Chapter 6: Biophysiology of Antineoplastic Chemotherapy for Head and Neck Cancer

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The otolaryngologist - head and neck surgeon frequently cares for patients with head and neck cancer who will receive chemotherapy as part of their treatment program. This therapy may involve chemotherapeutic agents for recurrent disease, such as squamous cancers, salivary gland cancer, melanomas, and sarcomas, or it may involve the use of chemotherapy as part of the standard primary treatment program, as with rhabdomyosarcoma. Chemotherapy may also be used in the primary treatment in an experimental combined modality program.

To evaluate the appropriate use of chemotherapy for these patients, the surgeon should be familiar with the following: (1) the principles of clinical trials, (2) the proper doses and expected toxic reactions of specific chemotherapeutic agents, (3) the basic principles of combination chemotherapy and combined modality programs, and (4) the standard use and experimental approaches of chemotherapy for head and neck squamous cancers, melanomas, sarcomas, and salivary gland tumors.

Principles of Clinical Trials

The efficacy of chemotherapy or combined modality programs is investigated through clinical trials (Simon, 1989). To evaluate the use of a particular treatment, it is important to establish at the onset the parameters to be evaluated: objective response rate, survival, disease-free survival or duration of response, and toxicity. The parameters of interest for a specific trial design must be defined before the initiation of the study and analyzed at the completion of the study. The primary end point will 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 if 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, disease-free survival, or response duration and survival are primary end points. The determination of sample size, patient entry criteria, and the follow-up and monitoring of patients are critical for a valid interpretation of a phase III trial (Piantadosi, 1988).

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 (see box). By convention, a "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 a period of at least 4 weeks. Therefore the response rate represents the total number of complete and partial responders. 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 thorough examination. Minor response or stable disease is usually of little value.

Box: Criteria for response and definitions

Complete response: complete disappearance of all evidence of tumor for a minimum of 4 weeks.

Partial response: a 50% or greater decrease in sum of products of perpendicular diameters of all measurable tumor for at least 4 weeks; no simultaneous increase in size any lesion or appearance of new lesions.

Minor response: a less than 50% decrease in sum of products of perpendicular diameters of all measurable tumor.

Stable disease: no appreciable change in tumor size.

Progression: increase of at least 25% in size of any measurable tumor or appearance of new lesions.

Once a study is completed, several ways exist to compute 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. Disease-free survival is calculated from study entry until disease progression or 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 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 imperative. This requirement is often accomplished by randomization with stratification for important prognostic variables. Prognostic variables are those factors known to influence response, regardless of treatment. One of the most 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 (see box) 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 less than 2 or less than 50% are poor candidates for phase II and III clinical trials and 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 randomized to one of the treatment groups and make it appear less efficacious than a second, when in fact it may be equal or better. Important prognostic variables should be defined at the onset of a study and analyzed in the results.

Box: Criteria for estimation of performance status

Zubrod, SWOG, and ECLOG Scales

0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physical strenuous activity but ambulatory and able to carry out work of a light sedentary nature (eg, light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out 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% odf waking hours.
4	Completely disabled; cannot carry out 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 of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do 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 supportive treatment necessary.
10	Moribund, fatal processes, progressing rapidly.
10	Dead.

It is important in designing and drawing conclusions from trials that one note whether the trial is prospectively randomized with concurrent controls or is a clinical trial with historical controls. Proponents of the randomized trial feel that one is more certain of equality between the two groups by a concurrent randomization process (Simon, 1989). This will reduce the bias of selecting controls from a historical pool. This will also reduce the problem of improvements in management or changes in treating physicians with time.

Specific Antineoplastic Chemotherapeutic Agents

The oncologist has a wide variety of drugs from which to choose. Each agent has a specific mechanism of action, toxicities, and spectrum of activity (Table 6-1). In this chapter

only those agents with efficacy in squamous cancers of the head and neck, parotid cancers, melanomas, and sarcomas will be covered.

Chemotherapeutic agents are classified into groups based on mechanisms of action or origin. Antimetabolites are drugs with structures that are similar to substrates such as amino acids or nucleosides that are necessary for important biochemical reactions. They can compete or substitute for that substrate and inhibit enzymes necessary for normal cellular function. Alkylating agents form highly reactive, positively charged carbonium ions that react with electron-rich sites on nucleic acids, proteins, sulfhydryl groups, and amino acids. The cytotoxic effect is a result of interaction with DNA. The vinca alkaloids are agents derived from a plant, and they have a common mechanism of action, binding to tubulin and subsequent arrest of cells in the metaphase of mitosis.

Antimetabolites

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 synthesis. 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 coenzymes requires 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 normal cells. Cancer cells may lack transport sites for leucovorin and are subject to the lethal effects of methotrexate. Mechanisms for resistance to methotrexate include 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 methotrexate is 40 to 60 mg/m^2 IV weekly. When higher doses of methotrexate are used, they may be in the moderate-dose range (250 to 500 $mg/^2$ IV) or the high-dose range (10 g/m^2).

These are both followed by leucovorin rescue, usually beginning at 24 hours and continuing until the plasma methotrexate level is less than 10^{-8} M. At this dose range the toxicity for patients with normal renal function is usually 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 very rarely and require intensive medical support. Renal failure may occur with high-dose methotrexate because of precipitation of the drug, especially in an acid urine. Hydration and alkalization of the urine before and following methotrexate administration can reduce the risk.

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 dose of 5-FU is 10 to 15 mg/kg IV weekly. An alternate method of delivery is a loading dose of 400 to 600 mg/m^2 daily for 5 days, followed by a weekly intravenous dose of 400 to 500 mg/m^2. 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. This allows delivery of up to 1 g/m^2/day for 5 days repeated every 3 to 4 weeks, without enhanced toxicity.

5-FU toxic reactions include myelosuppression with neutropenia and thrombocytopenia occurring at 1 to 2 weeks. Nausea, vomiting, and diarrhea may occur, and stomatitis is common with higher doses. Patients may develop alopecia, hyperpigmentation, or a maculopapular rash.

Alkylators

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 is usually given as a single dose of 500 to 1500 mg/m^2 repeated every 3 to 4 weeks. It can be given daily at 60 to 120 mg/m^2 but must be adjusted according to blood count results. It is important to hydrate the patient well before and after giving cyclophosphamide. Drugs that stimulate liver enzymes, such as barbiturates, should be avoided, or the cyclophosphamide dose should be modified. Following an intravenous dose, bone marrow suppression, predominantly neutropenia, can occur in 1 to 2 weeks, with a recovery at 2 to 3 weeks. Many patients have some degree of nausea and vomiting. Alopecia can occur, as well as ridging of the nails. 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.

Ifosfamide

Ifosfamide is structurally related to cyclophosphamide and has a similar mechanism of action leading to DNA interstrand and intrastrand 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/m^2 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- to 4-week intervals. MESNA (sodium mercaptoethane sulfonate) is a thiol compound that must 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 five divided doses given every 4 hours starting 30 minutes before ifosfamide is administered each day. Patients need to be well hydrated before drug administration.

The major dose-limiting toxicity is hemorrhagic cystitis. However, 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/m^2 over 5 days.

Dacarbazine

Dacarbazine (DTIC) can inhibit DNA and RNA synthesis. It must be given slowly intravenously. Conventional dosage schedules include either 250 mg/m^2 for 5 days or 850 mg/m^2 on day 1 repeated every 3 to 4 weeks.

One of the most dose-limiting toxic reactions is severe nausea and vomiting, which may last several hours. Myelosuppression occurs, with a nadir at 2 to 3 weeks. Patients may develop a flulike symptoms, with myalgias, malaise, and fever, that may last several weeks. Alopecia and changes in fertility may occur.

Antibiotics

Bleomycin sulfate

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 units/m^2 once or twice weekly given intramuscularly or intravenously. It may also be given by a continuous 24-hour infusion over 5 to 7 days at a dose of 10 units/m^2 each 24 hours. The major disposition 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 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 test dose of 1 unit 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. Patients may develop pneumonitis, a dry cough, and rales. Pulmonary function tests most commonly show a decreased carbon monoxide diffusion capacity, which can progress to

pulmonary fibrosis with associated hypoxia and restrictive lung disease. Bleomycin pulmonary toxicity is more common in elderly patients, patients who have had prior lung irradiation, and patients who have had a total dose greater than 200 units. Patients should be closely monitored with serial tests of diffusion capacity when the cumulative dose exceeds 150 units. Giving the drug by continuous infusion may lessen pulmonary toxicity (Weiss and Muggia, 1980).

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 90 mg/m^2 every 3 weeks. Alternate schedules that are associated with much lower risk of cardiac toxicity include doses of 20 to 30 mg/m^2 daily for 3 days repeated every 3 weeks, low doses given weekly, or prolonged infusions (Benjamin et al, 1988). The urine may be red for 1 to 2 days after adriamycin treatment.

If adriamycin infiltrates subcutaneous tissue, it can cause a 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 prior radiation therapy. The drug can also cause neutropenia and thrombocytopenia with a nadir at 1 to 2 weeks and a return to normal values by 3 weeks.

The most dose-limiting toxic effect of adriamycin is cardiac toxicity. This manifests as a cardiomyopathy (Von Hoff et al, 1982) leading to congestive heart failure in approximately 10% of patients who receive a cumulative dose greater than 550 mg/m^2. Other predisposing factors include age, prior cardiac irradiation, other cardiotoxic chemotherapeutic agents, and a prior 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.

Dactinomycin

Dactinomycin (actinomycin D) is an antitumor antibiotic that acts by intercalation into DNA with resultant inhibition of DNA-dependent RNA synthesis. Dactinomycin is given every 3 weeks in a 5-day course of 0.05 mg/kg per day (up to 0.5 mg) for children or 0.5 mg daily for adults. Because it is highly sclerotic, it should be given through a freely running intravenous line. The drug can cause severe damage to soft tissues if extravasation occurs.

Toxic reactions include myelosuppression with a nadir at 7 to 10 days. Nausea and vomiting may be severe. Up to one third of patients develop mucositis and diarrhea. Alopecia is common. Skin reactions include acne, hyperpigmentation, a maculopapular rash, and radiation recall.

Vinca alkaloids

Vinblastine

The vinca alkaloids act by disrupting microtubular spindle formation, causing mitotic arrest. Vinblastine (Velban) can be given weekly at 5 mg/m^2, or it may be given by continuous infusion over several days. The major toxic reactions are myelosuppression, alopecia, and myalgias.

Vincristine

Vincristine (Oncovin) is usually given at 1 to 1.5 mg/m^2 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 must take stool softeners with the drug. Vincristine causes alopecia but has almost no myelosuppressive effects.

Miscellaneous agents

Cisplatin

Cisplatin is an inorganic metal coordination complex with a significant 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 activation.

Cisplatin is administered by the IV route and requires aggressive hydration and diuresis to prevent renal tubular damage. A total dose of 80 to 120 mg/m^2 every 3 to 4 weeks is the usual dose given by IV infusion with mannitol diuresis (Hayes et al, 1977) or by 24-hour infusion (Jacobs et al, 1978). The drug is not schedule dependent; however, it has been shown that 5-day continuous infusion increases exposure to the active platinum species when compared to bolus dosing (Forastiere et al, 1988).

The major toxic reaction is renal dysfunction, manifested by a rise in serum creatinine levels or a fall in creatinine clearance. The peak serum creatinine level occurs at 1 to 2 weeks and returns to baseline by 3 to 4 weeks. A rise 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 secondary to bone marrow suppression; rarely patients manifest an acute hemolytic anemia. Hypomagnesemia can occur in part because of renal wasting. A peripheral neuropathy, predominantly sensory, occurs and is related to cumulative cisplatin dosage. Both ototoxicity and peripheral neuropathy are common toxicities when the cumulative cisplatin dose approaches or exceeds 600 mg/m^2.

These toxicities preclude long-term treatment with cisplatin in chemotherapy responders and dose intensification. This led to a search for analogs with similar efficacy but a different spectrum of toxicity.

Carboplatin

Over a dozen derivatives of cisplatin have been evaluated for clinical development. Of these, carboplatin (cis-diamine-cyclobutane dicarboxylato platinum II) is the first to become widely available. Carboplatin appears to have a mechanism of action similar to the parent compound. In most solid tumors its efficacy is also similar to cisplatin but it has a different toxicity profile. The dose-limiting toxicity is myelosuppression, primarily leukopenia and thrombocytopenia, which must be taken into consideration when carboplatin is combined with other myelosuppressing agents. However, renal toxicity, ototoxicity, and neurotoxicity are rare, and the emetogenic potential of carboplatin is less. The drug can be safely administered in the outpatient setting without the need for hydration. Based on pharmacokinetic parameters, a dose of 400 mg/m^2 by the IV route is considered the equivalent in potency to 100 mg/m^2 of cisplatin.

Hydroxyurea

Hydroxyurea (Hydrea) inhibits ribonucleotide reductase, interfering with the conversion of ribonucleotides to deoxyribonucleotides and causing inhibition of DNA synthesis. The drug is given orally, usually in an intermittent regimen of 80 mg/kg every third day. The major toxic responses are neutropenia and thrombocytopenia, so that the dose should be reduced or delayed if the white blood cell count decreases to less than 25.000/mm^3 or the platelets to less than 100.000000/mm^3. The nadir occurs approximately 10 days after starting the drug. Nausea and diarrhea are common. Stomatitis can occur, particularly if these is concurrent irradiation. Patients may also develop a maculopapular rash.

Combined Chemotherapy and Combined Modality Therapy

Combination chemotherapy is often used for recurrent disease or for combined modality programs. One theoretic reason for improvement in response is a lack of cross-resistance between two or more agents that have different mechanisms of action or represent different classes of drug. A basic principle of combination chemotherapy is that all agents are efficacious as single agents in the particular disease. Often one finds combinations used that include drugs having no proven efficacy as single agents. The goal of combination chemotherapy is to select agents that will result in synergistic effects (rather than additive or antagonistic). This may be achieved through combining agents with a different mechanism of action that have shown enhanced cytotoxic effects in vitro.

It is imperative when devising a combination to keep overlapping toxicities to a minimum so that each drug may be used in full dosage. Agents that have either different toxic effects or different timing of toxic effects should be chosen for a combination. Thus two drugs that are myelosuppressive may be used if the maximal points of myelosuppression differ.

Over the past decade interest in the use of combined modality approaches to cancer treatment has increased. The modalities include surgery or radiotherapy combined with chemotherapy. For those diseases that are treated primarily with surgery or radiotherapy, chemotherapy has the following roles:

1. To reduce tumor bulk before irradiation or surgery.
2. To sensitize tumors to irradiation.
3. To sterilize occult disease after surgery or irradiation.

Chemotherapy may be used before definitive treatment as induction or as a neoadjuvant. This use may reduce the size of tumor and facilitate surgery. Reduction of tumor size may also cause increased vascularization and, as a result, oxygenation, making tumors more sensitive to irradiation. Chemotherapy may also be used during radiotherapy as a radiosensitizer to improve tumor response to radiotherapy. Finally, chemotherapy may be given after definitive treatment. This is usually called adjuvant or maintenance chemotherapy. Griswold (1975) showed in animal models that chemotherapy is most effective when used against small tumor volumes. Theoretically, adjuvant chemotherapy is beneficial because of its ability to destroy micrometastases or small numbers of locally remaining tumor cells. Adjuvant chemotherapy is efficacious in other cancers, such as breast cancer.

Several potential disadvantages to the combined modality approach exist. If induction chemotherapy is used, a delay occurs before definitive surgery or radiation can proceed. If chemotherapy is ineffective, then tumor growth can occur during this time. If the tumor response is excellent or even complete, and the original cancer was not marked with diagrams or tattoo, the surgeon may be unable to find the original margins of tumor. Pathologists often have difficulty determining whether a margin is positive for cancer or has nonviable cancer cells. In patients who have had an excellent response to induction chemotherapy, surgeons may be tempted to perform less extensive surgery. A further problem is lack of patient compliance when response to chemotherapy is excellent.

When chemotherapy is used as a radiosensitizer, toxicity may be increased, resulting in excessive delay and lowered total dose of radiation. In addition to the acute toxic effects of chemotherapy, the long-term adverse effects including the potential for second tumors are unknown.

Squamous Cell Carcinomas

Overview of current concepts

Before 1970, chemotherapy had a very limited role in the management of squamous cell cancer of head and neck in both community practice and at academic centers. In part, this was because of the paucity of available drugs with documented antitumor activity for this disease. In fact, the only drug with clearly established activity, used worldwide, was the folic acid analog methotrexate. Many other drugs had been tested; however, 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, over the last two decades a rigid system has been applied to the testing of potentially useful drugs. There now exist clearly defined parameters for the objective evaluation of response,

duration of response, and survival time and statistical guidelines for the design of clinical research trials to establish efficacy or to demonstrate improvement compared to standard therapies.

The serendipitous identification of the metal compound cisdiaminedichloro platinum (II) (cisplatinum) as a potential anticancer agent by Rosenberg (1980) in 1968 spurred clinical research efforts to test new agents and combination chemotherapy regimens for the palliation of patients with locally recurrent and metastatic head and neck cancer. Several highly effective chemotherapy regimens were identified and then incorporated into a combined modality approach to treating the newly diagnosed patient. The goal was to improve survival. It became clear that chemotherapy administered before definitive surgery and/or radiation therapy could result in rapid regression of tumor in the majority of patients without increasing the morbidity of subsequent surgery or radiation. Further, a proportion of the responding patients would have no evidence of tumor in the resected specimen. This raised the possibility of altering the standard surgical approach at some sites to preserve organ function. In addition to these investigative trials utilizing chemotherapy before definitive local therapy, traditional adjuvant chemotherapy administered after surgical resection and chemotherapy used as a radiosensitizer concomitant with radiation therapy 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. Because squamous cell cancer of the head and neck is a heterogeneous disease, each factor must 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 prior radiation therapy and surgery (Amer et al, 1979). In these circumstances, any response to chemotherapy is likely to be marginal and brief without impact on overall survival. However, it seems clear that survival may be prolonged in patients who achieve a complete response to chemotherapy. These patients in general have a good performance status; they are not malnourished and have not received previous chemotherapy for recurrent disease. The impact of other factors such as histologic differentiation and primary site on response is unclear.

For the newly diagnosed patient treated with induction chemotherapy, the single 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 T_4 and N_3 stage disease in particular (Choksi et al, 1988; Ervin et al, 1987; Head and Neck Contracts Program, 1987). The significance of primary site as a prognostic factor for response to chemotherapy is unclear. Once investigator, in an analysis of 208 patients, reported that cancers within the oral cavity and nasopharynx were significantly associated with high response rates (Hill and Price, 1987). Nasopharynx cancer was found significant in two other trials (Al-Sarraf et al, 1987b; Ervin et al, 1987). Most trials have failed to demonstrate differences by site. This may be because of inadequate patient numbers and ineffective chemotherapy regimens.

Because of the importance of performance status as a predictor of outcome for the recurrent disease patient, induction chemotherapy trials have excluded patients with poor performance status (< 50% on the Karnofsky scale). Within the range of 50% to 100%, no differences have been observed. Tumor differentiation does not appear to be a predictive factor in studies that have utilized cisplatin-based combination chemotherapy regimens.

It is well established that overall survival correlates with performance status, T and N stage, and primary site (Al-Sarraf et al, 1987a; Ervin et al, 1987; Head and Neck Contracts Program, 1987). The survival of patients with cancers of the nasopharynx and larynx is longer than of those with oral cavity and hypopharyngeal primary cancers after other factors are corrected for in multivariate analyses of patients receiving induction chemotherapy.

The application of biologic factors such as DNA content (Ensley et al, 1989) and immunologic status and circulating immune complexes (Shantz et al, 1989) to predict response and survival outcome is under investigation.

Chemotherapy for palliation

Systemic treatment of recurrent head and neck cancer is a major concern because 30% to 50% of individuals diagnosed this year will die with recurrent local-regional disease within 5 years. Distant metastases will be present clinically in 20% to 40%, but occult disease determined at autopsy may be present in up to 60% (Kotwall et al, 1987). The primary goal of conventional chemotherapy used for palliation should be to prolong survival. Although one often hears that pain relief can be achieved with chemotherapy, this should not constitute the reason for treatment. Insignificant amounts of tumor regression may be associated with a transient diminution of pain; however, the aggressive use of a wide 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 squamous cell cancer to commonly used agents is provided in Table 6-2. 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 is brief, on the order of 2 to 4 months, and the median survival time is 6 months.

Methotrexate is the most widely used drug for squamous cancers of the head and neck and is the standard to which new agents or combinations should be compared. Response rates to conventional doses vary between 8% and 50%, averaging about 30% (Bertino et al, 1973). Weekly treatment, if tolerable, is superior to twice monthly or monthly treatments. Levit et al (1973) 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 normal tissue. The initial results of pilot trials of moderate- or high-dose methotrexate suggested improvement in response rates for head and neck cancers. However, there is no evidence of improved responses to the higher dose of drug from prospective randomized trials comparing conventional to moderate- or high-dose methotrexate (Vogler et al, 1979; Woods et al, 1981).

Cisplatin is one of the newer drugs to be used for squamous cancers of the head and neck. It has the same response rate as methotrexate, approximately 30%, with some reported complete responses and a duration of response of approximately 4 months (Jacobs et al, 1978; Wittes et al, 1977). Two controlled trials comparing methotrexate to cisplatin found no difference in response rate or survival between the two but only different toxicities (Grose et al, 1985; Hong et al, 1983). 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. However, methotrexate is more convenient, since it can be given on an outpatient basis, whereas the higher doses of cisplatin require hospitalization. Cisplatin has been studied at different doses to determine if a dose-response effect exists. In a comparison of 60 mg/m^2 and 120 mg/m^2 Veronesi et al (1985) found no difference in response rates. Forastiere et al (1987a) conducted a pilot trial evaluating 200 mg/m^2 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. The availability of platinum analogs may allow this concept to be definitively tested in the future.

Carboplatin has a 24% response rate in phase II trials in patients with recurrent squamous cell cancer of the head and neck. It appears to have an efficacy similar to cisplatin although no direct comparative trials have been performed in this patient population. It has several advantages over cisplatin. Carboplatin can be administered in the outpatient setting and requires no prehydration. There is less nausea and vomiting associated with carboplatin so that it is readily accepted by patients. For the patient with poor nutrition this is an important consideration. The major toxicity caused by carboplatin is myelosuppression. This limits the total dose that can be given and the frequency of drug administration. The availability of colony-stimulating factors (G0-CSF, GM-CSF, IL-3) that may lessen the degree and duration of myelosuppression is providing a new avenue for clinical investigations with this agent. It is likely that carboplatin will be more widely used in the future to treat 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 bleomycin, 5-FU, adriamycin, cyclophosphamide, hydroxyurea, and vinblastine (Al-Sarraf, 1988). Several of these, such as 5-FU and bleomycin, are only marginally effective as single agents for recurrent disease; however, when used in combinations or in patients with no prior treatment, they may be more efficacious.

Bleomycin and 5-FU have undergone testing using an intermittent bolus dosing schedule with response rates of 15% to 18%. A pharmacokinetic advantage may be achieved by continuous infusion because both agents have a very short plasma half-life. Continuous infusion 5-FU has been studied primarily in adenocarcinomas of the gastrointestinal tract. However, the results of one randomized trial in head and neck cancer comparing bolus and continuous infusion 5-FU showed improved response rates with continuous infusion (Kish et al, 1985).

Bleomycin and 5-FU are most frequently used in combination with other agents. Cyclophosphamide, hydroxyurea, adriamycin, and vinblastine represent second- and third-line choices because of a low order of response and less rigorous evaluation in disease-oriented trials. The lack of improvement in survival with single agents over that expected with no

treatment led to the evaluation of combination chemotherapy regimens.

Combination chemotherapy for recurrent disease

Many combination chemotherapy regimens have been evaluated in phase II trials in small numbers of 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 in general ranges from 2 to 6 months, and no one has yet documented improved survival over single-agent chemotherapy. Many of the regimens are quite complex, often with additional toxic effects.

Only through large comparative trials with patients randomized and stratified for prognostic variables can one determine if therapeutic benefit exists with combination chemotherapy. The results of 10 trials comparing combination chemotherapy to single-agent cisplatin or methotrexate are shown in Table 6-3. 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 prior treatment. However, three large multi-institutional trials that were well designed with respect to prognostic factors demonstrated a significant difference in response rates between the combination treatment and the single-agent control arm (Forastiere, 1990; Jacobs et al, 1991; Vogl et al, 1985).

The Eastern Cooperative Oncology Group (ECOG) compared an outpatient regimen of cisplatin, bleomycin, and methotrexate to weekly methotrexate (Vogl et al, 1985). The response to single-agent therapy with methotrexate was 35%, and to the combination 48%, a significant improvement ($p = 0.04$). However, toxicity was greater for the combination with no difference in survival.

The Southwest Oncology Group (SWOG) reported a comparison of cisplatin + 5-FU and carboplatin + 5-FU to weekly methotrexate (Forastiere, 1990). The response rates for the three arms were 32%, 21% and 10%. respectively. There was a significant difference comparing the cisplatin combination to methotrexate ($p < 0.001$); the difference between the response to the carboplatin combination and the response to methotrexate approached statistical significance ($p = 0.05$). The cisplatin + 5-FU arm was associated with significantly more toxicity than methotrexate; carboplatin + 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 to each drug used singly (Jacobs et al, 1991). The response rate to the combination was 40% compared to 18% for cisplatin and 15% for continuous infusion 5-FU ($p < 0.01$). 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 to 27% and 24% for the single-drug treatments ($p < 0.05$).

The latter two trials are also of interest in the similar response rates observed for cisplatin and 5-FU, which was administered using the same dose and schedule in both studies. Cisplatin and 5-FU is a commonly used drug regimen for the treatment of head and neck cancer both for palliation and in combined modality programs. Response rates to this

combination reported from small phase II trials in recurrent disease patients range from 11% to 79% (Urba and Forastiere, 1989). The results of these two large multi-institutional trials have served to establish a response rate of 32% to 40% that can be expected from the cisplatin and 5-FU combination in recurrent head and neck cancer.

Two comparative trials listed in Table 6-3 showed significant differences in median survival (Campbell et al, 1987; Morton et al, 1985). Morton et al (1985) compared the combination of cisplatin and bleomycin to each single agent and to a no treatment control arm. The response rate to each of the three chemotherapy arms was low; however, the two cisplatin arms had median survivals of 4.0 and 4.2 months, which was improved over a 2.1-month survival for the no treatment arm. In the four-arm trial reported by Campbell et al (1987), survival was significantly longer for single-agent cisplatin compared to 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. This serves to diminish 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 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 to single-agent therapy. The patients who are more likely to be in the subset showing improvement has a better performance status.

Combined modality therapy

Although surgery and radiation therapy 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. Since 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.

Induction chemotherapy

One of the first uses of induction chemotherapy involved methotrexate with leucovorin rescue given twice before surgery (Tarpley et al, 1975). It was reported that 77% of patients has some tumor shrinkage, although by strict criteria of tumor response (greater than 50% in all sites), the response rate was only 20%. Although one could not conclude that the result was better than with surgery alone, no increased incidence of postoperative complications occurred.

With the introduction of cisplatin into clinical trials in the mid-1970s therapy was cisplatin followed by a 5- to 7-day continuous infusion of bleomycin. Early series (Hong et al, 1979; Randolphet al, 1978) 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 (Al-Sarraf, 1988).

An alternate and probably more effective regimen tested in the 1980s is cisplatin (100 mg/m^2) followed by a 5-day infusion of 5-FU (1 g/m^2 per day by continuous infusion)

(Rooney et al, 1985). In phase II trials, this regimen was associated with as high as a 93% overall response rate 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 phenomen or lung toxicity.

In an effort to further increase the complete response rate and to improve survival, several strategies are being evaluated. The Southwest Oncology Group has a trial in progress evaluating the feasibility and efficacy of six cycles of cisplatin and 5-FU induction chemotherapy.

Ensley and co-investigators (1988; 1991) from Wayne State University have reported a high complete response rate using five or six courses of cisplatin + 5-FU alternating with methotrexate, leucovorin, and 5-FU. In one study, the complete response rate was 65% in 31 patients completing the protocol; however, 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 Center (Dreyfuss et al, 1990) and at the University of Chicago (Vokes et al, 1990) 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 (Moran, 1989). Dreyfuss et al (1990) administered cisplatin, 5-FU, and high-dose leucovorin (500 mg/m^2), 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. However, with dosage adjustment the regimen was tolerable and acceptable to patients. Vokes et al (1990) treated 31 patients with similar disease with a less intensive cisplatin, 5-FU, and leucovorin regimen. Leucovorin was administered orally in a dose of 100 mg every 4 hours during 5-days infusion of 5-FU. After two courses, the overall response rate in 29 evaluable patients was 90%, and the complete response rate was 30%.

The many uncontrolled trials of induction chemotherapy before surgery or radiation therapy have shown that this approach is feasible for locally advanced disease and does not add to the morbidity of subsequent definitive local treatment. With the cisplatin plus 5-FU regimen, 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 radiation therapy (Ensley et al, 1984; Glick et al, 1980; Hong et al, 1985). Thus patients who are resistant to cisplatin-based induction chemotherapy have a high likelihood of not responding to radiation therapy.

Large randomized trials that take into account all the important prognostic variables and have long-term follow-up are necessary to draw conclusions regarding disease-free survival and overall survival benefit. The results of six randomized controlled trials of induction chemotherapy before surgery or radiation therapy or both have been published in manuscript form (Table 6-4). The preliminary results of three other randomized trials were reported in abstract form only (Carugati et al, 1988; Martin et al, 1988; Paccagnella et al,

1990) and indicate no improvement in survival with the addition of induction chemotherapy to standard treatment.

Three of the trials listed in Table 6-4, The Head and Neck Contracts program (1987), the Southwest Oncology Group trial (Schuller et al, 1988), and the Veterans Affairs Laryngeal Cancer Study Group trial (1991), were large multi-institutional randomized studies. The patients had advanced resectable head and neck cancer, and the treatment arms were well balanced for T, N stage and primary site. The Head and Neck Contracts program randomized patients to 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 were 35%, 37%, and 45%, respectively, for the three regimens; 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 to the other two groups. On subgroup analysis, there was a significant difference in disease-free survival for patients receiving maintenance chemotherapy, for oral cavity primary tumors, and for N_1 or N_2 disease (Jacobs and Makuch, 1990). In retrospect it is not surprising that this trial did not show any improvement in overall survival because only one cycle of cisplatin and bleomycin was administered before surgery, resulting in a low response rate, 37%.

The Southwest Oncology Group (Schuller et al, 1988) randomized patients to receive either three cycles of cisplatin, bleomycin, methotrexate, and vincristine before surgery and radiation therapy or standard treatment with surgery and radiation therapy. The median survival time was 30 months for patients in the standard treatment arm compared to 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 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 randomized to induction chemotherapy completing the treatment per protocol.

The most encouraging data to emerge from induction chemotherapy trials are in the area of organ preservation. The Veterans Affairs Laryngeal Cancer Study Group (1991) recently completed a randomized trial in patients with resectable stage III and IV squamous cell cancer of the larynx. Patients were randomized to receive standard therapy with total laryngectomy and postoperative radiation therapy or to receive a maximum of three cycles of cisplatin and 5-FU chemotherapy followed by radiation therapy. Surgery was reserved to 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 98%. The pathologically confirmed complete response rate at the primary site was 64%. At a median follow-up of 33 months, there was no significant difference in survival. However, the patterns of relapse differed: recurrence at the primary site was 2% with surgery vs 12% with chemotherapy ($p = 0.0005$); regional node recurrence rates were similar ($p = 0.305$); distant metastases was 17% with surgery vs 11% with chemotherapy ($p = 0.016$); rate of second primary malignancies was 6% with surgery vs 2% with chemotherapy ($p = 0.029$).

The randomized trials published by Kun et al (1986), Toohill et al (1987), and Stell et al (1983) accrued much smaller numbers of patients and included a mix of patients with advanced resectable and unresectable disease. These studies contain design flaws that bring the interpretation of the results into question (Forastiere, 1991). The treatment groups were not balanced for known prognostic factors, the numbers of patients were small, and the chemotherapy selected was either a suboptimal regimen or given in reduced dosage for no apparent reason.

In spite of these criticisms of published randomized trials, no trial to date has demonstrated a survival benefit from induction chemotherapy. Therefore this approach must be considered experimental and its use limited to the research protocol setting. On the other hand, a role that does appear promising for induction chemotherapy is organ preservation. 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. However, the results of the Veterans Affairs Laryngeal Tumor Study Group (1991) must mature with longer follow-up and be confirmed before this approach can be advocated as a standard therapy.

Concurrent radiation therapy and chemotherapy

Concurrent radiation therapy and chemotherapy have been used primarily in patients with unresectable disease to improve local-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 (Fu, 1985; Steel and Peckham, 1979; Tannock and Rotin, 1988). Nearly all reported trials of concomitant chemotherapy and radiation therapy have noted enhanced acute radiation-induced toxicity, primarily mucosal. This has often 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 both chemotherapy and radiation in the optimal dose and schedule.

Single agents and radiation therapy (Table 6-5)

Methotrexate plus radiation therapy. Methotrexate can produce an S-phase block of the cell cycle, resulting in accumulation of cells in the G_1 phase causing increased radiosensitivity (Bagshaw and Doggett, 1969). In one early study 96 patients with inoperable disease were randomized to receive radiation therapy alone or radiation preceded by intravenous methotrexate (Knowlton et al, 1975). 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 as compared to 33% of patients who received radiation therapy alone (Lustlig et al, 1976). The Radiation Therapy Group (RTOG) randomized 712 patients to radiation therapy alone or radiation plus pretreatment methotrexate (Fazekas et al, 1980). No difference occurred in survival between the treatment groups, and more patients failed to complete irradiation in the combined therapy group. Thus three

randomized series with adequate patient numbers show negative results.

Hydroxyurea plus radiotherapy. Hydroxyurea kills cells in the S-phase and synchronizes cells into the more radiosensitive G_1 phase. Despite good theoretic activity, three randomized trials shown no advantage of hydroxyurea in addition to radiation therapy. In one series, 126 patients with advanced cancer were randomized to radiation alone or with hydroxyurea (80 mg/kg biweekly) (Stefani et al, 1971). The complete response rate at the primary site was 40% in both groups, but survival was inferior in the combination group. In addition, distant metastases developed in 23% of patients with combined treatment as compared to 8% with radiation alone. Another study of 40 patients comparing radiation therapy alone or with hydroxyurea (80 mg/kg three times per week) showed no difference in complete response rate or survival but a 40% incidence of mucositis in the combined group (Richards and Chambers, 1969).

Bleomycin plus radiation therapy. Bleomycin and irradiation have been studied in vitro, and the enhanced effects are believed to be caused by interference with cellular repair following irradiation. Four large randomized trials compared radiation therapy alone to radiation plus bleomycin. The first series included 227 patients with advanced oropharyngeal carcinomas (Cachin et al, 1977). Bleomycin was given as 15 mg twice weekly for 5 weeks. No difference in response rate or survival 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 (Eschwege et al, 1988). Similar results were reported by Vermund et al (1985). In contrast, the third large series (Shanta and Krishnamurthi, 1977), from India, included patients with advanced buccal mucosa cancers and compared radiation therapy alone to radiation plus bleomycin (10 to 15 mg three times per week for 6 weeks). The complete response rate in the radiotherapy group was 21% as compared to 77% in the combined therapy group.

An improvement in disease-free survival, local-regional control, and complete response rate but not overall survival was reported by Fu et al (1987). In this Northern California Oncology Group trial, patients received either radiation therapy alone or radiation with bleomycin (5 mg twice weekly) followed by 15 weeks of maintenance bleomycin and methotrexate. The complete response rates were 45% with radiation therapy alone and 67% for the combined treatment ($p = 0.056$). The 2-year local-regional control rate was significantly improved with the addition of bleomycin, 26% vs 64% ($p = 0.001$). 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 radiation therapy was well tolerated. A significant reduction in radiation dose or treatment delays did not occur as a result of enhancement of acute radiation toxicity.

5-Fluorouracil and radiation therapy. Several early trials indicated that 5-FU was an active radiosensitizer for head and neck cancer; however, only one randomized trial to date has shown efficacy (Lo et al, 1976). In that study 134 patients with advanced head and neck cancer were randomized to radiation therapy with or without 5-FU (10 mg/kg per day for 3 days, 5 mg/kg per day for 4 days, 5 mg/kg three times per week). The 5-year survival rate for radiation alone was 14% and for combined treatment, 32%. This improvement in survival occurred for patients with primary lesions in the tongue or tonsil only.

Mitomycin and radiation therapy. Mitomycin is an antibiotic that under hypoxic conditions is enzymatically reduced to form an active alkylating species (Sartorelli, 1988). 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 (Rockwell and Sartorelli, 1989). This concept was tested by Weissberg et al (1989) in a randomized trial by treating 120 patients with advanced head and neck cancer with radiation therapy alone or radiation with mitomycin (15 mg/m^2). Disease-free survival at 5 years was 49% for the radiation therapy alone and 75% for those treated with mitomycin ($p < 0.07$). Local and regional control rates were significantly improved with mitomycin, 55% vs 75% ($p < 0.01$). There was no difference in the incidence of distant metastases or overall survival between treatment groups.

Cisplatin and radiation therapy. 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 vitro systems (Devit, 1987). In a phase II trial the Radiation Therapy Oncology Group (RTOG) administered cisplatin (100 mg/m^2) every 3 weeks to 124 patients with locally advanced, unresectable head and neck cancer (Al-Sarraf et al, 1987b). 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 for nasopharynx and nonnasopharynx primary sites with over 5 years of follow-up have been published (Al-Sarraf et al, 1990; Marcial et al, 1990). A comparison to RTOG patients treated with radiation therapy alone suggested improvement in survival for the combined treatment.

Wheeler et al (1990) piloted high-dose cisplatin (200 mg/m^2) every 4 weeks with concurrent radiation therapy in 18 patients with unresectable disease and observed complete responses in 94%. The median survival 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 radiation therapy (Haselow et al, 1990). Through the Head and Neck Intergroup mechanism 371 patients with unresectable local regional squamous cell head and neck cancer were randomized to receive radiation therapy alone or radiation plus weekly cisplatin in low dose, 20 mg/m^2. There was a significant difference in overall response rate (complete and partial), 59% for radiation alone and 73% for the combined treatment ($p = 0.007$). However, there was no significant difference in complete response or survival. The lack of survival benefit may be because of the low total dose of cisplatin received, only 120 to 140 mg/m^2 over the 6 to 8 weeks of radiation treatment.

In summary, randomized trials of single agents and radiation therapy have shown improved survival with bleomycin and 5-FU (Lo et al, 1976; Shanta and Krishnamurthi, 1977). Improved disease-free survival but not overall survival has been shown in two other trials with bleomycin and mitomycin (Fu et al, 1987; Weissberg et al, 1989). Because mucosal toxicity is enhanced and overall survival, although improved, remains poor, none of these regimens has become a standard therapy.

Combination chemotherapy and radiation therapy. Combining several drugs with radiation will enhance acute toxicity, which may be severe in degree. Therefore investigators have piloted trials designed with split course radiation to allow for normal tissue recovery.

Most of these studies are limited to stage III and IV locally advanced unresectable squamous cell cancer and have improved survival as the primary goal. Recently published phase I and II studies have used infusional 5-FU as originally reported by Byfield et al (1984) adding cisplatin (Adelstein et al, 1990; Taylor et al, 1989) or hydroxyurea (Vokes et al, 1989) with concurrent split-course single daily fraction radiation. Alternatively, cisplatin and fluorouracil with leucovorin modulation have been combined with split-course accelerated radiation therapy (Wendt et al, 1989).

The most mature data were reported by Taylor et al (1989) using cisplatin plus continuous infusion 5-FU and radiation therapy alternating a week of treatment with a week of rest. The median survival time for 53 patients with a median follow-up in excess of 4 years was 37 months. The total dose received of radiation and 5-FU but not cisplatin correlated with outcome. Local control was poorest in stage IV patients with N_3 disease.

Although these pilot trials all report encouraging data for improved survival, randomized trials that use radiation therapy alone as the control are needed before these approaches can be recommended outside the research setting. Data from randomized trials is shown in Table 6-6. The South-East Cooperative Oncology Group (SECOG) (1986) compared alternating to sequential chemotherapy and radiation therapy. 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 prior pilot trial, and a significant improvement in disease-free survival was observed only for larynx primaries treated with the alternated schedule. The alternating regimen was associated with a higher frequency of severe mucosal reactions.

Merlano et al (1991a) published the final report of a randomized comparison of alternating sequential chemotherapy (vinblastine, bleomycin, methotrexate) and radiation therapy followed by surgical salvage if feasible. Four courses of chemotherapy were alternated with three courses of radiation therapy (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 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 to only 6% of those receiving chemotherapy before radiation therapy. The preliminary results of a follow-up trial reported by Merlano et al (1991b) showed a significant difference in relapse-free and overall survival for patients treated with alternating cisplatin + 5-FU and radiation therapy compared to radiation therapy alone. All patients had unresectable locally advanced squamous cell cancer of the head and neck.

In a small randomized trial Adelstein et al (199) compared simultaneous cisplatin + 5-FU and radiation therapy to sequential treatment. Patients with stage II, III or IV disease were eligible, both resectable and unresectable disease. 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 radiation therapy. In the sequential treatment, surgical evaluation occurred after three cycles of chemotherapy and before radiation therapy. The results with follow-up ranging between 9 and 41 months showed a significant difference in disease-free survival but not overall survival. At this point in follow-up 18 of 48 patients were complete responders and had not required surgery.

The results of these trials indicate that improved disease-free and overall survival is possible for patients with locally advanced squamous cell head and neck cancer using alternating or concomitant chemotherapy and radiation therapy. However, none of these approaches can be considered standard therapy. Well-designed clinical trials are still needed to determine optimal chemotherapy and radiation therapy schedules and to establish benefit compared to standard treatment.

Adjuvant chemotherapy

Adjuvant chemotherapy following primary surgery has been shown to be effective in breast cancer and osteogenic sarcoma. To date only one randomized trial has been designed to address this question in head and neck cancer. Through the Head and Neck Intergroup mechanism, a large multi-institutional trial was conducted to test whether the addition of chemotherapy to surgery and radiation therapy prolonged survival or altered the pattern of recurrence (Laramore). Patients with stage III or IV squamous cell carcinoma of the oral cavity, oropharynx, or larynx and stage II, III, or IV of the hypopharynx who had negative pathologic margins of resection were eligible. Randomization was to immediate postoperative radiation therapy or three cycles of cisplatin + 5-FU chemotherapy followed by radiation therapy. A preliminary analysis of the 503 patients randomized has shown no significant difference in disease-free survival, overall survival, and local-regional control. However, there was a significantly lower rate of distant metastases as a site of failure ($p = 0.016$) at any time for patients treated with adjuvant chemotherapy.

The same change in pattern of recurrence was observed by the Veterans Affairs Laryngeal Cancer Study Group (1991) for patients receiving induction chemotherapy compared to standard surgical management.

Two trials testing induction chemotherapy added maintenance chemotherapy to one treatment group and observed differences in outcome. The Head and Neck Contracts Program (1987) 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 et al (1987) randomized patients demonstrating a response to cisplatin, bleomycin, and methotrexate induction chemotherapy to receive three additional cycles or observation following definitive surgery and radiation therapy. The 3-year disease-free survival for patients receiving maintenance chemotherapy was 88% compared to 57% for the controls ($p = 0.03$).

In a phase II pilot, Johnson et al (1987) treated 42 patients with extracapsular spread of tumor in cervical lymph node metastases with 6 months of methotrexate and 5-FU after resection and radiation therapy. The 2-year disease-free survival was 66%, which was improved from an expected control rate of 38% based on historical experience.

Taken together, the results of these five trials indicate that adjuvant chemotherapy can affect micrometastatic disease and decrease the rate of distant recurrence. The data also suggest that disease-free survival may be improved. The major impediment to successfully conducting adjuvant or maintenance chemotherapy trials in head and neck cancer is patient noncompliance. The morbidity of the primary treatment, combined with the medical and

social situations of this group of patients, makes classical adjuvant chemotherapy unacceptable or not feasible in many patients.

Intraarterial chemotherapy

Poor response to chemotherapy after surgery or radiation therapy 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 (Frei and Canellos, 1980). 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 normal tissues (Chen and Gross, 1980; Collings, 1984). 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 in 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. (4) A drug should not require activation in the liver.

Intraarterial cisplatin has been shown to be effective and relatively nontoxic in several solid tumors. Pharmacokinetic studies have shown a regional increase in both plasma and tissue platinum concentrations in the infused area (Gouyette et al, 1986; Stewart et al, 1983). 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 (1972). Tumor regression lasted up to 13 months. Intraarterial methotrexate and bleomycin have been used before irradiation for advanced head and neck cancer, with a 28% partial response rate (Zielke-Temme et al, 1980). Intraarterial cisplatin given before surgery and/or radiation has produced responses in the 70% to 80% range (Grigoletto et al, 1982; Mortimer et al, 1988).

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 (Baker et al, 1981). This system has been used successfully in treating recurrent head and neck cancer with continuous infusion of dichloromethotrexate and fluorodoxyuridine (Forastiere et al, 1987b; Wheeler et al, 1984).

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 radiation therapy (Sato et al, 1967; Shibuya et al, 1982). More recently, investigators in the USA have evaluated superselective arterial catheterization and short-term intraarterial chemotherapy to debulk locally advanced resectable and unresectable paranasal sinus carcinomas. This approach minimizes potential toxic effects to adjacent normal tissues. Dimery et al (1990) reported evaluating intraarterial cisplatin and bleomycin by this technique combined with intravenous 5-FU. A complete response rate of 23% was achieved to the chemotherapy alone. Following surgery and/or radiation therapy, 63% of patients were disease free and 61% were

spared orbital exenteration.

Although intraarterial therapy has several theoretic advantages over systemic chemotherapy, it has not yet 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, but further investigation appears 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 radiation therapy, patients with advanced salivary gland cancers have a poor prognosis, with survivals ranging from 0% to 32% at 10 years. Survival varies with histology, with 10-year survival rates of 96% reported for low-grade mucoepidermoid carcinoma and 29% for adenoid cystic carcinoma (Friedman et al, 1986). Probability of recurrence also varies with site. Local or distal recurrence occurs in up to 66% of patients with cancers of major salivary glands and up to 92% of patients with cancers of the minor salivary glands (Conley and Dingman, 1974). 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 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 total number of patients who may have been treated. Suen and Johns (1982) showed that response to chemotherapy varies with histologic findings. They also found that response varies with site recurrence, with local-regional disease having a higher response rate than distal disease. In addition, patients without prior radiotherapy had a better response to chemotherapy. Drawing conclusions from most series is difficult, since they usually include a group of patients treated over 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 are difficult to interpret.

Suen and Johns (1982) 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 adenoid cystic carcinoma, the best single agents are cisplatin, 5-FU, and doxorubicin (see Table 6-7). Cisplatin has been reported to have a complete response rate of 29% and an overall response rate of 64% in 14 treated patients (Schramm et al, 1981; Suen and Johns, 1982). Complete responses lasted from 7 to 18 months. 5-FU has been reported to have a partial response rate of 46% in 13 patients (Johnson et al, 1964; Tannock and Sutherland, 1980). Adriamycin was noted to have a response rate of 13% in seven patients (Rentschler et al, 1977; Vermeer and Pinedo, 1979). 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 (Posner et al, 1982). Because of the poor prognosis of patients with advanced disease and the activity of cisplatin, Sessions et al (1982) treated four patients with intraarterial cisplatin before further therapy. All patients has 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 this carcinoma are not available. Methotrexate has been used in four patients with one achieving a complete response and one a partial response. Posner et al (1982) 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 (Alberts et al, 1981).

The small numbers of patients in each series preclude firm conclusions regarding the true level of antitumor activity of these drugs. However, the data do provide an indication of which drugs are reasonable to choose for single-agent or combination chemotherapy.

Creagan et al (1988) reported the results of cisplatin-based chemotherapy in 34 patients with locally recurrent or metastatic cancers originating from the salivary gland or contiguous structures (Table 6-7). Most patients received cyclophosphamide or mitomycin, plus adriamycin and cisplatin combination chemotherapy. A 38% response rate was observed, lasting 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 et al (1987) 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 et al (1987) 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 prior treatment.

In conclusion, cisplatin, adriamycin, and 5-FU or cyclophosphamide appear to be the most active agents and combinations for adenoid cystic carcinoma and adenocarcinoma. The most active agents for the other cancers have not been defined. Whether combination chemotherapy can improve survival in 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 of time. This slow growth rate in some cases may be one of the factors accounting for the poor response to chemotherapy. Studies of adjuvant chemotherapy in the disease have not been undertaken because of the small numbers of patients and relatively ineffective chemotherapy. Clearly, collaborative efforts by many investigators will be necessary before conclusions can be drawn concerning the use of chemotherapy for salivary gland cancers.

Melanomas of Head and Neck

Melanomas of the head and neck represent only about 2% of all melanomas. Nasal cavity and paranasal sinuses are the most common primary locations. Melanomas of this region are not usually separated from melanomas of other sites in cancer clinical trials. Whether talking about recurrent disease or combined modality therapy, conclusions often need to be drawn from studies based on various sites of melanoma. Several prognostic factors in addition to anatomic site determine outcome in melanoma. Level or depth of the lesion, type of melanotic lesion, and sex determine eventual relapse rate, and these should be stratification variables in all randomized studies of combined modality treatment. For patients with metastatic disease, the number of metastatic sites and location of metastases influence the clinical course (Balch et al, 1983).

Chemotherapy for recurrent disease

The site of metastatic disease will determine the treatment plan. Often the use of chemotherapy can be delayed. For example, a local recurrence may be treated with reexcision, intralesional bacille Calmette Guérin (BCG) vaccine, or isolated limb perfusion. Brain metastases are best treated with radiation therapy.

Dacarbazine (DTIC) is the most extensively studied single agent for melanoma and is the standard to which other agents should be compared. The overall response rate is 15% to 25%, and most are partial responses. Skin, lymph node, and pulmonary disease respond better than disease at other sites. A median duration of response has approached 1 year in some studies. The nitrosoureas, for example, lomustine (CCNU) or carmustine (BCNU), have defined activity in the 10% to 18% range. Other single agents with activity in melanoma are cisplatin and carboplatin (Evans et al, 1987).

Many combinations of drugs have been used. No combination, however, has been shown in a randomized trial to have a superior response rate to DTIC alone. Cisplatin-based combination chemotherapy has appeared promising in phase II pilot trials. Initial reports of cisplatin, vinblastine, and bleomycin indicated a 43% response rate. However, a large randomized trial showed no significant difference compared to DTIC (Luikart et al, 1984). Another promising regimen is DTIC, BCNU, cisplatin, and the antiestrogen tamoxifen (McClay et al, 1987). A 52% response was observed in 40 patients with metastatic melanoma. Tamoxifen appears to be a critical component of this regimen. Deleting tamoxifen resulted in a 20% response rate when studied by the same investigators. In vitro studies indicate that tamoxifen can modulate sensitivity to cisplatin although the exact mechanism is not understood (McClay et al, 1991).

Immunotherapy for recurrent disease

Through recombinant DNA technology interferons and interleukins have become available in large quantities for clinical testing. Type I interferons, specifically recombinant interferon-alpha, have been most extensively tested in metastatic melanoma. Responses occur in 10% to 20% of patients, are generally partial, and are of short duration. Skin, subcutaneous tissue, lymph nodes, and pulmonary metastases are the most responsive sites (Legha, 1989). Studies are ongoing to evaluate combinations of interferon with cytotoxic therapy and

interferon with interleukin-2; however, to date no improvement in response rate has been reported. The toxicity of interferons consists of flulike symptoms of fever, chills, headache, myalgias, and fatigue. Most of the side effects diminish as treatment progresses, however, fatigue can be severe and dose limiting.

Interleukin-2 and adoptive cellular therapy have perhaps the greatest potential for altering the course of this disease (Rosenberg et al, 1988). Laboratory and clinical investigations of this technology have been in progress since the early 1980s. This work stemmed from the observation that the rejection of established tumors was mediated by cellular immune responses. Rosenberg et al (1985) showed that high doses of interleukin-2 could induce regression of micrometastatic disease in liver and lung. When lymphocytes are incubated with interleukin-2 they acquire enhanced ability to lyse tumor cells. These lymphocyte-activated killer (LAK) cells could be expanded in vitro or in vivo under the influence of interleukin-2. Studies have been conducted at the National Cancer Institute Surgery Branch and by the Interleukin/LAK Working Group (ILWG) to determine response to high-dose interleukin-2 with and without LAK (McCabe et al, 1991). At the NCI Surgery Branch, Rosenberg (1991) observed no difference in response rates with 27% responding to IL-2 alone and 22% responding to IL2/LAK. There was a trend for a higher complete response rate and longer survival in patients receiving IL-2/LAK.

Although the overall response rate for metastatic melanoma to IL-2 or IL-2/LAK is low, durable remissions and prolonged survival are achieved in a small percentage of patients. This is in contrast to the results achievable with cytotoxic drugs reported to date. The toxicity of high-dose IL-2 or IL-2/LAK is severe and multisystem, requiring intensive supportive care in many patients. Treatment-related deaths range from 1% to 4% in reported series.

Cellular therapy with tumor-infiltrating lymphocytes (TILs) has also been under evaluation in melanoma patients where tumor is available for harvesting and in vitro culture (Topalian and Rosenberg, 1990). In murine models, TILs are 50 to 100 times more effective than LAK cells. In one protocol, TILs that have been expanded in vitro are infused with systemic administration of high-dose IL-2. The results in melanoma patients suggest higher response rates may be possible than with IL-2/LAK (Rosenberg, 1991).

Studies are continuing to develop improved adoptive immunotherapies. These include the introduction of genes that code for various cytokines into TIL cells. These gene transfer studies offer an exciting prospect for effective cancer therapies.

Unfortunately, for the practicing oncologist, none of the available cytotoxic or immunologic therapies (interferon) have demonstrated improvement in survival. Therefore no effective standard systemic therapy exists to treat metastatic melanoma. Patients should be referred to academic centers for participation in research studies.

Sarcomas of the Head and Neck

Sarcomas can originate from a wide variety of tissues in the head and neck region and include leiomyosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma, angiosarcoma, and osteogenic sarcoma. With the exception of rhabdomyosarcoma, the number of soft tissue sarcomas arising in the head and neck region is relatively small, and results of the use of

chemotherapy for these tumors usually include sarcomas in other sites. Generalizations often have to be made from data including all sites of sarcomas, rather than from head and neck sarcomas.

Soft tissue sarcomas

Recurrent disease

The chemotherapeutic agent that has been used most extensively for recurrent soft tissue sarcomas is dacarbazine (DTIC). In one early series the response rate was 17%, with the best responses seen in leiomyosarcoma (Gottlieb et al, 1976). Adriamycin soon became the most important agent in the management of sarcomas. In several series the response rate was approximately 30%, but most of these were partial responses (Blum, 1975). The alkylating agent ifosfamide has recently been identified as an active agent for the treatment of sarcomas. A 24% response rate was reported in a phase II trial in patients with metastatic disease refractory to other chemotherapy (Antman et al, 1989).

Combination chemotherapy may be superior in soft tissue sarcomas, although there are few randomized prospective trials comparing different regimens. Gottlieb (1974) used adriamycin and DTIC in combination for 200 patients, resulting in 22 complete responses and 63 partial responses for an overall response rate of 43%. The median duration of complete response was in excess of 12 months. Another widely used combination is CYVADIC (cyclophosphamide, vincristine, doxorubicin, and DTIC; Yel et al, 1980). Of 125 patients with soft tissue sarcomas, 50% achieved a response, with 17% complete responses. The median duration of response for complete responders was 9.5 months, and the median survival was 16 months. Significant toxicity, including neutropenia and vomiting, occurred.

The addition of ifosfamide with MESNA to adriamycin and DTIC (MAID regimen) is an effective new regimen. Elias et al (1989) reported a 47% overall response rate and 10% complete response rate in 105 patients. Myelosuppression, anorexia, and vomiting are the primary toxic effects of this regimen.

Three large multi-institutional comparative trials have been reported. The Eastern Cooperative Oncology Group (ECOG) compared two dosing schedules of adriamycin to the combination adriamycin + DTIC (Borden et al, 1987). The response rates were significantly inferior to the 30% response rate observed for adriamycin + DTIC ($p = 0.02$). However, time to treatment failure, complete response rate and survival were not different. Because there was no survival benefit for combination chemotherapy, ECOG conducted a follow-up trial comparing single-agent adriamycin to two combinations, ifosfamide + adriamycin and mitomycin + adriamycin + cisplatin (Edmonson et al, 1991). In a preliminary analysis, there was a significant improvement in response rate with ifosfamide + adriamycin compared to adriamycin alone but no significant difference in survival. The third randomized trial was conducted by the Southwest Oncology Group (Baker et al, 1987). Patients with metastatic soft tissue sarcoma received either adriamycin + DTIC or adriamycin + DTIC + cyclophosphamide or adriamycin + DTIC + actinomycin D. There was no significant difference in response rate, median duration of response, or survival among the three treatments.

In summary, combination chemotherapy, specifically adriamycin + DTIC and adriamycin + ifosfamide, achieves responses in approximately one third of patients compared to response rates of 18% to 20% for adriamycin used alone. However, there is no survival benefit. The MAID regimen appears to be more effective in pilot trials. Randomized comparisons need to be done to confirm its activity and to determine effects on survival.

Adjuvant chemotherapy

With the exception of rhabdomyosarcoma, studies of adjuvant chemotherapy for soft tissue sarcomas have included only chemotherapy following surgical resection and radiation therapy. Twelve randomized adjuvant trials in high-grade soft tissue sarcomas have been published with follow-up ranging from less than 2 years to over 10 years (Antman et al, 1990). Seven studies have compared single-agent adriamycin to observation, and five have tested combinations containing adriamycin. Only two of the trials show a significant survival advantage from adjuvant chemotherapy. Picci et al (1988) reported a 3-year actuarial survival of 68% vs 86% ($p < 0.05$) for high-grade extremity lesions either observed or treated with six cycles of adriamycin. Disease-free survival was also improved; however, median follow-up was only 28 months at the time of the report. In a small study (59 patients), investigators from the Foundation Bergonie in Bordeaux reported a 5-year actuarial survival of 83% vs 43% ($p = 0.002$), at a median follow-up of 40 months, for patients treated with the CYVADIC regimen or observation. An imbalance in extremity lesions and histologic findings in the two arms make this trial difficult to interpret (Antman et al, 1990).

In early reports, Rosenberg and colleagues (1983) at the National Cancer Institute observed a significant difference in survival after adriamycin, cyclophosphamide, and methotrexate chemotherapy for the subset of patients with extremity lesions. However, at 7.1 years of follow-up this difference is no longer apparent (Chang et al, 1988). In the subset of patients with trunk and head and neck primary soft tissue sarcomas there was a trend for a delay in the time to recurrence but there was no difference in survival.

In summary, to date, there is no convincing evidence that adjuvant chemotherapy is of benefit for any primary-site high-grade soft tissue sarcoma. Chemotherapy should only be used in the context of an investigational protocol.

Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft tissue sarcoma in children with an incidence of 0.2/100.000 children per year. Approximately 40% occur in head and neck sites. The most common location is the orbit, followed by the nasopharynx and paranasal sinuses (Feldman, 1982). The mode of spread is local extension, often with lymph node metastases. Distant metastases occur most commonly to the lungs, bone, and bone marrow.

The most favorable outcome occurs in those patients whose sarcoma can be totally resected and has a predominance of embryonal elements on histologic examination. Chemotherapy that includes vincristine, actinomycin D, and cyclophosphamide, given in an intermittent regiment concurrent with and following radiation therapy for a total of 2 years, has greatly enhanced curability.

The intergroup rhabdomyosarcoma study analyzed results from 202 patients with head and neck rhabdomyosarcomas (Sutow, 1982). Of this group 26% had primary lesions in the eye or orbit, 46% in parameningeal sites (middle ear, mastoid, ear canal, nasal cavity, paranasal sinuses, nasopharynx, and infratemporal fossa), and 28% in other head and neck sites. The majority of patients had microscopic residual disease following surgery, incomplete resection, or biopsy with gross residual disease. In only 5% was the sarcoma completely resected. Of the 103 patients who were rendered disease free, the relapse-free survival rate at 3 years was 91% for eye and orbit, 45% for parameningeal areas, and 75% for other head and neck sites. The less favorable results for patients with parameningeal primary sites occurred in part because of spread to the CNS with incomplete resection. It is now recommended that patients with parameningeal sites have CNS prophylaxis.

Osteogenic sarcoma

The most effective agents for the treatment of osteogenic sarcoma are methotrexate, adriamycin, cisplatin, and ifosfamide. Much of the early work on the use of very high doses of methotrexate (200 to 300 mg/kg) with the addition of leucovorin rescue was done in patients with osteogenic sarcoma (Jaffe, 1972). For patients with recurrent disease, the overall response rate was approximately 42%. Jaffe et al (1977) went on to demonstrate that high-dose methotrexate and leucovorin rescue preceded by vincristine could be given weekly in a very safe manner with response rates up to 74%. The role of methotrexate in the treatment of osteogenic sarcoma has been reviewed in detail (Grem et al, 1988). Adriamycin, cisplatin, and ifosfamide have response rates in the 20% to 30% range when tested in patients with metastatic disease.

Six percent of osteogenic sarcomas arise in the maxilla or mandible. They are more common in males than females and commonly occur between 20 and 40 years of age, with the median age in the fourth decade. Other features that distinguished these sarcomas from long bone osteogenic sarcomas are a lower metastatic rate (range of 6% to 51% in reported series) and a somewhat better 5-year survival rate of approximately 50% (Clark et al, 1983; Slootweg and Muller, 1985). These lesions can be either low or high grade. High-grade lesions have the potential for distant dissemination as well as local recurrence. Because wide surgical margins may not be feasible with jaw sarcomas, risk of local recurrence may be greater. This natural history would suggest the potential for benefit from a combined modality approach with preoperative chemotherapy or adjuvant chemotherapy, both of which have been shown effective with limb primary carcinomas (Eilber et al, 1987; Link et al, 1986). However, because these tumors are uncommon and may have a better prognosis, there are no data on the efficacy of chemotherapy used in this fashion for primary tumors of the mandible and maxilla.

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 (Fearon and Vogelstein, 1990). Chromosomal alterations and mutations of

specific oncogenes are associated with epithelial cancers (Harris et al, 1988; Wong, 1987). 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 may be useful as intermediate end points in future chemoprevention trials (Lippman et al, 1990a). 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 constant rate of 3% to 4% per year in these individuals (Cooper et al, 1989; Licciardello et al, 1989). The explanation for this risk if based on the concept of "field cancerization" first formulated in the 1950s (Slaughter et al, 1953; Strong et al, 1984). 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 (Boone et al, 1990). 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 regulate transcription of specific genes (Lotan, 1980; Wang et al, 1985).

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

The major limitation in the use of retinoids is the associated toxicity. Acute toxicity include dryness of conjunctival and oral mucous membranes, cheilitis, skin desquamation, hypertriglyceridemia, bone tenderness, arthralgias, and myalgias. Chronic toxicities include hepatotoxicity and bone remodeling (Heyne et al, 1991). These compounds are teratogenic, causing multiple malformations. Because of these toxicities, a number of retinoids have been synthesized. Four used clinically are vitamin A or retinol, beta-all-trans-retinoic acid or tretinoin, 13-cis retinoic acid or isotretinoin, and an aromatic ethyl ester derivative, etretinate (Heyne et al, 1991). In contrast to the retinoids, the major toxicity of the carotenoids is yellowing of the skin. Other compounds that may have utility in chemoprevention based mainly on in vitro and animal data are alpha-tocopherol (vitamin E), selenium, and N-acetylcysteine. The latter compound is a precursor of intracellular glutathione that enhances its antioxidant activity as a free radical scavenger. N-acetylcysteine is nontoxic and currently under investigation in Europe for the prevention of second malignancies in patients with a prior head and neck or lung carcinoma (Briggs and Forastiere, 1991; Heyne et al, 1991).

Studies with retinoid and carotenoids in patients with leukoplakia are listed in Table 6-8. Stitch et al (1988) reported two trials conducted in India and the Philippines in betel nut chewers. In one placebo controlled trial beta-carotene was compared to beta-carotene plus vitamin A. Complete response was observed in 3% of the placebo patients, in 15% of beta-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 series cytologic examinations. In a subsequent study patients were randomized to 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. In a small pilot study, Garewal et al (1990) observed a 71% complete and partial response rate in 24 patients treated with beta-carotene. There was no significant toxicity. The preliminary results of a fourth study (Toma et al, 1990) showed only a 27% response rate although the dose of beta-carotene was higher. Other investigators reported complete and partial response rates ranging from 60% to 100% with 13-cis retinoic acid (Koch, 1978; Shah et al, 1983).

These results led Hong et al (1986) to conduct a randomized placebo controlled trial of 13-cis retinoic acid (1 to 2 mg/kg/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 to the placebo group. Histologic reversal of dysplastic change was documented in 54%. Unfortunately, after stopping treatment the relapse rate was high within 2 to 3 months and the regimen was associated with considerable toxicity. In a successor trial (Lippman et al, 1990b) 56 patients received 13-cis retinoic acid (1.5 mg/kg/day) for 3 months followed by randomized to low-dose 13-cis retinoic acid (0.5 mg/kg/day) or beta-carotene maintenance therapy. Cis-retinoic acid proved superior in maintaining remissions and had an acceptable level of toxicity in this low dosage.

Most recently, Hong et al (1990) 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 radiation therapy. This placebo-controlled chemoprevention trial randomized 103 patients to receive high-dose 13-cis retinoic acid (50 to 100 mg/m^2/day) or placebo for 1 year. At a median follow-up of 32 months, second primary tumors had developed in 4% of those receiving retinoic acid compared to 24% of the placebo group ($p = 0.005$).

The results of this trial have led to the initiation of two multi-institutional confirmatory trials in the USA; two chemoprevention trials are in progress in Europe (Briggs and Forastiere, 1991). In the USA the North Central Cancer Treatment Group and the Eastern Cooperative Oncology Group are randomizing patients with stage I and II squamous cancers of the head and neck rendered disease free with surgery or radiation therapy to placebo or low-dose 13-cis retinoic acid (0.15 mg/kg/day) for 2 years. Patients must be randomized within 35 days of definitive local therapy. The MD Anderson Cancer Center will conduct a placebo-controlled trial for the same patient group. A higher dose of cis-retinoic acid will be tested, 30 mg/day, for the first year with dose reduction, if toxicity occurs, in years 2 and 3. Patients may enter the study if disease free between 16 weeks and 3 years after their primary treatment.

These trials along with those ongoing in Europe should establish both the benefits and risks of these particular retinoids in the prevention of second cancers in this patient population. Etritinate and isotretinoin (13-cis retinoic acid) are commercially available for other indications. Their use in patients with oral premalignant lesions or in patients with curatively treated early-stage head and neck cancer is not recommended outside an

investigational research trial. These agents are associated with considerable toxicity; moreover, the minimal effective dose and duration of treatment are not known. Less toxic retinoids or combinations of retinoids and carotenoids may prove to be more effective, but this can only be determined through carefully designed clinical and laboratory investigations.

Summary

Tumors of various histologic types occur in the head and neck. Excluding the thyroid, approximately 80% are squamous cell carcinomas. Data evaluating the impact of chemotherapy on survival, particularly for combined modality treatments are limited to this common histologic type where patient numbers are available for randomized comparative trials.

A number of effective cytotoxic agents have been identified in studies of patients with recurrent squamous cell carcinoma of the head and neck. There are now data indicating that combination chemotherapy does lead to improved response rates compared to treatment with single agents. A proportion of patients treated with these regimens may also achieve improvement in survival, although this needs to be confirmed. Prognostic factors have been identified that should be used by the physician to select patients most likely to be benefit from palliative treatment.

In the newly diagnosed patient with locally advanced disease, high response rates have been achieved with induction chemotherapy. Improved curability, however, has not been demonstrated. A more important role for chemotherapy may be to preserve organ function at selected sites. One randomized trial was successfully conducted to preserve laryngeal function. Chemotherapy concurrent with radiation therapy has improved local control and survival in selected series.

Chemotherapy for parotid cancers has been studied only for recurrent disease. Response rates are low, and impact on survival has not been demonstrated. For recurrent melanoma, chemotherapy is palliative in about 25% of patients. Immunotherapy is an exciting area of research that is promising for altering the natural history of this cancer.

The role of chemotherapy for sarcomas, with the exception of rhabdomyosarcoma, must be generalized from the results achieved at sites other than the head and neck. Multiagent chemotherapy is an important component of the primary management of rhabdomyosarcoma. However, for other soft tissue sarcomas and osteogenic sarcomas, chemotherapy is indicated only for recurrent and metastatic disease. Survival benefit from adjuvant chemotherapy for high-grade soft tissue sarcomas of any site and osteogenic sarcomas of the jaw has not been demonstrated. Treatment should be reserved for patients who can be enrolled in prospective randomized clinical trials.

Chemoprevention will 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 are in progress in the USA and Europe.

The management of head and neck cancer has become multidisciplinary. 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 and preserve organ function. Through well-designed and 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.