

TITLE: Chemotherapy for Head and Neck Cancer
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RESIDENT PHYSICIAN: Sarah Rodriguez, MD
FACULTY PHYSICIAN: Anna Pou, MD
SERIES EDITORS: Francis B. Quinn, Jr., MD and Matthew W. Ryan, MD

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Introduction

Worldwide, squamous cell cancer of the head and neck accounts for an estimated 500,000 new cancer cases annually and 40,400 new cases per year in the United States. One-third of patients present with early stage disease amenable to cure with surgery or radiation therapy. Two-thirds of patients present with locally advanced disease. For those patients presenting with locally advanced disease treated with surgery and/or radiation therapy, recurrence rates have remained at about 65% for the past 40 years. Thus far, the addition of chemotherapy has not changed this high recurrence rate but it has been shown to increase rates of organ preservation when combined with radiation therapy and decrease rates of distant metastasis. Chemotherapeutic agents also have a role in the palliative treatment of squamous cell cancer of the head and neck. In general, chemotherapy for squamous cell cancer of the head and neck has been used in three settings: as neoadjuvant or induction chemotherapy before locoregional treatment with surgery or radiation, as concurrent chemoradiotherapy for advanced disease, or as adjuvant post-op chemotherapy usually with radiation.

Types of Chemotherapeutic Agents

Alkylating Agents. The cytotoxic effects of this diverse group of chemical compounds relates to their interaction with DNA, causing substitution reactions, cross-linking reactions or strand-breaking reactions. These agents alter the information coded in the DNA molecule resulting in inhibition of or inaccurate DNA replication with resultant mutation or cell death. An important example is cisplatin.

Antimetabolites. This group of chemicals exerts cytotoxic effects by virtue of structural or functional similarity to naturally occurring metabolites involved in nucleic acid synthesis. They either inhibit critical enzymes involved in nucleic acid synthesis or become incorporated into the nucleic acid and produce incorrect codes. Both of these mechanisms result in an inhibition of DNA synthesis and ultimate cell death. An example is methotrexate.

Antitumor Antibiotics. These are a group of related antimicrobial compounds produced by Streptomyces species in culture. They are cytotoxic in that they affect the structure and

function of nucleic acids by: intercalation between DNA base pairs (doxorubicin), DNA strand fragmentation (bleomycin), or cross-linking of DNA (mitomycin).

Alkaloids. These chemicals bind to free tubulin dimers and thereby disrupt the balance between microtubule polymerization and depolymerization, resulting in the net dissolution of microtubules, destruction of the mitotic spindle, and arrest of cells in metaphase. Examples in this category are vincristine and vinblastine.

Taxanes. These agents disrupt equilibrium between free tubulin and microtubules causing stabilization of ordinary cytoplasmic microtubules and the formation of abnormal bundles of microtubules. Examples in this category are paclitaxel and docetaxel.

Neoadjuvant Chemotherapy

Neoadjuvant, or induction chemotherapy, is the use of chemotherapy alone prior to definitive surgery or radiation therapy. The intent of induction chemotherapy is to improve both local and distant control of disease and thereby allow for greater organ preservation and overall survival. Improved local control occurs through greater cytoreduction as a result of better drug delivery to a tumor in which the vasculature is not yet damaged by surgery or radiotherapy and the cells are not yet resistant to chemotherapy.

Squamous cell carcinoma of the head and neck is extremely sensitive to antineoplastic agents. The combination of 5-fluorouracil and cisplatin in newly diagnosed patients produces a reproducible overall response rate between 68 and 93 percent and a complete response rate as high as 54 percent. However, even in patients achieving a pathologic complete response after chemotherapy, relapse is invariable without definitive surgery or radiation. Neoadjuvant chemotherapy has been studied in numerous phase III trials. It has been followed by definitive surgery, by surgery and radiation therapy, or by radiation therapy alone and has been compared with definitive management without chemotherapy. Trials have consistently shown no survival advantage for the neoadjuvant treatment regimens. Even when studies demonstrated a statistically significant decrease in the likelihood of distant metastases in patients given chemotherapy, this did not translate into improvement in survival.

Although neoadjuvant chemotherapy has not shown a benefit in terms of survival, it has been shown to have benefits in terms of organ preservation. Two large randomized, controlled trials in patients with advanced, resectable laryngeal or hypopharyngeal cancer (the Department of Veterans Affairs and the European Organization for Research and Treatment of Cancer) have compared primary surgical management with a laryngeal preservation approach of induction chemotherapy followed by definitive radiation therapy. Results of these trials demonstrated no difference in overall survival between groups but showed laryngeal preservation was enjoyed by one-half to two-thirds of the surviving patients in the chemotherapy plus radiation therapy group but none of the primary laryngectomy patients at five years.

Standard induction chemotherapy for squamous cell head and neck cancer is a combination of cisplatin and fluorouracil. Improvement on this regimen is being studied with the addition of agents such as leucovorin and docetaxel. Preliminary results are promising; however, randomized trials are needed to evaluate these modified treatment programs.

Concomitant Chemoradiotherapy

Concomitant chemoradiotherapy is the simultaneous use of chemotherapeutic agents and radiation therapy. Concomitant chemoradiotherapy has the goal of systemic control through elimination of micro-metastatic disease and improved local control based on the concepts of additivity and synergy. In terms of additivity, chemotherapy may be more efficacious in certain radioresistant cell types such as hypoxic cells (mitomycin), cells with low pH, or cells in the radioresistant S phase (hydroxyurea). In terms of synergy, chemotherapy may hinder the repair of radiation-induced DNA damage (cisplatin), may synchronize or arrest cells during radiosensitive phases (hydroxyurea, paclitaxel), and may hinder regrowth between fractions.

Chemoradiotherapy has been studied mostly as an alternative to radiation alone in advanced, unresectable squamous cell cancer of the head and neck. Two recent meta-analyses of randomized trials evaluating chemotherapy in the treatment of squamous cell cancer of the head and neck have demonstrated a small but significant survival advantage associated with the use of chemoradiotherapy; both of these studies reported that the benefit achieved with chemoradiotherapy over radiation therapy alone was observed primarily in trials employing a strategy of concurrent or alternating chemoradiotherapy; no substantial gains were demonstrated with the use of neoadjuvant or adjuvant chemotherapy followed by radiation. Available literature suggests that carefully designed concurrent chemoradiotherapy programs can be administered with acceptable levels of toxicity without excessively prolonging radiation, without compromising chemotherapy scheduling, and with modest but clinically significant gains in locoregional control and in patient survival. Many different drug combinations and radiation schedules have been evaluated with each program having unique toxicities, risks, and benefits; so far, no specific chemoradiotherapy program has emerged as the definitive acceptable standard of care.

Adjuvant chemotherapy

Adjuvant chemotherapy is chemotherapeutic agents administered after definitive treatment with radiation or chemotherapy in an effort to reduce locoregional and systemic recurrence. Few studies have evaluated the use of adjuvant chemotherapy. Those studies that have been done failed to demonstrate any survival benefit.

Nasopharyngeal Carcinoma

Among head and neck cancers, nasopharyngeal cancer has one of the poorest prognoses because of the tumor proximity to the skull base and multiple vital structures, the invasive nature that typifies tumor growth, the subtlety of early symptoms, and the difficulty of nasopharyngeal examination that hampers early diagnosis. NPC is also unique in its epidemiologic profile: the incidence in Chinese 30 per 100,000 while the incidence in North American and European white populations is 1 per 100,000; increased incidence appears to be related to dietary intake of dried salted fish (environmental) and certain HLA haplotypes (genetic); a link has also been made between Epstein-Barr virus and NPC. Primary treatment for nasopharyngeal carcinoma is radiation therapy. Nasopharyngeal carcinoma is a radiosensitive and chemosensitive tumor. It usually presents at a locally advanced stage. Local, regional and systemic recurrences are high in patients presenting at a late stage and contribute to poor survival rates. Several studies show

concurrent single agent chemotherapy with cisplatin and radiation therapy improve survival rates substantially; and survival rates are increased further with the addition of adjuvant cisplatin and 5-fluorouracil following this concomitant chemoradiotherapy. Another recent study has shown promising increases in survival for very late stage nasopharyngeal carcinoma with neoadjuvant cisplatin, 5-fluorouracil and leucovorin followed by radiation therapy with low toxicity.

Novel Therapeutics

Epidermal Growth Factor Receptor. EGFR overexpression has been noted in human cancers including breast, ovarian, prostate, bladder, lung, brain, and pancreas. In squamous cell cancer of the head and neck, EGFR expression is reported in approximately 90% of specimens. EGFR appears to contribute to the growth and survival of tumor cells through various pathways including its effects on cell cycle progression, inhibition of apoptosis, angiogenesis, tumor cell motility, and metastases. Many EGFR blocking agents have been investigated including anti-EGFR antibodies and tyrosine kinase inhibitors. Small studies of patients with head and neck squamous cell cancer treated with IM-C225, a monoclonal antibody targeting EGFR, combined with cisplatin have shown promising results and continued study of this combination is ongoing.

RAS. Data suggest that approximately 27% of oral cavity cancers have mutations in the ras gene. Farnesyl transferase inhibitors are a class of compounds that inhibit a critical step in the expression of mutated ras genes. Small phase I trials have shown farnesyl transferase inhibitors to cause significant oral cavity tumor reduction. Combinations of this class of agents with paclitaxel have shown cytotoxic effects for head and neck squamous cell carcinoma and colon cancer cell lines.

p53. Mutations of p53 occur in 45-70% of head and neck squamous cell cancer patients. Ad-p53 is an adenovirus containing the wild-type p53 gene. In preclinical studies, this system induced apoptosis of cancer cells without affecting normal cells and reduced tumor growth in mouse xenograft models of head and neck squamous cell carcinoma and other cancers. Preliminary studies of Ad-p53 in patients with advanced recurrent head and neck squamous cell cancer revealed promising results; studies combining Ad-p53 with cisplatin and 5-fluorouracil are ongoing.

Chemoprevention

Main reasons for treatment failure in squamous cell carcinoma of the head and neck are the development of second primary tumors in patients with early stage disease and the development of local recurrence and metastasis in patients with locally advanced disease. Studies show there is a 2.7-4% risk per year of second primary tumors each year following initial treatment. Head and neck squamous cell cancer results from accumulation of genetic and tissue damage in a field exposed to a carcinogen. This process can be interrupted or reversed through the use of natural or synthetic agents, defined as chemoprevention. Molecular markers of tumorigenesis in head and neck squamous cell carcinoma include: increased frequency of chromosome polysomy, increased expression of cyclin D1, overexpression of epidermal growth factor receptor, loss of heterozygosity in chromosome arms coding for tumor suppressor genes such as p53. Proteolysis of cyclin D1 is retinoid dependent; retinoids have been shown to induce apoptosis, suppress carcinogenesis, decrease growth rate of epithelial cells, and reduce free

radicals. All of these effects of retinoids have made these compounds the most studied chemopreventive agents for head and neck squamous cell carcinoma.

Leukoplakia is considered to be a premalignant lesion of the oral mucosa; up to 17.5% of these lesions may transform into carcinoma. Depending on the severity of the dysplasia, a transformation risk of as high as 43% has been reported for leukoplakias. Retinoids have been shown to cause these lesions to regress or at least remain stable as long as treatment continues; many lesions recur after discontinuation of therapy. Hong et al recently conducted an adjuvant, randomized, double-blinded, placebo-controlled, chemopreventive trial of high dose 13-cis retinoic acid for one year in 103 patients curatively treated for head and neck squamous cell cancer. Trial endpoints were recurrence of the primary disease, development of a second primary, and survival. With a median follow up of 32 months, second primary tumors developed in only 4 % of 13-cis retinoic acid treated patients compared to 24 % of the placebo group. Problems with retinoid treatment are related to drug toxicity including dry skin, liver toxicity and teratogenesis.

Another group of potential chemopreventive agents are COX-2 inhibitors. There are 2 isoforms of cyclooxygenase, COX-1 and COX-2. COX-1 is present in most tissues and mediates the synthesis of prostaglandins required for normal physiologic function. COX-2 is not detected in most tissues. It can be induced by factors implicated in head and neck squamous cell cancer including oncogenes, growth factors, cytokines, and tobacco carcinogens. Wild-type, but not mutant p53, suppresses COX-2 transcription. p53 mutations can be detected in precancerous and cancerous lesions of the head and neck. Increased levels of COX-2 are found in premalignant and malignant lesions including oral leukoplakia and squamous cell carcinoma. Increased levels of COX-2 are also increased in normal appearing mucosa adjacent to head and neck squamous cell carcinoma. Experimental evidence suggests that COX inhibitors, including NSAIDS, protect against a variety of tumors. Sulindac, a COX-1 and COX-2 inhibitor, caused a decrease in the number of colorectal polyps in patients with familial adenomatous polyposis. Another study showed celecoxib, a selective COX-2 inhibitor, caused a 28% reduction in the number of colorectal polyps compared with 4.5% reduction for placebo in patients with familial adenomatous polyposis. Trials are ongoing to determine whether a selective COX-2 inhibitor is effective as a chemoprotective agent in oral leukoplakia and Barrett's esophagus.

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