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Review Article

Role of EGFR and Her-2 Expression in Oral Cancer

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Abstract

Therapeutic options in advanced oral cancers have not been successful in improving the morbidity and mortality rates in the past decades. Role of EGFR and Her-2 has received wide attention in head and neck Squamous cell carcinoma as potential targets for new therapies. Oral Squamous cell carcinoma (OSCC) shows 42 to 58% increase in epidermal growth factor receptor (EGFR) and 3 to 41% in Her-2 expression. Immunohistochemical staining is the most common method used for detection of overexpression of these receptors. Role of EGFR and Her-2 has received wide attention in head and neck Squamous cell carcinoma (HNSCC) as potential targets for new therapies. Use of immunohistochemical technique, has made the process of determining EGFR status simple and easily applicable in diagnostic strategies and prognostication. Oral tumors over expressing EGFR exhibit may benefit from specific target agents. Role of Her-2 expression in oral cancer is still in its infantile stage and further studies are required to establish its therapeutic approach.

Keywords: EGFR; Oral Cancer

Incidence of oral cancer is high in India and despite many advances in therapeutic approaches; 5 year survival rate has not improved significantly in head and neck cancers. Standard treatment of locally advanced oral cancer has been surgery and adjuvant radiotherapy with or without chemotherapy. But therapeutic options in advanced oral cancers have not been successful in improving the morbidity and mortality rates in the past decades. Staging of cancer helps in planning of treatment and prognostication, but it does not predict about onset of disease process. Clinical trials and many studies have been done on tyrosine kinase receptors to yield better results.

Tyrosine kinases are mediators in the signaling cascade having role in biological processes such as growth, differentiation, metabolism and apoptosis when affected by external or internal stimuli. They have received wide attention being part of pathophysiology of cancer. Activation of cancer cells can be blocked by use of therapies against the tyrosine kinase receptors. The tyrosine kinase receptors have been over expressed in many cancers. Trastuzumab for the treatment of advanced breast cancer, Imatinib for treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors, gefitinib for the treatment of lung cancer; all three have been successfully used in treatment of cancer and has translated basic research in cancer genomics into cancer therapeutics.

Oral cancer has also seen the use of targeted therapies against tyrosine kinase receptors. Oral Squamous cell carcinoma (OSCC) shows 42 to 58% increase in epidermal growth factor receptor (EGFR) [1] and 3 to 41% in Her-2 expression. Immunohistochemical staining is the most common method used for detection of overexpression of these receptors. Role of EGFR and Her-2 has received wide attention in head and neck Squamous cell carcinoma (HNSCC) as potential targets for new therapies [3-5].

EGFR signaling regulates cell proliferation and differentiation during development and it also contributes to proliferation, invasion and metastasis in tumor cells. EGFR is expressed in various carcinomas including head and neck cancers. EGFR overexpression

has been seen widely in OSCC, but Her-2 overexpression has been seen in few specimens of oral carcinoma. Few articles have reported association between poor differentiation of tumor and expression of EGFR in OSCC [6]. This is most probably related to degree of differentiation of keratinocytes [7].

EGFRs are members of the EGF growth factor receptor tyrosine kinase family and are generally found on the cell surface and are 170–180 kD transmembrane glycoprotein tyrosine kinase receptor identified in many cancers such as breast cancer, prostate cancer, pulmonary cancer, bladder cancer and head and neck cancers [8]. EGFR expression generally involves all the layers of epithelium in OSCC specimens while in normal oral epithelia it is localized to the basal cell layer [9,10].

Various studies showing the EGFR expression extent and intensity scores suggested that cancers having overexpression of EGFR display pathological features of more aggression which may be attributable to the activation of different signaling pathways that control diverse biological processes. Laimer., *et al*. reported high EGFR expression in oral and oropharyngeal squamous cell carcinoma patients on multivariate analysis and concluded EGFR antigen to represent an attractive target for targeted therapies with specific tyrosine kinase inhibitors or monoclonal antibodies [11]. Reports have also shown connection between the EGFR expression and the resistance to ionizing radiation. Inhibition of EGFR by a monoclonal antibody, cetuximab, increases the response of Squamous cell carcinoma to radiation [12,13]. Cetuximab represents a promising inhibiting agent that affects cellular proliferation, apoptosis and chemoradio sensitivity in squamous cell carcinoma cell lines of head and neck tumors. In these reports inhibition of EGFR has shown positive association with improved clinical outcome.

In contrast, studies published by Bernardes., et al. showed no significant association between EGFR, Her-2, and EGF salivary levels and immmuno expression of proteins EGFR and Her-2 in tumor specimen was seen. Also, the salivary levels of proteins were not associated with clinicopathological features of tumor [14,15]. Yamada., et al. has shown that EGFR expression is more common in well differentiated carcinomas. The correlation was strong between EGF receptors and differentiation, whereas, poorly differentiated tumors showed less intense staining. The study also revealed that EGFR-positive lesions presenting as low-grade tumours, has no association with patient outcome [16]. Smith., *et al.* emphasized on the fact that EGFR overexpression protects the patient from locoregional recurrence and the tumor has increased radio sensitivity. The confirmation of the results by new studies will help in prognosticating the patient [17]. These properties of EGFR show that it is a good target for therapeutic option and patients will be benefited by use of monoclonal antibodies against these receptors.

The EGFR2 (HER2/neu) oncoprotein is a ~185KD tyrosine kinase transmembrane receptor that belongs to the same family as epidermal growth factor receptor. It is encoded by a gene located on chromosome 17. Frequency of Her-2 expression and the prognostic role is still controversial. The over expression of Her-2 increases has been seen in many cancers such as breast, stomach and colorectal carcinomas. Therapy against this specific protein has also been used in treatment of cancers showing its overexpression. Her-2 neu over expression probably plays a role in carcinogenesis and increases the metastatic potential of a tumor, by promoting invasion through multiple stages and the metastatic cascade [18].

Few studies have shown that expression of Her-2 has no prognostic implication [14]. Seifi., et al. showed that Her-2 is not an effective protein in the carcinogenesis process of oral Squamous cell carcinoma [18]. On the contrary, Xia., et al. reported Her-2neu to be the most significant single factor in prediction of disease outcome [19]. The studied showed significant association between expression of Her-2 and Her-3 and lymph node metastasis and distant metastasis. They also stated correlation of Her-2 with EGFR expression.

The results are conflicting and me bay due to using different immunohistochemically methods (direct, indirect) or using different techniques (immunosorbent assay, radioimmunoassay, IHC) or there may be difference in subsite involvement and sex of patients with oral SCC. Fong., *et al.* suggested a dynamic change in Her-2 expression and development of oral squamous cell carcinoma. They showed low expression (10%) of Her-2 in normal oral mucosa, 20% in oral precancerous lesions of epithelial dysplasia and 40% expression in oral Squamous cell carcinoma. But clinicopathological variates like areca nut, tumor size and lymph node metastasis did not suggest any relation with expression of Her-2 in oral Squamous cell carcinoma [20].

Conclusion

To conclude, use of immunohistochemically technique, has made the process of determining EGFR status simple and easily applicable in diagnostic strategies and prognostication. Hence oral

tumors over expressing EGFR exhibit may benefit from specific target agents. Role of Her-2 expression in oral cancer is still controversial and further studies are required.

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