Chemotherapy of Head and Neck Cancer

Sarah Rodriguez, MD
Faculty Advisor: Anna M. Pou, MD
The University of Texas Medical Branch
Department of Otolaryngology
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Introduction

- 500,000 new cases of squamous cell cancer of the head and neck worldwide per year; 40,000 new cases per year in the United States

- Despite continuing improvements in diagnosis, local management and chemotherapy, there has been no significant increase in survival rates over the past 30 years
Chemotherapeutic Agents

- Alkylating agents
- Antimetabolites
- Antitumor Antibiotics
- Alkaloids
- Taxanes
Alkylating Agents

- Interact with DNA causing substitution reactions, cross-linking reactions or strand breaks
- Example: cisplatin
Antimetabolites

Cytotoxic effects via similarity in structure or function to naturally occurring metabolites involved in nucleic acid synthesis—either inhibit enzymes involved in nucleic acid synthesis or produce incorrect codes

Example: methotrexate
Antitumor Antibiotics

- Group of related antimicrobial compounds produced by *Streptomyces* species in culture
- Affect structure and function of nucleic acids by: intercalation between base pairs (doxorubicin), DNA strand fragmentation (bleomycin), or cross-linking DNA (mitomycin)
Alkaloids

- Bind free tubulin dimers thereby disrupting balance between microtubule polymerization and depolymerization resulting in arrest of cells in metaphase

Examples: vincristine, vinblastine
Taxanes

- Disrupt equilibrium between free tubulin and microtubules causing stabilization of cytoplasmic microtubules and formation of abnormal bundles of microtubules.
- Examples: paclitaxel and docetaxel
Neoadjuvant Chemotherapy

Use of chemotherapy prior to definitive surgery or radiation therapy

Intent is to improve both local and distant control of disease in order to provide greater organ preservation and overall survival

Chemotherapy in neoadjuvant setting benefits from drug delivery to a tumor with vasculature not damaged by surgery or radiation
Neoadjuvant Chemotherapy

- Standard induction chemotherapy is 5-fluorouracil and cisplatin
- Response rate between 68 and 93 percent; complete response as high as 54 percent
- Must be followed by definitive surgery or radiation
- No survival advantage even given decreased likelihood of distant metastases
Neoadjuvant Therapy and Organ Preservation

Two large randomized, controlled trials have compared primary surgical management with a laryngeal preservation approach of induction chemotherapy followed by radiation.

Survival comparable between groups; ½-2/3 patients in the chemotherapy plus radiation group retained larynx.
Concomitant Chemoradiotherapy

- Simultaneous use of chemotherapeutic agent and radiation therapy
- Intent is systemic control through elimination of micro-metastases and improved local control based on the concepts of additivity and synergy
Adjuvant Chemotherapy

Chemotherapeutic agents administered after definitive treatment with radiation or chemotherapy

The few studies that have been done failed to demonstrate any survival benefit
Nasopharyngeal Carcinoma

- Standard primary treatment is radiation therapy
- Several studies show increased survival rates with concurrent cisplatin and radiation
- Further survival benefits shown when this regimen followed by cisplatin and 5-fluorouracil
Epidermal Growth Factor Receptor

- EGFR overexpression in many human cancers including HNSCC
- EGFR blocking agents include anti-EGFR antibodies and tyrosine kinase inhibitors
- IM-C225 is a monoclonal antibody targeting EGFR; combined with cisplatin has shown efficacy against HNSCC
RAS

Farnesyl transferase inhibitors: class of compounds that inhibit a critical step in the expression of the mutated ras genes

Farnesyl transferase inhibitors have been shown to decrease oral cavity tumor bulk; combined with paclitaxel it has shown cytotoxic effects for head and neck cancer cell lines
Mutations of p53 occur in 45-70% of HNSCC

Ad-p53: adenovirus containing wild-type p53 gene

Preliminary studies of AD-p53 in patients with advanced recurrent HNSCC showed promising results
Chemoprevention

One of the main reasons for treatment failure in early stage HNSCC is development of a second primary.

Chemoprevention: the process of field cancerization can be interrupted or reversed through the use of natural or synthetic agents.
Retinoids

- Retinoids have been shown to cause regression or stabilization of leukoplakia.
- Recent use of 13-cis retinoic acid in patients curatively treated for HNSCC showed that second primary tumors developed in only 4% of patients treated with 13-cis retinoic acid compared with 24% of controls at 32 months.
COX-2 inhibitors

- Increased levels of COX-2 are found in oral leukoplakia and SCC as well as normal appearing mucosa adjacent to HNSCC

- Sulindac, an NSAID and celecoxib, a selective COX-2 inhibitor have been shown to reduce the number of colorectal polyps in patients with FAP


