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Integration of molecular targeted therapy with radiation in head and neck cancer☆

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ABSTRACT

Approximately 600,000 new cases of head and neck cancer arise worldwide each year. Of these, a large majority are head and neck squamous cell carcinomas (HNSCC). Conventional treatments, including surgical excision followed by radiation and/or chemoradiotherapy have limited efficacy and are associated with substantial toxicity. To date, key targets for molecular targeted therapy in HNSCC are epidermal growth factor receptors and angiogenesis-related factors. Cetuximab is a monoclonal antibody targeting the epidermal growth factor receptor (EGFR) and it is the only targeted therapy approved by the United States Food and Drug Administration for the treatment of HNSCC. Cetuximab in combination with radiotherapy represents a standard approach for newly diagnosed patients who are unable to tolerate platinum chemotherapy. Despite efficacy in preclinical HNSCC models, cetuximab is only effective in a subset of HNSCC patients, most likely due to the high heterogeneity of this cancer. Additional targets under active investigation include the PI3K/Akt pathway, the Ras-MAPK-ERK pathway and the JAK/STAT pathway, among others. Combining molecular targeted therapies and radiation may allow for deintensification of radiotherapy thereby reducing radiation toxicities and improving treatment outcomes. Here we review the preclinical and clinical data in support of treatment strategies that combined targeted therapy with radiation in HNSCC.

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1. Introduction

Head and neck cancer includes malignancies arising in the mucosal surfaces of the oral cavity, pharynx and larynx, and is generally referred to as head and neck squamous cell carcinoma (HNSCC). HNSCC is estimated to have 53,640 new cases in US in 2013 and accounting for 3% of all cancers. (Siegel et al., 2013) Risk factors for HNSCC include exposure to tobacco and alcohol. Increasingly, infection of the oropharynx with human papilloma virus (HPV) is emerging as a major cause of HNSCC. The incidence of HPV in head and neck cancer varies according to tumor site with most (about 70%) of HPV-associated tumors located in the oropharynx. (Perez-Ordonez et al., 2006) HPV-associated head

Abbreviations: 5-FU, 5-fluorouracil; COX-2, cyclooxygenase-2; DNA-PKcs, DNA-dependent protein kinase, catalytic subunit; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HNSCC, head and neck squamous cell carcinoma; IMRT, intensity-modulated radiation therapy; mAb, monoclonal antibody; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; PI3K, phosphatidyl inositol 3-kinase; RT, radiotherapy; SFK, Src-family kinase; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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and neck cancers are likely genetically distinct from HPV-negative tumors and are likely to be optimally treated with different therapeutic approaches. Individuals with HPV-associated head and neck cancers generally experience a better prognosis compared with patients with HPV-negative tumors. (Chung & Gillison, 2009). (Sivasithamparam et al., 2013) There are HNSCC treatment consists of surgical excision followed by radiation or chemoradiation, or chemoradiation alone. These conventional therapies have been used for decades in HNSCC but they have several limitations. Surgery may cause disfigurement and reduce patient quality of life. Radiation and chemotherapy are used in combination in an effort to preserve organ structure with a comparable effect on disease control. Concurrent chemotherapy and radiation in HNSCC likely provides a better outcome in terms of local disease control and organ preservation compared to radiation alone or radiation plus induction chemotherapy, but concurrent therapy also leads to more severe toxicity. (Forastiere et al., 2003) Mucositis occurs in about 80% of patients treated with radiation and is the most common severe toxicity observed, with an even higher incidence in those receiving radiation plus chemotherapy. (Trotti et al., 2003) Patients may also experience other toxicities including dysphagia, xerostomia, radiation dermatitis, hematologic toxicity, neurotoxicity and/or ototoxicity, moist desquamation, nausea or vomiting, fever, weight loss, fatigue, pneumonia and osteoradionecrosis, combinations of which may lead to termination of treatment or even death. (Tsao et al., 2006; Givens et al., 2009) The toxicities of conventional therapies are in large part due to their non-selective nature. Molecular targeted therapies are therefore in development with the goal of developing selective approaches to inhibit the growth of HNSCC cells. In the present review, we discuss molecular targeting agents and targets that are under investigation in combination with radiation in HNSCC with a focus on strategies that are in active clinical development (Fig. 1; Table 1).

2. Epidermal growth factor receptor targeted therapy

2.1. Epidermal growth factor receptor monoclonal antibodies

2.1.1. Cetuximab

HNSCC is characterized by high expression of the epidermal growth factor receptor (EGFR) where EGFR expression levels generally correlate with worse clinical outcome (Grandis et al., 1998). Preclinical studies using HNSCC cell lines and animal models suggested enhanced therapeutic effects when EGFR inhibitors were combined with radiation (Bonner et al., 1994; Huang et al., 1999; Bonner et al., 2000). Treatment with the EGFR-targeting monoclonal antibody cetuximab demonstrated

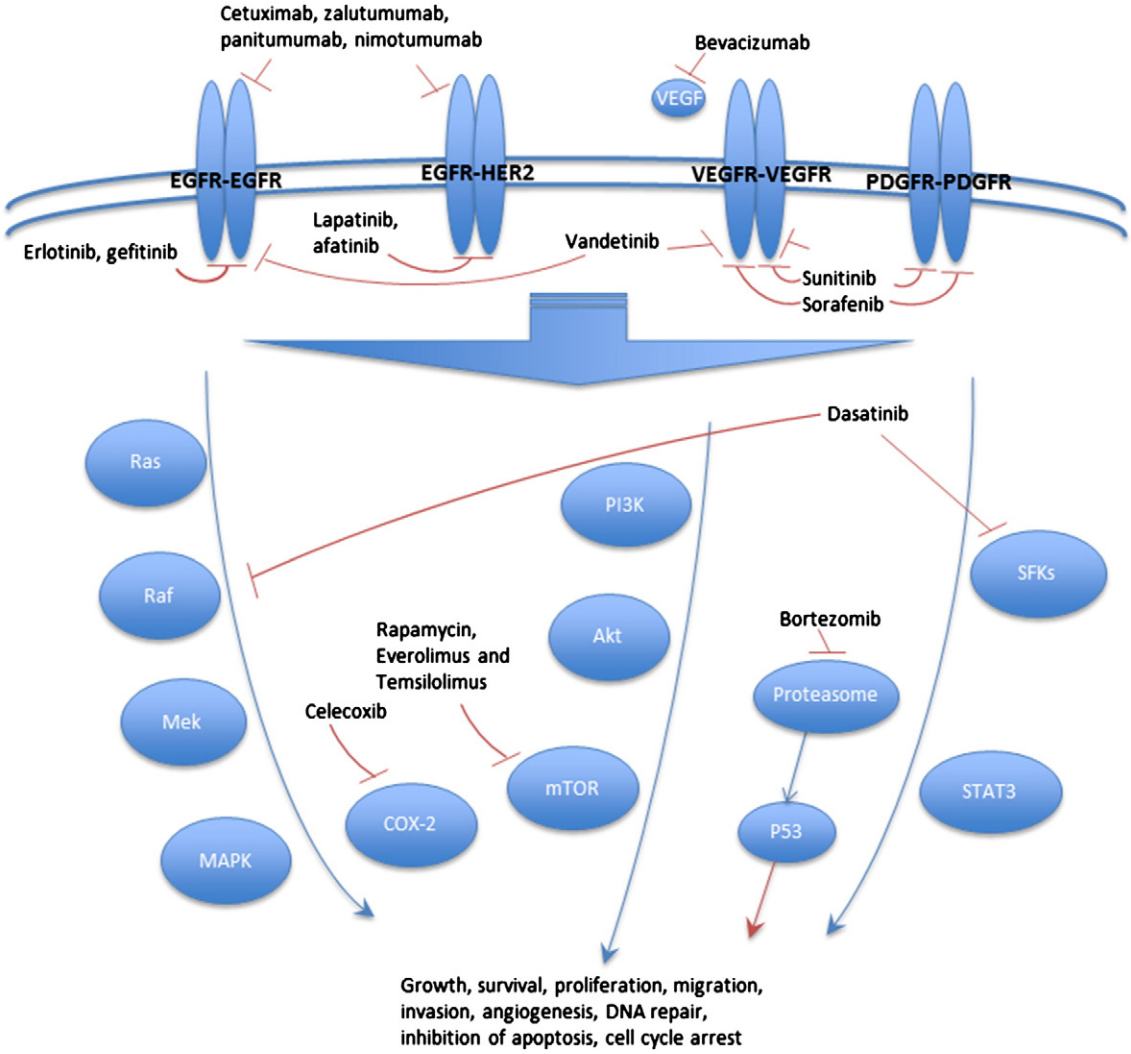

Fig. 1. Therapeutics under clinical investigation for combination with radiation in HNSCC. Red lines indicate inhibition and blue arrows indicate activation. EGFR: epidermal growth factor receptor; HER2: human epidermal growth factor receptor 2; VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet-derived growth factor receptor; MAPK: mitogen-activated protein kinase; PI3K: phosphatidylinositide 3-kinase; COX-2: cyclooxygenase-2; mTOR: mammalian target of rapamycin; SFK: Src family kinase; STAT3: signal transducer and activator of transcription 3.