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Cetuximab for Squamous Cell Carcinoma of the Head and Neck

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Abstract

Context: Treatment outcome for locally advanced squamous cell carcinoma of the head and neck is poor. Recently, anti-epidermal growth factor monoclonal antibodies, such as cetuximab have been used to improve outcome.
Evidence Acquisition: Medline, EMBASE, and SCOPUS were searched to identify published studies that evaluated cetuximab for loco regionally advanced and metastatic/recurrent squamous cell carcinoma of head and neck. Only published studies in English between 1990 and 2016 were included.
Results: Cetuximab may be administered concomitantly with radiation alone or in combination with chemotherapy during the induction phase of sequential modalities. Also, it has been used in combination with chemotherapy as first line or second line for treatment of metastatic/recurrent patients.
Conclusions: Cetuximab can be incorporated at some points in the course of treatment of patients with squamous cell carcinoma of the head and neck. The best protocols and the appropriate patients remain to be defined.

Keywords: Squamous Cell Carcinoma, Cetuximab, Anti-Epidermal Growth Factor Receptor, Radiotherapy, Chemotherapy

1. Context

Despite the current advances in treatment of locally advanced squamous cell carcinoma of head and neck (HNSCC), its prognosis is very poor (1). Adding chemotherapy to the conventional treatment has been used to improve survival, reduce metastasis, and increase organ preservation. Chemotherapy is used in 3 different settings: induction therapy, concomitant chemo-radiotherapy, and sequential treatment, which consists induction chemotherapy followed by concomitant chemo-radiotherapy (1-4). Recently, the incorporation of cetuximab to induction and/or concomitant phase of chemoradiation has been an area of interest (5-8). Cetuximab is an IgG1 monoclonal antibody against the ligand binding domain of EGFR and it is currently the only US Food and Drug Administration approved EGFR inhibitor for the treatment of HNSCC. The EGFR, a member of the ErbB family of receptor tyearosine kinases, is overexpressed in up to 90% of HNSCC (5, 9). In this article, the studies that evaluated the role of cetuximab for locally advanced and metastatic /recurrent HNSCC will be reviewed.

2. Evidence Acquisition

Medline, EMBASE, and SCOPUS were searched to identify published studies evaluating cetuximab for loco regionally advanced and metastatic/recurrent squamous cell carcinoma of head and neck. Only published studies in English between 1990 and 2016 were included. High quality retrospective and prospective studies were selected. Published review articles also were used. The studies can be categorized in 5 groups:

2.1. Radiation Concomitant with Cetuximab Versus Radiotherapy Alone (Table 1)

The only randomized trial that compared concomitant cetuximab with radiotherapy alone was conducted by Bonner et al. (10). The 5-year overall survival was significantly improved with the addition of cetuximab to radiation (45.6% versus 36.4%, P = 0.018).

2.2. Radiation Concomitant with Chemotherapy Versus Concomitant with Cetuximab (Table 1)

There are no phase III trials comparing concurrent chemoradiation and bioradiotherapy. The only randomized phase II trial was conducted by Magrini et al. to compare radiotherapy with concomitant cisplatin versus concomitant cetuximab. Cisplatin was given weekly

Table 1. Summary of Studies Evaluated Concomitant Cetuximab with Radiation

Authors	Protocol	Outcome	Toxicity
Bonner et al. (10)	RT vs. RT + Weekly CET	LRC-PFS and OS improved with CET	Higher acneiform rash with CET
Magrini et al. (11)	RT concomitant with CTX vs. CET	Similar LRC and OS	Higher cutaneous toxicity with CET, Higher hematology, renal and gastro intestinal toxicity with CTX
Koutcher L, et al. (12)	RT concomitant with CTX vs. CET	The 2-year PFS and OS was better with CTX	Similar high grade toxicity
Strom T.J et al. (13)	RT concomitant with CTX vs. CET	No difference in OS, LRC and DCR	Not assigned
Riaz N et al. (14)	RT concomitant with CTX vs. CET	The 3-year OS and LRC were inferior for CET	Not assigned
Levy A, et al. (15)	RT concomitant with CTX vs. CET	No difference in 2-year OS, LRC were inferior for CET	Higher mucositis and dermatitis with CET, Higher digestive toxicity with CTX
Ley J, et al. (16)	RT concomitant with CTX vs. CET	Better OS with CTX	76%Aceneiform rash with CET
Tang C et al. (17)	CET+ RTX, CTX+ RTX or: CTX+CET+RTX	OS and relapse rate were better for CTX+RTX	Not assigned
Shapiro et al. (18)	IMRT concomitant with CTX or CET	The 4-year OS and LRC were inferior for CET	Lower late toxicity with CET compared with CTX
Huang J et al. (19)	IMRT concomitant with CTX or CET	No difference in LRC and DCR, OS was better with CTX	Not assigned

Abbreviations: CET, Cetuximab; CTX, Chemotherapy; LRC, Locoregional Control; OS, Overall Survival; PFS, Progression Free Survival; RT, Radiotherapy.

with 40 mg/m^2 dose and cetuximab was prescribed with 400mg/m^2 loading dose followed by 250 mg/m^2 weekly concomitant with radiotherapy. Loco regional control, patterns of failure, and survivals were similar between the treatment arms. Hematologic, renal, and gastro intestinal toxicities were more frequent in the cisplatin arm. Skin toxicity and the need for nutritional support were seen more frequently in the cetuximab arm. Treatment related death occurred in 4 and 1 patients in cisplatin and cetuximab arm, respectively. The authors concluded that appropriate patient selection should be done for using concomitant cetuximab with radiation (11). There are several retrospective studies that have been constructed to compare chemotherapy versus cetuximab in concomitant regimen with radiation. In one of these studies conducted by Koutcher L et al., overall survival rate and the 2-year locoregional failure rate were better for chemotherapy arm (92.8% vs. 66.6%, P = 0.0003 and 5.7% vs. 39.9%, P < 0.0001, respectively) (12). In a study conducted by Strom T.J et al., no difference was seen in loco regional control (87% vs. 89%), or overall survival (91% vs. 90%) between patients treated with concurrent weekly cisplatin or cetuximab (13). In a study designed by Riaz N et al., the 3-year loco-regional failure and overall survival for cisplatin versus cetuximab concomitant treatment were 5.7% versus 40.2% (P < 0.0001) and 90.0% versus 56.6% (P < 0.0001), respectively (14).In another study conducted by Levy A et al., concurrent cisplatin or cetuximab with radiation was compared. The 2-year actuarial OS was not different between cisplatin and cetuximab groups (75% and 63%, respectively, P = 0.2). The 2 -year locoregional control was better for cisplatin compared with cetuximab (76% and 61%, respectively, P = 0.004) (15). Another retrospective study was done by Ley J et al. Disease specific survival at 3 years was 83% with concomitant chemoradiation and 31% with concomitant bioradiation (P = 0.01) (16). In a retrospective study conducted by Tang C et al., platinum-based concurrent chemoradiotherapy exhibited significantly better freedom from relapse and overall survival compared with bioradiotherapy (17). Two retrospective studies have been conducted to evaluate concurrent cetuximab with intensity-modulated radiation therapy (IMRT). Shapiro et al. compared concurrent cetuximab versus 5-fluorouracil/carboplatin or high dose cisplatin with IMRT. The 4-year overall survival for cisplatin, 5 FU/carboplatin and cetuximab group was 86.9%, 70.2%, and 40.9%, respectively (P < 0.0001) (18). In another study, IMRT with cetuximab compared with chemotherapy had significantly worse overall survival (58 vs. 83 %, P = 0.001) (19). A systematic review and meta-analysis was done by Petrelli F et al. to evaluate concomitant platinum-based chemotherapy or cetuximab with radiotherapy for locally advanced HNSCC. Platinum-based chemoradiation was associated with a better overall survival and progression free survival compared to bioradiotherapy (20).

2.3. Adding Cetuximab to Concomitant Chemoradiation (Table 2)

A phase II study of combination cetuximab in combination with cisplatin and radiotherapy in unresectable patients was conducted by Egolf A et al. The 2-year progression free survival and overall survival were 47% and 66%,

Table 2. Summary of Studies Evaluated the Addition of Cetuximab to Concomitant Chemoradiation

Authors	Protocol	Outcome	Toxicity
Egloff A.M et al. (21)	CET + CTX + RTX	2-year OS: 66% better OS for HPV+	High grade toxicity: Mucositis: 55%, Neutropenia: 26%
Pfister D.G et al. (22)	RTX + CTX + CET	The 3- year OS: 76%	Toxicity was typical of that expected with concurrent chemoradiation 2 treatment death
Ang K.K et al. (23)	RT + CTX with or without CET	No deferens in 3-year OS	More acute toxicity with cetuximab

Abbreviations: CET, Cetuximab, CTX, Chemotherapy, OS, Overall Survival; RTX, Radiotherapy.

respectively. Human papiloma virus positive patients had significantly longer survival (21). In another phase II study conducted by Pfister et al., cetuximab with concomitant chemoradiation showed the 3-year overall survival, progression free survival, and locoregional control rate of 76%, 56%, and 71%, respectively. Two treatments related death was occurred. Due to adverse treatment effects, they concluded that this regimen should not recommend outside of the clinical trial (22). In one phase III trial conducted by RTOG, the patients with locally advanced HNSCC were randomly assigned to receive accelerated radiotherapy plus cisplatin with or without cetuximab. Adding cetuximab resulted in more frequent interruption in treatment and more acute toxicity. No differences were seen between 2 arms in local recurrence, 3 -year overall survival, or metastasis rate. It was recommended that adding cetuximab to cisplatin-based chemotherapy should not be prescribed routinely (23).

2.4. Sequential Modalities (Table 3)

The addition of cetuximab to induction or concomitant phase of sequential chemoradiation protocols has been studied.

A phase II trial was conducted by Kies et al. to evaluate the combination of cetuximab with chemotherapy for induction treatment followed by local therapy in HNSCC. Induction chemotherapy consisted of 6 weekly cycles of paclitaxel 135 mg/m^2 and carboplatin (area under the curve: 2, with cetuximab 400 mg/m^2 in week 1 and, then, 250 mg/m^2. It proceed to definitive local therapy with radiation (for T1-2), concomitant chemoradiation (for T3-4), or surgery (for oral cavity). Cisplatin (100 mg/m^2) was administered on days 1 and 22 of radiation. Weekly carboplatin was administered in the patients not suitable for cisplatin. After chemoradiation, surgery was recommended for residual disease. The 3-year progression-free survival and overall survival rates were 87% and 91%, respectively. High grade skin rash and neutropenia occurred in 45 and 22% of the patients, respectively. They concluded that induction therapy with cetuximab/paclitaxel and carboplatin followed by risk-based local therapy seem to be feasible, effective, and well tolerated (24).

In another phase II study conducted by Mesia R et al., unresectable HNSCC were selected to receive induction therapy consisted of four 21-day cycles of TPF (docetaxel, 75 mg/m^2 day 1; cisplatin, 75 mg/m^2 day 1; 5-fluorouracil 750 mg/^{m2} day 1 - 5) and cetuximab, 250 mg/m^2 weekly (loading dose of 400 mg/m^2). Induction therapy was followed by radiation and weekly cetuximab. Accelerated radiation therapy with concomitant boost (69.9 Gy) was used. Objective response rate after induction was 86%. The 2-year loco regional control rate was 57%. The median overall survival was 40.7 months. The most common high grade toxicities were neutropenia (24%), neutropenic fever (24%), and diarrhea (20%). Three treatments related death occurred. The conclusion was that integration of cetuximab into induction regimens significantly enhances chemotherapy efficacy. But, toxicity rate does not allow to recommend this schedule at the current dose (25).

A phase II ECOG- ACRIN trial was designed to evaluate the efficacy and safety of induction cetuximab, paclitaxel, and carboplatin followed by chemoradiation for locally advanced HNSCC. Induction chemotherapy consisted of cetuximab (400 mg/m^2 IV day 1, then 250 mg/m^2/week); paclitaxel (90 mg/m^2) and carboplatin (AUC = 2) weekly for 6 weeks. Concurrent chemoradiation was started in week 9. Weekly cetuximab (250 mg/m^2/week), paclitaxel (30 mg/m^2/week) and carboplatin (AUC 1) were administered throughout radiation. After radiation, the patients were to receive maintenance cetuximab for 6 months. Overall survival was 78% at 3 years. Disease progression occurred in 37% of the patients. No treatment related death occurred. The most common toxicity was hematologic. They concluded that sequentional modality containing cetuximab is safe with high response rate and promising survival (26).

Another phase II study was done by Argiris et al. Locally advanced HNSCC were treated with 3 cycles of docetaxel (75 mg/m^2 day 1), cisplatin(75 mg/m^2 day 1), and cetuximab (loading dose of 400 mg/m^2 ,then 250 mg/m^2 weekly). It was followed by radiotherapy with concurrent weekly cisplatin (30 mg/m^2) and cetuximab .Maintenance cetuximab was prescribed for 6 months. The 3-year progression-free

Table 3. Summary of Studies Evaluated Cetuximab in Sequential Protocols

Authors	Protocol	Outcome	Toxicity
Kies MS, et al. (24)	CET + CTX followed by chemoradiation or radiation	Response to induction: 19% CR and 77% PR, the 3-year OS: 91%	High grade toxicity: Skin 45%, Neutropenia: 21%
Mesia R, et al. (25)	CET + CTX followed by RT + CET	Response to induction: 24% CR and 86% PR, 2-year LRC: 57%	Treatment death: 6%, Neutropenic fever: 24%
Wanebo HJ, et al. (ECOG-ACRIN) (26)	CET + CTX followed by RT + CET + CTX	Pathologic CR: 90%, 3-year OS: 78%	No toxicity death, Grade 3: 43 patients, Grade 4: 21patients
Argiris A, et al. (27)	CET + CTX followed by RT+ CET + CTX	Response to induction: 66%, 3-year OS: 74%	High grade neutropenia 77%
Lefebvre JL, et al. (TREMPLIN) (28)	CTX followed by RT + CET or CTX	Similar OS and larynx preservation rate	Similar high grade toxicity, Higher treatment compliance with CET

Abbreviations: CET, Cetuximab, CTX, Chemotherapy; CR, Complete Response; LRC, Loco Regional Control; PR, Partial Response; OS, Overall Survival; RT, Radiotherapy.

survival and overall survival were 70% and 74%, respectively (27).

The randomized phase II study (TREMPLIN study) was designed to compare the efficacy and safety of induction chemotherapy followed by chemoradiotherapy or bioradiotherapy for larynx preservation. Induction consisted of 3 cycles of docetaxel and cisplatin 75 mg/m^2 each on day 1 and fluorouracil 750 mg/m^2 per day on days 1 through 5. Responders were randomly assigned to conventional radiotherapy with concurrent cisplatin 100 mg/m^2 per day on days 1, 22, and 43 or concurrent cetuximab 400 mg/m^2 loading dose and 250 mg/m^2 per week.

There was no difference in larynx preservation rate and overall survival between 2 arms. More radio dermatitis was seen in bioradiotherapy arm. Protocol modification was necessary more frequently in chemotherapy arm. Receiving full protocol was achieved in 43% and 77% of patient with chemotherapy and biotherapy arm, respectively (28).

2.5. Cetuximab for Metastatic/ Recurrent Patients (Table 4)

In a phase II study, patients with disease progression after platinum therapy received single-agent cetuximab (initial dose 400 mg/m^2 followed by subsequent weekly doses of 250 mg/m^2) for at least 6 weeks. A 13% response rate was seen with cetuximab. Overall disease control rate was 46%. The median time to response and duration of response was 49 days (range, 37 to 251 days) and 126 days, respectively. It was concluded that single-agent cetuximab was active and generally well tolerated in the treatment of recurrent and/or metastatic SCCHN that progressed on platinum therapy (29).

The combination of cetuximab with platinum-based chemotherapy in patients with platinum refractory HNSCC was evaluated in a phase II multicentre study. The response rate was 10% and the disease control rate was 53%. The overall survival was 183 days (30).

The combination of cetuximab with chemotherapy was also evaluated by Herbst et al. Metastatic or recurrent HNSCC were to receive 3 cycles of cisplatin/pacitaxel or cisplatin/fluorouracil. Patients with complete or partial response continued standard treatment. Those patients with stable or progressive disease were enrolled in the study protocol consisted of cetuximab (400 mg/m^2 on day 1, then 250 mg/m^2/week) and cisplatin (75 - 100 mg/m^2 every 3 weeks). Objective response was seen in 18% and 20% of stable and progressive diseases, respectively. The median overall survival times for stable and progressive patients were 11.7 and 6.1 months, respectively. Sever hypersensitivity reaction due to cetuximab was 5%. Cetuximab did not exacerbate cisplatin toxicity (31).

In a phase III study conducted by Eastern cooperative oncology group, cisplatin plus cetuximab was compared with cisplatin plus placebo as the first line treatment for the patients with metastatic or recurrent HNSCC. The objective response rate was significantly improved with adding cetuximab (26% vs. 10%, P = 0.03). There was no difference in progression free survival and overall survival between 2 groups (32). The efficacy of cetuximab plus platinum-based chemotherapy as first-line treatment was investigated by EXTEME trial. The patients with recurrent or metastatic HNCC were randomized to receive cisplatin or carboplatin plus fluorouracil or the same chemotherapy plus cetuximab. Adding cetuximab to platinum-based chemotherapy significantly prolonged the median overall survival (10.1 months vs. 7.4 months, P = 0.04). The median progression free survival was 5.6 months and 3.3 months for cetuximab and non-cetuximab containing regimen, respectively (P < 0.001). Adding cetuximab improved response rate (36% vs. 20%, P < 0.0010). No cetuximab related death was occurred (33).

Table 4. Summary of Studies Evaluated Cetuximab in Metastatic/ Recurrent Patients

Authors	Patients	Protocol	Outcome
Vermorken J.B et al. (29)	CTX refractory	Weekly CET with salvage CTX after progression	RR: 13%, DCR: 46%
Baselga J et al. (30)	CTX refractory	Weekly CET with the same CTX before study	RR: 1O%, DCR: 50%
Herbst R.S et al. (31)	Progression or stable after CTX	Weekly CET with cisplatin	RR for progrression: 18%, RR for stable: 20%
Burtness B, et al. (ECOG) (32)	First line	Cisplatin with CET or placebo	RR: 10% vs. 26%, OS: no difference
Vermorken J.B et al. (33)	First line	Platinum CTX with or without CET	RR: 36% vs. 20%, P < 0.001, Median OS: 10.1 vs. 7.4 months, P = 0.04

Abbreviations: CET, Cetuximab; CTX, Chemotherapy; DCR, Distant Control Rate; OS, Overall Survival; RR, Response Rate.

3. Results

The superiority of concomitant cetuximab and radiotherapy compared with radiation alone has been proven with a phase III study (10). But, there is no phase III trial to compare chemoradiation with concomitant cetuximab and radiation. A phase II trial compared radiotherapy with concomitant cisplatin versus concomitant cetuximab. Loco regional control and survivals were similar between the treatment arms (11). Several retrospective studies have been conducted to compare concomitant chemoradiation versus bioradiotherapy (12-19, 34-36). The results have been variable. Four studies showed no difference in outcome. Chemoradiation showed better outcome in 5 studies. Toxicity profile differs significantly between cisplatin versus cetuximab containing regimens. This finding can be used for selection between chemotherapy and bioradiotherapy. According to a phase III trial, the addition of cetuximab to cisplatin base chemoradiation did not improve outcome. Treatment interruptions due to severe toxicity may be one explanation for this negative result (23). Also, the incorporation of cetuximab to induction and/or concomitant phase of sequentional modality has been studied. Response rate after induction therapy with cetuximab containing regimens has been between 66 % to 77%. Response rate after induction chemoterapy with docetaxel or paclitaxel and cetuximab followed by chemoradiation has been 77 to 100% with acceptable toxicity (24-28). There is no phase III study to compare concomitant chemoradiation with bioradiation, directly. A Phase II trial (TREMPLIN) showed no differences in treatment outcome between induction chemotherapy followed by chemoradiation or bioradiation. However, treatment compliance was higher in the bioradiotherapy arm. No renal toxicity was seen in cetuximab arm. The rate of renal toxicity was 15.5% in chemoradiation arm. According to this study, the substitution of cisplatin with cetuximab during concomitant phase can be administered to decrease nephrotoxicity following cisplatin-based induction phase (28). Metastatic and recurrent patients with platinum-refractory disease can achieve a treatment benefit with single-agent cetuximab. Promising response rate was seen in 3 studies evaluating the efficacy of single-agent cetuximab in these patients (29-31, 37). Cetuximab has also demonstrated activity in the treatment of recurrent and/or metastatic SCCHN in the first-line setting (32, 33).

4. Conclusions

It has been proven that concomitant radiotherapy with cetuximab results in a longer overall survival was compared to radiotherapy alone. Cetuximab can be combined safely with chemotherapy during the induction phase of sequential modalities and may be used alone during concomitant phase to reduce nephrotoxicity. The best protocols and the appropriate patients remain to be defined. The addition of cetuximab to cisplatin-based chemotherapy has a promising result for recurrent/metastatic patients.

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Footnotes

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