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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 (HNSCCs), 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

- Suh Y, Amelio I, Urbano T, Guerrero I, Tavassoli M (2014) Clinical update on cancer: Molecular oncology of head and neck cancer. *Cell Death Dis* 5: e1018.
- Saranath D, Panchal RG, Nair R, Mehta AR, Sanghavi VD, et al. (1992) Amplification and overexpression of epidermal growth factor receptor gene in human oropharyngeal cancer. *Eur J Cancer B Oral Oncol* 28B: 139-143.
- Cohen EE, Rosen F, Stadler WM, Recant W, Stenson K, et al. (2003) Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol* 21: 1980-1987.
- Soulieres D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, et al. (2004) Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol* 22: 77-85.
- Yun CH, Boggon TJ, Li Y, Woo MS, Greulich H, et al. (2007) Structures of lung cancer-derived EGFR mutants and inhibitor complexes: mechanism of activation and insights into differential inhibitor sensitivity. *Cancer Cell* 11: 217-227.
- Mitsudomi T, Yatabe Y (2007) Mutations of the epidermal growth factor receptor gene and related genes as determinants of epidermal growth factor receptor tyrosine kinase inhibitors sensitivity in lung cancer. *Cancer Sci* 98: 1817-1824.
- Yun CH, Mengwasser KE, Toms AV, Woo MS, Greulich H, et al. (2008) The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci USA* 105: 2070-2075.
- Baba Y, Fujii M, Tokumaru Y, Kato Y (2012) Present and future of EGFR inhibitors for head and neck squamous cell cancer. *J Oncol*.
- Loeffler-Ragg J, Witsch-Baumgartner M, Tzankov A, Hilbe W, Schwentner I, et al. (2006) Low incidence of mutations in EGFR kinase domain in Caucasian patients with head and neck squamous cell carcinoma. *Eur J Cancer* 42: 109-111.
- Lee JW, Soung YH, Kim SY, Nam HK, Park WS, et al. (2005) Somatic mutations of EGFR gene in squamous cell carcinoma of the head and neck. *Clin Cancer Res* 11: 2879-2882.
- Sok JC, Coppelli FM, Thomas SM, Lango MN, Xi S, et al. (2006) Mutant epidermal growth factor receptor (EGFRvIII) contributes to head and neck cancer growth and resistance to EGFR targeting. *Clin Cancer Res* 12: 5064-5073.
- Khattari A, Zuo Z, Brägelmann J, Keck MK, El Dinali M, et al. (2015) Rare occurrence of EGFRvIII deletion in head and neck squamous cell carcinoma. *Oral Oncol* 51: 53-58.
- Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, et al. (2008) K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 359: 1757-1765.
- Di Nicolantonio F, Martini M, Molinari F, Sartore-Bianchi A, Arena S, et al. (2008) Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol* 26: 5705-5712.
- Weber A, Langhanki L, Sommerer F, Markwarth A, Wittekind C, et al. (2003) Mutations of the BRAF gene in squamous cell carcinoma of the head and neck. *Oncogene* 22: 4757-4759.
- Schmid K, Oehl N, Wrba F, Pirker R, Pirker C, et al. (2009) EGFR/KRAS/BRAF mutations in primary lung adenocarcinomas and corresponding locoregional lymph node metastases. *Clin Cancer Res* 15: 4554-4560.
- Rekhtman N, Paik PK, Arcila ME, Tafe LJ, Oxnard GR, et al. (2012) Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung: lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations. *Clin Cancer Res* 18: 1167-1176.
- Vander Broek R, Mohan S, Eytan DF, Chen Z, Van Waes C (2015) The PI3K/Akt/mTOR axis in head and neck cancer: functions, aberrations, cross-talk, and therapies. *Oral Dis* 21: 815-825.

19. Mriouah J, Boura C, Pinel S, Chretien AS, Fifre A, et al. (2010) Cellular response to cetuximab in PTEN-silenced head and neck squamous cell carcinoma cell line. *Int J Oncol* 37: 1555-1563.
20. Baba Y, Maeda T, Suzuki A, Takada S, Fujii M, et al. (2017) Deguelin potentiates apoptotic activity of an EGFR tyrosine kinase inhibitor (AG1478) in PIK3CA-mutated head and neck squamous cell carcinoma. *Int J Mol Sci* 18: E262.
21. Rebucci M, Peixoto P, Dewitte A, Watzet N, De Nuncques MA, et al. (2011) Mechanisms underlying resistance to cetuximab in the HNSCC cell line: role of AKT inhibition in bypassing this resistance. *Int J Oncol* 38: 189-200.
22. Kim HS, Kwon HJ, Jung I, Yun MR, Ahn MJ, et al. (2015) Phase II clinical and exploratory biomarker study of dacomitinib in patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. *Clin Cancer Res* 21: 544-552.
23. Johnston PA, Sen M, Hua Y, Camarco DP, Shun TY, et al. (2015) HCS campaign to identify selective inhibitors of IL-6-induced STAT3 pathway activation in head and neck cancer. *Assay Drug Dev Technol* 13: 356-376.