Promising Biomarkers to Predict the Efficacy of Inhibitors of the Epidermal Growth Factor Receptor Tyrosine Kinase in Head and Neck Squamous Cell Carcinoma

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Abstract

The Epidermal Growth Factor Receptor (EGFR) is overexpressed in most Head and Neck Squamous Cell Carcinomas (HNSCs), making EGFR an important therapeutic target. Although specific mutations in EGFR sensitize inhibitors of the EGFR tyrosine kinase, these mutations are rarely observed in HNSCCs. Early clinical trials of monotherapy with EGFR inhibitors in patients with HNSCC have therefore yielded disappointing results. Clinical response rates to EGFR inhibitors may be improved by identifying suitable biomarker(s). One such promising biomarker is PIK3CA, which encodes phosphoinositide 3-kinase catalytic subunit α isoform; mutations in this gene may predict the efficacy of EGFR inhibitors.

Keywords: Head and Neck Squamous Cell Carcinoma (HNSCCs); PIK3CA; Biomarker; EGFR inhibitor

Introduction

Head and Neck Squamous Cell Carcinoma (HNSCC) is the sixth most common neoplasm worldwide [1]. Despite advances in treatment, patient survival remains poor, and HNSCC is associated with a high mortality rate. Therefore, research is needed to gain a better understanding of this disease and to develop novel treatment strategies.

Epidermal Growth Factor Receptor (EGFR) is a receptor tyrosine kinase that mainly activates two intracellular signalling pathways, the Phosphatidylinositol 3-Kinase (PI3K)/AKT signalling pathway associated with cell survival and the RAS/RAF/ Mitogen-Activated Protein Kinase (MEK)/ Extracellular-Signal-Regulated Kinase (ERK) signalling pathway associated for cell proliferation. EGFR is overexpressed in most HNSCCs, making this molecule a potential therapeutic target [2]. Nevertheless, early clinical studies with EGFR Tyrosine Kinase Inhibitors (TKIs) as single agents yielded disappointing results, with overall response rates to gefitinib and erlotinib, being in patients with recurrent and/or metastatic HNSCC being 11% and 4%, respectively. Clinical response rates to EGFR TKIs may be enhanced by identifying suitable biomarker(s).

Rarity of EGFR, KRAS and BRAF mutations in HNSCC

Somatic mutations in the TK domain of the EGFR gene, including in-frame deletions in exon 19 and missense mutations, such as L858R, G719X, and L861Q, increase the binding of EGFR TKIs to the ATP binding site of EGFR TK; these mutations are therefore strongly associated with sensitization to EGFR TKIs. Activating mutations of EGFR have been frequently detected in patient’s Non-Small Cell Lung Carcinoma (NSCLC) patients who respond to EGFR TKIs. In contrast, a resistance mutation has been detected in EGFR. The T790M mutation increases TK affinity for ATP, consequently reducing the competitive binding of EGFR TKIs to TK [3-7]. In contrast to lung cancer, the frequencies of mutations conferring sensitivity or resistance to TKIs are low in patients with HNSCC. Moreover, although one study reported that the frequency in HNSCC of the EGFR truncation mutation EGFRvIII was 42%, another study reported a frequency of only 0.31–0.37% [8-12].

Because mutations in KRAS and BRAF result in constitutive activation of their downstream signalling pathways through MEK/ERK, independent of EGFR activation, these mutations contribute to resistance to EGFR TKIs. Mutations in KRAS and BRAF have been observed in only 6% and 3% respectively, of patients with HNSCC [13-15]. In contrast, KRAS mutation frequencies are much higher in patients with colorectal cancer (30–42.3%) [13,14] and lung cancer (38%). BRAF mutation frequencies are also higher in colorectal cancer (13.9%) [14], but are low, 0–3%, in lung cancer [16,17]. Thus, routine screening for mutations in EGFR, KRAS, and BRAF will likely not
provide significant information for prediction of drug efficacy in HNSCC.

**PIK3CA mutations can predict the efficacy of EGFR inhibitors in HNSCC**

Activation of the phosphatase and tensin homolog deleted from chromosome ten (PTEN)/PI3K/AKT pathways enhances cell proliferation and invasion while suppressing apoptosis. PTEN antagonizes the enzyme PI3K, which converts phosphatidylinositol bisphosphate (PIP2) to phosphatidylinositol triphosphate (PIP3), thereby inhibiting EGFR signaling. Mutations in the gene encoding the PI3K catalytic subunit α isoform (PIK3CA), as well as in the PTEN and AKT genes, have been frequently detected in HNSCC. These mutations may stimulate survival signals independent of EGFR activation by activating AKT [18], suggesting that mutated PIK3CA may be a reliable and promising biomarker predicting the sensitivity of EGFR TKI in HNSCC. This hypothesis has been supported by results showing that cells expressing wild type PIK3CA, but with a loss of PTEN, are not resistant to EGFR inhibitors [19], whereas cells expressing mutant PIK3CA and harboring wild type PTEN are resistant to EGFR TKIs [20]. Moreover, the combination of the anti-EGFR monoclonal antibody cetuximab and a PI3K TKI was reported to be a good therapeutic option in PIK3CA-mutated HNSCC [21].

**Conclusion**

Although the overall survival of dacomitinib-treated patients did not depend on PI3CA gene status, overall survival was significantly shorter in patients with mutant PI3CA and high levels of expression of genes encoding inflammatory cytokines, such as IL6, IL8, IL1A, IL4, and TNF [22]. These results suggested that signalling via the STAT3 pathway involving inflammatory cytokines can compensate for signalling via EGFR [23]. Therefore, PIK3CA mutations, together with levels of inflammatory cytokines, are useful in predicting the efficacy of EGFR TKIs in HNSCC.

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**Conflicts of Interest**

The authors declare there are no conflicts of interest.

**References**


