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Introduction

Squamous-cell cancers of the head and neck with advanced primary lesions, with or without regional lymph-node metastases, are challenging to treat effectively while maintaining the function of vital healthy structures. Extensive surgical resection of the primary tumor and regional cervical lymphatics used to be the standard of care in the USA. More recently, additional organ-preserving strategies using either radiation alone or chemoradiotherapy have become a treatment option for these patients, and have been the focus of much investigation.

Increased understanding of molecular alterations in head and neck squamous cell carcinoma (HNSCC) and other cancers has ushered in efforts to develop molecularly targeted therapies. Among these alterations, overexpression of the epidermal growth factor receptor (EGFR) has been identified in many cancers, including 80% to 100% of HNSCC, where it has also been implicated in a more aggressive phenotype, increased resistance to treatment, and poorer clinical outcome.

Head and neck squamous cell carcinoma is the 5th most common cancer worldwide. In US alone 40,000 are newly diagnosed annually. It represents close to 11,000 Deaths annually, just in the US. Worldwide that figure grows to 200,000 deaths annually. The majority of the cases present in advanced stages, likely related to the poorer outcomes. It is estimated that 60% of patients develop local disease recurrence within 2 years. Improvements in surgery and chemoradiation offer better organ preservation but they have resulted in only modest improvement in the 5-year survival of HNSCC in the past three decades. 5-year survival rates of patients with locally advanced or metastatic disease are 48% and 26%, respectively. We need a better understanding of HNSCC at the cellular and molecular levels to guide development and use of new therapeutic interventions.

<i>Site</i>	<i>New Diagnoses</i>	<i>Deaths</i>
oral cavity & pharynx	30,990	7,430
larynx	9,510	3,740
nasal cavity, nasopharynx, paranasal sinuses, cervical esophagus, skin		

Figure 1.
Site of H&N cancers and related deaths annually.

Molecular Therapeutics

The systematic clinical investigation of organ-preserving radiotherapy and chemoradiotherapy regimens suggested that these regimens could produce overall survival results as good as surgical resection for patients with locoregionally advanced squamous-cell cancer of the head and neck (LASCCHN), thus radiation had become a cornerstone of treatment for patients with LASCCHN by the 1990s. The addition of chemotherapy to radiotherapy has also been extensively investigated. A recent meta-analysis of 87 randomised trials that compared locoregional treatment with or without chemotherapy found that the addition of chemotherapy to locoregional treatment was associated with an absolute survival advantage of 4 • 5% at 5 years.

There are many therapeutic agents being investigated to target the EGFR receptor in the head and neck. Of those, only cetuximab (erbitux) has been approved for unresectable head and neck SCCA. There are several drugs that are currently in phase III investigation. There are several tyrosine kinase inhibitors being investigated, such as erlotinib and gefitinib (already approved for lung cancers). Avastin, a VEGF monoclonal antibody is also being investigated. In addition COX-2 inhibitors, farnesyl inhibitors, and proteasome inhibitors are also being investigated in H&N.

These observations have led to interest in the development of molecularly targeted small-molecule inhibitors of EGFR for the treatment of HNSCC. Gefitinib (Iressa), an EGFR tyrosine kinase inhibitor, has been tested in clinical trials in solid tumors, including HNSCC, as a single agent, or in the combination with other chemotherapies or radiation, but has shown limited clinical efficacy with response rates of 10% to 15%. Molecular biomarkers that could identify patients responsive to gefitinib or other EGFR inhibitors would be useful in the selection of patients for therapy. The EGFR is a membrane-bound glycoprotein with an extracellular cysteine-rich ligand-binding domain linked by a short single transmembrane sequence to an intracellular tyrosine kinase and carboxyl-terminal scaffolding domains.

EGF Receptor

The EGF receptor is a 170–180 kD transmembrane glycoprotein tyrosine kinase receptor that is ubiquitous in cells in the upper aerodigestive tract. EGFR binds epidermal growth factor (EGF), transforming growth factor (TGF)-alpha, and other regulating proteins. Activation of EGFR results in a complex cascade of signaling pathways that influence normal cellular proliferation and differentiation and lead to strong mitogenic activity. Ligand binding results in:

- receptor dimerisation
- activation of the intrinsic kinase domain
- phosphorylation of tyrosine residues within the cytoplasmic tail.

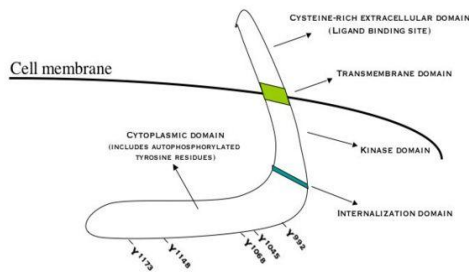


Figure 2.
EGF Receptor

Proteins dock on phosphorylated residues, leading to the activation of signaling pathways that promote cell growth, proliferation, differentiation, and migration. ErbB family ligands are EGF and transforming growth factor- α (TGF- α). The erbB family consists of four closely related members:

- erbB1
- erbB2
- erbB3
- erbB4

ErbB1 is also known as EGFR and HER1, it is targeted by gefitinib, cetuximab and erlotinib. ErbB2 is also known as Her2/neu and it is targeted by herceptin. Upon binding of the extracellular ligand EGFR forms homo-dimers and heterodimers with other erbB members, such as erbB2. Herein lays the rationale for targeting Her2/neu receptor in head and neck cancer. Other interesting features of the erbB family are that ErbB2 is unique, as none of the known ErbB family ligands activates ErbB2 homodimers. Instead, ErbB2 seems to function primarily as a hetero-dimerization partner for other ErbB family members. ErbB3 differs from the other ErbB receptors - possesses inefficient tyrosine kinase domain.

Overexpression of EGFR is observed in 42% to 80% of studied HNSCCs. 90% of trials showed a poorer outcome for patients with EGFR overexpression in a study that analyzed 756 patients. EGFR seems to be strongly correlated with worse prognosis in HNSCC in patients treated with either chemotherapy or RT. This finding suggests that overexpression of EGFR may be associated with chemotherapy resistance in these patients.

The presence of naturally occurring mutations of the EGFR gene in tumors may account for the limited clinical response to EGFR-targeted therapies. Various mutations of the EGFR gene have been described.

However, the presence of mutant EGFR (EGFRvIII) and/or EGFRwt has not been systematically evaluated in HNSCC tumors before treatment with EGFRtargeted therapy. Recently, somatic mutations in the tyrosine kinase domain of the EGFR gene have been described in non-small cell lung carcinomas that are associated with increased sensitivity to EGFR-specific TKIs. However, in HNSCC, the incidence of these mutations is low and varies according to ethnic origin (1% of Caucasians versus 7% of Asians with HNSCC).

A commonly described EGFR mutation is a truncation mutation, EGFR variant III (EGFRvIII). In gliomas, where it has been most extensively studied, EGFRvIII expression correlates with increased tumorigenicity in mouse models and poor prognosis in the clinical setting. Moreover, the expression of EGFRvIII is unique to cancer. EGFRvIII has not been observed in normal tissue, but it has been detected in other malignancies, such as non-small cell lung carcinoma, breast cancer, and ovarian carcinoma. This deletion produces a truncated 150-kDa protein that is weakly constitutively phosphorylated in a ligand-independent manner. Ligand-independent activation of EGFRvIII may explain the relative inability of blocking mAbs to downregulate this receptor.

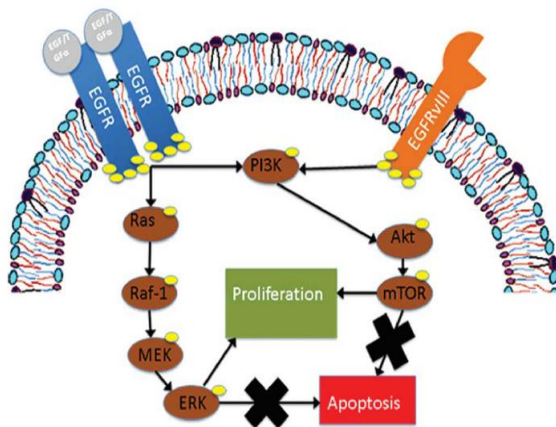


Figure 3. EGFRvIII preferentially activates cascade by PI3k

	Tyrosine Kinase Inhibitors (TKIs)	Monoclonal Antibodies (mAb)
Agents	gefitinib (<i>Iressa</i>) erlotinib (<i>Tarceva</i>) lapatinib	cetuximab (<i>Erbitux</i>) panitumumab
Mechanism	bind <i>selectively</i> to intracellular tyrosine kinase domain of EGFR	bind <i>specifically</i> to extracellular ligand-binding domain of EGFR
Administration	oral daily	intravenous every 1-3 weeks
Adverse Effects	rash diarrhea nausea	rash hypersensitivity reactions

Table 1. Comparison of TKIs and mABs

Updates in mAb Literature

First, Bonner and colleagues conducted a phase III study comparing cetuximab plus radiotherapy with radiotherapy alone in locoregionally advanced SCCHN. A significant improvement in locoregional control (median: 24.4 versus 14.9 months) and OS (median: 49 versus 29.3 months) was found in favor of the cetuximab and radiotherapy regimen. Second, cetuximab was investigated as a first-line treatment in patients with incurable recurrent and/or metastatic disease in combination with chemotherapy. Vermorken and colleagues showed that the addition of cetuximab to 5-fluorouracil (5-FU) and platinum-based therapy prolongs OS and progression-free survival (PFS) in this setting. Most researchers are foregoing comparing cetuximab to traditional chemotherapy but rather are working to integrate it into the doublet chemotherapy regimen that has become standard of care in Head and Neck Cancer treatment. One such study per Grandis and colleagues added cetuximab to docetaxel and cisplatin along with radiation for advanced stage. They identified that HPV expression resulted in better progression free survival and overall survival. In addition they also found EGFR expression was observed in 37 of 39 available biopsies and did not impact response to therapy or clinical outcome. They found the 3-year progression-free survival was 87% and the 3-year overall survival was 91%. In that study a complete response was seen in 70% of patients.

Tishler et. al. published the results of a phase I trial with 19 previously untreated patients with Stage III or IV SCCA. Their treatment algorithm was as follows:

- Panitumumab was administered weekly
- Paclitaxel was given weekly i.v. over 60 min after panitumumab
- Carboplatin was given i.v. over 30–45 min following paclitaxel
- Patients were treated using a dose-painting IMRT approach with a single plan to deliver 35 fractions once daily over 7 weeks

As this was a phase I trial, no definitive conclusions can be drawn regarding the utility of Panitumumab in the treatment of advanced head and neck cancer, but it was fairly well tolerated (comparable to cetuximab) and they demonstrated at median follow-up of 21 months, 18 of 19 patients (95%) remained disease free.

Other areas of the EGFR spectrum that remain to be extensively studied is EGFRvIII. As described above it is a mutant form of EGFR which is constitutively activated in a ligand dependent fashion. It does not have a binding site for a ligand. It does however retain its intra-cellular tyrosine kinase residue which can be targeted. In a study by Grandis et al. EGFRvIII was identified in 42% of patients with HNSCC. They demonstrated less in-vitro cellular death in cell treated with cetuximab and generally larger tumor volumes and decreased in response to cetuximab in a mouse model. They also concluded that EGFRvIII transfected cells are also less sensitive to cisplatin and cetuximab. Interestingly these cells remain equally susceptible to EGFR Tki targeting.

Cetuximab has been shown to produce a characteristic acneiform rash. The acneiform rash induced by cetuximab was initially thought to be reason to stop therapy. Now it seems we are findings that the more severe the rash the better response to cetuximab. The rash may be due to EGFR-R521K genotype or other EGFR variation. Specifically EGFR-R521K demonstrates increased cetuximab binding. Patients with EGFR-R521K developed more severe rash. Patients with the G/G genotype of EGFR-R521K who significantly developed skin rash showed a trend to prolonged progression-free survival on cetuximab/docetaxel treatment.

Updates in Tki Literature

EGFR pathway inhibition can be achieved with low molecular weight tyrosine kinase inhibitors (TKIs) or with MoAbs. TKIs bind intracellularly to EGFR tyrosine kinase and inhibit phosphorylation and downstream signaling pathways. The two main compounds are erlotinib and gefitinib. Besides cetuximab, panitumumab and zalutumumab are two fully humanized anti-EGFR MoAbs. Nimotuzumab is a humanized MoAb with intermediate affinity for EGFR. EGFR inhibitors have been investigated either with curative intent in combination with radiation therapy or in incurable SCCHN as palliation.

Very important to understand when thinking about targeting receptors at the cellular level is the tumor microenvironment. It is how tumor cells interact with each other, how well they oxygenate and how they will ultimately receive chemotherapy medications. The response of a tumor to radiation depends on cell-extracellular matrix interactions and tumor oxygenation. Manipulating this microenvironment has proven challenging. One potential method would be to target VEGF. Anti-angiogenic therapy has been used to normalize tumor microenvironment (VEGF) Pharmacologic inhibition of EGFR can decrease VEGF expression and therefore angiogenesis. The theory is that Erlotinib, a Tki, would indirectly lead to vascular normalization and decrease tumor hypoxia thereby leading to greater effects of chemo and radiotherapy. In a study by Maity et. al. they demonstrated that erlotinib decreased hypoxia and increased blood supply to tumors in a mouse model. In addition, they also identified chemo and radio sensitization properties of EGFR inhibition by erlotinib.

One of the potentially attractive properties of Tkis is their ability to inhibit nuclear translocation of EGFR. Nuclear translocation of EGFR has been shown to correlate with resistance to both chemotherapy and radiation. Cetuximab has been shown to paradoxically activate EGFR. Wheeler and colleagues demonstrated in a very nice investigation that cetuximab and radiation both induce EGFR translocation to the nucleus. Dasatinib was able to successfully block radiation and chemotherapy induced EGFR translocation to nucleus as well as inhibit phosphorylation of EGFR at residue 845.

Future

Work started by Bonner et. al. by adding cetuximab to XRT needs to be supplemented in view of doublet chemotherapy advanced in HNSCC treatment. Further studies combining EGFR targeted therapies with cisplatin/5FU are needed to prove it as an effective adjunct to standard therapy. Demonstrating the chemo and radio sensitizing properties of EGFR blockade in patients would also be beneficial in order to take advantage of sensitizing properties of EGFR biologics and design new medications for this purpose.

EGFR is highly over expressed in H&N cancer, we know that mutant forms exist, which are constitutively activated, resulting in decreased activity of extracellular EGFR blocking by cetuximab, but retained activity by Tkis. Early Phase II trial data suggests addition of cetuximab or erlotinib improves disease free progression and survival. HPV status may help target therapy as such there is an ongoing RTOG 0920 trial that will look in this. Acneiform rash is a marker of positive response to both monoclonal antibodies and TKi. Further work is needed to determine which tumors are responders to EGFR targets. And finally, further work is needed to develop new protocols that limit toxicities of combining chemo and EGFR biologics.

Discussant's Remarks: EGFR Therapy by Vicente A. Resto, MD, PhD March 31, 2011

The question was how often are we seeing an EGFR positivity in our patient population and we have instituted a prospective protocol to assess EGFR positivity among other markers in our cancer patients now for about a year and although the numbers don't come to mind immediately they seem not to be very high although there seems to be a concentration of positivity in patients with oral cavity cancers.

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