

The Role of Cetuximab for the Treatment of Squamous Cell Carcinoma of the Head and Neck

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Abstract: Squamous cell carcinoma of the head and neck (HNSCC), while curable in many cases with surgery, radiation, and chemotherapy, remains a disease that is associated with significant morbidity and mortality. Agents that target the epidermal growth factor receptor (EGFR) have demonstrated beneficial effects in this disease. The Food and Drug Administration approved cetuximab—a monoclonal antibody—in conjunction with radiation, for locally advanced, potentially curable disease, and also as a single agent for incurable recurrent/metastatic disease. In addition, there are more recent data showing a survival benefit for patients with recurrent/metastatic disease who were treated with a first-line regimen of platinum, fluorouracil and cetuximab. These promising results have had a significant impact on the standard of care for HNSCC, and have prompted further research on the role of EGFR inhibitors in the treatment of HNSCC. In the following review, we will discuss the history, mechanism, and clinical trials that pertain to the role of cetuximab in the treatment of HNSCC.

Squamous cell carcinoma of the head and neck (HNSCC) is diagnosed in over 500,000 patients worldwide each year with an estimated incidence in the United States of 45,000 new cases in 2007.¹ There is increasing evidence that the human papilloma virus (HPV) is pathogenic in oropharynx cancers, notably in patients lacking the usual risk factors of tobacco and ethanol use.²

Patients with stage I or II HNSCC are often cured with local modalities of radiation therapy or surgery. Unfortunately, more than half of patients present with locoregionally advanced disease, and have a 5-year survival rate of less than 50%.³ The use of platinum chemotherapy as a radiosensitizing agent improves treatment

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outcomes, but chemoradiation results in significant short- and long-term toxicities.

An emerging therapeutic option for HNSCC involves targeting the epidermal growth factor receptor (EGFR).^{4,5} A number of agents are in active clinical development; we have the most clinical data in the treatment of HNSCC with use of the monoclonal antibody cetuximab (Erbix, Bristol-Myers Squibb/ImClone). Cetuximab plus radiation has demonstrated a survival advantage compared with radiation alone in the treatment of patients with locoregionally advanced HNSCC, and an improved response rate compared to chemotherapy for patients with platinum-refractory metastatic/recurrent HNSCC. This review will summarize present data regarding the evolving role of cetuximab in the treatment of HNSCC.

EGFR Inhibition in HNSCC

Elevated EGFR expression detected by immunohistochemistry (IHC) is present in over 90% of HNSCC specimens. EGFR expression is associated with inferior survival, radioresistance, and locoregional failure.⁶⁻⁹ Multiple preclinical studies have confirmed that EGFR inhibition sensitizes head and neck squamous cancer cells to the effects of ionizing radiation.¹⁰⁻¹⁵ Also, there are preclinical data showing additive effects of cisplatin and EGFR inhibition in killing HNSCC cells, including in xenograft tumor models.¹⁶

The EGFR is a type 1 transmembrane receptor tyrosine kinase that is involved in numerous aspects of HNSCC pathogenesis. It is one member of a family of such receptors including c-erbB-2 (HER2 [human epidermal growth factor 2]/neu), c-erbB-3, and c-erbB-4. The EGFR is activated by ligand binding followed either by homodimerization or heterodimerization with another member of the EGFR family.^{17,18} EGF and transforming growth factor (TGF)- α appear to be the key ligands, although there are several other ligands such as epiregulin and amphiregulin that may be relevant to response and resistance to EGFR inhibitors in the clinic.¹⁹ EGFR stimulation results in downstream activation of signal transduction pathways for phosphatidylinositol-3-kinase (PI3K)-Akt relating to survival and apoptosis evasion and Ras-Raf-MAPK kinase (MEK)-mitogen-activated protein kinase (MAPK) relating to proliferation.²⁰ In addition, there is an interaction between EGFR expression and signal transducers and activators of transcription 3 (STAT3), which play a role in the regulation of gene transcription.^{21,22} STAT3 is often constitutively activated in HNSCC, and its activation and expression are associated with decreased survival. EGFR stimulation has been shown to activate STAT3. Pre-clinical investigation of HNSCC cell lines also indicates that STAT3 can be

activated independently of EGFR, and may thereby play a role in resistance to EGFR inhibitors.^{23,24} Treatment with STAT3 antisense has been shown to result in decreased STAT3 activation, decreased proliferation, and increased apoptosis in head and neck xenograft models.²⁵

In addition to membrane-based cell signaling, EGFR may also translocate to the nucleus where it can activate or repress the production of various effector proteins. It has been shown that irradiation stimulates EGFR nuclear localization.²⁶ One key nuclear function of EGFR is phosphorylation and activation of DNA-PK, an enzyme that can repair double-strand breaks that result from radiation therapy.^{27,28} The DNA repair process initiated by this pathway can be blocked by exposure to cetuximab.²⁶ EGFR localizing to the nuclear compartment can also enter transcriptional complexes and bind to the promoter region of cyclin D1 to promote cell cycle progression and increase cell proliferation.²⁹

A truncated variant of EGFR, EGFRvIII, was present in 42% of HNSCC cells in 1 series, and likely rendered these cells less responsive to treatment with cetuximab.³⁰ EGFRvIII has a deletion of exons 2 through 7, encompassing the ligand-binding domain and the cetuximab-binding site, but is weakly and constitutively active in a ligand-independent manner.

EGFR inhibition also delays the repair of chemotherapy-induced DNA damage via modulation of DNA repair genes such as XRCC1 and ERCC1.³¹⁻³⁴ Activation of other DNA repair pathways represents another potential mechanism for resistance to anti-EGFR therapy when combined with radiation therapy.^{35,36}

Cetuximab is a chimeric antibody (65% human and 35% murine) constructed on an immunoglobulin (Ig) G1 framework, which targets an extracellular epitope in the EGFR ligand-binding domain. Cetuximab infusion-related hypersensitivity reactions (HSR) were described by Chung and colleagues³⁷ in a recent report of preliminary data showing the presence, in serum, of an IgE antibody against glycosylation sites on cetuximab among patients who experienced HSR. Other investigators also suggested that these antibodies may cause the HSRs.³⁸

Several mechanisms that contribute to the anti-tumor activity of cetuximab have been identified; others may also be relevant. A dominant mechanism is interference by antibody with the binding of natural ligands, such as EGF and TGF, to the receptor itself, thereby disrupting EGFR signaling pathways.³⁹ The affinity of cetuximab for the receptor exceeds that of natural ligand EGF. Another mechanism is depletion of the targeted receptors from the cell surface. This occurs via induction of receptor endocytosis, albeit by a mechanism that is slower than for EGFR complexed to a natural ligand. Receptor internalization is followed by receptor recycling back to the cell surface,

receptor degradation in lysosomes, or translocation to the nucleus.⁴⁰

Finally, cetuximab's construction on an IgG1 framework would in theory allow this agent to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) via natural killer cells and macrophages, as well as complement-dependent cytotoxicity. While there is some support from preclinical studies for this mechanism in lung cancer and HNSCC, the relevance of ADCC in the therapeutic effect of cetuximab in patients with HNSCC requires further investigation.⁴¹⁻⁴³

History of Cetuximab

Cetuximab (formerly known as C225) was initially evaluated in phase I studies in which it was administered as either a single dose, weekly doses, or weekly doses in conjunction with cisplatin.⁴⁴ Doses in the range of 200–400 mg/m² were associated with pharmacokinetic evidence of saturation of systemic clearance. A separate phase I trial evaluated the safety of cetuximab in conjunction with radiation therapy in 16 patients with locoregionally advanced HNSCC.⁴⁵ A third study also looked at the optimal dosing of cetuximab in conjunction with cisplatin and studied EGFR binding to tumor as well as in vivo effects on tumor kinase activity.⁴⁶ Based on pharmacological parameters and an assessment of adverse events from all of these early studies, the recommended phase II regimen was a loading dose of 400–500 mg/m² followed by 250 mg/m² weekly. In the phase I study with radiation therapy, there was also preliminary evidence of a beneficial effect on treatment outcome, with 13 of 15 evaluable patients achieving a complete response (CR) and 2 having a partial response (PR). In this trial, most patients received conventional daily radiation therapy (2 Gy/day to a total dose of 70 Gy) and 3 patients received hyperfractionated radiation therapy (1.2 Gy/twice a day to a total dose of 76.8Gy). Skin toxicity was dependent on cetuximab dosing.

Treatment of Locally Advanced Disease

A phase III multicenter trial randomized 424 patients to definitive radiation therapy and radiation therapy with cetuximab. This study demonstrated a significant improvement with the addition of cetuximab; it was, in fact, the first statistically significant evidence of a survival benefit for the addition of EGFR-directed therapy to cytotoxic therapy.⁵ Patients with tumors in the oropharynx (60%), larynx (25%), or hypopharynx (15%) were enrolled and randomized to receive cetuximab as a 400 mg/m² loading dose followed by 250 mg/m² weekly for 8 planned doses designed to overlap the approximately 7 planned weeks of

radiation therapy or 7 weeks of radiation therapy alone. Prior to randomization, investigators chose between once-daily, twice-daily, or concomitant boost radiation therapy schedules, given the uncertainty at the time this study was designed and implemented regarding the optimal radiation therapy regimen.

Cetuximab plus radiation increased the duration of locoregional control from 14.9 to 24.4 months ($P=.005$). In addition, there was an improvement in median survival from 29.3 to 49 months ($P=.03$). There was no reduction in the rate of distant metastases. There has been some debate over the definition of locoregional control for the statistical purposes of the study, but overall, the benefit from cetuximab was not disputed.⁴⁷ The significance of the reduction in locoregional recurrence rates was greatest, in a post hoc subset analysis, for patients who received altered fractionation radiation therapy, but this was also the largest subset and had the greatest power. Thus, while radiation twice a day along with cetuximab administration seemed superior to daily radiation therapy with cetuximab, the study was not powered to determine the statistical difference between these 2 approaches. In a further post hoc subset analysis, patients with cancers in the oropharynx appeared to derive the greatest benefit from the addition of cetuximab. There appeared to be no benefit for patients with hypopharynx or larynx cancers, although the rate of larynx sparing was numerically superior in patients receiving cetuximab. The option of surgical salvage for patients with recurrent laryngeal cancer can also impact the detection of a survival benefit in these patients. Based on the design of this study, it is not possible to know whether cetuximab plus radiation would be equivalent to radiation with concurrent cisplatin. The favorable survival achieved in the control arm likely reflects the relatively favorable stage and prognosis of the patients who were entered into this trial, given the possibility of randomization to radiation alone. This study provided proof of principle for the activity of cetuximab with radiation in HNSCC. It also provided a step forward in care for patients who are not candidates for chemoradiation with high-dose cisplatin. Chemoradiation, however, continues to represent the standard of care for medically fit patients who can tolerate platinum-based therapy.

One notable observation from this phase III trial was that the reported acute toxicities of radiation were not exacerbated by the addition of cetuximab. In particular, the rates of grade 3 and 4 mucositis were the same in both study arms. Some severe cases of grade 4 dermatitis in patients who were irradiated while receiving cetuximab were reported subsequently.⁴⁸ An analysis of quality of life parameters during and after treatment on the phase III registration study did not show any significant differences between the 2 treatment arms.⁴⁹ However, the symptom

burden of uncontrolled disease would be expected to be greater in the radiation alone arm and to result in a worse quality of life for these patients. Perhaps this effect was not detected because there were more patients lost to quality of life follow-up in the control arm, or because the instruments employed to measure quality of life were insensitive to the consequences of local recurrence. Although acute toxicities do not appear to be exacerbated by the addition of cetuximab, more mature data from the registration study for cetuximab with radiation therapy in HNSCC suggest that the overall incidence of late radiation toxicities (grades 1 and 2) may be numerically greater with cetuximab and radiation therapy compared with radiation therapy alone.⁵⁰ Again, the impact of competing risks may not be fully accounted for in this analysis. The rate of late toxic effects remains to be established, ideally in prospective trials with appropriate instruments for assessment of late speech and swallowing function.

Given the largely nonoverlapping toxicity profiles of cetuximab and platinum chemotherapy, there is considerable interest in combining the 2 agents with radiation. An exploratory phase II study enrolled 22 patients to receive high-dose cisplatin (100 mg/m² every 3 weeks) and cetuximab (400 mg/m² followed by 250 mg/m² weekly) in conjunction with definitive concomitant boost radiotherapy.⁵¹ Long-term follow-up data were encouraging, with 3-year overall survival and locoregional control of 76% and 71%, respectively. Adverse events observed in this study resulted in its premature termination (2 on-study deaths of uncertain relation to cetuximab: myocardial infarction, bacteremia, and atrial fibrillation). A preliminary analysis of ECOG 3303, a phase II study of cetuximab at standard doses, cisplatin 75 mg/m² times 3 cycles, in conjunction with radiation to 70 Gy was recently reported. Results indicated grade 3/4 toxicities of anemia, neutropenia, hypomagnesemia, and skin toxicity and 2 grade 5 toxicities. Early survival data seem promising with a median progression-free survival of 15.3 months.⁵² In an effort to determine the value and safety of the addition of cetuximab to chemoradiation, there is an ongoing large randomized phase III trial (RTOG 0522) underway.⁵³ This study hopes to define the role and side-effect profile of cetuximab when incorporated into definitive cisplatin-based chemoradiotherapy.

Multiple studies are also underway in patients with locoregionally advanced HNSCC to assess the safety and efficacy of incorporating cetuximab into induction regimens. Investigators from MD Anderson Cancer Center have presented data utilizing cetuximab in an induction regimen with weekly carboplatin and paclitaxel.⁵⁴ This regimen was followed by risk-based definitive therapy. The initial results are quite promising, with a CR rate of 81% to induction therapy. Investigators from the Eastern

Cooperative Oncology Group (ECOG) conducted a study of induction carboplatin/paclitaxel and cetuximab followed by radiation with weekly carboplatin/paclitaxel and cetuximab (E2303).⁵⁵ Primary site tumor biopsies were performed after the induction component of treatment and again after chemoradiation to 50 Gy if clinically residual disease was not identified within this favorable response subset, the investigators reported complete pathologic responses in 65% and 100% of these serial biopsy samples, respectively. Chemoradiation was then completed for a total dose of 68–72 Gy, followed by a neck dissection and maintenance cetuximab for 6 months. This regimen clearly has substantial anti-tumor activity, however, the survival and safety data remain immature. Argiris and coauthors reported preliminary safety results of a trial in which patients received induction cisplatin, docetaxel (Taxotere, Sanofi Aventis), and cetuximab followed by cisplatin, cetuximab, and definitive radiation therapy and followed by maintenance cetuximab for 6 months.⁵⁶ Twenty-one patients with stage III/IV disease had the expected incidences of grade 3/4 toxicities, such as neutropenia, hypomagnesemia, fatigue, and rash.

Treatment of Recurrent or Metastatic Disease

A suggestion of the anti-tumor activity of cetuximab in patients with advanced head and neck cancer was apparent early on in phase I investigations, including an unconfirmed PR, as well as 2 PRs in patients with HNSCC who received cetuximab doses of 200 mg/m² and 400mg/m² along with cisplatin.⁴⁴ A single-institution phase I study also reported cetuximab activity in HNSCC patients, with 2 CRs and 4 PRs among 9 evaluable patients (response rate, 67%).⁴⁶ Based on these encouraging findings, randomized and nonrandomized studies were conducted in HNSCC patients with advanced, incurable disease.

A number of studies have shown that cetuximab may be combined safely with platinum regimens (Table 1).^{43,45,54} Burtness and co-investigators in ECOG randomized 117 patients with recurrent/metastatic HNSCC who had not received chemotherapy for recurrent/metastatic disease to either cisplatin 100 mg/m² every 4 weeks with placebo or to cisplatin at the same dose and schedule together with cetuximab (E5397).⁴ There was a statistically significant improvement in response rate from 10% to 26% ($P=.03$). The study was underpowered for its survival endpoints and the overall survival was confounded by crossover to cetuximab for patients in the latter half of the study who had disease progression on the control arm. The overall survival improved from 8 to 9.2 months with the addition of cetuximab, although this difference was not statistically

Table 1. Cetuximab in Recurrent/Metastatic Disease

First author	Study phase	No. of patients (n)	Treatment	Response	Median overall survival
Vermorken ⁵⁸	III	220 222	Platinum/FU Platinum/FU/cetuximab	20% 36%	7.4 months 10.1 months*
Burtness ⁵	III	57 60	CDDP CDDP/cetuximab	10% 26%*	8 months 9.2 months
Hitt ⁵⁹	II	46 (35 evaluable)	Cetuximab/paclitaxel	CR 24% PR 36%	NR
Vermorken ⁶²	II	103	Cetuximab	13%	178 days
Herbst ⁶¹	II	155	Cetuximab/platinum	11.5%	PD1 (6.1 months) PD2 (4.3 months) SD (11.7 months)
Baselga ⁶⁰	II	96	Cetuximab/platinum	10%	183 days

* Statistically significant

CDDP=cisplatin; CR=complete response; FU=fluorouracil, NR=not reported; PD1=patients who progressed on prior platinum therapy on protocol; PD2=patients who had prior platinum therapy off study; PR=partial response; SD=stable disease.

significant. In addition, there was an improvement in progression free survival (2.7 vs 4.2 months; hazard ratio [HR], 0.78). As with other studies incorporating EGFR inhibitors, the incidence of skin toxicity was associated with improved survival. One of the correlative endpoints for this study was an analysis of EGFR expression levels, expressed as an EGFR immunoreactivity score composed of EGFR staining density and intensity. Tumors were classified as very high EGFR immunoreactive if 3+ staining was present on 80% or more of cells, and low-moderate if there were lesser degrees of staining. The arms were well balanced with regard to the distribution of EGFR immunoreactivity scores, and approximately one-third of patients in each group with available EGFR stains had very high immunoreactivity. The addition of cetuximab led to a significant increase in response rate in the moderate staining group only, with no benefit from the addition of cetuximab for the very immunoreactive group. The results of E5397 provided proof of principle for the addition of cetuximab to cisplatin, and set up the design of a larger phase III study conducted in Europe, known as the EXTREME trial.⁵⁸

In this multicenter, phase III trial, 442 patients with recurrent/metastatic HNSCC not amenable to curative therapy were randomized between a platin-containing chemotherapy doublet and such a doublet given with cetuximab. Crossover of patients after disease progression was not allowed. Prior treatment for recurrent/metastatic disease excluded patients from participation. The chemotherapy regimen was either cisplatin 100 mg/m² on day 1 or carboplatin area under the concentration time curve 5 on day 1, in combination with 5-fluorouracil (5-FU) 1,000 mg/m² on days 1–4, for a maximum of 6 cycles.

Cetuximab was administered weekly at the standard loading and maintenance doses and continued beyond chemotherapy discontinuation. With the addition of cetuximab to standard chemotherapy, there was a statistically significant improvement in overall survival from 7.4 to 10.1 months (HR, .80). Patients treated with cetuximab had a greater incidence of diarrhea and vomiting. In a subset analysis, there was a greater benefit for the following subgroups: those under 65 years of age, those with better performance status, and those who received cisplatin (as three quarters of study participants did). The relative worth of cetuximab in first or later lines of therapy in metastatic/recurrent disease cannot be assessed from this study because there was no crossover. This study will likely establish cetuximab, cisplatin, and 5-FU as a standard first-line approach, while leaving open the question of whether cetuximab would have an equal benefit with lesser cost or toxicity if used later in the course of the disease, as appears to be the case, for example, in the treatment of colorectal cancer.

Other smaller studies support the activity of cetuximab in advanced, incurable HNSCC. Hitt and colleagues recently presented their results of a phase II study in which 46 patients received cetuximab and weekly paclitaxel. Among the 35 evaluable patients, the combined complete and partial response rate was 71%.⁵⁹ These patients had not received prior chemotherapy in the advanced disease/metastatic setting. EGFR gene copy number by fluorescent in situ hybridization (FISH) did not predict for a response to treatment in their study. While this is a small study, it does indicate that cetuximab may add value to cytotoxic agents besides cisplatin.

Patients with platinum-refractory disease may also achieve a treatment benefit with the addition of cetuximab as shown in a trial conducted by Baselga and coauthors, in which 96 patients with platinum-refractory disease were treated by adding cetuximab at the standard doses to the platinum dose and schedule that the patients had received previously and were failing.⁵⁷ The response rate was 10%, with a disease control rate of 53% and overall survival of 183 days. While these numbers are modest, they provide evidence of cetuximab activity in a platinum refractory population, which historically has a very low response rate to subsequent chemotherapy. The same result was reported in a phase II study of similar design conducted in the USA in patients who had progressive HNSCC on prior platinum-based therapy.⁶¹ In this trial, the addition of cetuximab yielded a response rate of 18% among patients who had stable disease on prior platinum therapy on protocol (SD), 20% among patients who had progressed on prior platinum therapy on protocol (PD1), and 6% among those who had progressive disease with prior platinum therapy off study (PD2; these patients were enrolled subsequent to a protocol amendment). Cetuximab has also shown activity as monotherapy in patients with recurrent and/or metastatic HNSCC who had failed platinum-based chemotherapy.⁶² The results of this phase II study showed a response rate of 12.6%, disease control rate of 46%, and median response duration of approximately 6 months. This study provided the main support for the regulatory approval of single-agent cetuximab for this population. The response rates to cetuximab in patients in the above 3 studies are highly concordant and support the conclusion that cetuximab monotherapy, rather than the combination of cetuximab and cisplatin, is the preferred approach for some platinum-refractory patients who have not received cetuximab as first-line treatment. The striking differences in objective response rates and survival among the 3 distinct cohorts in the study by Herbst and associates⁶¹ provide a reminder that cetuximab is likely to have differential efficacy among varying populations of patients. Little information is available from any of these studies about EGFR content, activation of downstream effectors that could be markers of response or resistance, or other features that would permit an assessment of how comparable the populations are. The study of cetuximab monotherapy by Vermorken and colleagues⁶² permitted the reintroduction of cisplatin for patients with initial progression on cetuximab alone; 53 such patients received cisplatin plus cetuximab, and objective responses were not reported. This does not prove that cisplatin/cetuximab may not be superior for some patients, as the decision to treat with the doublet at crossover may have involved a selection bias.

Review of cetuximab in HNSCC

Clinical Effectiveness

Presently, cetuximab has proven beneficial for the initial treatment of locally advanced potentially curable disease, first-line therapy of recurrent/metastatic incurable disease, and second-line treatment of refractory disease after platinum-based therapy. Given its clinical activity, treatment with cetuximab should now be incorporated at some point in the course of treatment of most patients with advanced HNSCC. The optimal use of cetuximab in this disease remains unclear with regard to timing, patient selection, and perhaps even dose. If one incorporates cetuximab earlier in the course of treatment of HNSCC, especially with concurrent chemoradiation therapy and in the induction setting, cetuximab may or may not still be effective under certain circumstances for patients who recur. It is not known whether cetuximab would offer advantages (or disadvantages) in the treatment of patients with the HPV-associated variant of HNSCC, although the favorable results seen for oropharynx cancers in the Bonner,⁶³ Wanebo,⁵⁵ and Kies⁵⁴ studies suggest cetuximab will be appropriate in such patients. Current research focuses on whether cetuximab will permit sparing of radiation therapy or cisplatin dose in such patients to reduce long-term toxicity.

Due to the paucity of other options for refractory disease, enrollment in clinical trials will continue to be an important component of care, including evaluation of novel combinations of drugs with cetuximab. An active area of study is to combine EGFR inhibitors, such as cetuximab, with other targeted agents, especially diverse cell signaling inhibitors and those targeting angiogenesis.

Possible Markers for Response to Cetuximab

Determining an appropriate means of patient selection based on rigorous study of biomarkers could improve the effectiveness of anti-EGFR therapy, but how to do this is far from clear. EGFR is present, if not overexpressed, on the majority of HNSCC cells. A subset analysis of a trial in which patients with advanced, incurable HNSCC were treated with cetuximab and cisplatin suggests that patients with low-to-moderate levels of EGFR expression had the best response to cetuximab.⁴ This observation may be due to the fact that patients with high EGFR expressing tumors have a worse prognosis at baseline regardless of the therapeutic intervention.⁸ In addition, this could also reflect a dose response (pharmacodynamic) effect if tumors with higher EGFR levels require greater doses of antibody, or the relative cetuximab resistance of EGFR-vIII expressing cancers. On the other hand, retrospective analyses have found no correlation between response rates to chemotherapy and EGFR expression.⁶⁴ Because of

uncertainty about the significance of the level of EGFR expression and the absence of a standardized assay for IHC analysis for EGFR in patient samples, such assays should not guide clinical practice.

Data from Chung and colleagues indicate that high gene copy numbers of EGFR detectable by FISH were present in 63% of the 41 HNSCC samples analyzed.⁶⁵ FISH-positive tumors were associated with a trend towards a worse recurrence-free survival. Further evaluation will be necessary to determine whether EGFR copy number will predict for therapeutic response to EGFR inhibitors in HNSCC.

Toxicities Associated with EGFR Inhibitor Therapy

The characteristic skin toxicity is considered a class effect of EGFR inhibitors. EGFR is expressed at the basal layer of the epidermis and therefore, it is not surprising that the skin expresses this mechanism-based toxicity.⁶⁶ Despite the typical skin toxicities caused by EGFR inhibitors (rash, hair and nail changes), the risk of poor wound healing appears to be low. In an analysis of a subset of patients treated with radiation therapy plus cetuximab or radiation therapy alone followed by a neck dissection, there was no significant difference in time to healing between the 2 groups of patients.⁶⁷

Other toxicities associated with cetuximab include infusion-related allergic reactions, possibly due to pre-existing anti-cetuximab IgE antibodies.³⁸ Such infusion reactions are less common with panitumumab (Vectibix, Amgen), a fully human IgG2 antibody. Hypomagnesemia is another class effect associated with anti-EGFR antibodies including cetuximab.

To date, it has been possible to incorporate EGFR inhibitors at full doses into chemo- and radiation therapy regimens, reflecting the nonoverlapping and unique toxicity profiles of EGFR inhibitors compared to traditional cytotoxic agents. Thus, in the pivotal trial of cetuximab and radiation therapy there were no significant differences in the rate, intensity, or duration of mucositis, xerostomia, pain, or dysphagia in patients in the 2 treatment arms.^{5,63} Although the data are less mature, similar observations were presented in the initial reports of the EXTREME study.⁵⁵ Late toxicities that might be the result of EGFR inhibitor-based therapy, especially in conjunction with radiation therapy, remain an issue that will require additional thorough analysis, preferably in the context of randomized trials and as a prospective endpoint.

The Future

Cetuximab is now firmly established as an active component of treatment for advanced HNSCC alone and in combination with other modalities, including radiation

therapy and induction therapy. Future studies will need to optimize the timing and duration of this treatment, including an assessment of maintenance therapy after definitive chemoradiation. Also, new generations of EGFR inhibitors are in development, including both small molecule inhibitors (multi-targeted kinase inhibitors that include anti-EGFR activity) and novel anti-EGFR monoclonal antibodies (nimotuzumab, panitumumab).

Markers that could predict for response to therapy, as well as markers that predict for resistance to EGFR inhibitor therapy, including pathways downstream of the EGFR and the role of the EGFRvIII, will need to be studied in larger, prospective trials. Markers of resistance may guide us to novel targets, which could sensitize tumors to EGFR inhibitors. Given the high rate of EGFR overexpression, it remains a mystery why the single-agent activity of cetuximab is so modest. We also need to consider whether anti-EGFR therapies might perform differently in patients with HPV-related and non-HPV-related tumors, as there are likely important differences in mechanisms of pathogenesis, as well as in their prognosis and responses to therapy.

Finally, as more focus is placed on chemoprevention, it will be interesting to see if cetuximab and other EGFR inhibitors could have a role in primary or secondary prevention. Currently, a multicenter trial is underway to study erlotinib (Tarceva, Genentech/OSI Pharmaceuticals) in this setting. The development of oral EGFR inhibitors with less skin and gastrointestinal toxicity would offer distinct advantages in this regard.

Conclusions

Cetuximab is an active drug in head and neck cancer, with randomized trial evidence that it improves survival when given with radiotherapy or cisplatin chemotherapy. Its favorable toxicity profile in combination with radiation offers an advance in the standard management of patients with locally advanced disease who are not good candidates for cisplatin. At this time, adequate biomarkers to define patients who are most likely to respond (or not respond) to EGFR-based therapies are lacking. Further study of the best way to integrate cetuximab, in conjunction with newer agents, into practice will improve the effectiveness of treatment for HNSCC and lead to a decrease in the morbidity of treatment.

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