

CHAPTER FOUR

GENERAL CONSIDERATIONS IN HEAD AND NECK: CHEMOTHERAPY FOR HEAD AND NECK CANCER

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INTRODUCTION

The otolaryngologist frequently cares for patients with head and neck cancer who will receive chemotherapy as a component of their treatment (Table 4-1). Most often, these patients have locally advanced squamous cancer or metastatic disease not amenable to curative therapy with surgery or radiation. Many patients have recurrent disease after earlier surgery and radiotherapy. Chemotherapy may also be indicated for patients with advanced carcinomas of the oropharynx or larynx as an aspect of primary management. Of course, chemotherapy is also administered in experimental protocols as an induction regimen, or it can be given concomitantly with radiotherapy for patients with a high risk of tumor relapse. The focus of this chapter will be on chemotherapy for squamous cell carcinomas of the head and neck, although salivary gland cancers, melanomas, and sarcomas are other processes that may be treated with systemic therapy.

Surgeons should be familiar with: (1) the principles of administering chemotherapy in a clinical trial; (2) the appropriate dose and expected side effects of specific chemotherapeutic agents; (3) the basic principles of combination chemotherapy in combined modality programs; and (4) the standard use and experimental approaches of chemotherapy for squamous cell carcinomas and salivary gland tumors.

PRINCIPLES OF CLINICAL TRIALS

The efficacy of chemotherapy or combined modality programs is investigated through clinical trials.²⁰¹ To evaluate the use of a particular treatment, clinicians establish at the onset the parameters to be evaluated: objective response rate, survival, disease-free survival or duration of response, and toxicity are commonly identified. The parameters of interest for a specific trial design are defined before the initiation of the study and analyzed at the completion of the study.

The primary end points depend on the nature of the clinical trial or phase of testing.

The evaluation of chemotherapeutic agents occurs in three steps or phases. The goals of phase I trials are to determine the toxic effects associated with a new drug and to establish the highest dose of the drug that can be safely administered. Patients with different tumor types refractory to conventional chemotherapy are enrolled. The purpose of phase II trials is to determine whether a drug or drug combination tested in patients with the same tumor type has enough activity to warrant further testing in a comparative trial. The primary end point is response rate. Phase III trials are randomized comparisons of two or more treatment options, often comparing a standard treatment to a new or more complex therapy. Response rate, progression-free survival, or response duration and survival are primary end points. The determination of sample size and patient entry criteria and the follow-up evaluation and monitoring of patients are critical for a valid interpretation of a phase III trial.¹⁶⁸

Standard definitions exist for the various end points in clinical trials that allow objective reporting of results. Definitions of response are complete, partial, minor, stable, and progressive disease (Box 4-1). The most meaningful response in terms of prolongation of survival is the attainment of a complete response in which no tumor is detectable after a clinical and radiographic examination. By convention, a partial response indicates that the disease has regressed by at least 50% as determined by serial bidimensional measurements and that no new lesions have appeared elsewhere for at least 4 weeks. The response rate represents the percentage of complete and partial responders. Minor responses and stabilization of disease have historically been of little value but may become significant as newer “targeted” treatments are tested.

TABLE 4-1

CHEMOTHERAPEUTIC AGENTS WITH ACTIVITY IN HEAD AND NECK CANCERS

Agent	Mechanism	Toxicity
Alkylators		
Cyclophosphamide	DNA cross-linker	Neutropenia, nausea, cystitis
Ifosfamide	DNA cross-linker	Myelosuppression, cystitis, confusion, alopecia
Antimetabolites		
Methotrexate	Binds dihydrofolate reductase	Mucositis, myelosuppression
5-Fluorouracil	Inhibits thymidylate synthetase	Mucositis, myelosuppression, diarrhea
Antibodies		
Bleomycin	Scission of DNA	Pulmonary fibrosis, rash, mucositis
Adriamycin	DNA intercalator	Cardiotoxicity, mucositis, myelosuppression, alopecia
Vinca alkaloids		
Vincristine	Mitotic arrest	Neurotoxicity, myelosuppression, alopecia
Vinblastine	Mitotic arrest	Neurotoxicity, myelosuppression, alopecia
Miscellaneous		
Cisplatin	DNA intercalator	Nephrotoxicity, vomiting, ototoxicity, neuropathy
Carboplatin	DNA intercalator	Myelosuppression
Taxanes		
Paclitaxel	Microtubule stabilizer	Myelosuppression, neuropathy
Docetaxel	Microtubule stabilizer	Edema, neutropenia, neuropathy

BOX 4-1

CRITERIA FOR RESPONSE

Complete response	Complete disappearance of all evidence of tumor for at least 4 weeks.
Partial response	Disease regression by at least 50% of the sum of the product of the perpendicular diameters of all measurable tumor for at least 4 weeks. No simultaneous increase in the size of any lesion or appearance of new lesions may occur.
Minor response	Regression by less than 50% of the sum of the products of the perpendicular diameters of all measurable lesions.
Stable disease	No appreciable change in dimensions of all evaluable lesions.
Progressive disease	Increase in the size of any detectable lesions by at least 25% or the appearance of new lesions.

When a study is completed, there are several ways to compute the response rate. In calculating the fraction of responders, the numerator should always be the number of patients who qualify in a particular response category, but the denominator often varies from study to study. Some investigators compute response rate using all patients entered into a study, whereas others evaluate response rates after eliminating early death or patients failing to receive a specific number of cycles of treatment. The latter method of computing a response rate results in a much larger value than the former.

Survival is usually calculated from date of study entry until date of death. Progression-free survival is calculated from study entry until disease progression and disease-free survival from achievement of complete response until disease progression. Duration of response is calculated from response date until date of disease progression. Toxicity should be strictly defined for every study before initiation. The National Cancer Institute (NCI) has developed a comprehensive set of standardized drug-induced toxicity criteria. Using a 0 to 4 grading scale, toxicity to each organ system can be objectively assessed. All toxic

reactions should be reported in detail in the final results.

In planning a clinical trial, particularly a phase III trial, having comparable patients in each group is critical. This requirement often is accomplished by randomization with stratification for important prognostic variables. Prognostic variables are those factors known to influence response, regardless of treatment. One of the more well-known, important prognostic variables is the Karnofsky Performance Status. In 1948, a 0-to-100 performance scale was devised by David Karnofsky to describe a patient's functional ability. This scale is used today interchangeably with a 0-to-5 point scale (Box 4-2) adapted by several cooperative groups. Performance status is an established prognostic variable that directly correlates with response to chemotherapy. Those patients with a performance status greater than 2 or less than 50% are poor candidates for phase II and III clinical trials and are poor candidates for chemotherapy with palliative intent. These patients usually have a large tumor burden, are malnourished, and have a very short survival time regardless of treatment. By definition, they are nonambulatory for more than 50% of their waking hours and require special care and assistance. If a trial is randomized but not stratified for performance status, a large number of patients with poor Karnofsky Performance Status could be randomly assigned to one of the treatment groups and make it appear less efficacious than a second, when it

actually may be equal or better. Important prognostic variables should be defined at the onset of a study and should be analyzed in the results.

It is important in designing and drawing conclusions from trials to note whether the trial is prospectively randomized with concurrent controls or is a clinical trial with historical controls. Proponents of randomized trials believe that one is more certain of equality between the two groups by a concurrent randomization process.²⁰¹ This will reduce the bias of selecting control subjects from a historical pool and will also reduce the influence of improvements in management or changes in treating physicians with time.

SQUAMOUS CELL CARCINOMA

Overview of Current Concepts

Before 1970, chemotherapy had a limited role in the management of squamous cell cancer of the head and neck in community practice and at academic centers. In part, this was because of the paucity of available drugs with documented antitumor activity for this disease. The only drug with clearly established activity, used worldwide, was the folic acid analog methotrexate. Many other drugs had been tested, although the assessment criteria used to define response were not uniform. Hence, the reported response rates were unreliable, representing an accumulation of observations of any degree of tumor regression. In contrast,

BOX 4-2

PERFORMANCE STATUS

ECOG, SWOG, Zubrid Scales

- 0 Fully active, able to carry on all predisease performance without restriction
- 1 Restricted in physical strenuous activity but ambulatory and able to do work of a light or sedentary nature, (e.g., light housework, office work)
- 2 Ambulatory and capable of all self-care but unable to do any work activities; up and about more than 50% of waking hours
- 3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 Completely disabled; cannot do any self-care; totally confined to bed or chair
- 5 Dead

Karnofsky Scale

- 100 Normal; no complaints; no evidence of disease
- 90 Able to carry on normal activity; minor signs or symptoms
- 80 Normal activity with effort; some signs or symptoms of disease
- 70 Cares for self; unable to do normal activity or active work
- 60 Requires occasional assistance, but is able to care for most needs
- 50 Requires considerable assistance and frequent medical care
- 40 Disabled; requires special care and assistance
- 30 Severely disabled; hospitalization indicated; death not imminent
- 20 Very sick; hospitalization and active support treatment necessary
- 10 Moribund; fatal process; progressing rapidly
- 0 Dead

during the past two decades, a rigid system has been applied to the testing of potentially useful drugs. There are now clearly defined parameters for the objective evaluation of response and survival time and statistical guidelines for the design of clinical research trials to establish efficacy or to show improvement compared with standard therapies.

The serendipitous identification of the metal compound cisdiamine-dichloroplatinum (II) (cisplatin) as a potential anticancer agent by Rosenberg¹⁸³ in 1968 spurred clinical research efforts to test new agents and combination chemotherapy regimens for the palliation of patients with locally recurrent and metastatic cancers. Several highly effective chemotherapy regimens were identified and then incorporated into a combined modality approach to treating the newly diagnosed patient. The ultimate goal was to improve survival time with squamous cancers of the head and neck. It became clear that chemotherapy administered before definitive surgery or radiotherapy could result in rapid regression of tumor in the majority of patients without substantially increasing the morbidity of subsequent surgery or radiation. Further, a proportion of the responding patients would have no histologic evidence of tumor in the resected specimen. This increased the possibility of altering the standard surgical approach at some sites to preserve organ function. In addition to investigative trials using chemotherapy before definitive local therapy, traditional adjuvant chemotherapy administered after surgical resection and chemotherapy used as a radiosensitizer concomitant with radiotherapy have been under active investigation.

Prognostic Factors

Many chemotherapy trials have been analyzed to determine factors that would predict response to chemotherapy and prolonged survival time. Because squamous cell cancer of the head and neck is a heterogeneous disease, each factor should be evaluated in the context of multiple primary sites. Most single-institution trials have only modest numbers of patients and therefore lack the statistical confidence to draw firm conclusions. For patients with recurrent disease, poor prognostic factors are a low performance status, poor nutrition, a large tumor burden, and extensive previous radiotherapy and surgery.¹² Tumor progression during or shortly after surgery or radiotherapy is also an ominous sign. In these circumstances, any response to chemotherapy is likely to be marginal and brief, without impact on overall survival time. However, it seems clear that survival time may be prolonged in patients who achieve a complete response to chemotherapy. These patients, in general, have a good performance status; they are not mal-

nourished and have not received previous chemotherapy for recurrent disease.

For newly diagnosed patients treated with induction chemotherapy, the most consistent prognostic factor for overall response and complete response is T and N stage. There is a significant correlation between tumor size and response, with lower response rates observed in T4 and N3 stage disease, in particular.^{39,73,106} The importance of primary site as a prognostic factor for response to chemotherapy is unclear. One investigator, in an analysis of 208 patients, reported that cancers within the oral cavity and nasopharynx were significantly associated with high response rates.¹⁰⁸ Nasopharynx cancer was found to be significant in two other trials.^{6,73} The pattern of failure for patients with nasopharyngeal carcinoma is also different than that of cases at other sites, with metastatic sites assuming a larger proportion. Besides nasopharyngeal carcinoma, most trials have failed to demonstrate differences by site, which may relate to inadequate patient numbers and only modestly effective chemotherapy regimens.

Because of the importance of performance status as a predictor of outcome for patients with recurrent disease, induction chemotherapy trials have excluded patients with poor performance status (<50% on the Karnofsky scale). Within the range of 50% to 100%, no clear differences have been observed. Tumor differentiation does not appear to be a predictive factor in studies that have used cisplatin-based combination chemotherapy regimens. It is well established that overall survival time correlates with performance status, T and N stage, primary site,^{5,73,106} and nodal extracapsular extension of tumor.^{124,203} The survival time of patients with cancers of the nasopharynx and larynx is longer than that of those with oral cavity and hypopharyngeal primary cancers after researchers correct for other factors in multivariate analyses of patients receiving induction chemotherapy.

The application of biologic factors (e.g., DNA content,⁷¹ immunologic status, and circulating immune complexes¹⁹⁵) to predict response and survival outcome is under investigation. Evidence exists that DNA ploidy and DNA content can predict survival and disease-free survival times.^{222,249} Molecular markers (such as *p53* and *p16*) that act as predictors for response and survival time are also under investigation.^{21,22}

CHEMOTHERAPY FOR PALLIATION

Systemic management of recurrent head and neck cancer is a major concern because 30% to 50% of patients diagnosed this year will die with recurrent local and regional disease within 5 years. Distant metastases will be clinically present in 20% to 40% of patients, but occult disease determined at autopsy

may be present in up to 60%.¹³⁵ The primary goal of conventional chemotherapy used for palliation should be to prolong survival time. Patients with locally advanced or disseminated recurrent squamous cell carcinomas of the head and neck have a median survival time of 6 to 8 months, and 20% survive 1 year. Chemotherapy has not yet altered these statistics, although it has been useful in palliation. One often hears that pain relief can be achieved with chemotherapy, but this should not constitute the sole reason for treatment. Tumor regression may be associated with a transient diminution of pain, although the aggressive use of a variety of available oral analgesics (tablet and elixir preparations) is a much more rational approach to pain management.

Single Agents

The response rate (complete and partial) of recurrent or metastatic squamous cell cancer to commonly used agents is provided in Table 4-2. In general, about one third of patients respond. The majority are partial responses, with less than 5% of patients achieving a complete response. Response duration tends to be brief, on the order of 2 to 4 months, and median survival time is 6 to 9 months.

Methotrexate

Methotrexate is a folic acid analog that is S-phase specific. Its mechanism of action involves binding to the enzyme dihydrofolate reductase, which blocks the reduction of dihydrofolate to tetrahydrofolic acid. Tetrahydrofolic acid is necessary for the synthesis of thymidylic acid and purine. This then interrupts the synthesis of DNA, RNA, and protein. The cytostatic

effects of methotrexate can be circumvented by the administration of reduced folates, such as leucovorin, which can be converted to the tetrahydrofolate coenzyme required for purine biosynthesis. The therapeutic index of methotrexate can be increased if leucovorin is administered at intervals after methotrexate is given. This results from a selective rescue of nonmalignant cells and forms the basis for the use of high doses of methotrexate followed by leucovorin to ameliorate methotrexate toxicity to healthy cells. Cancer cells may lack transport sites for leucovorin and are subject to the lethal effects of methotrexate. Mechanisms for resistance to methotrexate include the selection of cells with decreased transport of methotrexate into cells and increased dihydrofolate reductase activity.

Methotrexate can be administered by intramuscular injection or subcutaneous, intravenous, or oral routes. Weekly or biweekly administration is the preferred schedule. A conventional dose of intravenous methotrexate is 40 to 60 mg/m² weekly. When higher doses of methotrexate are used, they may be in the moderate-dose range (250–500 mg/m², intravenous) or the high-dose range (5–10 g/m²). These are both followed by leucovorin rescue, usually beginning at 24 hours and continuing until the plasma methotrexate level is less than 10⁻⁸ mol/L. At this dose range, the toxicity for patients with normal renal function usually is limited to mild stomatitis and myelosuppression. More severe, life-threatening reactions consisting of confluent mucositis, pancytopenia, liver function abnormalities, and an exfoliative maculopapular rash occur rarely and require intensive medical support. Renal dysfunction may occur with high-dose methotrexate administration because of precipitation of the drug, especially in the case of acidic urine. Hydration and alkalinization of the urine before and after methotrexate administration can reduce the risk.

Methotrexate was previously widely used for management of squamous cancers of the head and neck. Therapy with this drug is relatively nontoxic, inexpensive, and convenient. Response rates to conventional doses vary between 8% and 50%, averaging 30%.¹⁶ Weekly treatment, if tolerable, is superior to twice monthly or monthly treatments. Levitt and others¹⁴¹ have shown *in vitro* that when moderate-to-high doses of methotrexate are used with leucovorin rescue, an enhanced therapeutic index results from the high intracellular levels of drug associated with selective rescue of healthy tissue. The initial results of pilot trials of moderate- or high-dose methotrexate suggested improvement in response rates for those with head and neck cancers. However, there is no clear benefit to the higher dose (e.g., as much as 5000 mg) from prospective randomized trials comparing conventional

TABLE 4-2

ACTIVITY OF SINGLE AGENT CHEMOTHERAPY

Agent	Dosing Schedule	Response Rate (%)
Methotrexate	40–50 mg/m ² weekly	30
Cisplatin	80–120 mg/m ² every 3–4 weeks	33
Carboplatin	400 mg/m ² every 4 weeks	24
Paclitaxel	135–200 mg/m ² every 3–4 weeks	38
Docetaxel	75 mg/m ² every 3 weeks	38
Ifosfamide	1.5–2.5 g/m ² every 4 weeks	26
Bleomycin	15 mg/m ² twice weekly	18
5-Fluorouracil	500 mg/m ² weekly	15

with moderate- or high-dose methotrexate, with or without leucovorin rescue.^{233,248}

Cisplatin

Cisplatin is an inorganic metal coordination complex with major antitumor activity in a number of diseases. The drug behaves as a bifunctional alkylating agent binding to DNA to cause interstrand and intrastrand cross-linking. Cisplatin also binds to nuclear and cytoplasmic proteins. Resistance is believed to develop through increased metabolic inactivation. Cisplatin is administered by the intravenous route and requires aggressive hydration and diuresis to prevent renal tubular damage. A dose range of 80 to 120 mg/m² every 3 or 4 weeks¹⁰⁵ or by 24-hour infusion¹¹⁷ have been administered. More often, the 80 to 100-mg/m² dose is used. The drug is not schedule dependent, although it has been shown that 5-day continuous infusion increases exposure to the active platinum species when compared with bolus dosing.⁸⁴

The major toxic reaction is renal dysfunction, manifested by an increase in serum creatinine levels or a decrease in creatinine clearance. The peak serum creatinine level occurs at 1 or 2 weeks and returns to baseline by 3 or 4 weeks. An increase in serum creatinine level to 2 mg/dL has been noted in up to 20% of patients in several series. This drug should not be used in patients with a creatinine clearance below 40 mL/min. Nausea and vomiting are almost universal. Ototoxicity can occur, usually in the 4000- to 8000-Hz range. It tends to be dose-related and cumulative and may be permanent. Hematologic toxicity, including neutropenia and thrombocytopenia, is mild, with a nadir at 2 weeks. Anemia is common and appears to be a result of bone marrow suppression; rarely, patients manifest an acute hemolytic anemia. Hypomagnesemia can occur in part because of renal wasting. A peripheral neuropathy with predominantly sensory deficits occurs and is related to cumulative cisplatin dosage. Ototoxicity and peripheral neuropathy are very common toxicities when the cumulative cisplatin dose approaches or exceeds 600 mg/m². These toxicities preclude long-term management with cisplatin in chemotherapy responders and dose intensification. This led to a search for analogs with similar efficacy but a different spectrum of toxicity.

Cisplatin has the same response rate as methotrexate, approximately 30%, with some reported complete responses and a duration of response of approximately 4 months.^{117,247} Two controlled trials comparing methotrexate with cisplatin found no difference in response rate or survival time between the two but noted quite different toxicities.^{98,110} Advantages of cisplatin over methotrexate are its relatively rapid response rate and the fact that it needs to be given

only once every 3 or 4 weeks. Cisplatin has been studied at different doses to determine whether a dose/response effect exists. In a comparison of 60 mg/m² and 120 mg/m², Veronesi and others²²⁸ found no difference in response rates. Forastiere and others⁸¹ conducted a pilot trial evaluating 200 mg/m² and observed a 73% response rate or double that expected with conventional dosing. Although this suggested benefit from the higher dose, ototoxicity and neurotoxicity occurred frequently and limited treatment duration.

Carboplatin

More than one dozen derivatives of cisplatin have been evaluated for clinical development. Of these, carboplatin (cis-diamine-cyclobutane dicarboxylatoplatinum II) was the first to become widely available. Carboplatin appears to have a mechanism of action similar to the parent compound, but it has a different toxicity profile. The dose-limiting toxicity is myelosuppression, primarily leukopenia and thrombocytopenia, which should be considered when carboplatin is combined with other myelosuppressing agents. Renal toxicity, ototoxicity, and neurotoxicity are rare, and the emetogenic potential of carboplatin is less. The drug can be administered in the outpatient setting without the need for hydration. Based on pharmacokinetic parameters, an intravenous dose of 400 mg/m² is considered the equivalent in potency to 100 mg/m² of cisplatin and can be safely administered to patients with creatinine clearance of 60 mg/mL or more. Most clinicians calculate carboplatin dose using the Calvert³¹ formula, which accounts for delayed renal excretion leading to increased drug exposure.

Carboplatin has a 24% response rate in phase II trials in patients with recurrent squamous cell cancer of the head and neck. It may not be as active as cisplatin; one comparative trial in patients with untreated disease has documented an inferior outcome for carboplatin.¹⁰ Thus, carboplatin is often reserved for patients who are not candidates for cisplatin therapy because of excessive nausea, renal impairment, or preexisting peripheral neuropathy. Carboplatin can be administered in the outpatient setting and requires no prehydration. The major toxicity caused by carboplatin is myelosuppression, which limits the total dose that can be given and the frequency of drug administration. The availability of colony-stimulating factors that can lessen the degree and duration of myelosuppression may provide a means to compensate for marrow toxicity.

Taxanes

The taxanes are a new class of compounds that include paclitaxel (Taxol) and docetaxel (Taxotere). These drugs act by stabilizing microtubules after bind-

ing to the *b* subunit of tubulin, thereby inhibiting microtubule depolymerization, which results in a cell cycle arrest at G₂. Preclinical studies showed that the taxanes were active against a variety of solid tumors and that prolonged infusions were more effective.^{90,99,176,230} Trials involving patients with head and neck cancer have shown response rates of approximately 30% to 40%.^{34,66,80,83,219}

Paclitaxel has been administered at doses of 135 to 250 mg/m² given over 3 or 24 hours, and docetaxel has been given at 60 to 100 mg/m² by bolus injection every 3 weeks. The major toxicity is neutropenia, particularly with high doses, and infection is a chief concern. Growth factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) may be used to shorten the neutropenic nadir duration and hopefully lessen the risk of infection.¹⁸⁴ Given this risk, patients with good performance status are better candidates for treatment at 175 to 200 mg/m². Paclitaxel has been given over several schedules, and the optimal dosing schedule is being investigated. Docetaxel is a semisynthetic agent and may be more effective than paclitaxel. In two small phase II studies, response rates of 32% and 50% were observed.^{34,63}

Ifosfamide

Ifosfamide is structurally related to cyclophosphamide (to be discussed) and has a similar mechanism of action, leading to DNA interstrand and intrastand cross-linking that disrupts DNA replication. It is activated by hepatic p-450 mixed-function oxidase, and its metabolites are excreted in the urine. Ifosfamide in total doses of 7 to 10 g/m² is usually administered as a 5-day continuous infusion or over 3 to 5 days in equally divided doses. The drug is repeated at 3- or 4-week intervals. Sodium mercaptoethane sulfonate (MESNA) is a thiol compound that should be administered concomitantly with ifosfamide to limit urothelial toxicity. The total daily dose of MESNA should equal the daily dose of ifosfamide. It may be administered as a continuous infusion or in divided doses. Patients need to be well hydrated before drug administration. The major dose-limiting toxicity is hemorrhagic cystitis, although with the use of MESNA, myelosuppression, nausea, vomiting, and hyponatremia are more frequent toxicities. Central nervous system toxicities, which include cerebellar dysfunction, seizures, confusion, and lethargy, occur in up to 30% of patients treated with doses of 8 to 10 g/m² over 5 days. Early phase II results with this drug are promising, with reported response rates ranging from 6% to 43% with a median of 26%.*

*References 53, 56, 95, 127, 136, 138, 167, 172, 200.

Bleomycin

Bleomycin (Blenoxane) is an antineoplastic antibiotic that binds to DNA and produces DNA strand breaks by generating oxygen free radicals. The conventional dose of bleomycin is 10 to 20 U/m² once or twice weekly given intramuscularly or intravenously. It also may be given by a continuous 24-hour infusion over 5 or 7 days at a dose of 10 U/m² each 24 hours. The major metabolism of bleomycin is via the kidneys. It is important that the dose of bleomycin be reduced if the level of serum creatinine is abnormal. A 50% dose reduction is recommended for a creatinine clearance of 15 to 30 mL/min, and a 75% reduction is recommended if the creatinine clearance is below 15 mL/min. Approximately half of the patients receiving this drug will develop fever or chills during the first 24 hours, which can be reduced with the use of antipyretics. A rare complication is an anaphylactic reaction. It has been recommended that a dose of 1 U be given several hours before the first dose of bleomycin. Alopecia can occur, particularly with the higher dosage of drug. Skin toxicity, including erythema, thickening, and hyperpigmentation, is common. Patients may develop stomatitis, which necessitates discontinuing a prolonged infusion.

Pulmonary toxicity is potentially one of the most serious complications of bleomycin administration. Patients may develop pneumonitis, a dry cough, and rales. Pulmonary function tests most commonly show a decreased carbon monoxide diffusion capacity. Pulmonary fibrosis with associated hypoxia and restrictive lung disease can result. Bleomycin pulmonary toxicity is more common in elderly patients, in patients who have had previous lung irradiation, and in patients who have had a total dose higher than 200 U. Patients should be closely monitored with serial tests of diffusion capacity when the cumulative dose exceeds 150 U. Giving the drug by continuous infusion may lessen pulmonary toxicity.²⁴⁰

Bleomycin has undergone testing using an intermittent bolus dosing schedule with response rates of 18%. A pharmacokinetic advantage may be achieved by continuous infusion because both agents have a short plasma half-life. Bleomycin is most frequently used in combination with other agents, and is not currently in common usage.

5-Fluorouracil

5-Fluorouracil (5-FU) is a fluorinated pyrimidine similar to uracil. 5-FU competes for the enzyme thymidylate synthetase by displacing uracil, which in turn inhibits the formation of thymidine, an essential factor in DNA synthesis. The conventional intravenous dose of 5-FU is 10 to 15 mg/kg weekly. An alternate method of delivery is a loading dose of 400 to 500

mg/m² daily for 5 days, followed by a weekly intravenous dose of 400 to 500 mg/m². It is recommended that no more than 800 mg be given as a single bolus. The therapeutic index of 5-FU may be enhanced by giving it by continuous infusion, which allows delivery of up to 1 g/m² per day for 5 days, repeated every 3 or 4 weeks, without marked enhanced toxicity. Continuous infusion of 5-FU has been studied primarily in patients with adenocarcinomas of the gastrointestinal tract. However, the results of one randomized trial studying patients with head and neck cancer and comparing bolus with continuous infusion of 5-FU showed improved response rates with continuous infusion.¹³¹ 5-FU toxic reactions include myelosuppression with neutropenia and thrombocytopenia occurring at 1 or 2 weeks. Nausea, vomiting, and diarrhea may occur, and stomatitis is common with higher doses. Patients may develop alopecia, hyperpigmentation, or a maculopapular rash. In patients with head and neck carcinomas, treatment with 5-FU can produce response rates of 15%, thus it has most often been used in combination with other agents, particularly cisplatin.^{8,169}

Other Single Agents with Activity in the Treatment of Head and Neck Cancer

Several other chemotherapeutic agents were reported to have response rates in excess of 15% for patients with recurrent disease. They include Adriamycin, cyclophosphamide, hydroxyurea, and vinblastine.⁹ Several of these are only marginally effective as single agents for recurrent disease, although when used in combinations or in patients with no previous treatment, they may be more efficacious. These agents will be discussed.

Cyclophosphamide

Cyclophosphamide is activated in the liver by microsomal enzymes. Its major mechanism of action is cross-linking DNA strands, preventing further division. Cyclophosphamide can be given orally or intravenously. When given intravenously, it usually is given as a single dose of 500 to 1000 mg/m² repeated every 3 or 4 weeks. It is important to hydrate patients well before and after giving cyclophosphamide. Drugs that stimulate liver enzymes, such as barbiturates, should be avoided, or the cyclophosphamide dose should be modified. After an intravenous dose, bone marrow suppression, predominantly neutropenia, can occur within 1 or 2 weeks, with a recovery at 2 or 3 weeks. Many patients have some degree of nausea and vomiting. Alopecia and ridging of the nails can occur. Azoospermia and cessation of menses, often with permanent infertility, can occur with most alkylating agents.

Acute hemorrhagic cystitis occurs most commonly in patients who are poorly hydrated. It is recommended that patients drink at least 2 quarts of fluid per day while taking cyclophosphamide. Toxicity may occur as microscopic hematuria or gross bleeding. This can eventually result in a fibrotic bladder, and a few cases of bladder carcinoma have been described in patients who have received cyclophosphamide.

Adriamycin

Adriamycin (doxorubicin) is an anthracycline derivative that intercalates between nucleotide pairs in DNA to interfere with nucleic acid synthesis. This drug is given intravenously, usually at doses of 60 to 75 mg/m² every 3 weeks. Alternate schedules that are associated with a much lower risk of cardiac toxicity include doses of 20 to 30 mg/m² daily for 3 days repeated every 3 weeks, low doses given weekly, or prolonged infusions.¹⁵ The patient's urine may be red for 1 or 2 days after Adriamycin treatment.

If Adriamycin infiltrates subcutaneous tissue, it can cause severe necrosis of skin and subcutaneous tissue. The drug causes alopecia, which can be decreased by using scalp hypothermia. Stomatitis, nausea, vomiting, and diarrhea are common. Adriamycin, like actinomycin D, can cause radiation recall in patients who have had previous radiotherapy. The drug can also cause neutropenia and thrombocytopenia with a nadir at 1 or 2 weeks and a return to normal values by 3 weeks.¹⁷

The most dose-limiting toxic effect of Adriamycin is cardiac toxicity, which manifests as a cardiomyopathy,²³⁸ leading to congestive heart failure in approximately 10% of patients who receive a cumulative dose greater than 550 mg/m². Other predisposing factors include age, previous cardiac irradiation, other cardiotoxic chemotherapeutic agents, and a previous history of heart disease. Many methods of observing patients have been used, including endomyocardial biopsy. Radionuclide ejection fraction is a relatively easy and accurate way to determine the amount of damage to the heart from Adriamycin.

Vinca Alkaloids

Vinblastine and vincristine are vinca alkaloids. These agents act by disrupting microtubular spindle formation, causing mitotic arrest. Vinblastine (Velban) can be given weekly at 5 mg/m², or it may be given by continuous infusion over several days. The major toxic reactions are myelosuppression, alopecia, and myalgia. Vincristine (Oncovin) is usually given at 1.0 to 1.5 mg/m² once or twice monthly. It is recommended for adults that a single dose not exceed 2 mg. The drug is neurotoxic, which is most commonly manifested as a sensory motor peripheral neuropathy or hoarseness

that will progress if the drug is not discontinued. Most patients will experience constipation, and they should take stool softeners with the drug. Vincristine causes alopecia, but it has almost no myelosuppressive effects.

Hydroxyurea

Hydroxyurea (Hydrea) inhibits ribonucleotide reductase, interfering with the conversion of ribonucleotide to deoxyribonucleotide and causing inhibition of DNA synthesis. The drug is given orally. The major toxic responses are neutropenia and thrombocytopenia, so the dose should be reduced or delayed if the leukocyte count decreases to less than 2500/mm³ or the platelet count decreases to less than 100,000/mm³. The nadir occurs approximately 10 days after starting the drug. Nausea and diarrhea are common. Stomatitis can occur, particularly if there is concurrent irradiation. Patients also may develop a maculopapular rash. This drug is most commonly used as a radiation sensitizer.

New Single Agents

Many new drugs are being investigated for their activity in patients with head and neck cancer in phase I and II studies. Topoisomerase I inhibitors are under study.¹⁸⁰

Gemcitabine is a pyrimidine antimetabolite that may have antitumor activity in patients with head and neck carcinomas. This agent is converted to an active triphosphate metabolite, which is then incorporated into DNA and terminates transcription. Early phase II results have demonstrated only modest activity with response rates of 18%.³⁵

Vinorelbine is a semisynthetic vinca alkaloid with dramatically less neurotoxicity than other agents of its class. Early studies have demonstrated response rates of 22%.^{94,218} Finally, analogs of methotrexate have been evaluated for response in small series. Trimetrexate, edatrexate, and piritrexim are active in squamous cell carcinomas of the head and neck but offer no special advantage over methotrexate.^{55,179,188,223,236}

COMBINATION CHEMOTHERAPY FOR RECURRENT DISEASE

In an effort to improve response rates and, hopefully survival time, combination chemotherapy was developed. Many combination chemotherapy regimens have been evaluated in phase II trials involving a few patients with recurrent head and neck cancer. Often, the results indicate a high response rate that suggests improvement over that expected from single agent methotrexate or cisplatin. However, the median duration of response ranges from 2 to 6 months, and no one has yet documented improved survival time over single-agent chemotherapy. Many of the regimens are complex, often with additional toxic effects.

Only through large comparative trials with patients randomized and stratified for prognostic variables can it be determined whether therapeutic benefit exists with combination chemotherapy. The results of 12 trials comparing combination chemotherapy to single-agent cisplatin or methotrexate are shown in Table 4-3. Some of the studies had small numbers of patients and lacked balance between treatment groups for prognostic factors such as performance status and extent of previous treatment. However, four large multiinstitutional trials that were well designed with respect to prognostic factors showed a significant difference in response rates between the combination treatment and the single-agent control arm.^{41,79,86,119,232}

The Eastern Consortium Oncology Group (ECOG) compared an outpatient regimen of cisplatin, bleomycin, and methotrexate to weekly methotrexate.²³² The response to single-agent therapy with methotrexate was 35%, and to the combination 48%—a significant improvement ($P = .04$). However, toxicity was greater for the combination, with no difference in survival time.

The Southwestern Oncology Group (SWOG) reported a comparison of cisplatin and 5-FU vs carboplatin and 5-FU to weekly methotrexate.^{79,86} The response rates for the three arms were 32%, 21%, and 10%, respectively. There was a significant difference comparing the cisplatin combination with methotrexate ($P < .001$); the difference between the response to the carboplatin combination and the response to methotrexate approached statistical significance ($P = .05$). The cisplatin and 5-FU arm was associated with significantly more toxicity than methotrexate; carboplatin and 5-FU were intermediate in toxicity. Despite these findings, the median survival times were not different, varying between 4.7 and 6.6 months.

The third study to show a difference in response rates compared the combination of cisplatin and 5-FU with each drug used alone.¹¹⁹ The response rate to the combination was 40% compared with 18% for cisplatin and 15% for continuous infusion 5-FU ($P < .01$). Although the median survival times were not different, an analysis of patients surviving longer than 9 months showed a 40% survival rate for the combination treatment group compared with 27% and 24% for the single-drug treatments ($P < .05$).

The latter two trials are also of interest because of the similar response rates observed for cisplatin and 5-FU, which were administered using the same dose and schedule in both studies. Cisplatin with 5-FU is a commonly used drug regimen for the treatment of patients with head and neck cancer for palliation and in combined modality programs. Response rates to this combination reported from small phase II trials in patients with recurrent disease range from 11% to 79%.²²⁴ The results of these two large multiinstitutional

TABLE 4-3

RANDOMIZED TRIALS OF CHEMOTHERAPY FOR RECURRENT HEAD AND NECK CANCER			
Author	Regimens	CR + PR (%)	Survival (months)
Davis and Kessler, 1979 ⁵²	PMB	11	
	P	13	
Jacobs, 1983 ¹¹⁸	PM	33	6.3
	P	18	6.9
Drelichman, 1983 ⁶³	P		
	Vb	41	5.6
	M	33	4.0
Vogl, 1985 ²³²	PMB	48	5.6
	M	35	5.6
Morton, 1985 ¹⁶²	PB	24	4.0
	P	13	4.2
	B	14	2.8
	No chemotherapy		2.1
Williams, 1986 ²⁴⁶	PVbB	23	6.8
	M	16	7.2
Campbell, 1987 ³²	PF	19	2.7
	PM	40	8.7
	P	31	5.3
	M	33	6.7
Eisenberger, 1989 ⁶⁸	CM	25	6l
	M	25	6l
Liverpool Study, 1990 ¹⁴⁶	P	14	6l
	PF	12	6l
	M	6	2l
	PM	11	6l
Forastiere, 1992 ⁸⁶	PF	32	6.6
	CF	21	5.0
	M	10	5.6
Jacobs, 1992 ¹¹⁹	PF	32	5.5
	P	17	5.0
	F	13	6.1
Clavel, 1994 ⁴¹	PMBVb	34	7.0
	PF	31	7.0
	P	15	7.0

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CR, Complete response; PR, partial response; P, cisplatin; M, methotrexate; B, bleomycin; Vb, vinblastine; C, carboplatin; F, fluorouracil.

trials have served to establish a response rate of 32% that can be expected from the cisplatin and 5-FU combination in patients with recurrent head and neck cancer.

Clavel and others⁴¹ also observed significant differences between combination chemotherapy and single agents. They found significant differences in response rates for two cisplatin-containing combinations compared with single agent methotrexate—34%, 31%, and 15%, respectively. These data corroborate the work of Vogl, Jacobs, and Forastiere.

Two comparative trials listed in Table 4-3 showed significant differences in median survival time.^{32,162} Morton and others¹⁶² compared the combination of cisplatin and bleomycin to each single agent and to a control arm featuring no treatment. The response rate to each of the three chemotherapy arms was low, although the two cisplatin arms had median survival times of 4.0 and 4.2 months, which was improved over a 2.1-month survival time for the no-treatment arm. In the four-arm trial reported by Campbell and others,³² survival time was significantly longer for single-agent

cisplatin compared with methotrexate, and there was no advantage for the combination treatments. Both of these trials had small numbers of patients and were unevenly balanced for prognostic factors, which serves to decrease the reliability of the statistical interpretation. Thus, from these randomized trials, it appears that higher response rates can be achieved with some combination chemotherapy regimens. Toxicity is more severe, and overall survival time as measured by median survival time is not improved. However, one study did find that a significantly greater proportion of patients treated with cisplatin and 5-FU lived longer than 9 months when compared with those receiving single-agent therapy. The patients who are more likely to be in the subset showing improvement have a better performance status.

As for other sites, the most effective combinations for treating those with nasopharyngeal carcinoma are cisplatin-based regimens. Higher complete and partial response rates than those from other sites have been reported in several phase II trials.* A few long-term disease-free survivors have been seen as a result of cisplatin-based combinations.^{20,40,76} French investigators have formed a collaborative group to study nasopharyngeal cancer. They have reported a series of studies evaluating cisplatin combination chemotherapy. Their regimen of cisplatin, bleomycin, and 5-FU resulted in a 20% complete response rate and an 86% overall response rate. Four patients with metastatic disease were long-term, disease-free survivors for 52 to 58 months.^{20,50,150} In their series, 131 patients with metastatic nasopharyngeal carcinoma were treated between 1985 and 1991. Ten percent of the members of this group were long-term, disease-free survivors. Thus, this disease entity shows a unique chemosensitivity even in patients with either bone or visual metastasis.⁷⁶ Brownman and Cronin²⁵ summarized all of the available data regarding combination therapy by use of a metaanalysis. They analyzed all randomized trials published between 1990 and 1992 and concluded that cisplatin was the most effective single agent. Further, they found that the combination cisplatin and 5-FU was more efficacious than any single agent or other reported combinations. The combination of cisplatin and 5-FU is the gold standard to which all new combinations should be compared. Response rates achieved with this combination are approximately 32%, and the complete response rate ranges from 5% to 15%. Given these low response rates, one of the goals of clinical trials is to find new single agents and new combinations that may be more effective. Patients with locally advanced or metastatic disease should be considered for trials in an effort to improve on these statistics. Patients who have undergone previous surgery and radiation with good per-

formance status and no previous chemotherapy are the best candidates to test new treatment protocols.

COMBINED MODALITY THERAPY

Although surgery and radiotherapy cure a high percentage of patients with early-stage squamous cell carcinoma of the head and neck, conventional treatment will not cure the majority of those with advanced disease. Because treatment for recurrent disease with chemotherapy is far from satisfactory, much effort has been directed toward improvements in the primary treatment program by using combined modality therapy. To this end, three general approaches have been undertaken: (1) induction, also known as neoadjuvant therapy, in which chemotherapy is given before surgery or radiation; (2) chemoradiation, in which chemotherapy is given simultaneous with radiation to enhance its effect; and (3) adjuvant therapy, in which chemotherapy is given after surgery or radiation in an effort to decrease metastatic disease burden.

Induction Chemotherapy

Theoretically, treatment with chemotherapy before surgery or radiation—known as induction chemotherapy—has several advantages. This neoadjuvant chemotherapy allows for the delivery of drugs to the best possible host in terms of medical condition, which leads to increased compliance and better tolerance of therapy. Chemotherapy, when given first, can reduce tumor burden and downstage patients, resulting in the preservation of organ function by obviating the need for surgery. Further, induction therapy can reduce metastatic seeds and eliminate problems with poor vascularity that often occur after surgery or radiation, thus reducing a potential pharmacologic sanctuary.

One of the first uses of induction chemotherapy involved methotrexate with leucovorin rescue given twice before surgery.²¹⁵ It was reported that 77% of patients had some tumor shrinkage, although by strict criteria of tumor response (>50% in all sites), the response rate was only 20%. Although it could not be concluded that the result was better than with surgery alone, no increased incidence of postoperative complications occurred. Many other studies followed using single-agent methotrexate and bleomycin. The complete response rate was approximately 5% in these studies.

With the introduction of cisplatin into clinical trials in the mid-1970s, combination therapy consisted of cisplatin followed by a 5- to 7-day continuous infusion of bleomycin. Early series^{111,173} reported overall response rates of 71% to 76%, with a 20% complete response rate. Other investigators added vinblastine, vincristine, or methotrexate to the two-drug

combination with similar results.⁹ An alternate and probably more effective regimen tested in the 1980s at Wayne State University was cisplatin (100 mg/m²) followed by a 5-day infusion of 5-FU (1 g/m² per day by continuous infusion).¹⁸² In phase II trials, this regimen was associated with an overall response rate as high as 93% and a 54% complete response rate when three cycles were administered. Although the toxicity from cisplatin is the same, 5-FU appears to be better tolerated than bleomycin, without the associated allergic phenomena or lung toxicity.

Ensley and others^{69,70} from Wayne State University have reported a high complete response rate using five or six courses of cisplatin and 5-FU alternating with methotrexate, leucovorin, and 5-FU. In one study, the complete response rate was 65% in 31 patients completing the protocol, although toxicity was formidable, and approximately one third of patients withdrew from the study early. Despite the potential for improvement in response rate, the feasibility of this approach has yet to be demonstrated.

Investigators at the Dana Farber Cancer Center⁶⁴ and at the University of Chicago²³⁵ have used leucovorin to biochemically modulate the cytotoxic effects of 5-FU. Leucovorin results in an increase in intracellular-reduced folate levels and inhibition of thymidylate synthase.¹⁵⁹ Dreyfuss and others⁶⁴ administered cisplatin, 5-FU, and high-dose leucovorin (500 mg/m²), all by continuous infusion, over 6 days to 35 patients with local regionally advanced head and neck cancer. The overall response rate was 80%, and 66% had a complete response by clinical assessment. A pathologic complete response was documented in 14 of 19 patients (74%). Moderate-to-severe mucositis occurred in the majority of patients, although with dosage adjustment, the regimen was tolerable and acceptable to patients. Vokes and others²³⁵ treated 31 patients with similar disease with a less intensive regimen of cisplatin, 5-FU, and leucovorin. Leucovorin was administered orally in a dose of 100 mg every 4 hours during the 5-day infusion of 5-FU. After two courses, the overall response rate in 29 evaluable patients was 90%, and the complete response rate was 30%.

Since the early 1980s, the many uncontrolled trials of induction chemotherapy before surgery or radiotherapy have shown that this approach is feasible for those with locally advanced disease and does not add to the morbidity of subsequent definitive local treatment.^{137,207} With the cisplatin plus 5-FU regimen, a response can be expected in 80% to 90% of patients with, on average, a 40% complete response rate. Approximately two-thirds of complete responses by clinical examination will be confirmed pathologically. Response to induction chemotherapy correlates with response to subsequent radiotherapy.^{72,96,113}

Thus, patients who are resistant to cisplatin-based induction chemotherapy have a high likelihood of not responding to radiotherapy. Large randomized trials that consider all the important prognostic variables and have long-term follow-up periods are necessary to draw conclusions regarding disease-free survival and overall survival benefit.⁸⁵ The results of 17 randomized controlled trials of induction chemotherapy before surgery, radiotherapy, or both have been published.

Three of the most important trials are listed in Table 4-4; The Head and Neck Contracts program,¹⁰⁶ the SWOG trial,¹⁹⁰ and the Veterans Affairs Laryngeal Cancer Study Group trial²³¹ were large multiinstitutional randomized studies. The patients had advanced resectable head and neck cancer, and the treatment arms were well balanced to TN stage and primary site. The Head and Neck Contracts program randomly assigned patients to receive one of three treatments: (1) surgery followed by radiation, (2) induction chemotherapy with one cycle of cisplatin plus bleomycin followed by surgery and radiation, or (3) induction chemotherapy, surgery, radiation, and maintenance chemotherapy with cisplatin for 6 months. The 5-year survival rates for the three regimens were 35%, 37%, and 45%, respectively; the differences were not significant. However, the time to development of distant metastases and the frequency of distant metastases as a site of first recurrence were significantly less in patients in the maintenance chemotherapy arm compared with the other two groups. On subgroup analysis, there was a significant difference in disease-free survival time for patients receiving maintenance chemotherapy for oral cavity primary tumors and for N1 or N2 disease.¹²⁰ In retrospect, it is not surprising that this trial did not show any improvement in overall survival time because only one cycle of cisplatin and bleomycin was administered before surgery, resulting in a low response rate of 37%.

In the SWOG¹⁹⁰ trial, patients were randomly assigned to receive either three cycles of cisplatin, bleomycin, methotrexate, and vincristine before surgery and radiotherapy or standard treatment with surgery and radiotherapy. The median survival time was 30 months for patients in the standard treatment arm compared with 18 months for the induction chemotherapy arm. The distant metastatic rate was 49% with standard treatment and 28% with induction chemotherapy. Although differences in survival time and pattern of recurrence are striking, statistical significance was not reached. This trial fell short of its accrual goals and had a high rate of noncompliance, with only 56% of patients assigned to induction chemotherapy completing the treatment per protocol.

TABLE 4-4

RANDOMIZED TRIALS OF NEOADJUVANT CHEMOTHERAPY BEFORE SURGERY OR RADIOTHERAPY

Author	Regimen	Sites	Number of Patients	Operability	Survival Benefit	Other Outcomes
HN Contracts, (1987, 1990) ¹⁰⁶	PB	OC,L,HP	443	O	For N ₂ disease in subset analysis	Disease in distant metastases
Carugati (1988) ³³	PB ± M	OC,OP,L	120	O	None	
Toohill (1987) ²²⁰	PF	OC,OP,HP,NP	60	O + I	None	
Jaulerry (1992) ¹²¹	PFV		108	NS	None	
Spirglas (1987) ²¹²	PBVM	OC,OP,HP,L	100	NS	None	
Mazeron (1992) ¹⁵⁵	DVcBP	OC,OP	114	I	None	
Martin (1990, 1995) ^{153,154}	PFBM	OC,OP	107	O + I	None	
Schuller (1988) ¹⁹⁰	PF	OC,OP,HP,L	75	O + I	None	
VA Study (1991) ²³¹	PBMF	OC,OP,HP,L	158	O	None	Decrease in distant metastases
	PF	L	332	O	None	Larynx preserved in 64% at 2 years
Paccagnella (1994) ¹⁶⁴	PF	OC,OP,HP	237	O + I	For inoperable patients in subset analysis only	Decrease in distant metastases
Depondt (1993) ⁵⁷	CF	OC,OP,HP,L	324	O	None	Decrease in distant metastases; improved L-R control for inoperable patients
DiBlasio (1994) ⁵⁹	PF	NS	69	O	Significantly worse with chemotherapy	Larynx preserved in 42% at 3 years
Hasegawa (1994) ¹⁰³	PF	OC,OP,HP,L	50	O	None	
Chan (1995) ³⁷	PF	HP	82	NA	None	
Eschwege (1995) ⁷⁵	BEP	NP	339	NA	Significant improvement	
Dalley (1995) ⁵¹	PF	HP	91	O	Survival at 7 years	
Lefebvre (1996) ¹⁴⁰	PF	HP	202	O	Statistically equivalent survival	Decrease in distant metastases
Domenge (2000) ⁶¹	PF		318	O+I	Yes	

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P, Cisplatin; B, bleomycin; OC, oral cavity; L, larynx; HP, hypopharynx; O, operable; M, methotrexate; OP, oropharynx; F-5, fluorouracil; NP, nasopharynx; I, inoperable; V, vinblastine; Vc, vincristine; L-R, locoregional; C, carboplatin; NS, not specified; NA, not applicable; E, epirubicin.

Shigematsu (1971)¹⁹⁸ Chemotherapy 000 (tongue) Response Yes-DFS.

Doméngue and others⁶¹ have recently reported a phase III trial in which 318 patients with locally advanced oropharyngeal squamous cancers were randomly assigned to receive induction chemotherapy with cisplatin and 5-FU followed by locoregional treatment or locoregional therapy alone. Overall survival was better in the chemotherapy group (median, 5.1 vs 3.3 years; $P = .03$).

Encouraging data emerge from induction chemotherapy trials in the area of organ preservation (see Organ Preservation section to follow). The Veterans Affairs Laryngeal Cancer Study Group²³¹ completed a randomized trial in patients with resectable stage III and IV squamous cell cancer of the larynx. Patients were randomly assigned to receive standard therapy with total laryngectomy and postoperative radiotherapy or to receive a maximum of three cycles of cisplatin and 5-FU chemotherapy followed by radiotherapy. Surgery was reserved for salvage patients with persistent or recurrent disease. If patients did not have at least a partial response at the primary site after two cycles of chemotherapy, they underwent immediate surgery. The complete and partial response rate after two cycles of chemotherapy was 85%, and after three cycles it was 98%. The pathologically confirmed complete response rate at the primary site was 64%. At a median follow-up period of 33 months, there was no significant difference in survival time. However, the patterns of relapse differed: recurrence at the primary site was 2% with surgery vs 12% with chemotherapy ($P = .0005$); regional node recurrence rates were similar ($P = .305$); distant metastases were 17% with surgery vs 11% with chemotherapy ($P = .016$); and the rate of second primary malignancies was 6% with surgery vs 2% with chemotherapy ($P = .029$). After 3 years of follow-up, 66% of surviving patients in the induction chemotherapy treatment group had a preserved, functional larynx. Similar results were reported by the EORTC comparing cisplatin and 5-FU induction chemotherapy followed by radiotherapy to laryngopharyngectomy and radiation in patients with locally advanced cancer of the hypopharynx. No survival time differences were observed, and 28% of patients were alive with a functional larynx. The larynx preservation rate was 42% at 3 years, considering only deaths from local disease as failure.¹⁴⁰

In follow-up to the VA study, the Head and Neck Intergroup has conducted a prospective three-arm study comparing induction chemotherapy with cisplatin and 5-FU followed by radiotherapy; radiotherapy alone; and radiotherapy with concomitant cisplatin.⁸⁷ For entry, patients had stage III/IV disease, but T1 and advanced T4 lesions conferred ineligibility. Infiltrating tumors greater than 1 cm into the tongue base or the demonstration of thyroid cartilage

destruction were not allowed. Five hundred ten patients were entered, 65% of whom had stage III disease. Two thirds of patients had supraglottic primary sites. No unexpected toxicity was observed. With no difference in overall survival, the concomitant treatment arm resulted in superior larynx preservation, 88% compared with 74% resulting from sequential chemotherapy and radiation and 69% with radiotherapy alone. Notably, patients with destructive T4 primary tumors were excluded from this study. Long-term outcomes including quality of life and functional data are awaited.

The Doméngue trial⁶¹ in Table 4-4 demonstrated a survival benefit from induction chemotherapy. Two trials showed an improvement in survival time for chemotherapy-treated patients after subset analysis. In a large Italian study, Paccagnella and others^{163,164} observed an improvement in local control, metastatic rate, and survival time for inoperable patients. In a follow-up study to the Head and Neck Contracts Program, Jacobs and others¹¹⁹ reported an improvement in survival time for the subgroup with oral cavity primaries and limited nodal disease. In terms of patterns of failure, five trials showed a decrease in the rate of distant metastasis.^{119,140,164,190}

These trials have helped to clarify many issues. First, the overall response rates range from 60% to 90% with complete response rates of 20% to 50%. Survival time is improved in patients with a complete response compared with nonresponders, and pathologic complete response can be seen in 30% to 70%. Second, response to chemotherapy predicts for response to radiotherapy. Patients who fail to respond to chemotherapy do not respond well to radiation. Third, neoadjuvant chemotherapy increases neither surgical nor radiotherapy complication rates. Fourth, the most critical prognostic factors for response are TN stage and type of chemotherapy. Biologic behavior appears to differ per site. Fifth, although no benefit in overall survival time has yet been shown, a significant reduction in the rate of distant metastases has been observed. Finally, organ preservation and improved quality of life can result with induction chemotherapy. For patients with advanced laryngeal cancer who would require a total laryngectomy, the available data indicate that laryngeal function can be preserved in two thirds without jeopardizing survival time.

Neoadjuvant chemotherapy has been used to manage advanced nasopharyngeal carcinoma similarly to other sites. To date, two randomized prospective trials have been conducted. The International Nasopharyngeal Study Group¹¹⁶ randomly assigned 339 patients, who were at high risk for relapse (i.e., N₂, N₃ disease), to receive three cycles of bleomycin, epirubicin, and cisplatin chemotherapy followed by

radiotherapy or radiotherapy alone. At a median follow-up period of 49 months, there was a significant difference in disease-free survival time, 42% vs 29% at 4 years ($P = .006$) in favor of the chemotherapy arm. No difference in overall survival time was observed, 50% vs 42%, although median survival time was superior for the chemotherapy and radiation arm compared with radiation alone, 50 and 37 months, respectively.

In the second study, Chan and others³⁷ randomly assigned 82 patients to receive either radiotherapy alone or two cycles of cisplatin and 5-FU followed by radiotherapy. These patients had tumors 4 cm or larger or N₃ nodal disease. The overall response rate to chemotherapy was 81%, and this increased to 100% after radiation vs 95% for radiation alone. However, at a median follow-up period of 28.5 months, 2-year survival and disease-free survival time were not significantly altered by the addition of chemotherapy. This lack of difference may be accounted for partly by the less intensive nature of the chemotherapy with the 5-FU being given at 1000 cy/m² per day over 3 days.

Concurrent Radiotherapy and Chemotherapy

Concurrent radiotherapy and chemotherapy have been used primarily in patients with unresectable disease to improve local and regional control. The major drugs with efficacy for this tumor type and in

vitro evidence of radiation enhancement capability have been tested as single agents since the 1960s. The theoretic rationale and mechanism for the interaction between cytotoxic drugs and radiation that results in additive or synergistic enhancement have been reviewed in detail.^{91,205,213} This biologic phenomenon rests on several mechanisms. These include (1) inhibition of DNA repair, (2) redistribution of cells in sensitive phases of the cell cycle, and (3) promoting oxygenation of anoxic tissues. The net effect is to improve cellular cytotoxicity.²³⁵ Most of the single agents used to treat patients with head and neck cancer have been combined with radiation.

Nearly all reported trials of concomitant chemotherapy and radiotherapy have noted enhanced acute radiation-induced toxicity, primarily mucosal, which often has resulted in dose reductions and lengthy interruptions in radiation without evidence of survival benefit. Thus, in combining these two treatment modalities, it is essential that toxicity not preclude the use of chemotherapy and radiation in the optimal dose and schedule.

Single Agents and Radiotherapy

For an outline of randomized trials of simultaneous single-agent chemotherapy with radiotherapy vs radiotherapy, see Table 4-5.

TABLE 4-5

RANDOMIZED TRIALS OF SIMULTANEOUS SINGLE AGENT CHEMOTHERAPY WITH RADIOTHERAPY VS RADIOTHERAPY

Investigations	Chemotherapy	Number of Patients	Response Rate	Survival Benefit
Richards (1969) ¹⁷⁵	HU	40	Yes	NR
Stefani (1971) ²⁰⁶	HU	150	No	No
Hussey (1975) ¹¹⁵	HU	42	No	No
Condit (1968) ⁴⁴	MTX	40	Yes	NR
Gupta (1987) ¹⁰⁰	MTX	313	Yes	Yes
Kapstad (1978) ¹²⁶	Bleomycin	29	Yes	NR
Shanta (1980) ¹⁹³	Bleomycin	157	No	Yes
Morita (1980) ¹⁶⁰	Bleomycin	45 (tongue)	No	No
Scandolaro (1982) ¹⁸⁷	Bleomycin	30	No	No
Parvinen (1985) ¹⁶⁶	Bleomycin	46	NR	No
Shetty (1985) ¹⁹⁶	Bleomycin	38	No	No
Vermund (1985) ²²⁷	Bleomycin	222	Yes	No
Fu (1987) ⁹²	Bleomycin	104	No	Yes-DFS
Eschwege (1988) ⁷⁴	Bleomycin	199	NR	No
Shigematsu (1971) ¹⁹⁸	5-FU	63	Yes	Yes-DFS
Lo (1976) ¹⁴⁷	5-FU	163	Yes	Yes
Browman (1993) ²⁶	5-FU	175	Yes	No
Weissberg (1989) ²⁴¹	Mitomycin-C	117	Yes	Yes
Haselow (1990) ¹⁰⁴	CDDP	319	Yes	NR

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Methotrexate plus radiotherapy. Methotrexate can produce an S-phase block of the cell cycle, resulting in accumulation of cells in the G₁ phase and causing increased radiosensitivity.¹³ In one early study, 96 patients with inoperable disease were randomly assigned to receive radiotherapy alone or radiation preceded by intravenous methotrexate.¹³³ The complete response rate was the same in both groups, as was the 3-year survival rate. However, the incidence of mucositis increased in those patients who received chemotherapy. A second large study of patients with stage III and IV squamous cell carcinoma, similar to the previous study, again showed no difference in the 3-year survival rate, although the rate of distant metastases was only 19% in patients who received chemotherapy plus radiation compared with 33% of patients who received radiotherapy alone.¹⁴⁹ The Radiation Therapy Oncology Group (RTOG) randomly assigned 712 patients to receive radiotherapy alone or radiation plus pretreatment methotrexate.⁷⁷ No difference occurred in survival time between the treatment groups, and more patients failed to complete irradiation in the combined therapy group. In a randomized study published by Condit,⁴⁴ there was no improvement in survival time in the combined group. In another study, Gupta and others¹⁰⁰ observed an improvement in survival time and better control of the primary tumor. This was especially true for those with oropharyngeal tumors. Thus, three randomized series with adequate patient numbers showed negative results, and a fourth study showed improved survival time.

Hydroxyurea plus radiotherapy. Hydroxyurea kills cells in the S-phase and synchronizes cells into the more radiosensitive G₁ phase. Despite good theoretic activity, three randomized trials have shown no advantage of hydroxyurea in addition to radiotherapy. In one series, 12 patients with advanced cancer were randomly assigned to receive radiation alone or with hydroxyurea (80 mg/kg biweekly).²⁰⁶ The complete response rate at the primary site was 40% in both groups, but survival time was inferior in the combination group. In addition, distant metastases developed in 23% of patients receiving combined treatment as compared with 8% receiving irradiation alone. Another study of 40 patients comparing radiotherapy alone or with hydroxyurea (80 mg/kg three times per week) showed no difference in complete response rate or survival times, but it did show a 40% incidence of mucositis in the combined group.¹⁷⁵

Bleomycin plus radiotherapy. Bleomycin and irradiation have been studied *in vitro*, and the enhanced effects are believed to be caused by interference with

cellular repair after irradiation. Nine randomized trials have compared radiotherapy alone with radiation plus bleomycin. The first series included 227 patients with advanced oropharyngeal carcinomas.²⁹ Bleomycin was given at 15 mg twice weekly for 5 weeks. No difference in response rate or survival time was noted, and bleomycin was not well tolerated, causing a significant amount of mucositis. The results were unchanged in a recent update of this trial.⁷⁴ Similar results were reported by Vermund and others.²²⁷ In contrast, a third large series from India¹⁹⁴ included patients with advanced buccal mucosa cancers and compared radiotherapy given alone with radiation plus bleomycin (10 to 15 mg three times per week for 6 weeks). The complete response rate in the radiotherapy group was 21% compared with 77% in the combined therapy group.

An improvement in disease-free survival time, local and regional control, and complete response rate, but not overall survival time, was reported by Fu and others.⁹² In this Northern California Oncology Group trial, patients received either radiotherapy alone or radiation with bleomycin (5 mg twice weekly) followed by 16 weeks of maintenance bleomycin and methotrexate. The complete response rates were 45% with radiotherapy alone and 67% for the combined treatment ($P = .056$). The 2-year local and regional control rate was significantly improved with the addition of bleomycin, 26% vs 64% ($P = .001$). The incidence of distant metastases as a site of failure was similar in both treatment groups, indicating that the bleomycin and methotrexate maintenance regimen was ineffective in controlling micrometastatic disease. In this trial, in contrast to the others reported, the dose of bleomycin used with radiotherapy was well tolerated. A significant reduction in radiation dose or treatment delays did not occur as a result of enhancement of acute radiation toxicity.

Nine randomized trials of bleomycin and radiation have been completed. Only three of these showed a response benefit.^{92,126,193}

5-Fluorouracil plus radiotherapy. Several early trials indicated that 5-FU was an active radiosensitizer for patients with head and neck cancer. Three randomized trials have been published. Lo and others¹⁴⁷ randomly assigned 134 patients with advanced head and neck cancer to receive radiotherapy with or without 5-FU (10 mg/kg per day for 3 days, 5 mg/kg per day for 4 days, 5 mg/m² three times per week). The 5-year survival rate for radiation alone was 14%, and for combined treatment it was 32%. This improvement in survival time occurred for patients with primary lesions in the tongue or tonsil only. In another study, Shigematsu and colleagues¹⁹⁸ used intraarterial 5-FU

with radiotherapy to treat patients with maxillary sinus carcinoma and observed an improvement in disease-free survival time. Browman and others²⁶ randomly assigned patients to receive infusional 5-FU and radiation or radiation alone and observed a higher complete response rate but no change in survival time.

Mitomycin and radiotherapy. Mitomycin is an antibiotic that during hypoxic conditions is enzymatically reduced to form an active alkylating species.¹⁸⁵ It is selectively toxic to hypoxic cells. Therefore, because hypoxic cells within tumors have reduced sensitivity to the effects of radiation, it has been hypothesized that combined treatment could improve the therapeutic ratio.¹⁸¹ This concept was tested by Weissberg and others²⁴¹ in a randomized trial by treating 120 patients with advanced head and neck cancer with radiotherapy alone or with radiation with mitomycin (15 mg/m²). Disease-free survival time at 5 years was 49% for the radiotherapy-alone patients and 75% for those treated with mitomycin ($P < .07$). Local and regional control rates were significantly improved with administration of mitomycin, 55% vs 75% ($P < .01$). There was no difference in the incidence of distant metastases or overall survival time between treatment groups.

Cisplatin and radiotherapy. The exact mechanism of interaction between cisplatin and radiation is not known. Hypoxic and aerobic cell sensitization and the inhibition of cellular repair processes for sublethally damaged cells contribute to the effects observed in *in vitro* systems.⁵⁸ In a phase II trial, the RTOG administered cisplatin (100 mg/m²) every 3 weeks to 124 patients with locally advanced, unresectable head and neck cancer.⁶ Sixty percent of patients completed the combined treatment per protocol, and 69% of all patients achieved a complete response. Separate analysis of the disease-free and overall survival times for those with nasopharynx and non-nasopharynx primary sites with more than 5 years of follow-up have been published.^{7,151} A comparison to RTOG patients treated with radiotherapy alone suggested improvement in survival time for the combined treatment.

Wheeler and others²⁴⁴ piloted a study involving the administration of high-dose cisplatin (200 mg/m²) every 4 weeks with concurrent radiotherapy in 18 patients with unresectable disease and observed complete responses in 94%. The median survival time was 23 months with 56% and 41% alive and disease-free at 1 and 2 years, respectively. A high rate of distant relapse was observed. Only one randomized trial has been conducted to evaluate concomitant cisplatin and radiotherapy.¹⁰⁴ Through the Head and

Neck Intergroup mechanism, 371 patients with unresectable local regional squamous cell head and neck cancer were randomly assigned to receive radiotherapy alone or radiation plus weekly low-dose cisplatin, 20 mg/m².

There was a significant difference in overall response rate (complete and partial), 59% for those receiving radiation alone and 73% for those receiving the combined treatment ($P = .007$). However, there was no significant difference in complete response or survival time. The lack of survival benefit may be because of the low total dose of cisplatin received—only 120 to 140 mg/m² over the 6 to 8 weeks of radiation treatment.

Concomitant chemotherapy and radiotherapy have been useful for the treatment of patients with nasopharyngeal carcinoma. A head and neck intergroup trial closed in November 1995 demonstrating favorable results for the combined approach in this disease.⁷ In this study, patients received either radiotherapy alone or cisplatin (100 mg/m² days 1, 22, and 43) during radiotherapy followed by adjuvant chemotherapy with cisplatin and 5-FU (three cycles). An analysis of 147 randomized patients revealed significant differences in 3-year survival time (78% vs 47%) and progression-free survival time (69% vs 24%) favoring the chemotherapy group. This exciting result has now changed the standard of care for those with nasopharyngeal carcinoma in the United States. Patients with stage III or IV disease should be treated with concomitant chemoradiotherapy followed by adjuvant chemotherapy.

Randomized trials of single agents and radiotherapy have shown improved survival time with methotrexate, bleomycin, and 5-FU.^{147,194} Improved disease-free survival, but not overall survival time, has been shown in two other trials with use of bleomycin and mitomycin.^{92,241} Because mucosal toxicity is enhanced with these regimens and because overall survival time, although improved, remains poor, none of these regimens has become a standard therapy. The exciting results of the intergroup trial using concurrent cisplatin in patients with locally advanced nasopharyngeal cancer cannot be generalized to other sites, but they will form a basis for further investigation.

The favorable results from concurrent cisplatin treatment and radiotherapy followed by adjuvant chemotherapy establish this as a standard management approach for locally advanced nasopharyngeal cancer in the United States.

Multiple Agents and Radiotherapy

Combining several drugs with radiation will enhance acute toxicity, which may be severe. Therefore, investigators have piloted trials designed with split-course

radiation to allow for healthy tissue recovery. Most of these studies are limited to patients with stage III and IV locally advanced unresectable squamous cell cancer and have improved survival time as the primary goal. These regimens alternate chemotherapy and radiotherapy or use split-course radiotherapy to maximize tumor cell kill and to minimize tissue toxicity. For those with head and neck cancer, protracted radiation results in decreased local control rates because of accelerated repopulation of cancer cells that survive the initial insult.^{11,165} Thus, alternating two non-cross-resistant agents may potentially eliminate not only tumor cell repopulation but primary drug resistance.

Early phase I and II studies have used infusional 5-FU as originally reported by Byfield and others,²⁸ adding cisplatin^{1,216} or hydroxyurea²³⁴ with concurrent split-course single daily fraction radiation. Alternatively, cisplatin and fluorouracil with leucovorin modulation have been combined with split-course accelerated radiotherapy.²⁴² Several studies with long follow-up periods reported promising survival and response data but also severe toxicity.^{3,102,216,237,242}

Mature data were reported by Taylor and others²¹⁶ using cisplatin plus continuous-infusion 5-FU and radiotherapy and alternating 1 week of treatment with 1 week of rest. The median survival time for 53 patients with a median follow-up period in excess of 4 years was 37 months. The complete response rate was 55%. The total dose received of radiation and 5-FU but not cisplatin correlated with outcome. Local control was poorest in stage IV patients with N3 disease.

Although these pilot trials all report encouraging data for improved survival time, randomized trials that use radiotherapy alone as the control are needed before these approaches can be recommended outside the research setting. Data from selected randomized trials are shown in Table 4-6. The South-East Cooperative Oncology Group (SECOG)²⁰⁴ compared alternating with sequential chemotherapy and radiotherapy. The chemotherapy selected was vincristine, bleomycin, and methotrexate with a further randomization to inclusion of 5-FU or not. Survival rates were lower than observed in a previous pilot trial, and a significant improvement in disease-free survival time was observed on subset analysis for larynx primaries managed with the alternating schedule. The alternating regimen was associated with a higher frequency of severe mucosal reactions.

Merlano and others¹⁵⁶ published the final report of a randomized comparison of alternating and sequential chemotherapy (vinblastine, bleomycin, methotrexate) and radiotherapy followed by surgical salvage if feasible. Four courses of chemotherapy were alter-

nated with three courses of radiotherapy (20 Gy each). All patients had unresectable stage III or IV squamous cell cancer. The complete response rate before and after surgical intervention and the overall survival time at 4 years were significantly superior for patients receiving concomitant treatment. Severe mucosal toxicity was observed in 30.5% of patients in the alternating regimen compared with only 6% of those receiving chemotherapy before radiotherapy. The results of a follow-up trial reported by Merlano and others^{156,157} showed a significant difference in relapse-free and overall survival time for patients treated with alternating cisplatin plus 5-FU and radiotherapy compared with radiotherapy alone. All patients had unresectable locally advanced squamous cell cancer of the head and neck.

In a small randomized trial, Adelstein and others² compared simultaneous cisplatin plus 5-FU and radiotherapy to sequential treatment. Patients with stage II, III, or IV, either resectable or unresectable disease, were eligible. In the simultaneous treatment, patients were evaluated for surgery after chemotherapy and 30 Gy. Complete responders and those with unresectable disease continued treatment with chemotherapy and radiotherapy. In the sequential treatment, surgical evaluation occurred after three cycles of chemotherapy and before radiotherapy. The results with follow-up period ranging from 9 to 41 months showed a significant difference in disease-free survival time but not overall survival time. At this point in follow-up, 18 of 48 patients were complete responders and had not required surgery. Taylor,²¹⁷ similarly to Adelstein and others,³ compared cisplatin plus 5-FU and concomitant radiotherapy with sequential treatment. They found a significant improvement in local and regional control in patients receiving concomitant treatment.

The use of concurrent combination chemotherapy and radiation has continued to be under intense study in recent years.¹³⁰ There has been clear demonstration of enhancement of tumor control and improvement of survival over radiation treatment alone (see Table 4-6). There has also been a substantial increase in acute toxicities, especially dermatitis and mucositis, and longer follow-up evidence for increased late toxicity has begun to emerge.

As a generalization, patients admitted to these studies have had variable head and neck primary T sites, although oropharynx primaries tend to predominate. Brizel and others²⁴ have compared a hyperfractionated radiotherapy arm to a total dose of 75 Gy with the same radiation schedule, to 70 Gy, and concurrent cisplatin and 5-fluorouracil. The concurrent treatment was followed by two cycles of adjuvant chemotherapy. There was a statistically significant

TABLE 4-6

RANDOMIZED TRIALS OF CONCOMITANT OR ALTERNATING COMBINATION CHEMOTHERAPY AND RADIATION

Author (Ref)	Treatment	Number of Patients	Survival other Outcomes
Keane (1993) ¹²⁸	Concurrent MMC + F/RT	104	NS
	RT	105	
Merlano (1992) ¹⁵⁸	Alternating PF/RT	80	Significant increase
	RT	77	Significant improvement in CR + L-R control with PFS/RT
Taylor (1994) ²¹⁷	Concurrent PF/RT	108	NS
	Sequential PF → RT	107	Significant improvement L-R control for T ₃₋₄ N ₂ subset with PFS/RT
Adelstein (1990) ²	Concurrent PF/RT	24	NS
	Sequential PF → RT	24	Significant improvement in DFS with concurrent PFS/RT
Merlano (1991) ¹⁵⁶	Alternating VBM/RT	61	Significant increase
	Sequential VBM → RT	55	Significant increase in CR and PFS with concurrent VBM/RT
SECOG (1986) ²⁰⁴	Concurrent VBM ± F/RT	136	
	Sequential VBM ± F → RT	NS	DFS improved for larynx with concurrent VBM ± F/RT
Brizel (1998) ²⁴	Concurrent PF/RT	56	L-R Control improved (P = .1)
	HFRT	60	
Wendt (1998) ²⁴³	Concurrent PFL/RT	130	Improved survival (P = .0003)
	HFRT	140	
Calais (1999) ³⁰	Concurrent Pc/RT	109	Improved survival (P = .02)
	RT	113	
Jeremic (2000) ¹²³	Concurrent C/RT	65	Improved survival (P = .008)
	HFRT	65	

(Reprinted with permission from *Tumors of the nasal cavity and paranasal sinuses, nasopharynx, oral cavity, and oropharynx*. In Schantz SP, Harrison LB, Forastive AA: *Cancer-principles and practice of oncology*, ed 5. Philadelphia, Lippincott-Raven, 1997.) MMC, Mitomycin C; F-5, fluorouracil; L, leucovorin; Pc, carboplatin; RT, radiotherapy; NS, not significant; PFS, progress-free survival; CR, complete response; DFS, disease-free survival; SECOG, Southeast Cooperative Oncology Group; P, cisplatin; V, vinblastine; B, bleomycin; M, methotrexate; L-R, locoregional.

improvement in local disease control and a strong trend toward improved overall survival. In this trial, neck dissection was recommended in patients with N2/3 disease. Clayman and others⁴² reviewed the M.D. Anderson experience examining the indication for neck dissection in this patient population. This report suggests that neck dissections are required only when there is radiographic evidence of residual disease 6 to 8 weeks after the completion of definitive chemoradiation. Wendt and others²⁴³ reported a statistically significant 3-year survival advantage after the concurrent use of cisplatin, 5-FU and leucovorin given as a single therapeutic modality. Calais and others³⁰ compared a more standard once-daily fractionation radiation schedule with the same radiotherapy and concurrent carboplatin and 5-FU, demonstrating a statistically significant advantage in local regional tumor control and overall survival at 3 years. This report is particularly germane because the study group consisted of oropharyngeal patients only. Finally, Jeremic and colleagues¹²³ investigated the

value of adding cisplatin given daily to a hyperfractionated radiation therapy program vs the same radiation schedule given alone in patients with locally advanced squamous cell cancers of the head and neck. In this recent report, locoregional and distant disease control, as well as overall survival were improved at the 5 years. The clearest benefit in all four studies was an improvement in locoregional control that translated into a survival advantage. Acute toxicity was increased, especially mucositis and hematologic effects, but there was no obvious escalation of long-term sequelae. However, this potential problem area has not been fully studied. In aggregate, overall 3-year survival exceeded 50% in these experimental programs, underscoring the potential therapeutic efficacy of concomitant chemotherapy and radiation in advanced head and neck cancers.

Concurrent chemotherapy, particularly with multiple drugs, leads to a marked increase in acute toxicity. "In-field" mucositis and dermatitis can be severe, are associated with much discomfort, and may lead to

increased risk of infection, poor nutritional intake, and interruption of radiotherapy or chemotherapy dose reductions. This may compromise tumor control and ultimate survival. There also is the potential for an increase in serious long-term toxicities as survival increases after these intensive treatment programs. For optimal results, concurrent treatments should be administered in centers with sufficient training and expertise and with experienced supportive care teams available.

The results of these trials indicate that improved disease-free and overall survival times were obtained for patients with locally advanced squamous cell head and neck cancer using alternating or concomitant chemotherapy and radiotherapy. Well-designed clinical trials are needed to determine optimal chemotherapy and radiotherapy schedules. Randomized trials are currently in progress to help clarify these issues.

Adjuvant Chemotherapy

Adjuvant chemotherapy after primary surgery has been shown to be effective in patients with breast cancer and osteogenic sarcoma. To date, three randomized trials have been designed to address this question in those with head and neck cancer. Adjuvant chemotherapy has several potential advantages over neoadjuvant treatment. With adjuvant treatment, surgery is not delayed, and a patient with resectable disease can undergo surgery sooner. Secondly, induction therapy can blur the margins of disease, making the degree of surgical resection less obvious. Finally, induction chemotherapy, if successful, can lead to symptom abatement, resulting in patient refusal of surgery afterward.

Through the Head and Neck Intergroup mechanism, a large multiinstitutional trial was conducted to test whether the addition of chemotherapy to surgery and radiotherapy prolonged survival time or altered the pattern of recurrence.¹³⁹ Patients with stage III or IV squamous cell carcinoma of the oral cavity, oropharynx, or larynx and those with stage II, III, or IV of the hypopharynx who had negative pathologic margins of resection were eligible.

Randomization was to immediate postoperative radiotherapy or to three cycles of cisplatin plus 5-FU chemotherapy followed by radiotherapy. A preliminary analysis of the 503 patients in the study has shown no significant difference in disease-free survival time, overall survival time, and local and regional control. However, there was a significantly lower rate of distant metastases as a site of failure ($P = .016$) at any time for patients treated with adjuvant chemotherapy. Perhaps more important was the finding that a high-risk subset of patients (those with extracapsular extension, carcinoma in situ, or close

surgical margins) appears to benefit from adjuvant chemotherapy with increased survival time and local control that approached statistical confidence when compared with those receiving radiation alone.

Two trials testing induction chemotherapy added maintenance chemotherapy to one treatment group and observed differences in outcome. The Head and Neck Contracts Program¹⁰⁶ trial of one course of cisplatin and bleomycin induction chemotherapy before surgery and radiation included 6 months of maintenance chemotherapy in one of the three treatment arms. There was a significant decrease in the distant metastatic rate observed for those patients. Ervin and others⁷³ randomly assigned patients showing a response to cisplatin, bleomycin, and methotrexate induction chemotherapy to receive three additional cycles or observation after definitive surgery and radiotherapy. The 3-year disease-free survival time for patients receiving maintenance chemotherapy was 88% compared with 57% for the control subjects ($P = .03$). In a phase II pilot, Johnson and others¹²⁴ treated 42 patients with extracapsular spread of tumor in cervical lymph node metastases with 6 months of methotrexate and 5-FU after resection and radiotherapy. The 2-year disease-free survival rate was 66%, which was improved from an expected control rate of 38% based on historical experience.

Shin and others¹⁹⁹ have recently reported the potential benefit of adjuvant cis retinoic acid interferon- α and vitamin E in advanced-stage patients treated for 1 year after completion of primary therapy. In a phase II experience with eligible patients considered disease-free at the start of the adjuvant program, they reported 90% failure-free survival at median 2-year follow-up. This adjuvant regimen is currently being tested in a prospective phase III trial.

Considered together, the results of these trials indicate that adjuvant chemotherapy can affect micrometastatic disease and decrease the rate of distant recurrence. The data also suggest that disease-free survival time may be improved. The major impediment to successfully conducting adjuvant or maintenance chemotherapy trials in patients with head and neck cancer is patient noncompliance and physician fatigue. The morbidity of the primary treatment, combined with the medical and social situations of this group of patients, makes classical adjuvant chemotherapy difficult or not feasible for many patients. In addition, there appears to be no role for adjuvant chemotherapy in low-risk patients, although high-risk patients may benefit.

ORGAN PRESERVATION

Many squamous cell cancers of the head and neck are diagnosed at a late stage. Stage III and IV tumors often

necessitate extensive or radical surgery that can alter function. Problems with radical surgery include loss of speech, loss of swallowing function, or disfigurement without a concomitant improvement in survival time. Therefore, preservation of function became one of the major challenges of the 1990s. A role for combined modality treatment in preserving organ function has already been noted for laryngeal preservation as in the VA larynx study.²³¹ In this study, neoadjuvant chemotherapy followed by radiotherapy was more successful in preserving voice function compared with surgery without a loss in survival time.

Neoadjuvant chemotherapy has been used to preserve organ function for patients with hypopharyngeal, laryngeal, and oropharyngeal cancers. Several nonrandomized studies have been completed using cisplatin-based chemotherapy. In these studies, patients were required to have achieved either partial or complete response to go on to conventional radiotherapy. Nonresponders then went on to undergo radical surgery. In these pilot studies, there were no survival differences between the surgical groups and the groups that avoided surgery, suggesting that quality of life may be improved without worsening survival.

In addition to the VA larynx study,²³¹ another large randomized study has been completed. This study¹⁴⁰ was done in Europe by the European Organization for Research and Treatment of Cancer (EORTC) beginning in 1990 and compared a larynx-preserving therapy (induction chemotherapy plus radiation) with conventional surgery plus postoperative radiation. The design of the EORTC study was similar to the VA larynx study; the patients were randomly assigned to either treatment, and patients receiving induction chemotherapy received cisplatin plus 5-FU. After two cycles of chemotherapy, only responders (i.e., partial or complete responders) received a third cycle. Patients achieving a complete response then received definitive radiotherapy. Nonresponding patients or those with partial response underwent conventional surgery followed by postoperative radiation. As in the VA study, the overall survival data were not different between the two arms, and the median duration of survival time was longer for the chemotherapy arm. Local failures occurred more commonly in the chemotherapy arm, but the distant metastatic rate was lower. In both studies, a large number of patients were enrolled, and of the surviving patients, a significant percentage were able to retain their larynx.

The intergroup study, previously discussed, further supports the concept that for selected patients definitive treatment with chemotherapy and radiation may allow for organ preservation with no compromise in terms of survival. In the R91-11 trial, there was

comparison between induction chemotherapy, radiotherapy alone, and radiotherapy with concurrent cisplatin. The results indicated a significant advantage for concomitant cisplatin treatment with preservation of the larynx in 88% of patients treated in the concomitant arm. It can be concluded that the option of organ preservation therapy with chemotherapy and radiation therapy is becoming a reality for many patients with squamous cancers of the head and neck. Certainly, enrollment of patients with advanced cancers of the oropharynx and hypopharynx to clinical trials of multimodel therapy.

INTRAARTERIAL CHEMOTHERAPY

Poor response to chemotherapy after surgery or radiotherapy may be caused by impaired drug delivery into the region. Intraarterial chemotherapy has been used in attempts to overcome this for almost three decades. The rationale for intraarterial therapy is based on the steep dose-response curve exhibited by most cytotoxic drugs.⁸⁸ Maximum cell kill occurs when the tumor exposure to a high concentration of drug is optimized. Drug toxicity also follows a steep curve. Therefore, regional drug delivery has the potential to increase tumor drug exposure and reduce systemic exposure that affects critical healthy tissues.^{38,43} The principal determinant of a drug's therapeutic advantage is the ratio of total body clearance to the regional exchange rate.

Several factors should be considered when choosing a drug for intraarterial delivery: (1) drug concentration, not time of exposure, is the major factor in cell killing; (2) the drug should be deactivated in the systemic circulation; (3) there should be a high tissue extraction; and (4) a drug should not require activation in the liver.

Intraarterial cisplatin has been shown to be effective and relatively nontoxic in patients with several solid tumors. Pharmacokinetic studies have shown a regional increase in plasma and tissue platinum concentrations in the infused area. Several studies indicate significant palliation in patients with head and neck squamous cancers in whom irradiation and surgery failed to eradicate the tumor. A response rate of 87% using intraarterial 5-FU, methotrexate, and bleomycin was reported by Donegan and Harris.⁶² Tumor regression lasted up to 13 months. Intraarterial methotrexate and bleomycin have been used before irradiation for patients with advanced head and neck cancer, with a 28% partial response rate.²⁵⁰ Intraarterial cisplatin given before surgery or radiation has produced responses in the 70% to 80% range.¹⁶¹

One of the major drawbacks of intraarterial therapy is catheter-related complications: air and plaque emboli, sepsis, and patient immobility during chemotherapy administration. These problems have been

overcome by the introduction of an implantable infusion pump.¹⁴ This system has been used successfully to treat patients with recurrent head and neck cancer with continuous infusion of dichloromethotrexate and fluorodeoxyuridine.^{82,245}

One primary site for which intraarterial chemotherapy has been more extensively studied is paranasal sinus cancer. Japanese investigators have favored cannulation of the superficial temporal artery and infusion of 5-FU integrated with surgery and radiotherapy.^{186,197} More recently, investigators in the United States have evaluated superselective arterial catheterization and short-term intraarterial chemotherapy to debulk locally advanced resectable and unresectable paranasal sinus carcinoma. This approach minimizes potential toxic effects to adjacent healthy tissues.

Dimery and colleagues⁶⁰ reported evaluating intraarterial cisplatin and bleomycin by this technique combined with intravenous 5-FU. A complete response rate of 23% was achieved in those receiving the chemotherapy alone. After surgery or radiotherapy, 63% of patients were disease free, and 61% were spared orbital exenteration. Papadimitrakopoulou and others⁹⁷ further evaluated intraarterial cisplatin with systemic paclitaxel and ifosfamide induction therapy for maxillary cancers in an attempt to determine the efficacy of the regimen in patients who otherwise would require orbital exenteration or a major cranial facial resection. The organ preservation rate was 74% with 17 of 24 patients disease free at 1.6 years' medial follow-up.

More recently, Robbins and colleagues^{177,178} have reported an extensive experience in 213 patients with stage III/IV squamous cell carcinomas treated with weekly intraarterial infusion of cisplatin, simultaneous intravenous thiosulfate, and external beam radiotherapy. Complete tumor response in the primary and regional sites was observed in 80% and 61% of patients, respectively. Cancer-specific 5-year survival was 54%, and six treatment-related deaths occurred.

Although intraarterial therapy has several theoretic advantages over systemic chemotherapy, it has not been established as a superior approach. Most series contain small numbers of selected patients. This therapy should not be viewed as a standard of care by the community, and further investigation appears to be warranted.

SALIVARY GLAND CANCERS

Cancers of the salivary gland represent approximately 3% of all neoplasms in the head and neck region. The majority originate in the parotid gland. Despite optimal treatment with surgery and postoperative radiotherapy, patients with advanced salivary gland cancers have a poor prognosis, with survival times

ranging from 0% to 32% at 10 years. Survival time varies with histology, with 10-year survival rates of 96% reported for low-grade mucoepidermoid carcinoma and 29% reported for adenoid cystic carcinoma.⁸⁹ The probability of recurrence also varies with site. Local or distal recurrence occurs in up to 66% of patients with cancers of the major salivary glands and in up to 92% of patients with cancers of the minor salivary glands.⁴⁵ The reasons for recurrence include failure of local control and spread of disease to distant sites, particularly the lung.

Chemotherapy in the management of salivary gland cancers has been used mainly for the treatment of patients with recurrent disease. Because of the relatively small number of patients, trials often contain few patients with a variety of histologic findings. Many reports document single cases, leaving uncertainty as to the number of patients who may have been treated. Suen and Johns²¹¹ reported that response to chemotherapy varies with histologic findings. They also found that response varies with the site of recurrence, with local and regional disease having a higher response rate than distant disease. In addition, patients without previous radiotherapy had a better response to chemotherapy. Drawing conclusions from most series is difficult because they usually include a group of patients treated for many years with a variety of combinations and single agents. In addition, some cancers with distal spread, such as adenoid cystic carcinoma, can grow at such a slow rate that responses and impact on survival time are difficult to interpret.

Suen and Johns²¹¹ reported large series of patients treated at their institutions and at others in an attempt to define the best single agents or combinations of drugs for salivary gland cancers of specific histologic categories. For those with adenoid cystic carcinoma, the best single agents are cisplatin, 5-FU, and doxorubicin. Cisplatin has been reported to have a complete response rate of 29% and an overall response rate of 64% in 14 treated patients.^{189,211} Complete responses lasted from 7 to 18 months. 5-FU has been reported to have a partial response rate of 46% in 13 patients.^{125,214} Adriamycin was noted to have a response rate of 13% in seven patients.^{174,226} Methotrexate, vincristine, and cyclophosphamide appear to have little activity for adenoid cystic carcinoma. The combination of Adriamycin and cyclophosphamide has been used in five patients with a 40% partial response rate.¹⁷¹ Because of poor prognosis of patients with advanced disease and the activity of cisplatin, Sessions and others¹⁹¹ treated four patients with intraarterial cisplatin before further therapy. All patients had some tumor shrinkage, but only two had a partial response. There was minimal toxicity.

Very few studies of single-agent chemotherapy for mucoepidermoid carcinoma exist. Several of the studies were done before the widespread use of cisplatin, and data on its use as a single agent for the management of this carcinoma are not available. Methotrexate has been used in four patients, with one achieving a complete response and one having a partial response. Posner and others¹⁷¹ used two different combinations for recurrent mucoepidermoid carcinoma. Two of three patients responded to a combination of cisplatin, bleomycin, and methotrexate. Three patients failed to respond to a combination of cyclophosphamide and Adriamycin. Further studies need to be done to determine the most active agents for mucoepidermoid carcinoma.

Only scattered reports of the use of chemotherapy for the other salivary gland cancers exist. The combination of Adriamycin, cisplatin, and cyclophosphamide achieved one complete response and two partial responses in three treated patients with adenocarcinoma.⁴ The small numbers of patients in each series preclude firm conclusions regarding the true level of antitumor activity of these drugs. However, the data provide an indication of which drugs are reasonable to choose for single-agent or combination chemotherapy. Creagan and others⁴⁹ reported the results of cisplatin-based chemotherapy in 34 patients with locally recurrent or metastatic cancers originating from the salivary gland or contiguous structures. Most patients received cyclophosphamide or mitomycin, plus Adriamycin and cisplatin combination chemotherapy. A 38% response rate was observed, listing a median of 7 months. The median survival time was 18 months for responders to chemotherapy and 15 months for nonresponders. Thus, response to treatment did not appear to confer a survival advantage. Dreyfuss and others⁶⁵ also evaluated cyclophosphamide, Adriamycin, and cisplatin in a series of 13 patients (nine with adenoid cystic carcinoma and four with adenocarcinoma), observing responses in 46% (three complete and three partial responses). In another combination chemotherapy trial, Venook and others²²⁵ treated 17 patients with advanced or recurrent salivary cancer with cisplatin, Adriamycin, and 5-FU. Thirty-five percent of patients responded to chemotherapy. In this small series, response rate was not influenced by the extent of previous treatment.

Whether combination chemotherapy can improve survival time in patients with recurrent disease is not clear. In some patients with recurrent disease, particularly adenoid cystic carcinoma, the pace of disease can be so slow that patients often do not need to be treated with chemotherapy for a prolonged period. This slow growth rate in some patients may be one of the factors accounting for the poor response to

chemotherapy. New agents need to be evaluated in adequate numbers of patients to determine activity with statistical confidence. A recent paclitaxel trial showed evidence of activity in mucoepidermoid and adenocarcinoma of salivary origin with 7 of 29 (25%) patients achieving partial response.¹²² In contrast, adenoid cystic carcinomas were not responsive to therapy. Studies of adjuvant chemotherapy in salivary cancer have not been undertaken because of the small numbers of patients and relatively ineffective chemotherapy. Clearly, collaborative efforts will be necessary before conclusions can be drawn concerning the use of chemotherapy for salivary gland cancers.

CHEMOPREVENTION OF HEAD AND NECK CANCER

Chemoprevention is defined as the administration of pharmacologic agents to inhibit the events occurring during the multistep process of carcinogenesis or the reversal of a premalignant condition. The biology of carcinogenesis leading to upper aerodigestive tract malignancies is not well understood. Tumor formation is believed to be a multistep process involving biochemical and molecular changes that result in dysregulated differentiation and proliferation.⁷⁸ Chromosomal alterations and mutations of specific oncogenes are associated with epithelial cancers. Investigators studying various genomic, proliferation, and differentiation biomarkers have found alterations in specific markers (keratin, involucrin, transglutaminase) during the process of abnormal squamous differentiation. These biomarkers can be useful as intermediate end points in future chemoprevention trials.¹⁴³ Our understanding of the biology of carcinogenesis for head and neck cancer and other aerodigestive tract tumors is expected to rapidly expand in the next decade.

Chemoprevention is particularly relevant to patients who are curatively treated for an early stage head and neck squamous cell cancer. It is recognized that second primary malignancies develop at a rate of 3% to 4% per year in these patients.^{46,129,142} The explanation for this risk is based on the concept of field cancerization first formulated in the 1950s.^{202,210} Repeated exposure of the entire epithelial surface to carcinogens, such as tobacco and alcohol, can lead to the development of multiple sites of premalignant and malignant change. The ability of retinoids and carotenoids to affect epithelial growth and differentiation is supported by *in vitro*, animal, and epidemiologic studies.¹⁹ Although the exact mechanism by which retinoids inhibit carcinogenesis is not known, retinoids have been shown to modify genomic expression at the level of messenger RNA synthesis and to regulate transcription of specific genes.^{148,239} Clinically,

retinoids and carotenoids have been used to prevent malignant transformation of dysplastic leukoplakia lesions. Most recently, retinoids have been studied in the prevention of second primary cancers. Retinoids are the synthetic and natural analogs of vitamin A. β -carotene is the major source of vitamin A in the diet.

The major limitation in the use of retinoids is associated toxicity. Acute toxicity includes dryness of conjunctival and oral mucous membranes, cheilitis, skin desquamation, hypertriglyceridemia, bone tenderness, arthralgias, and myalgias. Chronic toxicities include hepatotoxicity and bone remodeling.¹⁰⁷ These compounds are teratogenic, causing multiple malformations. Because of these toxicities, a number of retinoids have been synthesized. Four that are used clinically are vitamin A (retinol); β -all-transretinoic acid (retinoid); 13-cis retinoic acid (isotretinoin); and an aromatic ethyl ester derivative, etretinate.¹⁰⁷ In contrast to the retinoids, the major toxicity of the carotenoids is yellowing of the skin. Other compounds that may have use in chemoprevention based mainly on in vitro and animal data are α -tocopherol (vitamin E), selenium, and N-acetyl cysteine. The latter compound is a precursor of intracellular glutathione that enhances its antioxidant activity as a free-radical scavenger. N-acetyl cysteine is nontoxic and currently under investigation in Europe for the prevention of second malignancies in patients with a previous head and neck or lung carcinoma.¹⁰⁷ EGFR, farnesyl transferase, and COX-2 inhibitors are also under study as potential chemoprevention agents.

Studies with retinoids and carotenoids in patients with leukoplakia are listed in Table 4-7. Stich and others^{208,209} reported two trials conducted in India and

the Philippines in betel nut chewers. In one placebo-controlled trial, β -carotene was compared with β -carotene plus vitamin A. Complete response was observed in 3% of the patients taking placebo, in 15% of β -carotene-treated patients, and in 28% of those taking the combination. These patients demonstrated significant suppression of micronuclei expression and index of DNA damage on serial cytologic examinations. In a subsequent study, patients were randomly assigned to receive placebo or twice the dose of vitamin A (200,000 IU/wk) received in the first trial. A 57% complete response rate was observed with total suppression of the development of new leukoplakic lesions. In the placebo group, the complete response rate was 3%, and there was a 21% rate of new lesion formation.²⁰⁹ In a small pilot study, Garewal and others⁹³ observed a 71% complete and partial response rate in 24 patients treated with β -carotene. There was no significant toxicity. Other investigators reported complete and partial response rates ranging from 60% to 100% with 13-cis retinoic acid.^{134,192}

These results led Hong and others¹⁰⁹ to conduct a randomized placebo-controlled trial of 13-cis retinoic acid (1 or 2 mg/kg per day) in oral leukoplakia with dysplastic change. All patients were assessed with pretreatment and posttreatment biopsies. Patients were treated for 3 months and observed for 6 months. There was a highly significant difference in response rate, 67% vs 10%, comparing the treated group with those taking placebo. Histologic reversal of dysplastic change was documented in 54%. Unfortunately, after stopping treatment, the relapse rate was high within 2 or 3 months, and the regimen was associated with considerable toxicity. In a follow-up trial,¹⁴⁴ 56 patients received 13-cis retinoic acid (1.5 mg/kg

TABLE 4-7

RESULTS OF RANDOMIZED CHEMOPREVENTION TRIALS IN THE HEAD AND NECK

Study	Design	Number of Patients	Intervention and Dose	Results
Oral premalignancy				
Hong and others, 1986 ¹⁰⁹	Induction	44	Isotretinoin (2 mg/kg/d)	Positive
Lippman and others, 1993 ¹⁴⁵	Maintenance	70	Isotretinoin (0.5 mg/kg/d)	Positive
Stich and others, 1988 ²⁰⁹	Induction	65	Vitamin A (200,000 IU/wk)	Positive
Han and others, 1990 ¹⁰¹	Induction	61	Retinamide (40 mg/d)	Positive
Costa and others, 1994 ⁴⁸	Maintenance	153	Fenretinide (200 mg/d)	Positive
Previous cancer				
Hong and others, 1990 ¹¹²	Adjuvant	103	Isotretinoin (50 to 100 mg/m ² /d)	Positive
Bolla and others, 1994 ¹⁸	Adjuvant	316	Etretinate (50 mg/d; 25 mg/d)	
Pinto and other, 2001 ¹⁷⁰	Adjuvant	189	Isotretinoin (7.5-10mg/d)	Negative
Khuri and others, 2003 ¹²⁹	Adjuvant	1190	Isotretinoin (300mg/d)	Negative

(Reprinted with permission from Lippman and others: Strategies for chemoprevention study of premalignancy and second primary tumors in the head and neck, *Curr Opin Oncol* 7:234, 1995.)

per day) for 3 months, followed by randomization to low-dose 13-cis retinoic acid (0.5 mg/kg per day) or β -carotene maintenance therapy. cis-Retinoic acid proved superior in maintaining remissions and had an acceptable level of toxicity in this low dosage.

Hong and others¹¹² reported the results of using 13-cis retinoic acid to prevent second primary malignancies in patients with squamous cell cancer of the head and neck rendered disease free with surgery and radiotherapy. This placebo-controlled chemoprevention trial randomly assigned 103 patients to receive high-dose 13-cis retinoic acid (50 to 100 mg/m² per day) or placebo for 1 year. At a median follow-up period of 32 months, second primary tumors had developed in 4% of those receiving retinoic acid compared with 24% of the placebo group ($P = .005$). The results of this trial have led to the initiation of two multiinstitutional confirmatory trials in the United States; two chemoprevention trials are in progress in Europe.²³ In the United States, the North Central Cancer Treatment Group and ECOG have randomly assigned patients with stage I and II squamous cancers of the head and neck rendered disease free with surgery or radiotherapy to placebo or low-dose 13-cis retinoic acid (0.15 mg/kg per day) for 2 years.¹⁷⁰ Preliminary results suggest no benefit for the experimental regimen, with respect to the incidence of second primary tumors or survival. The M.D. Anderson Cancer Center and Radiation Therapy Oncology Group have conducted a placebo-controlled trial for the same patient group testing a higher dose of cis-retinoic acid, 30 mg/day, for 3 years. Dose reductions for toxicity were allowed. Khuri and others¹²⁹ have recently reported that no long-term disease-free or survival benefit was clearly demonstrated.

SUMMARY

Tumors of various histologic types occur in the head and neck. Excluding thyroid malignancies, approximately 80% are squamous cell carcinomas. Data evaluating the impact of chemotherapy on survival time, particularly for combined modality treatments, are limited to this common histologic type for which patient numbers are available for randomized comparative trials. Phase I, II, and III studies in patients with locally recurrent or metastatic disease have shown that chemotherapy can produce response rates of 30% to 40%, and combination chemotherapy is more effective than single agents. However, responses tend to be brief (2 to 4 months) and may not be associated with longer survival time. Thus, chemotherapy for these patients is palliative. An exception to this is for patients with tumors of the nasopharynx in whom higher response rates and a small proportion of long-term disease-free survivors are observed. Prognostic

factors have been identified that should be used by the physician to select patients most likely to benefit from palliative treatment.

In newly diagnosed patients with locally advanced disease, high response rates have been achieved with induction chemotherapy; and this approach remains under study. An important role for chemotherapy may be to preserve organ anatomy and function at selected sites. Three large multicenter randomized trials were successfully conducted with preservation of laryngeal function. Chemotherapy administered concurrently with radiotherapy has improved local control and survival time in selected series. The increase in toxicity associated with these regimens should be carefully considered when selecting patients for this combined treatment. Chemotherapy for those with parotid cancers has been studied only for recurrent disease. Response rates are modest, and impact on survival time has not been demonstrated.

Figure 4-1 shows an algorithm for management of late-stage (locally advanced) squamous cell carcinomas of the head and neck. Patients with earlier-stage disease (i.e., stage I or II) should receive conventional therapy with either surgery, radiotherapy, or both. Patients with stage III or IV disease can be divided into those with resectable or unresectable disease. Those with unresectable disease should often be treated with chemotherapy and radiation or entered into a combined chemoradiation treatment protocol. Those with stage III disease also benefit from combination treatment as part of a clinical trial. Patients with metastatic disease should receive chemotherapy with palliative intent if performance status is favorable. Patients with "resectable" disease can be further divided by site. Those with primary oral cavity tumors would be best served by surgery followed by radiotherapy, whereas patients with oropharynx, hypopharynx, or laryngeal tumors are treated with radiation, with or without chemotherapy depending on the site and stage.

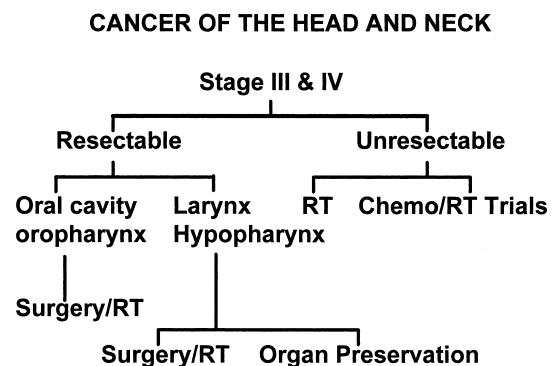


Figure 4-1. Management of late-stage squamous cell carcinomas of the head and neck.

Chemoprevention will continue to be an important area of research in the coming decade. One randomized trial has shown a decreased rate of second primary tumors in patients with curatively treated upper aerodigestive tract primary tumors. Confirmatory trials have been unsuccessful thus far, but multiple new strategies are to be considered for further testing.

The management of head and neck cancer is a multidisciplinary activity. The identification of effective chemotherapeutic agents and their integration into the initial curative therapy of head and neck cancer has the potential to improve survival time and preserve organ function. Through well-designed and well-executed clinical trials, coupled with basic research of the biology of upper aerodigestive tract tumors, further advances in the management and prevention of these cancers can be achieved.

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