Keynote Lecture 3

Molecular Target Approaches in Genomics Era in the Management of Head and Neck Cancer

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Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common malignancy world-wide, with an estimated 38,000 new cases and 11,000 deaths predicted in the United States in 2004. Survival in the advanced SCCHN has improved little in the past two decades, despite the fact that increasing sophisticated combined modality approaches have been explored. Molecular alterations, particularly the epidermal growth factor receptor (EGFR) have been focused in the management of SCCHN. Activation of the EGFR protein tyrosine kinase results in the recruitment and phosphorylation of several intracellular substrates. A major downstream signaling route of the EGFR family is via MAPK pathway, initiation of multistep phosphorylation cascades that lead to the activation of several key steps including transcription of intermediate molecules that are linked to cell proliferation, survival, angiogenesis, differentiation, and/or metastasis. EGFR inhibition decreases SCCHN tumor metastasis and angiogenesis in xenograft models, reduces activity of molecules downstream from EGFR, and inhibits proliferation of EGFR-dependent squamous carcinoma cells in vivo. Monoclonal antibodies (Erbitux, ABX-EGF, h-R3, EMD-72,000 and others) and tyrosine kinase inhibitors (Iressa, Tarceva, CI-1033, and others) specifically targeting EGFR are the most well-studied and hold substantial promises of success. This lecture will address each of these agents alone or in combination with radiation or chemotherapy and highlight some of the promising recent clinical trials. A recent multi-institutional trial randomized radiation therapy plus Erbitux or radiation therapy alone for 424 patients with locally advanced SCCHN. The study clearly showed that the Erbitux combination had better locoregional control and survival rates than radiation therapy alone. EGFR targeted small molecules such as Iressa or Tarceva are currently being investigated in clinical trials as single agents or in combination with cytotoxic agents. The antitumor activity of EGFR targeted agents have been closely related to the mutation status of the DNA binding pockets of the tyrosine kinase domain of the EGFR gene in non-small cell lung cancer, and such sensitivity to the TKIs may possibly be associated with SCCHN, although further investigation is necessary. Other molecularly targeted agents such as COX-2 inhibitors, farnesyl transferase inhibitors, intermediate growth signaling blockers, cell cycle inhibitors and antiangiogenic factors are being actively investigated in preclinical and clinical settings for SCCHN. Development of innovative technologies, such as multifunctional nanoparticle probes based on semiconductor quantum dots (QDs) for cancer targeted therapy and imaging are highly promising and will be addressed.