Contributions of Targeted Agents

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KEY POINTS

- The cellular growth receptors epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) play a strong role in the biology of head and neck squamous cell carcinoma (HNSCC).
- A series of promising molecularly targeting agents that impact EGFR and VEGFR signaling are under active preclinical and clinical investigation in HNSCC.
- Toxicity profiles are generally less with molecular targeting agents than with conventional cytotoxic chemotherapy.
- It may prove possible to substitute selected molecular inhibitors for cytotoxic agents, thereby lessening toxicity and enhancing quality of life.
- Personalized cancer treatment strategies that derive from molecular biology and genetics of individual tumors are within our future reach.

19.1 Introduction

The dominant pattern of spread and recurrence for head and neck squamous cell carcinoma (HNSCC) is locoregional; therefore, surgery and radiation have historically played the central role in curative treatment. More recently, a beneficial role for cytotoxic chemotherapy in both the curative and palliative setting for patients with HNSCC has become better defined. However, even with this aggressive multidisciplinary approach, the overall survival rate for advanced HNSCC has only begun to show modest improvement. In addition, modern treatment regimens used
for HNSCC are quite toxic, and often result in compromised functional status and impaired quality of life (QOL). Therefore, the development of novel therapeutic alternatives to standard therapy is highly desired. Recent advances in targeted molecular therapy have identified the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF) and its receptor (VEGFR) as highly promising therapeutic targets. This chapter focuses on current molecular targeting agents used in HNSCC, promising molecular targets in HNSCC and the impact molecular targeting agents may have on patient QOL.

19.2 Molecular Targeting Agents in HNSCC

19.2.1 Epidermal Growth Factor Receptor – EGFR Biology

The EGFR is a member of the HER (human epidermal growth factor receptor) family of receptor tyrosine kinases and consists of four members: EGFR (ErbB1/HER1), HER2/neu (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). Stimulation of the receptor through ligand binding leads to receptor oligomerization at the plasma membrane. This activates the receptor tyrosine kinase and thereby causes autophosphorylation of tyrosine residues in the cytoplasmic tail. These phosphorylated tyrosines serve as docking sites for various proteins that contain Src homology domains and phosphotyrosine binding domains. These events lead to the activation of several signaling cascades most notably the Ras/RAF/MEK/ERK, phosphotyrosylinositol-3-kinase (PI3K)-Akt, Stat, and phospholipase C gamma pathways (Fig. 19.1). The activation of these pathways ultimately promotes tumor cell proliferation, survival, invasion, and angiogenesis. Aberrant expression or activity of the EGFR is identified as a central regulator of proliferation and progression in many human cancers, including HNSCC, non-small cell lung cancer (NSCLC), metastatic colorectal cancer (mCRC), and brain cancer. Therefore, the EGFR is considered a promising molecular target for therapeutic modulation in oncology.

19.2.2 EGFR Blockade

Targeting the EGFR with molecular inhibitors has been intensely pursued in the last decade as a cancer treatment strategy. Two primary strategies have been developed to target the EGFR, including anti-EGFR monoclonal antibodies (mAbs) and small molecule tyrosine kinase inhibitors (TKI) (Table 19.1). Dating back to the early 1980s, Mendelsohn and colleagues purified a series of mAbs to the EGFR to test these agents as inhibitors of tumor growth. Born out of these efforts, cetuximab (IMC-C225, Erbitux) was developed to target the extracellular ligand binding domain of the EGFR and thereby block natural ligand binding. Cetuximab prevents receptor activation and dimerization and ultimately induces receptor internalization and downregulation. Cetuximab exhibits promising antitumor activity as monotherapy or in combination with chemotherapy and/or radiation.