INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is one of the significant causes of morbidity and mortality worldwide. Developments in the field of evaluation and treatment in the last decade have resulted only in a modest improvement in survival rate.\(^1\) Hence, targeted therapies for HNSCC are actively tried with the goal of reducing morbidity and improving the survival. Epidermal growth factor receptor (EGFR) is over expressed in 80 to 90% of head and neck cancers\(^2\) and play a role in its pathogenesis and clinical course. Several EGFR-targeted therapies have therefore been developed and tried in clinical trials in the past decade resulting in the approval of cetuximab, an EGFR monoclonal antibody as a treatment agent for HNSCC by US FDA. Even though, EGFR monotherapy so far does not have a significant effect, cetuximab in combination with radiotherapy has enhanced the overall effect of radiotherapy in these patients without enhancing significantly the overall toxicity. Hence, understanding the mechanisms of resistance and exploring new combination treatments with EGFR targeting agents are important.

RECEPTOR BIOLOGY

EGFR is a glycoprotein that belongs to ErbB receptor family. Other members of this family include Her-2, Her-3 and Her-4.\(^3\) These receptors are composed of an extracellular ligand-binding domain, a hydrophobic transmembrane segment and an intracellular tyrosine kinase domain. The gene necessary for expression of the human EGF receptor is located on human chromosome 7.\(^4\) When a natural ligand like EGF or transforming growth factor alpha (TGF-α) binds to the receptor, it undergoes a conformational change promoting homodimerization with other EGFR molecules (ErbB1-ErbB1) or heterodimerization with other HER family members (e.g. ErbB1-ErbB2) resulting in subsequent autoactivation of the tyrosine kinase from the intracellular domain of the receptor.\(^5\) Other mechanisms that may lead to constitutive receptor activation include receptor overexpression (common in HNSCC) and mutations of the receptor. Activation of EGFR triggers activation of the mitogen-activated protein kinase (MAPK), phospha-tidylinositol 3-kinase (PI3K)/Akt, and protein kinase signal transducers and activators of transcription (STAT) signaling pathways.\(^3,6,7\)

EGFR AND PROGNOSIS

Expression of EGFR has been shown to be an independent prognostic factor for overall survival.\(^8\) Expression of EGFR is associated with higher incidence of radiation resistance.\(^9\) Phosphorylated EGFR without mutations\(^10\) and increased EGFR gene copy number may also be associated with poor prognosis in head and neck squamous cell carcinomas.\(^11\)

RATIONALE FOR TARGETING EGFR

While EGFR signaling is tightly controlled in normal cells, the tumor cells show several alterations like overexpression of ligands, receptors or receptor mutations leading to an increased activation of its tyrosine kinase activity, and thereby promoting cell proliferation, angiogenesis and inhibition of apoptosis. These will ultimately result in an environment favoring tumor growth and metastasis.\(^12\) Several in vivo and in vitro studies have shown that inhibition
of the EGFR (ErbB1) and Her-2 (ErbB2) signaling cascade could block cell cycle progression and induce apoptosis, providing the rationale for anti-EGFR therapy.\textsuperscript{13,14}

**THERAPEUTIC STRATEGIES FOR TARGETING EGFR**

Two major therapeutic strategies have been developed in targeting the EGFR pathway. The first one targets the extracellular domain of the receptor with the anti-ErbB monoclonal antibodies (MoAbs) like cetuximab (Erbitux\textsuperscript{®}). The second strategy is to use tyrosine kinase inhibitors (TKIs), such as Gefitinib (AstraZeneca) or Erlotinib (Roche) to block the binding of adenosine triphosphate to the intracellular TK domain of EGFR, thereby blocking TK activity and subsequent intracellular signaling.\textsuperscript{15} MoAbs like cetuximab and panitumumab has been approved for the treatment of head and neck carcinomas.

Even though EGFR is commonly expressed in HNSCC, treatment with anti-EGFR agents alone has only been modestly active in patients. However in combination with radiotherapy, they appear to enhance the effect of radiation. Bonner and colleagues in 2000 showed that cetuximab and concurrent radiation resulted in a greater decrease in cell proliferation in number of HNSCC cell lines.\textsuperscript{16} Subsequently, a multinational phase III study conducted by the same authors showed that treatment of locoregionally advanced head and neck cancer with concomitant high-dose radiotherapy plus cetuximab improved locoregional control and reduced mortality without increasing the common toxic effects associated with radiotherapy to the head and neck.\textsuperscript{17}

However, the efficacy of cetuximab with radiotherapy compared with standard concomitant chemoradiotherapy remains under investigation. The Erbitux in first-line treatment of recurrent or metastatic head and neck cancer (EXTREME) phase III trial compared platin-5-fluorouracil alone versus combined with cetuximab as first-line treatment in recurrent or metastatic SCCHN.\textsuperscript{18} Subsequently, a multinational phase III study conducted by the same authors showed that treatment of locoregionally advanced head and neck cancer with concomitant high-dose radiotherapy plus cetuximab improved locoregional control and reduced mortality without increasing the common toxic effects associated with radiotherapy to the head and neck.\textsuperscript{17}

A systematic review by the head and neck cancer disease site group of cancer care Ontario’s program in evidence-based care (PEBCC) identified four phase III trials to develop evidence-based recommendations for the use of cetuximab and other anti-EGFR agents in advanced HNSCC.\textsuperscript{19} Based on the review of available clinical trial results, they made the following observations/recommendations:

- Cetuximab in combination with platinum-based chemotherapy is superior to chemotherapy alone in patients with recurrent or metastatic HNSCC.
- In patients with locally advanced HNSCC who are medically unsuitable for concurrent platinum-based chemotherapy, the addition of cetuximab to radical radiotherapy should be considered to improve overall survival, progression-free survival and time to local recurrence.

**EMERGING STRATEGIES**

Understanding the mechanisms of resistance to EGFR targeted therapies and prediction of response to treatment, many patients are refractory to EGFR inhibitor treatment despite higher levels of EGFR within the tumor. Even in patients with an initial clinical response, acquired resistance can occur after prolonged treatment. Several factors may be contributing to this effect:

a. **EGFR mutations and structural variants**: EGFR mutations, though rare compared to lung cancers, have been described in HNSCC and their incidence differ between ethnic groups ranging from 0 to 4% in whites to 7% in Asians.\textsuperscript{20} Several structural variants of EGFR have been identified and the most frequently detected genomic variant is the EGFRvIII, which is expressed in 42% of HNSCC tumors.\textsuperscript{21} EGFRvIII is a 145 kDa protein resulting from the deletion of amino acids 6 to 273 of the wild-type EGFR (wtEGFR) extracellular domain causing a reduction in the binding affinity of monoclonal antibodies. The transmembrane and intracellular domains are structurally identical to that of wtEGFR and have the ability to initiate intracellular signaling by itself due to persistent phosphorylation of its protein kinase domain.

b. **Ras mutations**: K-ras (v-KI-RAS2 Kirsten rat sarcoma viral oncogene homolog) mutations are also associated with resistance to EGFR inhibitors.\textsuperscript{22} However, H-ras mutations are more common in HNSCC and may play an important role in resistance to EGFR. Incidentally, H-ras mutations are more common in patients from south asia.\textsuperscript{23}

c. **Other mechanisms**: These include epithelial-mesenchymal transition (EMT), cyclin D1 upregulation, PI3KCA mutations\textsuperscript{24} or by activation of downstream or alternative cytoplasmic signaling pathways and germline polymorphisms of EGFR.\textsuperscript{25} Based on these findings, a series of predictive markers can be developed in the future to guide the selection of appropriate patients who are sensitive for EGFR targeted therapies.

**EFFORTS TO OVERCOME TREATMENT RESISTANCE (COMBINATION TREATMENTS)**

Combining therapeutic agents with different mechanisms of action like STAT or SRC inhibitors may be more effective...
than using a single agent. By this method, parallel pathways activated during HNSSC pathogenesis can be effectively targeted. Combination treatments may play a great role in targeted therapies for HNSSC. 24

CONCLUSION

Despite high expression of EGFR, single agent EGFR targeted therapies have not been effective. However, EGFR monoclonal antibody, cetuximab, enhanced the effect of radiotherapy and improved survival in advanced HNSSC when given along with chemotherapy. Future studies will be directed to understand the mechanisms of resistance, and identification of suitable markers to predict response to EGFR targeted therapy. Combining two or more molecular targeting agents may improve the overall tumor response.

REFERENCES


