by RT plus cetuximab at the recommended dose. After completion of ICT, 44 of 49 patients received RT plus cetuximab. Three months after therapy completion, tumor response was observed in 33 patients and after 2 years, 25 patients still had a complete response. The most common grade 4 toxicity during the whole treatment period was dermatitis (30%), followed by mucositis (27%), and neutropenia (17%) without fever. One toxic related death was observed during ICT. The 2-year PFS rate was 59% and the 2-year OS rate was 63%.

Reirradiation

Promising efficacy data with acceptable toxicity were reported with reirradiation and cetuximab in a small series of studies of patients with locoregional recurrent and inoperable SCCHN.^{61–64} Balermipas et al⁶² treated 18 patients with an inoperable recurrence of SCCHN after prior adjuvant or definitive RT and simultaneous or sequential cisplatin-based chemotherapy for primary SCCHN, with cetuximab and RT (1.8 Gy/fraction/day over 5–6 weeks resulting in a median total dose of 50.4 Gy). Overall response rate was 47%. The median OS and PFS were 8.4 months and 7.3 months, respectively. The OS rate was 44% at 1 year, with a 1-year local control rate of 33%.

Comet et al⁶³ treated 40 patients with an inoperable recurrent, or new primary tumor, in a previously irradiated area

with 36 Gy in six fractions to the 85% isodose line covering 95% of the planning target volume. Fifteen patients received concomitant cetuximab without major additional toxicity.

Akmansu et al⁶¹ reirradiated nine patients with doses ranging between 20–70 Gy with concomitant cetuximab. During RT, four patients had grade 2 and five patients had grade 3 skin toxicity.

A single institution matched case–control study comparing two groups of 35 patients each, treated with stereotactic body reirradiation therapy alone or with weekly cetuximab infusion during RT, suggests an OS benefit with the addition of cetuximab (24.5 months versus 14.8 months), without a significant increase in grade 3 or 4 toxicities.⁶⁵ Concomitant cetuximab with reirradiation seems to be a reasonable approach for unresectable recurrent SCCHN and should be tested in a prospective randomized trial.⁶⁵

Cetuximab with postoperative CRT

In a Phase II trial conducted by RTOG,⁶⁶ patients with high-risk pathologic features, were randomized to receive a combination of RT (60 Gy) and cetuximab plus either weekly cisplatin 30 mg/m² (arm A) or weekly docetaxel 15 mg/m² (arm B). Treatment-related toxicity was moderate and comparable between the treatment arms. With a median follow-up of 2.5 years, 2-year OS rates were 69% (95% CI, 60%–79%) and 79% (95% CI, 71%–87%) for arms A and B, respectively; 2-year disease-free survival rates were 57% (95% CI, 47%–67%) and 66% (95% CI, 56%–75%), respectively. The study suggests that further studies with taxane-based chemo-bio-radiation with cetuximab are warranted.

R/M-SCCHN

First line R/M-SCCHN

ECOG⁶⁷ randomly assigned 117 evaluable R/M-SCCHN patients to receive cisplatin 100 mg/m² every 4 weeks, with weekly cetuximab (arm A) or placebo (arm B). Median PFS was 2.7 months for arm B and 4.2 months for arm A. The HR for progression (primary endpoint) of arm A versus arm B was 0.78 (95% CI: 0.54–1.12; $P = 0.09$). The 22% reduction in risk of progression was not significant in a study powered to detect a 50% reduction in hazard rates. To detect a 2-month prolongation of median PFS from 2.7 months with 90% power, approximately 173 patients would have been required, rather than the 123 enrolled in the study. Median OS was 8.0 months for arm B and 9.2 months for arm A ($P = 0.21$). The objective response rate was 26% for arm A and 10% for arm B ($P = 0.03$). Although the ECOG study failed to meet its primary endpoint, the results nevertheless were in line

with the outcome in the Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer (EXTREME) trial, which indeed met its primary endpoint.⁶⁸ In that trial, Vermorken et al⁶⁸ randomized 442 patients with previously untreated R/M-SCCHN to receive cisplatin (100 mg/m²) or carboplatin (AUC 5) on day 1, followed by 5-FU 1000 mg/m²/day as a continuous infusion for 4 days, every 3 weeks for a maximum of six cycles or the same chemotherapy plus cetuximab at the SPC recommended dose. Patients with at least stable disease who received chemotherapy plus cetuximab continued to receive cetuximab until disease progression or unacceptable toxic effects, whichever occurred first. The median OS was 7.4 months in the chemotherapy-alone group and 10.1 months in the group that received chemotherapy plus cetuximab (HR for death, 0.80; 95% CI: 0.64–0.99; $P=0.04$). The addition of cetuximab prolonged the median PFS from 3.3 months to 5.6 months (HR for progression, 0.54; 95% CI: 0.43 to 0.67; $P < 0.001$). The response rate was 20% (95% CI: 15–25) and 36% (95% CI: 29–42) ($P < 0.001$), respectively. Neither the amount of EGFR expression nor the tumor EGFR copy number were a predictive marker for any benefit from the addition of cetuximab.⁶⁹

Taxanes are among the most active cytotoxic agents in SCCHN.⁷⁰ Promising results were observed in non-randomized Phase II trials when cetuximab was added to a taxane, either as a single agent or in combination with cisplatin.^{71–74} Hitt et al⁷¹ enrolled 46 patients who were unlikely to benefit from platinum-based chemotherapy in a Phase II trial combining weekly paclitaxel 80 mg/m² and cetuximab at the recommended dose. The overall response rate was 54% (95% CI: 39%–69%) (complete response rate: 22%, disease control rate: 80%). Median PFS and OS were 4.2 months (95% CI: 2.9–5.5 months) and 8.1 months (95% CI: 6.6–9.6 months), respectively. Common grade 3 or 4 adverse events were acne-like rash (24%), asthenia (17%), and neutropenia (13%). The development of acne-like rash was associated with tumor response. Patients who had not previously received chemotherapy as part of a multimodal treatment of locally advanced disease had a significantly better tumor response ($P=0.020$) than those who had received prior chemotherapy.

In the GORTEC 2008-3 trial,⁷² 54 patients with previously untreated R/M-SCCHN were treated with weekly cetuximab and four 3-week cycles of docetaxel 75 mg/m² and cisplatin 75 mg/m², followed by maintenance cetuximab until disease progression or unacceptable toxicity. Toxicity was manageable with granulocyte colony-stimulating factor support. The overall response rate (primary endpoint) was 54%. Median PFS and OS were 7.1 months and 15.3 months, respectively.

These data compare favorably with the results observed with cisplatin, 5-FU, and cetuximab in the EXTREME trial.

Clark et al⁷³ conducted a Phase I pilot study combining oxaliplatin, 5-FU, and cetuximab in patients with untreated R/M-SCCHN. Oxaliplatin 100 mg/m² on day 1, 5-FU 750 mg/m²/day over 96 hours beginning on day 1, and weekly cetuximab every 21 days was determined as the maximum tolerated dose. However, observed responses were short-lived.

Vermorken et al⁷⁴ treated 60 R/M-SCCHN patients who had received no more than one prior systemic therapy for LA-SCCHN with pemetrexed 500 mg/m² with vitamin supplementation and cisplatin 75 mg/m² on day 1, administered every 3 weeks, and weekly cetuximab. Median PFS was 4.4 months (95% CI: 3.6–5.4 months) and median OS was 9.7 months (95% CI: 6.5–13.1 months). The overall response rate was 29.3% (95% CI: 18.1%–42.7%). Drug-related grade 3 or 4 toxicities included neutropenia (33.4%), fatigue (24.2%), anorexia (12.1%), and infection (10.6%). There were five drug-related deaths (7.6%) on treatment. The authors concluded that this regimen could not be seen as a favorable alternative for the presently standard EXTREME PFE (cisplatin 100 mg/m² on day 1, followed by 5-FU 1000 mg/m²/day day 1–4, every 3 weeks plus cetuximab) regimen.

Pretreated R/M-SCCHN

The role of cetuximab in platinum-refractory or platinum-resistant disease was evaluated in Phase II trials which showed similar overall response rates (10%–13%), irrespective of whether cetuximab was administered as a single agent or in association with a platinum compound.^{75–78} The median OS of around 6 months compares favorably to the median OS observed in platinum-refractory historical controls.⁷⁹ Therefore, single agent cetuximab seems to be a valuable option for patients with R/M-SCCHN who progressed on platinum-based chemotherapy.

Fury et al⁸⁰ conducted a multicenter randomized prospective Phase II study in patients who had received no more than two prior cytotoxic chemotherapy regimens for R/M-SCCHN. Patients were treated with cetuximab every 2 weeks either at 500 mg/m² (Group A) or 750 mg/m² (Group B). The primary end point was response rate. Confirmed partial response rates were 11% for Group A and 8% for Group B. Median PFS and median OS were similar for both groups (PFS: 2.2 months and 2.0 months; OS: 7.0 months and 9.4 months for Groups A and B, respectively). The most common cetuximab-related adverse events (all grades) included rash, fatigue, and hypomagnesemia. Cetuximab 500 mg/m² administered every 2 weeks, although not directly compared

with a 250 mg/m² weekly dose, seems to have similar efficacy as conventional dosing for patients with R/M-SCCHN and might be a convenient alternative. Escalating the dose to 750 mg/m² every 2 weeks clearly does not seem to offer a therapeutic advantage.

Massa et al⁸¹ combined vinorelbine on day 1, 8, and 15 every 28 days, and weekly cetuximab in 24 patients with R/M-SCCHN progressing after at least two chemotherapy regimens. Overall response rate and disease control rate was 17% and 69.5%, respectively. Median PFS was 5.2 months. The regimen was well tolerated.

Knoedler et al⁸² treated 84 platinum-pretreated R/M-SCCHN patients with weekly cetuximab and docetaxel 35 mg/m² (3 weeks out of 4). The observed partial response rate and disease control rate were 12% and 39%, respectively. The response rate was independent of previous platinum sensitivity. High expression of EGFR variant III and the EGFR ligand amphiregulin was associated with a worse outcome.⁸³

Cetuximab in combination with other targeted agents

Combinations of targeted agents should be explored with caution as illustrated by the outcome of a Phase I trial conducted by Argiris et al.⁸⁴ In that study of seven SCCHN patients, the addition of bortezomib to cetuximab and radiation therapy led to unexpected early disease progression. Bortezomib antagonized cetuximab- and radiation-induced cytotoxicity, degradation of EGFR, and enhanced pro-survival signal pathway activation in SCCHN tumor biopsies. Argiris et al⁸⁵ enrolled 46 patients with R/M-SCCHN in a Phase II trial combining weekly cetuximab at the recommended dose and bevacizumab 15 mg/kg administered on day 1 every 3 weeks. A potent reduction in tumor vascularization was observed. The objective response rate was 16% and the disease control rate 73%. The median PFS and OS were 2.8 months and 7.5 months, respectively. Grade 3–4 adverse events were as expected and occurred in less than 10% of patients. These promising data support further evaluation of the combination.

Safety and tolerability

The most common adverse events with cetuximab administered as a single agent in SCCHN patients are summarized in Table 2. The vast majority of cetuximab-related adverse events are grade 1 or 2.⁷⁷

In the pivotal randomized Phase III trial conducted by Bonner et al,²⁷ cetuximab did not exacerbate the common adverse events of RT in SCCHN, including mucositis,

Table 2 Adverse events with second line single agent cetuximab in squamous cell carcinoma of the head and neck

	All grades	Grade 3–4
Dermatological		
Rash	49%	1%
Acne	26%	0%
Dry skin	14%	0%
Nail disorder	16%	0%
Other		
Fever	14%	1%
Nausea	13%	1%
Vomiting	11%	2%
Dyspnea	5%	4%
Infusion-related reactions	6%	1%

xerostomia, dysphagia, pain, weight loss, and performance-status deterioration. With the exception of acneiform rash and infusion-related events, the incidence rates of grade 3 to 5 adverse events were similar in the two treatment groups. Adverse events occurring more commonly with the combination of cetuximab and RT than with RT alone in that randomized trial are summarized in Table 3.²⁷

However, after the introduction of concurrent RT and cetuximab in routine clinical practice, higher incidences of severe radiation dermatitis than observed in the Bonner trial²⁷ were reported.^{33,36,86–97} Potential explanations include the use of different toxicity grading systems and publication bias, but also differences in radiation dose and techniques.⁹⁸ Detailed consensus guidelines, including general and grade-specific measures, for the management of radiation dermatitis in patients receiving RT plus EGFR inhibitors were published in 2008⁹⁹ and updated in 2011.¹⁰⁰

In the EXTREME trial,⁶⁸ the safety profile of the study treatment was consistent with what could be expected with the agents used. For the most part, there was no significant difference in the overall incidence of grade 3 or 4 adverse events between the groups. However, there were nine cases of sepsis (4%) in the cetuximab group, as compared with one case (<1%) in the chemotherapy-alone group ($P = 0.02$), and there were eleven cases (5%) of severe hypomagnesemia in the cetuximab group, as compared with three cases (1%) in the chemotherapy-alone group ($P = 0.05$). Grade 3 skin reactions occurred in 9% and <1% of the patients, respectively ($P < 0.001$).

In the ECOG trial,⁶⁷ the addition of cetuximab to cisplatin was associated with a statistically significant increase of grade 3 or 4 adverse events (90% versus 73%; $P = 0.02$). Neutropenia (30% versus 14%; $P = 0.04$), overall grade 3 or 4 hematological toxicity (36% versus 18%; $P = 0.04$), and hypomagnesemia

Table 3 Adverse events occurring more frequently with the addition of cetuximab to radiotherapy

	All grades			Grade 3–5		
	Radiotherapy	Radiotherapy + cetuximab	P-value	Radiotherapy	Radiotherapy + cetuximab	P-value
Acneiform rash	10%	87%	<0.001	1%	17%	<0.001
Weight loss	72%	84%	0.005			
Nausea	37%	49%	0.02			
Fever	13%	26%	0.001			
Headache	8%	19%	0.001			
Pruritus	4%	16%	<0.001			
Infusion reaction	2%	15%	<0.001	0%	3%	0.01
Chills	5%	11%	0.03			

Note:

(14% versus 0%; $P = 0.006$) were more common in the cetuximab containing arm than with single agent cisplatin.

Data from the French pharmacovigilance database analysis suggest that (severe) infusion reactions were more common in SCCHN than in colorectal cancer patients,¹⁰¹ confirming an earlier report from North Carolina.¹⁰²

Patient and society focused perspectives

Quality of life (QoL)

Adding cetuximab to platinum/5-FU does not adversely affect the QoL of patients with R/M-SCCHN.¹⁰³ The EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) and QLQ-Head and Neck 35 (QLQ-H&N35) modules were used to assess QoL of the patients included in the EXTREME trial.¹⁰³ For QLQ-C30, mean scores at the end of the third cycle and sixth month for platinum/5-FU plus cetuximab were not significantly worse than those for platinum/5-FU alone. Pattern-mixture analysis demonstrated a significant improvement in the global health status/QoL score in the cetuximab arm ($P = 0.0415$) but no treatment differences in the social functioning scale. For QLQ-H&N35, the mean score for the cetuximab arm was not significantly worse than that for the chemotherapy arm for all symptom scales at all post-baseline visits. At the third cycle, some symptom scores significantly favored the cetuximab arm (pain, swallowing, speech problems, and social eating).¹⁰³

QoL using the EORTC QLQ-C30 and QLQ-H&N35 was also assessed at baseline, week 4, and at months 4, 8, and 12 post-baseline in the Phase III trial in patients treated with RT with or without cetuximab.^{27,104} Compliance with completion of QoL questionnaires was high in both arms. QoL worsened during treatment and improved after cessation of treatment, reaching baseline levels at 12 months. There were no significant differences in QoL scores between the treatment arms. This was particularly notable for global health status/

QoL, social functioning, social eating, and social contact. Pretreatment global health status/QoL was identified as a significant prognostic variable in these patients.¹⁰⁴

Cost effectiveness

The cost effectiveness of cetuximab in the treatment of SCCHN has been evaluated for several health care systems. Overall, the incremental cost effectiveness ratio (ICER) of the addition of cetuximab to RT falls within the range which is generally considered acceptable in the respective countries that were studied. In contrast, the ICER of the addition of cetuximab to chemotherapy in R/M-SCCHN exceeds the commonly accepted thresholds. An evidence review group (ERG)¹⁰⁵ evaluated the cost effectiveness of cetuximab plus RT for the treatment of LA-SCCHN considered inappropriate for chemoradiotherapy but appropriate for RT. The evaluation was based upon the evidence submitted by Merck Pharmaceuticals to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The results suggested that cetuximab plus RT was cost effective compared with RT alone under a broad range of different assumptions on the basis of a cost effectiveness threshold of £20,000. In the base case, the ICER of cetuximab plus RT compared with RT alone in the treatment of patients with LA-SCCHN was £6390 per additional quality adjusted life year gained (QALY).¹⁰⁵

Brown et al¹⁰⁶ estimated the cost effectiveness of cetuximab in combination with RT compared to RT alone for the treatment of LA-SCCHN for five countries (Belgium, France, Italy, Switzerland, and the United Kingdom). Country-specific costs of care from official sources were applied in the analysis for each country. In the base-case analysis, the ICER/QALY by ICER and state xxx dollars/qaly for patients receiving RT with cetuximab compared to RT alone among all countries was in the range of €7538 to €10,836. Sensitivity analysis showed the results to be robust.¹⁰⁶ In Taiwan, the ICER/QALY by ICER and

state xxx dollars/qaly for patients receiving RT in combination with cetuximab compared with RT alone was estimated at US\$36,992.¹⁰⁷ The Liverpool Reviews and Implementation Group ERG evaluated the cost effectiveness of cetuximab for R/M-SCCHN based upon a review of the manufacturer's submission to the NICE as part of the single technology appraisal process.¹⁰⁸ The manufacturer reported an ICER/Qaly by ICER and state xxx dollars/qaly of £121,367 and an incremental cost per life-year gained of £92,226. The ERG was confident that neither model assumptions nor parameter values were likely to introduce sufficient uncertainty to result in cetuximab plus chemotherapy being cost effective for this group of patients.¹⁰⁸ According to Hannouf et al,¹⁰⁹ the addition of cetuximab to standard platinum-based chemotherapy in first line treatment of patients with R/M-SCCHN has an ICER that exceeds 100,000 CAD per QALY gained from the perspective of the Canadian public healthcare system, which again is not considered to be cost effective.

Conclusion and place in therapy

The addition of cetuximab to RT improves locoregional control and OS when compared to RT alone in patients with LA-SCCHN. However, the addition of cetuximab to CRT, although feasible, does not lead to a further improvement.

Moreover, efficacy results of an adequately sized Phase III trial comparing cetuximab plus RT with cisplatin-based CRT have not been reported thus far. Therefore, CRT remains the standard of care for patients with LA-SCCHN for whom surgery is not considered the optimal treatment, provided they can tolerate CRT.

The addition of cetuximab to platinum-based chemotherapy prolongs survival in patients with R/M-SCCHN. The combination of a platinum-based regimen and cetuximab should be considered as the standard first line regimen for patients who can tolerate this treatment.

Single agent cetuximab is a valuable option for patients with R/M-SCCHN who progressed on platinum-based chemotherapy.

Disclosure

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