

Targeting epidermal growth factor receptor for head and neck squamous cell carcinoma: still lost in translation?

Christopher H. Chapman¹, Nabil F. Saba², Sue S. Yom¹

¹Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA; ²Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA

Correspondence to: Sue S. Yom, MD, PhD. UCSF Radiation Oncology, 1600 Divisadero St. H1031, San Francisco, CA 94143-1708, USA. Email: yoms@radonc.ucsf.edu.

Abstract: The epidermal growth factor receptor (EGFR) is preferentially expressed in head and neck squamous cell carcinoma (HNSCC), and is a promising therapeutic target. Yet other than cetuximab, no agent targeting EGFR has been approved for this disease, and none has shown benefit over the standard of care. Several randomized trials of antibody and small molecule agents have found no new indication for these agents, despite their initial promise. In this review, we examine the major clinical evidence and discuss potential future developments of translational science in this area, including use of these agents in risk-stratified subgroups, inhibition of downstream/parallel targets, and combination with immunotherapy.

Keywords: Epidermal growth factor receptor (EGFR); head and neck cancer; targeted therapy

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Prognostic importance of epidermal growth factor receptor (EGFR)

For locoregionally advanced head and neck squamous cell carcinoma (HNSCC), radiation with concurrent cisplatin-based chemotherapy has been established as the standard of care (1). Despite this, the prognosis of most patients with HNSCC remains poor with overall long-term survival around 65% (2). Furthermore, cisplatin is associated with significant toxicities. In an effort to find more targeted and less toxic agents, interest has developed around the epidermal growth factor receptor (EGFR), which is highly expressed in HNSCC and is correlated with worse outcomes (3). In March 2006, the FDA approved the EGFR monoclonal antibody (MAb) cetuximab to be used in combination with radiation therapy for the definitive treatment of locoregionally advanced HNSCC, based on phase III data showing improved overall survival compared to radiation alone (4). Nearly 10 years later, despite numerous trials of agents targeting the EGFR pathway, cetuximab remains the only FDA approved targeted compound for this indication and no trial has yet identified

a regimen including targeted agents that is superior to standard chemoradiotherapy.

EGFR (also known as ErbB1) is in the ErbB family of receptor tyrosine kinases, along with ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). Binding ligands allow members of the ErbB family to homo- or heterodimerize, autophosphorylating the intracellular domain and creating binding sites for signaling proteins. The two primary pathways activated are RAS/RAF/MEK/ERK and PI3K/AKT/mTOR. Typical downstream effects include promotion of cell survival, mitosis, and altered adhesion (5). The ErbB network is complex, with various fine-tuning responses; activated signaling proteins and downstream effects are dependent on the involved ligands, dimeric partners, and the cellular context (6). Furthermore, EGFR can also act as a transcription factor itself. Radiation triggers translocation of EGFR to the nucleus, where it takes part in complexes related to DNA damage repair. The EGFR antibody cetuximab blocks this translocation and causes increased DNA strand breaks following radiation (7).

These preclinical findings are in agreement with clinical data showing that increased quantitative expression of

EGFR was correlated with worse local control and survival in patients treated with radiation alone (3,8). However, these analyses failed to account for the emerging factor of human papilloma virus (HPV) status, recently found to be a strong favorable prognostic factor (9). HPV-association is often measured by the surrogate marker of p16^{Ink4A} (p16) protein overexpression, which has the highest concordance with HPV DNA *in situ* hybridization in oropharyngeal tumors (10). HPV-associated tumors appear to have less frequent EGFR amplification (11,12), as well as fewer genetic alterations overall (13).

Targeting of epidermal growth factor receptor (EGFR) through the extracellular domain

Initial efforts to target EGFR in HNSCC used MAbs. Results using cetuximab, a chimeric IgG1 MAb with high affinity for the extracellular domain of EGFR, were first published by Bonner *et al.* in 2010 (4). In this phase III trial, patients receiving cetuximab had an improvement in median survival of nearly 20 months over those receiving radiotherapy alone. However, the trial was criticized for not having a control arm of radiotherapy with a platinum agent, considered the current standard of care. Regardless, the trial confirmed the radiosensitizing effects of cetuximab, and it also confirmed previous observations that acneiform rash is a clinical marker of cetuximab response, with patients experiencing rash having median overall survival over 40 months longer than those without. In 2011, the FDA expanded the indication for cetuximab to include recurrent and metastatic HNSCC based on the European EXTREME trial (14).

In attempts to improve upon the standard definitive treatment based on chemoradiotherapy, trials were also performed adding cetuximab to platinum-based regimens concurrent with radiation. The major phase III trial using this strategy was RTOG 0522, with results originally presented at the American Society of Clinical Oncology (ASCO) conference in 2011, then published in 2014 (12). In this study, patients with locoregionally-advanced HNSCC were randomized to chemoradiotherapy with concurrent cisplatin, with or without concurrent cetuximab. No significant differences were found in 3-year locoregional failure, distant metastasis, progression-free survival, or overall survival (72.9% control *vs.* 75.8% cetuximab). The cetuximab arm had significantly higher rates of acute side effects, and treatment completion was lower than the control arm. However, subgroup analysis showed

improved overall survival with cetuximab in patients younger than 50 (hazard ratio for death 0.45, P=0.02). EGFR immunohistochemical expression was evaluated as a biomarker for response, but no interaction effect with treatment arm was found.

Similar studies using other EGFR antibodies met with similar results. Panitumumab was used in the CONCERT-1 trial added to cisplatin chemoradiotherapy (15). There were no significant differences in local control or survival, and more acute toxicity and treatment discontinuation occurred in the panitumumab arm. Zalutumumab was used in the DAHANCA 19 trial added to radiotherapy with concurrent cisplatin and nimorazole (16). Preliminary results were presented at the 2013 European Cancer Congress; locoregional control, disease-specific survival, and overall survival were statistically equivalent between arms. At present, the addition of EGFR antibodies to platinum-based chemoradiotherapy has only resulted in greater acute toxicity without advantages in oncologic outcome, although attempts at refinement of this approach continue. A randomized study sponsored by the National Cancer Centre of Singapore (NCT00957086) is currently enrolling patients to examine the combination of chemoradiotherapy with nimotuzumab, which has lower affinity towards EGFR than cetuximab. Preclinical data suggests this may confer selectivity for high EGFR-expressing patients, and lower toxicity rates have been reported in phase I/II trials (17).

Targeting of epidermal growth factor receptor (EGFR) by tyrosine kinase inhibition

Another strategy for targeting EGFR is orally administered tyrosine kinase inhibitors (TKIs) that directly prevent autophosphorylation of the intracellular signaling domain. In 2013, two randomized trials using TKIs were published in the same issue of the *Journal of Clinical Oncology* (18,19). In the study by Martins *et al.* (18), patients with locoregionally advanced HNSCC were randomized to cisplatin-based chemoradiotherapy with or without the TKI erlotinib. No significant difference was found between arms in the primary endpoint of complete response rate, although there was a trend towards improvement (40% control *vs.* 52% erlotinib, P=0.08). Adverse effects were minimal compared to those seen with the addition of MAbs, and no differences were seen as far as completion of radiotherapy or cisplatin. Tissue evaluation was performed for less than 50% of study patients, and no biomarkers for erlotinib response were identified.

Along with this trial, the Eastern Cooperative Oncology Group (ECOG) 1302 trial results were published (19). In this phase III trial, patients with recurrent or metastatic HNSCC with poor performance status or prior failure of platinum therapy were randomized to docetaxel with or without gefitinib, another oral EGFR-TKI. There was no statistically significant difference in the primary endpoint of overall response rate. In an unplanned subgroup analysis, patients younger than 65 years showed an improved median overall survival with gefitinib, but there were higher rates of infections and treatment interruption in patients over 65.

Harrington *et al.* examined the addition of the TKI lapatinib, publishing phase III data in 2015 (20). Lapatinib has the theoretical advantage of being a dual-TKI, inhibiting activation of both EGFR and ErbB2. Heterodimers of EGFR-ErbB2 have been shown to be more potent signaling complexes than EGFR homodimers (6). This trial was conducted in a group of high-risk post-operative HNSCC patients who would typically receive adjuvant chemoradiotherapy (20). Patients were randomized to post-operative cisplatin chemoradiotherapy with or without concurrent/maintenance lapatinib. There was no difference in the primary endpoint of 3-year disease-free survival (62.2% control *vs.* 61.1% lapatinib), and no differences in secondary end points. While more acute side effects were seen in the lapatinib group, there was no significant difference in completion of chemoradiotherapy.

Future strategies to improve outcomes using epidermal growth factor receptor (EGFR) targeted therapies

This review of major randomized trials illustrates the repeated failure of EGFR-targeted agents to add benefit to standard platinum-based therapies. One reason may be the lack of maintenance EGFR inhibition after completion of the concurrent regimen; a maintenance cetuximab phase might have contributed to the improved outcome in the recurrent metastatic setting. Another reason may be that the addition of these extra agents is too toxic, particularly in elderly patients. Acute toxicity caused more treatment delays in RTOG 0522, CONCERT-1, and ECOG 1302, which may have nullified any benefit from EGFR inhibition. In RTOG 0522 and ECOG 1302, the addition of EGFR inhibition were found on post hoc analyses to be associated with survival benefits limited to younger patients. This differential effect by age may be more pronounced with MABs than TKIs, given their higher toxicity profiles

overall. No treatment delays were seen in the Martins *et al.* gefitinib trial and the Harrington *et al.* lapatinib trial. ECOG 1302 (combined docetaxel and gefitinib) did see treatment interruptions, but this trial included poorer performing patients for whom even an added TKI may be too difficult.

Future trials might limit enrollment to younger patients to test this hypothesis, although support for additional trials of this nature may be low at this point given the risk of harm. A converse approach would be reducing platinum dose while adding EGFR-targeted therapy, to maintain therapeutic effect while limiting platinum-related toxicity. Following this concept, a phase I study examined chemoradiotherapy with reduced-dose cisplatin but with addition of cetuximab for locally advanced HNSCC (21). In this study, 87% of patients completed therapy as planned, and 2-year overall survival was a promising 80%.

Reexamining the biological mechanisms of these agents' action may help to shed light on future directions. As mentioned above, the radiosensitization effect of cetuximab appears to be related to its ability to prevent translocation of EGFR to the nucleus, limiting DNA damage repair (7,22). Cisplatin may similarly interfere with protein transcription and DNA damage repair, making any added benefit from cetuximab unneeded (23). Combining EGFR-targeting agents with chemotherapeutics that operate based on a different mechanism may therefore be more effective. Docetaxel is an anti-mitotic agent targeting microtubule activity, and has been shown *in vivo* to have combinatorial radiosensitizing effects with cetuximab (24). The phase II trial RTOG 0234 showed that that cetuximab/docetaxel compared favorably to cetuximab/cisplatin for post-operative high-risk HNSCC (25), and the currently recruiting RTOG 1216 will test this comparison at the phase III level (NCT01810913).

Unlike MABs, TKIs have found no role in either the definitive or palliative setting for HNSCC. One prominent difference between the two classes is immunogenicity. MABs are able to provoke antibody-dependent cellular cytotoxicity through interaction with Fc-gamma receptors on immune effector cells (26). It may be that this effect is more important than inhibition of EGFR activity. EGFR activating mutations are fairly rare in HNSCC (13), implying that they are not a common cause of oncogenesis. However, EGFR amplification is seen more often in HPV-negative tumors, which are more associated with tobacco use. EGFR is not amplified just in tumor cells, but also in histologically normal mucosa of HNSCC patients (27). Thus, EGFR

amplification may be a reaction to carcinogen exposure, but not necessarily an oncogenic driver. In non-small cell lung cancer, patients without EGFR activating mutations derive no benefit from TKIs (28,29). Thus, it is not surprising that TKIs also have little benefit for unselected HNSCC patients. The combination of cetuximab and an immune checkpoint inhibitor has shown activity in murine models (30), and clinical translation of this combination could be promising.

Another consideration is that EGFR is only one signaling molecule in a network of pathways ultimately promoting cell survival and mitosis (6). EGFR expression by gene copy number has not been shown to have any predictive value for response to cetuximab, indicating escape mechanisms may be in play (31). For example, recent evidence suggests that HER3 activation is induced by cetuximab exposure, bringing into consideration the use of an alternative approach to patients with *de novo* or acquired resistance to cetuximab (32). In support of this theory, the HER3 ligand (neuregulin) has been suggested as a possible prognostic marker in HNSCC (33). Other members of the ErbB family and related tyrosine kinases (FGFR, IGF-1) are also under active investigation as therapeutic targets (34). A recent examination of HNSCC genetics shows a diverse array of mutations (13). Activating mutations of a signaling molecule downstream to EGFR, PIK3CA (PI3K), were seen in high proportions of tumor samples, possibly bypassing effects of EGFR inhibition. Numerous stage I/II trials of agents targeting the PI3K/AKT/mTOR pathway are underway (35).

While new agents and combinations remain to be tested in the future, selection of the appropriate population may be the appropriate priority for designing future studies of EGFR-targeting agents. Low-risk HPV-associated tumors respond excellently to platinum chemoradiotherapy, showing long term survival rates near 95% (9). However, cetuximab is also radiosensitizing, with fewer side effects than expected from cisplatin (4). Therefore, trials such as RTOG 1016 are examining whether EGFR-targeted MAb can be used instead of cisplatin for HPV-associated cancers. In the CONCERT-2 trial, patients with locally advanced HNSCC were randomized to radiation with concurrent cisplatin or panitumumab. While outcomes were equivalent in the subset of patients with p16-positive tumors, adverse effects were not improved (36). The need for careful selection was also highlighted, as patients with p16-negative tumors did worse with panitumumab than with standard chemoradiotherapy. Maturing randomized data will provide further information (NCT00820248, NCT01302834,

NCT01855451).

While these trials hold promise for HPV-associated disease, the majority of HNSCC patients treated with concurrent chemoradiotherapy have HPV-negative cancers. In these higher risk patients, treatment intensification remains the dominant strategic approach. One such intensified approach is being tested by the ongoing TRYHARD study (RTOG 3501; NCT01711658). This study randomizes patients with non-HPV-associated locoregionally-advanced HNSCC to accelerated cisplatin chemoradiotherapy with or without concurrent/maintenance lapatinib. Unfortunately, since the initiation of this trial the results of Harrington *et al.* have been released, showing no effect of added lapatinib even in a selected postoperative high-risk subgroup. In the future, other novel agents may be added to chemoradiotherapy, in the search to improve outcomes for this higher risk population.

Predictive biomarkers to select patients likely to manifest EGFR-targeted therapy response could lead to the formulation of more effective studies, but truly prognostic biomarkers remain elusive. While HPV-association is a powerful prognostic factor in HNSCC, no EGFR-containing trial has shown any significant interaction effect with treatment. Likewise, EGFR expression has failed to be predictive of response to EGFR-targeted therapy, although the major trials in which this was evaluated used immunohistochemistry (12,20), which is dependent on staining protocol and may be less accurate than other methods. Failure of EGFR expression to predict response may ultimately be a reflection of the mutational diversity of HNSCC and the many alternative signaling pathways by which a cell may retain oncogenic drive (13). As we advance with targeted agents related to the PI3K/AKT/mTOR pathway, individualized genetic profiling may be necessary to determine choice of drug combinations (37). Development of acneiform rash remains the strongest biomarker of EGFR-targeted therapy response as of now. Immunological mechanisms by which this rash occurs are still under investigation, however molecular markers of immune-escape pathways may help predict response to anti-EGFR therapy (38).

Conclusions

Despite early positive clinical trials, EGFR targeting has generally not had the impact on HNSCC treatment it initially promised. However, as our understanding of the underlying biology deepens, combination with other agents

and targeting escape and resistant mechanisms as part of a broader pathway-targeting strategy may provide an answer as to the causes of innate and acquired resistance to EGFR inhibition. Multiple maturing clinical trials will provide a greater opportunity to better answer these questions over the next few years. We hope that the growing scientific understanding of EGFR's role in HNSCC will someday improve outcomes for our patients and no longer be lost in translation.

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Footnote

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