Editorial

EGFR in head and neck squamous cell carcinoma: exploring possibilities of novel drug combinations

Hina S. Rehmani[1], Natalia Issaeva[1,2,3]

[1]Department of Otolaryngology/Head and Neck Surgery, [2]Department of Pathology and Laboratory Medicine, [3]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Correspondence to: Natalia Isaeva. 450 West Drive, UNC at Chapel Hill, Lineberger Cancer Center, Room 22-044, Chapel Hill, NC 27599, USA. Email: natalia.isaeva@med.unc.edu.

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The standard care for head and neck squamous cell carcinoma (HNSCC) patients involving postoperative radiation therapy (RT) with concurrent cisplatin-based chemotherapy remains the same to this day since it's conceptualization in the 1960s (1). Though this treatment plan does improve locoregional control and disease-free survival in head and neck cancer patients, rates for overall 5-year survival is unimpressive in advanced HNSCC, ranging from 30% to 60%.

The human epidermal growth factor receptor (EGFR), also known as ErbB-1 or HER1, is a member of the ErbB receptor family. It is an extensively studied oncogenic gene influencing gene expression, proliferation, angiogenesis, apoptosis inhibition, cell motility, metastasis, adhesion, and angiogenesis. As one of the top targets of precision therapy, especially due to high levels of mutations found in lung cancer, it was natural to assume that head and neck cancer patients may benefit from EGFR-targeted therapies. This is due to the fact that EGFR is overexpressed in over 90% of head and neck tumors (2) and the association translates to shorter survival for patients (3-5). HNSCCs have significantly increased EGFR expression, high frequency of EGFR amplification, and low rates of single nucleotide variations (SNV)/indels (6).

In 2006, Cetuximab (Erbitux), a monoclonal antibody (mAb) targeting the extracellular domain of EGFR, was approved for head and neck cancer for either local/regional advanced squamous cell carcinoma in combination with RT, or as a monotherapy for recurrent or metastatic squamous cell carcinoma progressing after platinum-based therapy. Then in November 2011, the FDA approved Cetuximab for late-stage head and neck cancer in combination with chemotherapy (recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with Fluorouracil).

However, it became clear later that the response rate for Cetuximab was less than 20% in HNSCC patients, despite high amplification of EGFR and independent of human papillomavirus (HPV) status. The addition of Cetuximab to platinum-based chemoradiation (CRT) did not lead to an improved outcome (7) and Cetuximab with RT yielded inferior overall survival in comparison with cisplatin for the nonoperative management of stage III to IVb HNSCC (8). Additionally, for patients with HPV-positive oropharyngeal carcinoma, radiotherapy plus Cetuximab showed lower overall survival and progression-free survival compared with radiotherapy plus cisplatin (9). Yet, these results coincide with recent findings that the addition of Cetuximab to either carboplatin/paclitaxel chemotherapy or high-dose radiotherapy treatment provided no survival benefit for nonresectable stage III non-small cell lung cancer (NSCLC), a cancer subtype that displays high EGFR expression and mutation rates (10).

Another arm of targeting EGFR, besides monoclonal antibodies, involves tyrosine kinase inhibitors (TKI) that

target the intracellular domain of EGFR. Many have been FDA approved for patients whose tumors have EGFR alterations or mutations. For example, Gefitinib (Iressa) is approved for NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Unfortunately, many fail to show impressive results in terms of desired clinical parameters. For example, in the case of Gefitinib (Iressa), it has shown limited clinical efficacy with response rates of 10–15% in HNSCC patients, as a single agent or in combination with radiation treatment (11).

Osimertinib (Tagrisso), a mono-anilino-pyrimidine small molecule, is an FDA-approved selective novel third-generation irreversible EGFR inhibitor that was designed to inhibit both EGFR-sensitizing and EGFR T790M-resistance mutations without affecting wild type EGFR; therefore, Osimertinib is well tolerated in patients with advanced or metastatic EGFR mutation-positive lung cancer. In addition to mutant EGFR, Osimertinib also displays remarkable activity against tumors overexpressing another member of the ErbB/HER tyrosine kinase family, HER2 (ERBB2), in a mouse model (12).

On top of relatively low response rates to EGFR-targeted therapies with mAb and TKIs in head and neck cancer, several reports also show that patients often acquire resistance (13,14). Several publications point out that despite EGFR inhibition, there are multiple downstream signaling pathways that serve as alternatives and that are found to be persistently activated, thus permitting cancer resistance to EGFR-inhibitors (15). Additionally, less than 5% of head and neck cancers contain EGFR mutations, which may partially explain limited efficacy in using TKIs and the current lack of FDA-approved TKIs for HNSCC (16).

The frustrations with mediocre improvements in head and neck cancer therapy involving EGFR have been somewhat quelled with the potential seen in using drug combinations. Additionally, there is greater appreciation of using "repurposing drugs"—existing drugs that are used for new therapeutic purposes—to speed up the availability of options for head and neck cancer patients and potentially reduce a treatment-associated cost for patients.

In *Annals of Translational Medicine*, Chaib *et al.* described the results of *in vitro* and *in vivo* experiments where combinations of Osimertinib with dihydroartemisinin (DHA) exhibited synergistic cytotoxicity in HNSCC cell lines (17). The authors used FaDU and Cal27 head and neck cancer cell lines that both overexpress wild type EGFR for their analysis, which is a good representation since few head and neck cancers contain EGFR tyrosine kinase domain mutations, but many have EGFR amplifications and/or overexpression.

DHA, the most potent synthetic derivative of artemisinin, is a European Medicines Agency (EMA)-approved antimalarial drug with antibacterial and antiviral properties; however, several publications indicate that it may inhibit tumorigenesis in many cancer types, including head and neck (18-20), thus providing a scientific basis for repurposing DHA for cancer treatment. Interestingly, DHA was found to inhibit STAT3 (19), while STAT3 activation was shown to induce resistance of HNSCC to targeted therapy including EGFR monoclonal antibody Cetuximab (21).

To address the issue of multiple downstream signaling pathways activated with EGFR suppression and leading to acquired resistance to EGFR inhibitors, Chaib *et al.* explored a combination of DHA and Osimertinib. DHA suppressed STAT3 and Src phosphorylation in head and neck cancer cells; moreover, the combination was able to inhibit AXL expression—another event that was associated with resistance to Osimertinib (22). In addition, while exerting a notable tumor suppressing activity, the combination did not display any notable side effects in FaDu and CAL27 mice xenografts, which is a hopeful finding. Currently there are no clinical trials using Osimertinib in head and neck cancer patients and DHA has never clinically been tested in cancer patients.

Surprisingly, despite the fact that FaDu and Cal 27 cells contain wild type EGFR, Osimertinib alone suppressed cell growth and had a significant antitumor effect in mouse xenografts (17). It remains to be tested whether expression of HER2 and significant levels of HER2 phosphorylation that are exhibited by both cell lines (23) play a role in a sensitivity of these cells to Osimertinib. Further investigation into DHA's antitumorigenic properties in HNSCC also merit further study as we strongly believe it may involve in more than just suppression of STAT3. Overall, we believe that the novel combination of Osimertinib with DHA for head and neck cancer explored by Chaib *et al.* warrants further investigation.

HNSCC is a heterogeneous disease and despite high expression of EGFR, targeted monotherapies against this oncogene have produced average results or led to resistance. Due to the interplay of other oncogenic pathways involved with EGFR, involving combination therapies to target multiple pathways will be essential.

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Footnote

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