Oral Oncology 51 (2015) 399–408

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Mechanisms of and therapeutic approaches for overcoming resistance to epidermal growth factor receptor (EGFR)-targeted therapy in squamous cell carcinoma of the head and neck (SCCHN)

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ARTICLE INFO

Article history:
Received 22 April 2014
Received in revised form 19 January 2015
Accepted 28 January 2015
Available online 26 February 2015

Keywords:
Epidermal growth factor receptor
Molecular targeted therapy
Squamous cell carcinoma of the head and neck
Clinical trial
Drug resistance
HER2
HER3

SUMMARY

The majority of squamous cell carcinoma of the head and neck (SCCHN) overexpress epidermal growth factor receptor (EGFR), which has been associated with poor treatment response and survival. However, only modest success has been achieved with the use of single agents that target EGFR, possibly due to primary and acquired resistance. This review will discuss key mechanisms of and therapeutic approaches to overcoming resistance to EGFR-targeted therapy in SCCHN. Recent preclinical and clinical investigations have demonstrated that other ErbB family receptors (eg, HER2 and HER3) and other horizontal resistance mechanisms, as well as activation of downstream signaling pathways, epigenetic events, and nuclear EGFR, are possible mediators of resistance to anti-EGFR therapeutics. Key downstream pathways that may be implicated in EGFR resistance include phosphatidylinositol-3-kinase/protein kinase B, vascular endothelial growth factor (VEGF), and mammalian target of rapamycin (mTOR). Multiple agents that target EGFR and other ErbB family members (ie, lapatinib, afatinib, and dacomitinib), as well as combination therapies that target EGFR and selected other pathways (eg, VEGF, mTOR, and c-Met) are being investigated clinically. In addition, several phase II and III trials continue to investigate strategies to enhance the efficacy of EGFR-targeted therapy in SCCHN.

Introduction

Recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) has a poor prognosis for which palliative chemotherapy provides a low likelihood of 1-year overall survival (OS) [1]. More than 90% of SCCHN overexpress the epidermal growth factor receptor (EGFR; also known as ErbB1 or human epidermal growth factor receptor 1 [HER1]) [1], which has been associated with poor treatment response and survival [2,3].

EGFR and other ErbB family members are known therapeutic targets for several malignancies, including EGFR in lung and colon cancer and HER2 in breast cancer [4,5]. To date, clinical development of EGFR-targeted agents has achieved mixed success for SCCHN. Presently, the only US Food and Drug Administration (FDA)-approved EGFR-targeted agent for the treatment of SCCHN is cetuximab (Erbitux®; Bristol-Myers Squibb, Princeton, NJ), a chimeric monoclonal antibody (mAb), which has been shown to have single-agent activity in platinum-refractory R/M SCCHN and to prolong OS when added to radiation therapy for locally advanced SCCHN or to first-line platinum/5-fluorouracil chemotherapy (5-FU) for R/M disease [6–10]. In contrast, the reversible EGFR tyrosine kinase inhibitor (TKI) gefitinib (Iressa®; AstraZeneca, Wilmington, DE) failed to prolong OS when added to chemotherapy for R/M SCCHN [11,12], and poor accrual led to early closure of trials evaluating erlotinib (Tarceva®; Genentech, Inc., South San Francisco, CA) with first-line chemotherapy for R/M SCCHN (NCT00448240) or maintenance monotherapy for resected disease (NCT00412217). The new generation of mAbs directed against EGFR, including zalutumumab (formerly HuMax-EGFr; Genmab, Princeton, NJ), a human IgG1 mAb targeting EGFR domain III, and panitumumab (Vectibix®; Amgen Inc., Thousand Oaks, CA), a human IgG2 mAb targeting EGFR domain III, also failed to demonstrate an OS benefit in phase III trials [13,14]. The humanized anti-EGFR IgG1 mAb nimotuzumab (formerly h-R3; Oncoscience AG, Germany and YM Biosciences Inc, Ontario, Canada) is approved for treating SCCHN in some countries outside the United States [15], and several phase III studies in combination

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http://dx.doi.org/10.1016/j.oraloncology.2015.01.018
1368-8375/

with radiation or chemoradiation therapy (CRT) are ongoing or planned (NCT01345084; NCT00957086).

The success of EGFR-based therapeutics may be impeded by primary and acquired resistance, with substantial research focused on characterizing the underlying mechanisms of resistance [16]. This review will discuss key mechanisms of and therapeutic approaches to overcoming resistance to EGFR-targeted therapy for SCCHN.

Lack of predictors of response to EGFR inhibitors or primary EGFR resistance

Despite EGFR overexpression, only a small percentage of patients have a major response to EGFR inhibition [17]. In lung cancer, activating mutations in *EGFR* are known to be the primary predictor of benefit from erlotinib, gefitinib, and afatinib [18,19], and in colon cancer, the presence of a *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*) mutation is predictive of primary resistance to EGFR-targeted therapy [20]. To date, a biomarker that can predict response or primary resistance to EGFR inhibition in SCCHN has yet to be identified. Biomarker analyses of the phase III EXTREME trial of cetuximab plus first-line platinum/5-FU chemotherapy for SCCHN found that improvements in survival and efficacy outcomes were not influenced by tumoral EGFR expression level or *EGFR* copy number, with no utility of these parameters as predictive biomarkers [21,22].

Resistance mechanisms to SCCHN-directed EGFR inhibition

Recent preclinical and clinical investigations have demonstrated that other ErbB receptors, activation of downstream pathways, and epigenetic events are probable mediators of resistance to anti-EGFR therapeutics (Fig. 1). In preclinical models of cetuximab-resistant non-small cell lung cancer (NSCLC), several mechanisms have been identified, including EGFR internalization leading to activation of HER2 and HER3; EGFR upregulation leading to increased HER2/HER3 dimerization and signaling; and activation of v-src sarcoma viral oncogene homolog (Src) family kinases causing prolonged EGFR activity, HER3 activation, and increased signaling through downstream prosurvival pathways, such as phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) [23,24]. These various mechanisms and others are discussed below.

Horizontal resistance mechanisms/compensatory receptors

HER2 and HER3 have been implicated in resistance to EGFR-targeted agents in SCCHN (Fig. 1A). In cetuximab-resistant SCCHN cell lines, increased activation of EGFR, HER2, and HER3 was reported [25,26]. A preclinical study in SCCHN reported a significant association between increased expression of HER2 and HER3 and resistance to gefitinib [27]. Yonesaka et al. published comprehensive in vitro and in vivo preclinical data, mainly in colon cancer cell lines, that identified ErbB2 (HER2) signaling as a cause of cetuximab resistance by 2 distinct mechanisms, *ErbB2* amplification and upregulation of heregulin (HER3 ligand) [28]. The experiments conducted in a cetuximab-sensitive SCCHN cell line showed that the primary mechanism of HER2-mediated resistance was through downstream signaling of extracellular signal–regulated kinase 1/2 (ERK1/2) [28]. Recent preclinical data in a xenograft model using SCCHN cell lines showed increased antitumor activity with dual inhibition of HER3 and EGFR [29]. Tumor samples from patients with SCCHN have been reported to have high levels of heregulin expression, suggesting that a subset of patients could benefit from HER3 blockade [30].

Several other signaling pathways have been implicated as mediators of resistance to EGFR-targeted agents, including vascular endothelial growth factor (VEGF), the hepatocyte growth factor (HGF)/c-MET pathway, the insulin-like growth factor receptor (IGFR) pathway, and the Notch pathway (Fig. 1A). In a human SCCHN cell line with acquired resistance to EGFR-targeted mAbs, increased expression of VEGF has been described [31]. In preclinical models of SCCHN, bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA), an anti-VEGF mAb, has shown potential when combined with erlotinib and radiation [32] or with cetuximab [33].

The HGF/c-Met pathway is similar to the EGFR pathway, as both are overexpressed in SCCHN and are known to confer similar downstream signaling. There is preclinical evidence to suggest that c-Met can compensate for EGFR inhibition (and vice versa), suggesting that dual blockade may be a strategy for overcoming resistance [34]. At the same time, however, clinical biomarker analyses of EGFR inhibitor-treated patients have not revealed an association between high c-Met expression and efficacy outcomes [35,36].

Blockade of EGFR signaling can result in a switch to signaling through the IGFR pathway [37]. In SCCHN cell lines sensitive to gefitinib, activation of the IGF-1 receptor (IGF1R) blocked apoptosis and induced gefitinib resistance [38].

The Notch pathway is believed to crosstalk with the EGFR pathway, and may be involved in EGFR resistance [39,40]. Overall, the EGFR pathway plays a key role in cellular self-renewal while the Notch pathway is a promoter of differentiation, yet both pathways ultimately promote cell survival [40]. Preclinical data have shown that when Notch signaling is suppressed in squamous cell carcinomas, the ability of EGFR inhibitors to induce cellular differentiation is blunted [41]. Recent genomic findings, including those from The Cancer Genome Atlas, support that a subset of SCCHN (10%–20%) harbor mutations in *NOTCH1*, suggesting a potential role for these mutations in EGFR resistance [39,42–44].

Vertical/downstream resistance mechanisms

Vertical and downstream resistance mechanisms are depicted in Fig. 1B. EGFR activation leads to downstream activation of the PI3K/AKT pathway, resulting in tumor growth and survival; alterations to this pathway, from the ligand to downstream effectors, are implicated in resistance to EGFR inhibition. Increased expression of the ligand heparin-binding EGF-like growth factor (HB-EGF), resulting from downregulation of its regulator miR-212, was found to confer cetuximab resistance in SCCHN cell lines; this resistance was reversed with knockdown of HB-EGF using HB-EGF–specific shRNA [45]. Of note, average plasma HB-EGF levels were 5 times higher in patients with recurrent disease compared with that of patients at diagnosis, suggesting that cetuximab may be more effective when incorporated into front-line therapy [45]. Morris et al. performed a genomic analysis of the EGFR/PI3K pathway using samples of oral cancer and matched normal tissue, and found that activating alterations in the EGFR/PI3K pathway were present in 74% of the tumors [46]. They also reported that the protein tyrosine phosphatase receptor S (PTPRS), which is known to inactivate EGFR, was deleted in 26% of studied samples, and this deletion led to EGFR/PI3K pathway activation and promoted resistance to EGFR inhibition [46]. A recently published genomic analysis showed PI3K pathway mutations in both human papillomavirus (HPV)-positive and HPV-negative SCCHN, despite markedly different overall genomic profiles [47]. Rebucci et al. reported data suggesting that cetuximab sensitivity is correlated with AKT phosphorylation and ERK inhibition, and AKT phosphorylation is inhibited by cetuximab in cetuximab-sensitive cells but not in cetuximab-resistant cells [48]. Furthermore, they demonstrated that treatment with a PI3K inhibitor restored cetuximab sensitivity, and postulated that AKT activation contributes to cetuximab resistance [48]. Recently, a biomarker