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REVIEW

Cetuximab: The Emerging Evidence of its Therapeutic Value in Squamous Cell Carcinoma of the Head and Neck

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Abstract: The worldwide incidence of head and neck cancer exceeds half a million cases annually with squamous-cell histology as the most predominant. Almost half of newly diagnosed cases have advanced disease at diagnosis. The high morbidity and mortality associated with the malignancy has brought more attention to this cancer. The improvement in the diagnosis and management has resulted in considerable improvements in quality of life and survival. EGFR is constitutively expressed in squamous-cell carcinoma of the head and neck (SCCHN) paving the path for evaluation of EGFR targeted agents. Cetuximab is a chimeric monoclonal antibody that targets the extracellular epitope in the EGFR ligand-binding domain. It was initially approved by the Food and Drug Administration, FDA, in 2006 for use in SCCHN in combination with radiation therapy based on improvement in both locoregional control and survival. In addition, it is efficacious as a single agent in patients with failure after prior platinum-based chemotherapy and is also indicated in combination with platinum-based chemotherapy in first-line recurrent or metastatic SCCHN. This paper reviews the mechanism of action, clinical studies, safety and efficacy of cetuximab in SCCHN.

Keywords: cetuximab, squamous cell carcinoma head and neck

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Introduction

Head and neck cancers account for about 6% of all cancers worldwide, with about 35,720 expected to be diagnosed in 2009 in the United States with almost 8000 estimated deaths.[1] Over the past three decades, the long-term survival for squamous cell carcinoma of the head and neck (SCCHN) remains roughly 30%–40%.[2–4] The successful management of head and neck cancer often requires multimodality approach: complete surgical excision of the primary tumor and nodal metastasis, along with chemotherapy and radiotherapy in the adjuvant setting. For locally advanced, non-operable disease and metastatic disease, systemic chemotherapy and chemoradiation have been the corner stone of management. Multiple cytotoxic chemotherapeutic agents have been evaluated with or without radiation with varying degree of activity. Recently, agents that target the epidermal growth factor receptor (EGFR) have demonstrated benefit leading to their incorporation in the overall treatment paradigm. EGFR is overexpressed in 90–100% of SCCHN and the overexpression of this receptor often correlates with a more advanced stage of the disease, poor response to chemotherapy and poor prognosis.[5,6]

Cetuximab is a recombinant, human/mouse chimeric monoclonal antibody, specifically against EGFR. It improves locoregional control and overall survival when used in combination with definitive radiation therapy (Table 1).[7] In addition, it is also active as a single agent in patients with progressive disease post-treatment with platinum-based therapy (Table 1).[8] Cetuximab was approved in 2006 by the FDA in head and neck cancer in combination with radiation therapy for locoregional disease and as monotherapy for metastatic and recurrent disease after failure from prior platinum-based chemotherapy. This article provides a summary of the role of cetuximab in the management of SCCHN.

Mechanism of Action, Metabolism and Pharmacokinetics

EGFR is a 170 kd transmembrane tyrosine kinase receptor expressed ubiquitously. EGFR binds multiple ligands including EGF, tumor growth factor alpha (TGF-α), epiregulin, betacellulin, amphiregulin.[9] Upon ligand binding, the receptor undergoes conformational change and activation of its kinase activity followed by initiation of intracellular signaling cascade (MAPK, PI3K/Akt, Jak/Stat pathways). The biological effect of activation of EGFR results in cell proliferation and tumor progression. Cetuximab binds to the extracellular domain of EGFR with a 2-log higher affinity than that of its natural ligand, EGF.[10] This binding of cetuximab to the receptor induces dimerization with eventual internalization of the antibody-receptor complex and abrogates signaling cascade through EGFR. Hence, cetuximab is able to inhibit EGFR function by competing with its natural ligands, blocks phosphorylation and activation of receptor-associated kinase and its associated downstream signalling resulting in inhibition of many cellular processes such as induction of apoptosis, inhibition of cell growth, and decreased vascular endothelial growth factor (VEGF) production.[10] Preclinical data demonstrated significant anti-proliferative activity of cetuximab in tissue culture and mouse xenograft models.[11,12] In addition to its direct inhibitory effect on EGFR, cetuximab may also exert its anti-tumor activity via antibody-dependent cell cytotoxicity.[13] EGFR blockade with cetuximab also delays the repair of chemotherapy-induced DNA damage via modulation of DNA repair genes such as XRCC1 and ERCC1, providing the rationale for its synergy with cisplatin.[14–16] Nonetheless, the exact mechanism of the anti-tumor activity of cetuximab remains unclear.

In 2000, cetuximab was first brought into human usage. Baselga and colleagues reported their phase I study in patients with solid tumors.[17] The study enrolled a total of 52 patients with 13 patients treated with single dose, 17 patients treated with multiple doses and 22 patients treated with combination of cetuximab and cisplatin. Cetuximab demonstrated nonlinear dose-dependent pharmacokinetics without reaching any dose-limiting toxicity (DLT) or maximum tolerated dose (MTD). The agent was very fairly well tolerated. However, there was no difference in drug clearance when the dose reached 200 mg/m^2 to 400 mg/m^2 indicating that the clearance system was saturated at this dose range. The clearance of cetuximab did not change with the addition of cisplatin. The combination of cisplatin with cetuximab was also well tolerated[17] and partial response was observed in 2 patients; among them one of the patients had SCCHN. The most common side effects were fever and chills, skin

Table 1. Selected studies of cetuximab in SCCHN.

Study	Agents	Phase	No. of patients	RR	PFS	OS
Baselga et al[8]	Cetuximab followed by platinum chemotherapy	2	96	10%	85 days	183 days
Herbst et al[19]	Cisplatin/paclitaxel or cisplatin/5FU and then cetuximab and cisplatin	2	132	20% 6% 18%		6.1 4.3 11.7
Vermorken et al[18]	Cetuximab in patients with recurrent and/or metastatic	2	103	13% 0%		178 days
Burtness et al[20]	Cisplatin vs. cisplatin + cetuximab in metastatic/recurrent SCCHN	3	117	10% vs. 26%	2.7 m vs. 4.5 m	8 m vs. 9.2 m
Bonner et al[7]	Radiotherapy vs. radiotherapy plus cetuximab in locally advanced SCCHN	3	424		12.4 m vs. 17.1 m $P = 0.006$	29.3 m vs. 49 m $P = 0.03$ 5-yr OS 46%
Vermorken et al[21]	Platinum-based chemotherapy plus cetuximab vs. cisplatin plus 5FU	3	442		From 3.3 to 5.6 m $P < 0.001$	7.4 m vs. 10.1 m $P = 0.04$

Summary of previous studies on cetuximab previously published including study phase, response rate, progression free survival, overall survival and the number of patients involved in the study.

toxicities (flushing, acneiform rashes, and seborrheic dermatitis), asthenia, diarrhea, nausea, and vomiting. However, most of these adverse events were less than grade 3 and manageable. One patient experienced aseptic meningitis at dose level of 100 mg/m^2 and one patient had grade 4 dyspnea at a dose of 5 mg/m^2. The half-life of cetuximab was approximately 7 days and the current recommended dose was established at 400 mg/m^2 loading dose followed by weekly 250 mg/m^2.

Clinical Studies

Second line use in metastatic/recurrent SCCHN

The efficacy of cetuximab was assessed in metastatic SCCHN for second line use. Multiple phase II studies evaluated the utility of cetuximab in the second line setting either alone or in combination with platinum in platinum-refractory disease. Vermorken and co-workers examined the efficacy of single agent cetuximab in metastatic or recurrent SCCHN resistant to platinum therapy.[18] A 13% response rate was observed with single cetuximab with an overall disease control rate of 46%. The overall survival for the study patients was 178 days. Fifty-one percent of the patients on the study progressed and eventually received combination therapy. In the study by Baselga et al, 96 patients with platinum-refractory disease were treated with cetuximab and cisplatin or carboplatin.[8] The intent-to-treat response rate was 10% and overall disease control rate was 53%. The progression and overall survival were 85 and 183 days respectively. Herbst et al also assessed the efficacy of cetuximab in platinum-refractory SCCHN in a multicenter phase II study.[19] This study enrolled a total of 132 patients with metastatic or recurrent SCCHN. All patients were initially treated with cisplatin and paclitaxel or fluorouracil for two cycles and then evaluated for tumor response. Fifty-one (51) patients with stable disease and 25 patients with progressive disease received combination therapy with cetuximab and cisplatin (75 or 100 mg/m^2) every 3 weeks. Although the protocol for this study was later amended to accommodate patients with progressive disease within 90 days after platinum-based therapy, the response

Table 2. Recently completed trials of cetuximab and concurrent radiotherapy for SCCHN.

Study	Sponsor	Phase	Primary outcome	Secondary outcome
Cetuximab with concurrent carboplatin, paclitaxel and radiotherapy-advanced locoregional SCCHN	University of MD	2	Locoregional control	Local control (2 yrs) PFS RR
Adjuvant cetuximab and chemotherapy with either cisplatin or docetaxel in resected stage III or IV	RTOG	2	Local-regional DFS OS Treatment tolerance	
Cetuximab, cisplatin and radiotherapy in patients with locally advanced cancer	ECOG	2	PFS	OS Local control Toxicity
Study of albumin-bound paclitaxel for treatment of recurrent/metastatic SCCHN with cetuximab	University of CA, Irvine	2	RR	OS PFS Toxicity
Radiation therapy and cisplatin with and without cetuximab in patients with stage III or stage IV	RTOG	3	DFS	OS LRC Toxicity
Cetuximab, combination chemotherapy and radiation therapy in patients undergoing surgery for stage III/IV	ECOG	2	EFS	RR (path) LRC DFS OS

Selected studies involving cetuximab in which recruitment have been completed, but not yet published. This include the study phase, sponsor, primary and secondary outcome measurement.

rate (RR) for patients with earlier stable disease (SD) was 18%; 20% in patients with progressive disease (PD), and 6% in patients with progressive disease admitted to the protocol after the amendment (PD2). The median progression-free-survival was 4.9 months in SD group, 3 months in PD group and 2 months in PD2 group. The median overall survival (OS) were 11.7, 6.1 and 4.3 months for the SD, PD and PD2. Thirty (30) of the patients with complete or partial response were ineligible for the study and continued on chemotherapy. Acne-like rashes were the most common adverse events associated with cetuximab. These two studies demonstrate that the addition of cetuximab to platinum could re-sensitize tumors from platinum-resistant to platinum-responsive.

First line use in metastatic/recurrent SCCHN

Burtness and co-workers[20] (Table 1) compared cisplatin plus cetuximab with cisplatin plus placebo as the first line treatment in 117 patients with recurrent or metastatic SCCHN in a phase III ECOG study. Cisplatin was given at 100 mg/m^2 every 4 weeks while cetuximab was given at a dose of 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly. The objective response rate was significantly increased with the addition of cetuximab to cisplatin (26% for the combination vs. 10% for cisplatin with placebo, $P = 0.03$). The median progression-free survival (PFS) was 4.2 months in cisplatin plus cetuximab and 2.7 months in cisplatin plus placebo arm (hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.54–1.12). The median OS was 9.2 months in cetuximab arm and 8 months in placebo arm ($P = 0.21$). The addition of cetuximab to cisplatin significantly improves response rate. The trend towards survival benefit with the addition of cetuximab, though modest, was not statistically significant and the overall effect was additive.

Perhaps the study reported by Vermorken et al, EXTREME Trial,[21] is the largest randomized trial to show the survival benefit of cetuximab when combined with chemotherapy as the first line treatment. A total of 442 patients with recurrent or metastatic SCCHN were randomized to receive either platinum with 5-FU doublet or platinum, 5-FU and cetuximab triplet. The OS was 7.4 months with doublet alone arm and 10.1 months in the cetuximab triplet arm (HR 0.80, 95% CI 0.64–0.99, $P = 0.04$). The PFS

Table 3. Ongoing studies of cetuximab for SCCHN.

Study	Sponsor	Phase	State date	Stop date	Trial no.
Sorafenib/cetuximab in SCCHN	Duke University	1/2	01/08	01/10	NCT0081529
Adjuvant cetuximab and Chemoradiation in SCCHN	Heinrich-Hein University, Dusseldorf	2	08/08	09/12	NCT00791141
Combination of cisplatin, cetuximab and Temsirolimus in recurrent/metastatic SCCHN	University of TN	1/2	12/09	06/12	NCT01015664
IMC-A12, alone or in combination with cetuximab in patients with recurrent/metastatic SCCHN	ImClone LLC	2	01/08	06/10	NTC00617734
Docetaxel, cisplatin, fluorouracil follow by cetuximab in locally advanced H and N cancer	Wake Forest University	2	09/08	09/10	NTC00721513
Cetuximab, cisplatin, radiation therapy in patients with recurrent SCCHN	Simmons Cancer Center	2	12/08	01/12	NTC00833261
A study of dasatinib, cetuximab and radiation therapy with or without cisplatin in SCCHN	Sidney Kimmel Cancer Center	1/2	06/09	01/14	NTC00882583
Bevacizumab, cetuximab and cisplatin with IMRT for patients with stage III/IV SCCHN	Memorial Sloan Kettering Cancer Center	2	08/09	08/12	NTC00968435
Temsirolimus and erlotinib in platinum-refractory/ineligible, advanced SCCHN	New Mexico Cancer Care Alliance	2	12/09	11/12	NTC01009203
Study of RAD001 in combination with cetuximab and cisplatin in recurrent and metastatic SCCHN	Sidney Kimmel Cancer Center	1/2	10/09	1/14	NTC01009346

This table list studies of ongoing cetuximab including study phase, government registered number, sponsors, date in which recruitment begins and the proposed date for study closure.

was also significantly higher in the cetuximab arm (3.3 months in the doublet arm vs. 5.6 months in cetuximab triplet arm, HR 0.54, $P < 0.001$) along with significant improvement in response rate (20% vs. 36%, $P < 0.001$). This study demonstrated definitively that addition of cetuximab to combination chemotherapy increases response rate, PFS and OS. Thus cetuximab should be considered as the first line therapy for patients with metastatic or recurrent disease.

Concurrent with radiation in locally advanced disease

Majority of patients with head and neck cancer usually present with locally advanced, stage III or IV disease. The management usually involves the combination of chemotherapy, chemoradiation or surgery (Table 1 and 2). Several randomized phase III studies and meta-analysis have shown that chemoradiation is superior to radiotherapy alone in managing localized SCCHN.[2,3,22–27] Chemoradiation (platinum-based) has thus become the 'standard of care' for these patients with locoregional unresectable disease. However, the results are far from ideal as recurrence is frequent.

The concept of combining cetuximab with radiation is attractive as it has radiosensitizing effects with no DLT.[28,29] Early phase I study reported by Robert et al[30] showed that standard dose of cetuximab could be safely used in combination with radiotherapy. Among the 16 patients enrolled, 13 patients achieved a complete response and 2 had a partial response. With these provocative results, a phase III study was conducted and has now been reported by Bonner and

colleagues.[7] More than 400 patients were randomized to receive either radiotherapy alone (70 to 76.8 Gy) or cetuximab with radiotherapy. The OS survival was significantly better in the cetuximab arm (49 months in cetuximab arm vs. 29.3 months in radiation alone arm, HR = 0.74, $P = 0.03$). The PFS was also increased in the cetuximab/RT group (HR = 0.7, $P = 0.006$). It resulted in overall improvement in local control (24.4 months vs. 14.9 months) and the side effects were very manageable. The major adverse effects included mucositis, acneiform rash, radiation dermatitis, weight loss, xerostomia, dysphagia and asthenia in the combined modalities. Six percent of patients in the radiotherapy alone and 1% in the combined treatment arm had grade 3–5 anemia.

To further elaborate the efficacy of cetuximab, Pfister et al combined cisplatin with radiotherapy.[31] This single arm phase II study had 21 patients who were treated with cisplatin 100 mg/m^2 and standard dose of cetuximab with simultaneous radiotherapy. At 52 month follow-up, 3 year OS was 76% and 3 year PFS was 56%. The toxicity profile was very similar to the regimen of cisplatin with radiation but there were two fatal events. Although these survival data are encouraging, this regimen is not recommended for use outside of a study.

In the induction setting, addition of docetaxel to cisplatin and 5-fluorouracil has been shown to significantly improve PFS and OS.[32] Along the same line, cetuximab has been incorporated in the induction regimen of carboplatin and paclitaxel. In a phase II study published by Kies et al,[33] patients received weekly paclitaxel and carboplatin with cetuximab. 19% patients achieved a complete response and 77% patients experienced partial response. The 3-year PFS and OS were 87% and 91% respectively. The authors have recommended further evaluation of this approach.

Safety

The major toxicity seen with cetuximab is skin rash, an expected manifestation and well documented problem with EGFR inhibitor.[16,17,25,27,29] Cetuximab was discontinued because of severe rash in 8 of 9 patients in the phase 3 study comparing cetuximab and radiotherapy vs. radiotherapy alone.[25] Another study reported skin toxicity rate of 77% in the cetuximab-containing arm, compared with 24% of patients on cisplatin and placebo arm, $P < 0.001$.[16] The mechanism of rash is unclear but it may be the result of EGFR expression in the basal layer of the epidermis of the skin.[34] The rash is usually managed with local creams, topical steroids, and oral antibiotics such as doxycycline and minocycline and if severe one may consider discontinuation of the agent.

Hypersensitivity reactions with cetuximab have been noted in a minority (approximately 3%) of patients.[25,29] Whether this is enhanced in patients with prior history of allergy, is unclear but the reactions occurred in 22% of patients treated with cetuximab in three centers from Tennessee and North Carolina.[35] In the study by Chung et al 17 of 21 patients with an allergic reaction had pre-existing IgE antibodies against galactose-α-1,3-galactose, an oligosaccharide present on cetuximab.[36] There was no significant difference in hypersensitivity reactions in the study where cetuximab was compared to cisplatin.[16]

Ocular toxicities including corneal erosions and keratitis.[37–39] can also occur but are rare. Other toxicities include headache, nausea, and diarrhea.[29] Cetuximab has not been found to exacerbate the common toxic effects of radiation therapy.[25] Unusual grade 2 painful bilateral periungual lesions on the finger have also been reported following treatment with cetuximab.[29] Meanwhile, Vermorken reported no difference in the incidence of grade 3 or 4 adverse events between the 2 groups of patients in the study that involved platinum-based chemotherapy in patients with recurrent or metastatic SCCHN.

The EXTREME trial utilized European Organization for Research and Treatment of Cancer (EORTC) and Quality of Life Questionnaire (QLQ) as tool. The result showed that there was no difference in the quality of life between the cetuximab arm of the trial and the chemotherapy arm alone arm.[21]

Biomarkers for response

Like in many other cancers, patient selection for appropriate targeted therapy is necessary to determine which subset of patients would derive the most benefit from the therapy. A subset analysis of a trial by Burtness et al[20] in which patients with advanced, incurable SCCHN were treated with cetuximab and cisplatin suggests that patients with low-to-moderate

levels of EGFR expression had the best response to cetuximab. This was hypothesized that in the high immunoreactive group, perhaps the agent is unable to fully saturate a greater number of receptors. It has also been shown that overexpression of EGFR often correlates with a more advanced stage of the disease, a poorer prognosis and a worse response to chemotherapy.[5] The lack of standardization of the EGFR expression assay measurement makes definitive recommendation of its use improbable. Use of fluorescence in situ hybridization (FISH) method by Chung et al[40] showed that high gene copy numbers of EGFR were present in 63% of the 41 SCCHN samples. They also demonstrated that FISH+ tumors were associated with a worse recurrence-free survival. Other observers have also reported EGFR gene amplification with a range between 12%–58%.[41–45] There have been reports of expression of truncated form of EGFR, EGFR variant III (VIII), in about 40% of SCCHN and this ultimately has shown to confer resistance to EGFR monoclonal antibodies in preclinical models.[41] Unlike colon and lung cancers, there are no significant EGFR activating mutations in SCCHN. Finally, matrix-assisted laser desorption ionization (MALDI) mass spectrometry (MS) on serum specimens has been used to identify a favorable proteomic profile that may predict for response to cetuximab.[46] In this retrospective analysis of 314 patient samples, the favorable proteomic profile predicted for a survival benefit in cohorts of patients treated with EGFR inhibitors, but not in the control group. This observation has not been validated in a prospective trial.

Thus, to date there have been no consistent molecular markers identified to correlate with SCCHN response to EGFR inhibitors. The prevalence of other markers such as Kras mutation, PI3K-AKT pathway mutation and PTEN mutations is quite low to warrant widespread use.[47–50]

Perhaps the most intriguing data is the association of the human papillomavirus (HPV) with a subset of SCCHN. This is believed to be sexually acquired as a result of a high lifetime number of oral-sex partners.[40] In a meta-analysis involving 5046 cases of squamous cell cancers, the prevalence of HPV ranged between 23%–35%.[41] HPV serotypes 16 and 18 are frequently associated with malignancy with the former been the most common subtype in SCCHN.[40,41]

HPV positivity is associated with favorable outcomes in patients with oropharyngeal cancers[42] and those with positive HPV and wild type p53 have best overall survival and lowest recurrence after surgical resection.[43] Furthermore, HPV positive tumors also have better outcomes with chemoradiation.[44] Although the exact molecular mechanism of this observation is not delineated, it has been hypothesized in one of the models that HPV16 oncoprotein E6 and E7 inactivate tumor suppressors p53 and pRB via protein-protein interactions and therefore, frequently leave the p53 and pRB gene intact without creating mutations, making the cells more sensitive to chemoradiation. Thus, HPV status should be considered to stratify patients in all future studies. At the present time, clinical data of cetuximab in HPV positive tumors are very limited. In a phase II study published by Kies et al, cetuximab was used in combination with carboplatin and taxol in the induction chemotherapy in SCCHN. An improved PFS and OS were observed in patients with positive HPV in the biopsy specimen.[45]

Place in therapy and conclusions

The use of cetuximab has been well established as an active treatment either alone or in combination with radiation or chemotherapy for the treatment of advanced SCCHN. Its use is well documented in both the first-line and in the recurrent/metastatic setting. Its role as in patients who are unable to tolerate high dose cisplatin is equally well elucidated. The addition of cetuximab to a platinum doublet significantly improves overall median survival of patients with incurable SCCHN. Cetuximab monotherapy is also a reasonable approach for patients who become refractory to platinum therapy. The toxicity profile of cetuximab is acceptable. We hope that cetuximab will continue to be part of the armamentarium for oncologists when deciding the best option to treat patients with this malignancy. The future holds for identifying validated biomarkers for proper patient selection to optimize the use of cetuximab in patients with SCCHN. Incorporation of cetuximab with novel combinations of chemotherapy (Table 3) or other signal transduction inhibitors are underway based on the increasing evidence of efficacy of this agent in the management of SCCHN.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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