Paparella: Volume I: Basic Sciences and Related Disciplines

Section 6: Pharmacology

Chapter 29: Principles of Chemotherapy and Immunotherapy for Head and Neck Cancer

Reinhard W. von Roemeling, William J. M. Hrushesky

Cancer of the head and neck presents a profound continuing challenge in the optimal use of combined modality therapy, which requires the expertise of surgeons, radiotherapists, medical oncologists, prosthodontists, plastic surgeons, and pathologists.

Nearly 50.000 new cases of primary head and neck cancer will occur in the United States in 1990. Figure illustrates the sites of origin of these malignancies. As a group, head and neck cancer accounts for only 5 per cent of all malignancies in the United States. However, the pronounced cosmetic deformities and social stigma associated with these diseases increase their relative importance. Real and imagined disability or disfigurement and the loss of key physiologic functions such as swallowing, speech, and vision have prompted some desperate treatment approaches in order to control the disease or to achieve palliation, since there is no cure (McQuarrie, 1986).

Etiology of Head and Neck Cancer

In the majority of head and neck cancers there is no clear-cut etiology. Smoking and high ethanol intake (particularly the combination) are strikingly common in head and neck cancer patients and are implicated as etiologic factors. Poor oral hygiene is another important factor. Epstein-Barr virus is associated with nasopharyngeal carcinoma. Carcinomas of the nasal cavities have shown an increased incidence in furniture workers and are somehow related to wood dust inhalation (Hadfield and Macbeth, 1971). Chronic iron deficiencies are an etiologic factor in tongue and postcricoid carcinomas in women (Zagars and Norante, 1983).

Prognostic Factors

Many prognostic indicators have been used to predict the clinical course of squamous cell carcinoma of the head and the neck. These can be grouped into patient, tumor, and treatment factors. Patient factors include the age, sex, race, state of nutrition, and performance status. Tumor factors include the site of the primary cancer, the sites of the tumor, and the presence or absence of regional or distant metastases. Treatment factors, namely the response of a given cancer to surgery, radiation therapy, and chemotherapy, are of prognostic value and constitute major variables affecting patient survival.

Staging

Currently, the best prognostic indicator is the staging system developed by the American Joint Committee. This system is most helpful in determining the prognosis in stage 1 and stage IV cancers. Caution must be exercised in stage I cancers of the oral cavity, which

tend to be more threatening. The major need for careful prognostic indicators beyond simple staging is clearly evident in stage II and stage III cancers. Furthermore, information on tumor cell parameters (differentiation, nuclear pleomorphism, and mitoses) and tumor-host relationship (mode of invasion, stage of invasion, and cellular response) might help further subclassify different prognostic groups (Davis, 1985).

Histology

More than 90 per cent of primary head and neck malignancies resemble squamous cell carcinoma of various degrees of differentiation (Barnes, 1985). Because of the rarity of other cell types and because there are not interpretable data defining the optimal systemic treatment of these rare diseases, our discussion is predominantly restricted to epidermoid or squamous cell carcinomas. These epidermoid cell carcinomas are intrinsically less sensitive to chemotherapy than are other tumor types, such as malignant lymphoma or testicular cancers that are curable by chemotherapy alone. The degree of differentiation and the site of the primary tumor allow statistical predilection of the likelihood of response to chemotherapy and patient survival.

Multifocal Disease

Multiple primary neoplasia is common in patients with head and neck cancer; however, the true incidence is unknown and may be between 1.8 and 20 per cent (Lyons et al, 1986). Recent reports demonstrate a histologic shift toward nonsquamous lung carcinoma in patients with multiple primary neoplasia. These multiple lesions are probably related to chronic exposure to the same carcinogens.

Treatment Goals

The goals of treatment in head and neck oncology have been summarized as (1) eradication of cancer, (2) maintenance of adequate physiologic function, and (3) achievement of socially acceptable cosmesis. Treatment decisions are based mainly on an appraisal of the patient's tumor, but the patient also plays an important role. Emphasis is given to host factors such as age and general condition; co-morbidity such as extensive dental disease, premalignant mucosa, leukoplakia, erythroplasia, second primary cancer, or other significant diseases (eg, chronic obstructive pulmonary disease); and patient desires. Surgery and radiation therapy are the major curative modalities. Chemotherapy may be potentially effective as an adjuvant to these modes and may add to cure rates. The rationale for its potential values relates to local disease control, especially in advanced stages (T3 and 4, N2 and 3), and to the control of metastases.

Prognosis

Two of every three patients with this neoplasm present with disease not easily curable by surgery or radiation therapy. Although these local treatment modalities result in a cure in about 30 per cent of cases, they do not provide adequate tumor control for the majority of patients who present with advanced local, regional, or distant metastatic disease.

Head and neck cancers are most commonly fatal through local extension and invasion of nearby vital structures. Local recurrences occur following primary resection or irradiation in up to 60 per cent of these patients, and distant metastases develop in about 20 to 30 per cent, with malnutrition, infection, hemorrhage, and suffocation often causing serious side effects.

The Role of Chemotherapy

A number of antitumor drugs have been tested during the past several years. Initial research has focused upon the identification of effective single chemotherapeutic agents. The difficulty of this identification process must be understood. Recognizing that drug activity may not be accurately assessed in patients who have already endured extensive surgery, radiation therapy, or especially prior chemotherapy, this search is continuing. In a next step, which is also currently in process, drug combinations more effective than the best single agents must be identified. Non-cross-resistant drugs or drug combinations may be employed in alternating cycles. Administration of scheduled drugs needs to be varied until optimal dose intensity and the best therapeutic index are achieved. This includes a search for optimal circadian drug timing, a regulated sequence and interval between single drugs, and noncross multiagent cycles.

Randomized phase III comparisons of these regimens and schedules must be continued in order to demonstrate survival advantage in patients receiving different regimens.

Until recently, chemotherapy has been reserved for those patients with advanced or recurrent disease. Extensive prior surgery and radiation therapy and the patient's commonly poor performance and nutritional status each contributed to low tumor response rates and poor quality responses. These were most often of brief duration with little obvious benefit for the patient. The search for new chemotherapeutic agents and the development of effective drug combinations have been the objectives of many recent clinical trials. These drug combinations have been traditionally tested initially in patients with primarily inoperable, relapsing, or metastatic disease. More recently, these approaches have been used in patients with lower-staged head and neck cancer receiving multimodality treatment. This "neoadjuvant" chemotherapy is given prior to "definite local treatment" with radiation therapy and/or surgery and/or subsequent additional adjuvant chemotherapy.

Single-Agent Chemotherapy

Among the most active and thoroughly evaluated of the currently noninvestigational cytotoxic agents are methotrexate, cisplatin, bleomycin, and 5-fluorouracil. Several other single agents have been found to have such activities in broad phase-II tumor trials that usually result in treatment of small numbers of a variety of different malignancies. The precise activity of these agents remains to be defined.

Methotrexate

Methotrexate (MTX) has most commonly been given either weekly, bi-weekly, or monthly. It can be administered by intravenous (IV), intramuscular (IM), and oral (PO) routes. The oral route has not been employed extensively in patients with head and neck cancer.

Concurrent chemotherapy with other agents that are toxic to the gut may make absorption erratic.

One theoretic approach to increase the therapeutic index of MTX has been its administration at higher, actually lethal, doses from 60 mg/m^2 up to 30 gm/m^2 and more together with subsequent "rescue" doses of leucovorin (folinic acid). MTX is a competitive inhibitor of the essential enzyme dihydrofolate reductase. This enzyme normally catalyzes the reduction of folates to dihydro and tetrahydro forms that are required for DNA synthesis. Leucovorin, which is the formyl derivative and active form of folic acid, supplies the product of the inhibited reaction and thereby prevents the major effect of MTX.

Dose-limiting toxicities of standard-dose MTX at 40 to 60 mg/m^2 are stomatitis and myelosuppression with neutropenia, thrombocytopenia, and megaloblastic anemia. In addition, there is possible accentuation of toxicity secondary to impairment of renal function. With the use of very high doses, the drug can actually precipitate in the kidney tubules, causing kidney damage, prolonged excretion, and resultant increased systemic toxicity. This can usually be avoided by ensuring adequate hydration and alkalization of the patient's urine. However, if MTX is combined with another highly nephrotoxic drug like cisplatin, renal toxicity may become dose limiting. Caution is also warranted in patients with effusions, since the drug is retained in third spaces.

There are indications from animal experiments that MTX toxicity is dependent on the circadian stage of its administration. The time of day associated with best tolerance for this drug is probably early morning for diurnally active patients, at the time of their highest cortisol serum levels (English et al, 1984).

Representative Studies

In a Southwest Oncology Group study reported by Grose and co-workers (1985), MTX was given at a dose of 16 mg/m^2 IM daily for three consecutive days, repeated at 3-week intervals, to 50 patients with advanced, inoperable squamous cell carcinoma. MTX produced a complete response rate of only 16 per cent, with an 18-week median duration of response. The corresponding median survival was 20 weeks. Good pretreatment performance status had a significantly positive effect on survival, but prior therapy did not. There was a single MTX-related death from pneumonia with secondary-to-severe leukopenia. Another leading toxicity was mild to moderate stomatitis.

DeConti and Schoenfeld (1981) treated 81 patients with recurrent squamous cell cancers, at stages III and IV, with MTX IV weekly at an initial dose of 40 mg/m^2, which was increased to 60 mg/m^2 if no significant leukopenia or mucositis occurred. These patients were compared with 80 patients receiving MTX at a dose of 240 mg/m^2 every 2 weeks, followed by leucovorin, 25 mg PO 42 hours later and then every 6 hours, for a total of eight doses. Complete plus partial objective responses were achieved in 26 and 24 per cent, respectively. Methotrexate alone produced a median duration of response of 105 days compared with 42 days following the high-dose MTX leucovorin regimen. Weekly administration of MTX alone resulted in significantly more skin and mucosal toxicity than higher doses of the combination of MTX and leucovorin. Moderate hematologic toxicity was observed in about 15 per cent of the cases in both regimens. A 5 per cent drug-related fatality rate resulted from profound

myelosuppression, dehydration, and shock following severe vomiting and marked azotemia. This study failed to support and improved therapeutic index for high-dose MTX with leucovorin rescue.

In summary, MTX is an active agent in squamous cancer of the head and neck. No dose response relationship has been described. Objective response rates of 16 to 33 per cent have been of short duration. Most of these responses have been only partial; complete responses are rare, and survival has remained poor. Weekly or bi-weekly MTX administration may be superior to monthly administration. Other schedules that have proved activity include infusions over 24 hours at 1 to 3 mg/kg, followed by leucovorin rescue, if higher doses are used. Well-controlled drug sequencing studies and studies of optimal circadian drug timing remain to be done.

Cisplatin

Cisplatin (CP) has been the subject of numerous investigations in patients with head and neck cancer. Of the several platinum compounds tested in experimental tumor systems, CP has been found to have, by far, the greatest antitumor activity. The precise mechanisms of action are not known but are shown in some systems to cause DNA intra- and interstrand crosslinks (Lippard, 1984). A relatively large percentage of an intravenous dose is bound to plasma proteins. The reversibility of this binding has not been well studied. Free (unbound) CP is said to be primarily responsible for its anticancer activity.

Hecquet and associates (1985) have described time dependency of the plasma protein binding of CP. Circulating levels of free CP were lower when the drug was injected during the afternoon or evening hours in diurnally active patients. This supports the experimental and clinical observations of Hrushesky (1984) that circadian timing of CP reduces its toxicity substantially without adversely affecting the drug's anticancer activity. A safe time of day for its administration is early evening (around 6 pm).

CP has little hematologic toxicity aside from a rather profound and long-lasting progressive multifactorial anemia. This anemia results from (1) a relative erythropoietic deficiency, (2) primary erythroid precursor suppression, and (3) a slightly shortened red blood cell survival time (Wood and Hrushesky, 1984). The major problems associated with CP are nausea and vomiting, nephrotoxicity, and neurotoxicity, including ototoxicity. Prehydration minimizes renal toxicity without compromising CP antitumor activity. In addition, concurrent mannitol diuresis, hypertonic salt solutions, and a variety of "rescue" agents have been introduced in order to reduce renal toxicity. Diethyldithiocarbamate (DDTC) is one of those rescue substances that has been used together with high-dose CP; it may protect tubular enzymes in the kidney (Borch et al, 1984) and act as an immunorestorative drug (Newman et al, 1986). However, since DDTC may chelate CP, it could interfere with the drug's antitumor activity. Therefore, it is usually given 1 to 2 hours after CP. This may not be the case concurrent with oral disulfiram, a DDTC-dimer (Roemeling et al, 1986a), which also exerts renal protection without interfering with CP-induced anticancer activity.

Representative Studies

In a recent study by Veronesi and colleagues (1985), high-dose CP at 120 mg/m^2 was compared with low-dose CP at 60 mg/m^2 in a randomized trial, given to 62 patients as short-term infusion over 30 to 45 minutes every 3 weeks, together with hydration and mannitol diuresis. Response rates for both high-dose and low-dose CP were 16.1 and 17.8 per cent, respectively. Survival was superimposable in the two treatment arms. There was no evidence for a dose response relationship. Since this lack of dose response is unusual for this particular agent (Hryniuk and Levine, 1986), the low response rates may be explained by patient selection. A number of Veronesi's patients had previously failed other types of chemotherapy. Another unfavorable factor was the exclusion of the patients eligible for intra-arterial chemotherapy who may represent a group with more favorable reaction to chemotherapy. In any event, primary tumor size did not influence response in this study.

In a later study by the Northern California Oncology Group (Jacobs et al, 1983), CP at a dose of 80 mg/m^2 IV every three weeks was compared with CP plus weekly administration of MTX at 200 mg/m^2 with leucovorin rescue. The overall response rate for CP was 18 per cent versus 33 per cent for the combination therapy (10 per cent versus 18 per cent complete responses). There was no difference in response duration, time to progression, or survival rates between the two regimens.

Frustaci and associates (1986) gave CP in the form of *intra-arterial* continuous infusion to untreated patients with head and neck cancer. Twenty mg of CP was infused per 24 hours for 5 to 10 days via an external infusion pump. After a rest period of 5 to 7 days, treatment was restarted with the same schedule until a cumulative CP dose of 400 mg or significant dose-limiting toxicity was reached. Response was evaluated in patients who received a total dose of at least 200 mg of CP. Of 41 evaluable patients, 19.5 per cent obtained a complete response and 48.8 per cent obtained a partial response. The most frequent grade 1 and 2 drug-related toxicities were anemia, transient renal impairment, and nausea and vomiting, whereas grade 3 toxicities were observed in 5 of 43 patients. Catheter-related toxicity accounted for five central nervous system complications (including transient motor weakness, hemiparesis, and embolism) and six local problems (including clotting around the catheter, catheter displacement, and drug extravasation). This treatment seemed to be effective, especially in lower-staged head and neck cancers.

In summary, CP is active in head and neck cancer, with response rates for single-agent IV bolus therapy in the range between 16 and 18 per cent in recurrent head and neck cancer. Twice the response rates may be expected in patients with good performance status who have received no previous chemotherapy or irradiation. No clear dose-response relationship has been shown, but these studies are far from being definitive. Improved response rates have been found in selected groups of patients receiving high concentrations of CP infused intra-arterially to the tumor site. Convincing evidence for the survival advantage of single-agent CP chemotherapy is lacking.

Bleomycin

In 1966, bleomycin (BLM) was discovered by Umezawa (1976). The clinical formulation is a mixture of cytotoxic glycopeptides (major compounds are A2 and B2 bleomycins), which are natural products of *Streptomyces verticillus.* Tumors with a large fraction of resting cells and hypoxic cells are less sensitive than dividing or well-oxygenated cells. The amount of selective drug uptake by malignant target cells is low; the mechanism of drug uptake is unknown. The major mechanism of resistance is thought to be an increase in the level of a cytosolic catabolic enzyme (a bleomycin hydrolase). This enzyme is lacking in normal skin and lung, making these organs most susceptible to BLM-induced damage.

The major toxicity of BLM therapy is interstitial pneumonitis that may progress to pulmonary fibrosis, which is clinically evident in 10 per cent of the patients who receive a cumulative dose of 200 to 250 mg/m^2 (Carter, 1985; Wiemann and Calabresi, 1985). This toxicity can be lethal. The incidence and severity of this toxic effect are related to both the acute dose and the cumulative dose. Exacerbation is caused by high concentrations of inspired oxygen and by radiation to the lungs. BLM hypersensitivity reactions can occur less frequently. The picture of rapidly progressive hypoxia and interstitial fibrosis cannot reliably be stemmed by the administration of corticosteroids. Immediate cessation of the drug is mandatory. Various skin changes such as hyperpigmentation and erythema have been described. The incidence and the severity of all toxicities increase with cumulative doses of the drug. Mucositis is frequent, especially in combination with other cytotoxic agents (MTX, radiation therapy); BLM-induced mucositis is additive (sequential applications are strongly recommended).

Minor toxicities include slight nausea and alopecia. Important for combination chemotherapy is BLM's relative lack of bone marrow toxicity. Fever to 38.9°C (102°F) without chill is a common, almost universal, side effect of BLM treatment and can last for up to 2 days after its administration.

Various administration routes and schedules have been tried, including IV, IM, and subcutaneous (SC) injections and continuous infusion. In animal models, there is clear evidence that continuous infusion is less toxic and more effective than bolus injection (Peng et al, 1980). The toxicity of continuous infusion seems to be qualitatively and quantitatively similar to that of bolus injection; however, no direct comparison from randomized trials is available (Krakoff et al, 1977). In patients with recurrent head and neck cancer, single-agent BLM therapy produces objective (mainly partial) responses in 15 to 31 per cent of the cases, and the response duration is usually short (2 to 3 months)(Blum et al, 1973; Carter, 1985; Ichikawa, 1976).

BLM has been used together with MTX, CP, and other agents, with or without concurrent radiation therapy. Improvement in local regional control of the disease has been established in many clinical trials; however, only a single positive study has demonstrated survival advantage (Shanta and Krishnamurthi, 1976). The most effective dose and schedule have not yet been established. The safest and most effective time of day for the administration of BLM is currently not known.

5-Fluorouracil (FU)

5-Fluorouracil (FU) and the closely related 5-fluoro-2'-deoxyuridine (FUDR) act as antimetabolites after activation to fluorodeoxyuridine monophosphate (FdUMP) and fluorodeoxyuridine diphosphate (FUDP). FdUMP blocks thymidylate-synthetase and interferes with DNA synthesis by starving the process of the necessary thymidine. Both folinic acid and MTX are able to enhance this enzyme blockage. Secondly, fluoro-deoxyuridine triphosphate (FUTP) competes with uridine triphosphate and thus interferes with RNA and protein synthesis. FU and FUDR both have very short plasma half-lives and are predominantly metabolized and cleared by the liver.

There is an important circadian rhythm in drug toxicity. Administration during the late activity and early rest phase of diurnally active patients reduces toxicity by at least 50 per cent, regardless of route or mode of drug administration (Roemeling et al, 1986b). Dose-limiting toxicities of bolus injection are hematotoxicity and mucositis; mild nausea is frequent. Toxicity of continuous infusion is qualitatively and quantitatively different. Less hematotoxicity but more gastrointestinal toxicity is observed, which becomes dose limiting. There are also epidermal changes including the "hand-foot syndrome", which is a painful skin reaction that occurs secondary to long-term fluorodeoxyuridine therapy.

A recent retrospective analysis by Tapazoglou and associates (1986) has focused on the efficacy of continuous FU IV infusion over 96 to 120 hours at a dose of 1000 mg/m^2/24 h. The rationale for continuous FU infusion is a prolonged exposure time of the tumor to the drug and the avoidance of toxicity accompanied with peak drug levels. Eight of eleven patients (72 per cent) responded to this therapy, which was accomplished by stomatitis and leukopenia in 55 and 18 per cent, respectively.

The use of a single-agent FU bolus given weekly or daily on 4 to 5 consecutive days every 4 weeks has produced a 15 to 30 per cent overall response rate in advanced or recurrent head and neck cancer patients (Amer et al, 1979). However, data for therapy with standard-dose FU bolus injection (10-15 mg/kg) are scanty. Continuous infusion mode is probably more effective than bolus injection. This is especially relevant because of the availability of programmable infusion pumps (implantable, wearable, or bedside drug-delivery devices) for automatic long-term infusions.

FU is used most frequently in combination therapy or as a single agent in intra-arterial infusion programs.

Other Cytotoxic Substances

Doxorubicin (Adriamycin) is an antitumor anthracycline antibiotic with a broad spectrum of activity. It is moderately water soluble and stable in solution (Ausman et al, 1986). The time of day at which anthracycline drugs are given determines their therapeutic index (Hrushesky, 1985). Circadian stage-dependent toxicity stems from the time of day the drug is given, varying bone marrow suppression, mucositis, gastrointestinal irritation, alopecia and, most importantly, from myocardial damage. The dose-limiting cardiotoxicity results in congestive heart failure in about 1 of 10 patients after cumulative doses of more than 500 mg/m^2. Split doses or continuous infusion are probably equally effective but are less

cardiotoxic (Legha et al, 1982; Weiss and Mathel, 1977). This drug and other anthracycline analogues have not been adequately tested in squamous cell head and neck cancer. Cobleigh and associates (1985) administered doxorubicin as bolus injections of 60 mg/m^2 IV every 3 weeks to 20 previously untreated patients with stage IV cancers. In 18 evaluable patients, a 44 per cent overall response rate was found with one complete response. This study did not address response duration or rate of survival. Doxorubicin may also have significant activity in head and neck cancer cell types other than squamous cell cancer (eg, in tumors arising from salivary glands)(Eisenberger, 1985).

Magee and co-workers (1985) tested 4, epi-doxorubicin in 31 patients. In 25 patients with squamous cell carcinoma, antitumor activity was very limited. However, activity was observed in two of three patients with minor salivary gland carcinoma.

A number of otherwise widely used anticancer drugs have limited activity in head and neck cancer and are not or are only occasionally included in more recent chemotherapy protocols. This is the case for alkylating agents such as cyclophosphamide (Harrison et al, 1963; Livingston and Carter, 1970), hydroxyurea (Bloedan, 1964), vinca alkaloids (Eisenberger et al, 1984; O'Connor et al, 1982; Smart et al, 1964), and procarbazine (Carter and Livingston, 1982).

Negative trials have recently been reported for a number of investigational drugs, including aclarubicin (Carugati et al, 1986), misonidazole (NSC number 261037)(Davila et al, 1985), mitoguazone (Luedke et al, 1986), diaziquone (Kish et al, 1986), Baker's antifol (Krasnow, 1986), and mitolactol (McHale, 1986). Drugs with minimal activity include amsacrine, bisantrene, dianhydrogalactitol, etoposide (VP-16), PALA, ftorafur, pyrazofurin, maytansine, thioprolin, and ICRF 159 (Eisenberger et al, 1984; Rozencweig et al, 1977).

It is noteworthy that the CP compound iproplatin (CHIP, JM-9) had no antitumor activity in squamous cell cancer of the head and neck (Abele et al, 1986), whereas the combination of carboplatin and FU resulted in an objective response rate of 44 per cent with one-third having complete responses (Forastiere et al, 1986). Although the parent compound CP has been established as an active drug, the therapeutic role of carboplatin remains uncertain. Carboplatin was introduced because of its lack of renal toxicity. Of course, the antitumor activity observed in this uncontrolled study may be secondary to FU.

Among numerous investigational drugs evaluated in advanced head and neck cancer, only three other compounds have induced a response in more than 10 per cent of patients treated. These include methyl-G, vindesine, and dibromodulcitol (Eisenberger et al, 1984).

The development of new drugs has not recently resulted in any breakthroughs in the systemic control of head and neck cancer (Bertino, 1982). The latest new drugs have not represented any significant improvements, even if given at an earlier treatment phase or in combination with established agents such as CP.

Single-Agent Chemotherapy Versus Drug Combination

Several authors have compared single-agent MTX therapy in head and neck cancer with other single agents or with combination chemotherapy in prospective randomized studies.

DeConti and Schoenefeld (1981) compared therapy using single-agent MTX with therapy using MTX/leucovorin plus cyclophosphamide plus cytosine-arabinoside (Ara-C). Combination chemotherapy did not improve the therapeutic index over that with single-agent MTX alone.

Hong and Bromer (1983) studied 20 patients with recurrent cancer who received MTX weekly at 40 to 60 mg/m^2 IV, and 22 patients who received CP at a dose of 50 mg/m^2 as a 6-hour infusion on days 1 and 8 every 4 weeks. Objective responses were achieved in 23.5 per cent of patients following MTX and in 28.6 per cent following CP. The median duration of response was 84 days versus 92 days, and the median survival of patients was 6.1 months versus 6.3 months. Significant mucositis occurred in 38 per cent of the patients receiving MTX, and gastrointestinal and renal toxicity was prominent in the group treated with CP.

Drelichman and associates (1983) reported results in 51 patients with recurrent head and neck cancer after the administration of single-agent MTX at a dose of 40 mg/m^2 IV weekly versus a combination of CP (100 mg/m^2 IV on days 1, 22, and 43), vincristine (1 mL IV on days 1 and 5) and bleomycin (30 units as continuous infusion for 4 days, starting 24 hours after administration of CP). The overall response rate was 33.3 per cent for patients treated with the combination therapy. The difference was not significant, nor was the survival of patients. Nausea and vomiting were more common side effects of the combination therapy, whereas hematologic toxicity was more frequent and more severe in the MTX segment (75 per cent).

Vogl and co-workers (1985) gave a similar MTX regimen (40 to 60 mg/m^2 IV weekly) versus a combination of MTX, bleomycin, and CP to 163 patients with recurrent or metastatic disease. In this combination, MTX was given at a dose of 40 mg/m^2 IM on days 1 and 15, BLM at 10 units IM on days 1, 8, and 15, and CP at 50 mg/m^2 IV on day 4. Courses were repeated every 21 days. The combination produced an objective response in 48 per cent of patients versus 35 per cent after MTX, with 16 per cent of patients in complete remission versus 8 per cent, respectively. Toxicity was similar in the two groups. The median survival rate was 5.6 months in each group, indicating that the addition of BLM and CP to MTX did not have a major impact on the course of far-advanced head and neck cancer.

Williams and colleagues (1986) treated 191 evaluable patients with recurrent or metastatic squamous cell carcinoma with either weekly MTX at 45 mg/m^2 IV with escalation to 60 mg/m^2 IV at week 5 in the absence of significant toxicity, or with a combination of CP, vinblastine, and BLM (CP, 60 mg/m^2 IV on day 1; vinblastine, 0.1 mL/kg on days 1 and 15; and BLM, 15 units IV weekly, repeated monthly). MTX induced responses in 16 of 989 patients (16 per cent), whereas 22 of 92 (24 per cent) responded to the combination. Remission duration was similar in both segments of the study, as was average survival at 30 weeks. MTX produced more mucositis, and the combination therapy produced more gastrointestinal and renal toxicity. However, antitumor activity was not significantly different in either case.

These randomized trials failed to show a statistically significant advantage with the use of combination therapy. However, a persistent trend points to more and longer-lasting responses following combination therapy. Current studies show an improvement of chemotherapy combination schedules (continuous infusion versus bolus-injection, drug intensity), which might eventually improve treatment results.

Combination Chemotherapy

CP and FU

In a number of recent reports, authors have investigated the effect of CP and FU combinations.

In an Eastern Cooperative Oncology Group pilot study reported by Rowland and co-workers (1986), 34 patients with recurrent cancer were treated with CP bolus and continuous infusion of FU every 3 to 4 weeks. All but one patient had failed prior radiation therapy or surgery; 27 had failed both. Among 30 evaluable patients with squamous cell carcinoma, five achieved a complete response and 13 achieved partial responses. Durations of response for patients with a complete response or a partial response were 10.4 and 3.1 months, respectively. The median time to disease progression for all patients was 4.5 months, and the median survival rate was 9.1 months. Toxicity was moderate with 7 patients having grade 3 mucositis, and 11 patients having grade 3 to 4 hematologic toxicity. One treatment-related death was due to nephrotoxicity.

In an earlier study, an almost identical therapy was given to 30 patients with recurrent disease (Kish et al, 1984). The overall response rate was 61 per cent; 27 per cent of patients obtained a complete response and 34 per cent had partial responses. Response and survival rates were better in patients with recurrent and local disease without distant metastases, versus disseminated disease, and in patients with good performance status compared with those with poor performance status. The overall median survival was 6.8 months. A lower incidence of mucositis was observed as compared with the 5-day FU-infusion regimen mentioned above; the remaining toxicity types were comparable.

The same two-drug combination of CP and FU was given by Merlano and co-workers (1985) in a different mode of administration: CP, IV bolus days 1 to 5; and FU, IV bolus days 1 to 5, repeated every 21 days. All but 2 of 30 patients had a relapse. Of 27 evaluable patients, four had complete responses and 12 had partial responses (objective response rate, 59.2 per cent). The median survival rate was 7 months; toxicity was due to myelosuppression, whereas other toxicities were rare.

Rooney et al (1985) compared the effectiveness of 96-hour FU infusion plus CP (two courses). A total of 164 consecutive patients were enrolled in these three separate pilot studies (no randomized assignment to one treatment modality). All patients were previously untreated and suffered from advanced, inoperable epidermoid head and neck cancer but had no distant metastases. The numbers of patients in the three studies were unequal but the groups were prognostically comparable. Seventy-seven patients received COB, 26 received the 96-hour FU regimen, and 61 received the 120-hour FU regimen. Overall response rates to each of the three induction regimens were very high at 80, 88, and 93 per cent, respectively. A superior

complete response rate was observed in the group receiving three courses of 120-hour FU infusion plus CP, with 54 per cent versus 29 per cent for the COB and 19 per cent for two courses of 96-hour 5-FU infusion plus CP. There was also a significant survival advantage at 18-month minimum follow-up for the group receiving the longer term FU infusion. As expected, toxicity (hematotoxicity, renal toxicity) was more severe for the higher intensity FU and CP regimen. As patients were further randomized to receive surgery plus radiation or radiation therapy alone, survival could not be exclusively related to the initial treatment.

Amrein and Weitzman (1985) studied 24-hour infusion of CP plus FU, 800 mg/m^2/24 hour, over 5 days. Among the 31 *untreated* patients, 7 had complete response and 19 had partial responses, producing an overall response rate of 84 per cent. In a group of 30 patients with *recurrent* disease after surgery or radiotherapy, or both, receiving the same regimen, there were 5 complete responses and 10 partial responses (50 per cent total response rate). Among an additional 9 patients who had failed prior chemotherapy, there were 2 complete responses and 1 partial response (33 per cent response rate). Performance status and stage had little bearing on response frequency. Projected survival for the group without prior treatment was 59 per cent at 22 months versus 9 months for the group with recurrent cancer. Toxicity was mild.

The combination of CP and FU was also tested in a randomized study reported by Kish and associates (1985). Two different schedules were compared: CP bolus plus FU continuous infusion, days 1-4, versus CP bolus, day 1, plus FU bolus, days 1 and 8. Thirty-eight patients were evaluable for three induction courses. Response for the infusion arm was 72 per cent, with 4 complete responses and 9 partial responses in 18 patients. Response for the segment treated by bolus was 20 per cent (2 complete responses and 2 partial responses in 20 patients). Hematotoxicity was severe in the bolus-treated segment; the infusion-treated segment had a greater incidence of generally mild and reversible stomatitis. The median survival rate was 6.8 months for the infusion-treated segment versus 5 months for the bolus-treated segment. However, Choksi and associates (1986) were not able to reproduce the impressive response rates in the CP bolus and FU infusion segment in Kish's study. When they applied CP as a 24-hour infusion and FU as a 120-hour infusion, results were only 10 per cent and 15 per cent for complete and partial responses, respectively.

Results for the same drug combination differ substantially, depending on the treatment schedule and the patient selection.

Other Drug Combinations

Browman and co-workers (1986) tested the combination of MTX and FU in a randomized study comparing concurrent versus sequential administration of drugs. The survival rate was 22 months for untreated and 14 months for recurrent disease patients. In the 79 patients studied, no difference could be detected in the survival rates between simultaneous and sequential chemotherapy.

Vogl and colleagues (1986) reported results of a single-arm study with a four-drug combination of sequential MTX, FU, BLM, and CP. The response rate was 75 per cent for patients with regional disease without prior radiation therapy (only partial responses), and 41 per cent for recurrent or metastatic disease. The median survival rate was short, even for

previously untreated patients.

CP, BLM, and sequential MTX, FU, and leucovorin were used in a study reported by Panasci and associates (1985). In 30 patients with recurrent disease, the objective response rate was only 33 per cent, with a brief duration of response and a median rate of survival of 6 months in responders and 4 months in nonresponders.

CP, BLM, MTX, and leucovorin were used by Weichselbaum and colleagues (1985). This combination was tested as a form of induction chemotherapy for patients with untreated advanced disease. After two courses, the complete response rate was 26 per cent and the partial response rate was 52 per cent in 109 evaluable patients. Myelosuppression and nephrotoxicity were dose limiting in only a few patients. Patient age, performance status, histologic grade of tumor, and tumor size did not predict response to chemotherapy in this study. The size of the tumor after induction therapy was strongly correlated with local control. Local and regional recurrences after a complete response to induction chemotherapy and subsequent definitive surgery or radiotherapy, or both, were uncommon, occurring in only 14 per cent of the patients. None of these 22 patients developed distant metastases.

Price and Hill (1986) analyzed 7-year survival statistics in 175 untreated patients with stage III and IV cancers but without metastatic lesions. They used a four-drug combination of vincristine, MTX with leucovorin rescue, BLM, and FU as the initial treatment (a non-CP-containing regimen). Response to chemotherapy was a good prognostic sign for patients with nasopharyngeal tumors, was less of an indicator for those with oral cavity lesions, and held little significance for those with laryngeal tumors. Patients with nasopharyngeal and laryngeal tumors had the best rate of survival, whereas patients with hypopharyngeal, oropharyngeal, or oral cavity lesions had the poorest rates. Improved survival rates were noted for lower stage disease and for patients younger than 49 years of age. However, response to chemotherapy was a good prognostic sign, regardless of tumor stage.

Clark and co-workers (1986) compared two types of induction regimens for untreated, advanced disease. CP bolus and FU infusion was compared with CP, BLM infusion, and MTX bolus with leucovorin rescue. Partial responders after two treatment courses had additional benefits from continuation of either of the chemotherapy regimens, which were both comparable for response and toxicity, except for severe interstitial pulmonary disease in 3 of 28 patients receiving BLM infusion.

Another two-drug combination was claimed to be superior to CP and FU in a small randomized study. In 18 patients, 7 had complete responses (35 per cent), with an overall objective response rate of 89 per cent (Gonzalez et al, 1986).

Spaulding and associates (1986) compared a two-induction regimen prior to surgery: CP bolus, vincristine bolus, and BLM-infusion versus CP bolus, vinblastine infusion, and FU infusion. The BLM-containing regimen yielded a 24 per cent complete response rate and better long-term disease control. However, the overall response rate of about 80 per cent was similar for both regimens.

Ensley and colleagues (1986) used the combination of CP bolus and FU 120-hour continuous infusion, alternating with MTX, FU bolus, and leucovorin rescue. In 20 patients

with advanced, untreated tumors, with histologic confirmation in 67 per cent during subsequent surgery. Preliminary results after 5 months of treatment revealed a high complete clinical response rate of 85 per cent.

In summary, recent complex multidrug combination have resulted in response rates two to four times as high as those achieved with single-agent combination. Optimal drug combinations and drug timing are being defined (Lane et al, 1985; Hrushesky, von Roemeling, and Sothern, 1989). It should be possible to translate 80 per cent response rates into survival advantage. In any event, a complete response to many of these combinations definitely improves a patient's quality of life. This is a desirable goal, even in the absence of survival advantage.

Intra-Arterial Therapy

The possibility of intra-arterial chemotherapy infusion was mentioned earlier. The objective is to deliver the highest possible drug doses to the tumor area with a maximum local effect but with minimal systemic toxicity. Only a few reports are available. Milazzo and co-workers (1985) used a combination of CP, vinblastine, BLM, and FU. All drugs were given as continuous infusion. In 12 patients, the overall response rate was 67 per cent, with only 8 per cent having complete responses. This relatively low rate of complete responses is disappointing and does not support the concept of an obvious dose-response relationship. In addition, there was substantial local toxicity, requiring the shortening of therapy courses in 9 of 12 patients. The advantage of this arterial infusion approach was seen in reduced systemic toxicity and shorter treatment periods necessary for response induction as compared with systemic chemotherapy; however, additional surgery for pump and catheter placement is required and adds to the overall complication rate. This treatment is possible in only a small group of selected patients.

In most of the patients treated with intra-arterial chemotherapy, high anticancer drug concentrations are achieved in the tumor-bearing areas with little systemic shunt (Wheeler et al, 1986). Neurologic complications are probably less frequent than expected (Baker et al, 1985), but pump or catheter-related failures plus infection, hemorrhage, skin necrosis, thrombosis, embolism, and shunting of highly concentrated drug to the internal carotid circulation have to be considered. Intra-arterial therapy is technically feasible and may be effective if the right drug is chosen. CP seems to be more active than MTX or BLM, although resulting fibrosis may add to the complication rate (Taylor, 1984). The fact that the brain and eyes are fed by nearby or even the same arteries that are cannulated for intra-arterial chemotherapy obviously limits the usefulness of this approach.

Combination of Chemotherapy and Radiation Therapy as Induction Treatment

In patients with locally advanced cancer without distant metastases, preoperative chemotherapy and radiation are used to reduce the tumor burden to make the extent of the subsequent operative procedure as small as feasibly possible. This process can help save functional anatomic structures without the increased risk of relapse. Although chemotherapy may also destroy micrometastases locally or distally, the addition of radiotherapy is thought to improve local control by eradicating cells that have survived chemotherapy.

Chemotherapy and radiation have been used simultaneously as well as sequentially. When given in sequence, there were sandwich-type designs of therapy with chemotherapy, radiation therapy, surgery, and more chemotherapy, or alternating short courses of chemotherapy and radiation therapy.

In a study reported by Slotman and associates (1986), CP was administered synchronously with radiation therapy. The rationale for this application is a possible radiosensitizing effect and increased recruitment of dormant cells. Seventy-two per cent of patients had complete responses, which were obtained in 18 primary tumors following two courses of CP at 20 mg/m^2/day IV bolus on days 1 to 4 and 21 to 24 plus 4.500 rad external beam radiation given at 180 rad daily fractions over a 5-week period. When patients underwent curative surgery following the combination of chemotherapy and radiation therapy, complete pathologic responses were confirmed in 50 per cent, as compared with a 72 per cent complete clinical response rate. The morbidity of the surgical procedure was low in spite of the pretreatment phase, but significant survival advantage was not documented.

Similar results have been reported by Zerillo and colleagues (1986), again in a small group of 16 patients. With the same treatment approach, the complete response rate in their study was 75 per cent.

Only a few papers have addressed the questionable advantage of combining radiation therapy and chemotherapy over radiation therapy alone in randomized trials. Cachin and co-workers (1977) were among the first researchers to compare the effects of radiation therapy alone in 87 patients (cobalt 60, 6400 rads within 7 to 8.5 weeks) with a group of 99 patients who underwent radiation therapy combined with BLM single-agent chemotherapy (50 mg IM twice a week for 5 weeks) in a cooperative EORTC study. Complication rates of mucositis and epidermitis were significantly increased (71 per cent) in the group treated with radiotherapy and chemotherapy and were considered responsible for frequent denutrition and weight loss. Such side effects necessitated a delay of radiotherapy in 22 per cent of patients and definite interruption in 5 per cent in the combined treatment group, whereas in the group treated with radiation therapy alone, no interruption of treatment was reported and only 6 per cent of treatments were postponed. Considering tumor regressions measured 6 weeks after completion of radiation therapy, total regression rates were not significantly different in both groups as far as primary tumor or neck nodes were concerned. Survival curves showed the same 50 per cent survival rate in both groups at 15 months of follow-up.

A similar study was conducted by the Northern California Oncology Group and was reported by Fu and co-workers (1985). Radiotherapy alone was compared with radiation therapy plus single-agent chemotherapy of BLM concurrently with radiation at 5 units IV twice a week, followed by BLM 15 units IV and MTX 25 mg/m^2 IV weekly for 16 weeks as maintenance therapy after completion of radiation therapy. Fifty-one patients received radiation therapy alone and 45 patients had combined treatment. BLM and concurrent radiation therapy produced a more favorable local regional control rate and relapse-free survival overall, but the length of survival was not statistically significant. The compliance to maintenance chemotherapy was poor because of the high toxicity of the combined regimens.

In a randomized study, Taylor and associates (1985a) selected 95 previously untreated patients with locally advanced disease to receive either induction chemotherapy plus subsequent definite treatment (surgery or radiation or both) or definite treatment only.

Induction chemotherapy consisted of MTX 60 mg/m^2 IM for 96 hours on days 1, 5, and 9, plus leucovorin, 25 mg PO for 96 hours divided into 8 doses on days 2-3, 6-7, and 10-11 (starting 6 hours after the last MTX injection). MTX-dose escalations to 90 mg/m^2 and 120 mg/m^2 were done in the absence of significant toxicity.

Following treatment, patients were further randomized to receive additional adjuvant chemotherapy (MTX, which was then poorly tolerated, or CP 40 mg/m^2 IV, plus Adriamycin 40 mg/m^2 IV over 93 weeks). Disease-free survival in 86 evaluable patients was better only for the chemotherapy-treated group during the first 3 years; the expected three-year disease-free survival was then equal for the control group.

In a randomized study, Holoye and co-workers (1985) compared combination chemotherapy (two courses of FU, cytoxan, BLM, and MTX before and after radiation plus surgery) with preoperative radiation plus surgery alone. Forty-three evaluable patients of the group undergoing chemotherapy did not do better than 40 patients in the control group in terms of rates of residual and recurrent disease, distant metastases, or survival.

In a randomized study by Merlano and colleagues (1986), the question was addressed as to whether alternation or sequential polychemotherapy and radiotherapy were superior in patients with advanced, untreated cancer. Induction chemotherapy with vinblastine, BLM, and MTX/leucovorin was given either in four cycles prior to radiation therapy or as an alternation of four cycles of chemotherapy with three interim courses of radiotherapy (2000 rads in 10 days per course). Twenty patients were evaluable in the segment undergoing alternating therapy. No significant differences were detected in either response or survival rates during a preliminary evaluation.

Two other uncontrolled studies applied "sandwich" therapy: Combination chemotherapy with vinblastine, BLM, and MTX was rotated with split courses of radiation therapy. Rosso and co-workers (1985) treated 46 inoperable, previously untreated patients after O'Connor and associates (1982) had applied this regimen to 198 patients. Treatment-related toxicity in O'Connor's trial was substantial, including 15 deaths in 198 patients (7.5 per cent). He later found this treatment approach superior to his previous experience with radiotherapy and surgery alone (historical controls). Overall survival was 41 per cent at 60 months, whereas in Rosso's study, actuarial survival was 28 per cent at 55 months.

Preoperative simultaneous induction by radiation therapy and chemotherapy was used in a number of uncontrolled studies. Chemotherapy consisted of CP in the study of Slotman and co-workers (1986); CP and FU infusion were used by Taylor and associates (1985b) and Adelstein and colleagues (1986); CP, FU, and folinic acid was administered by Hartenstein and associates (1986); and FU-infusion and mitomycin-C bolus was administered by Cortes and co-workers (1986). Complete response rates following combined modality treatment ranged between 53 and 72 per cent in these smaller studies, in which 18 to 53 patients were enrolled. Because of good local control, subsequent surgical procedures could be cautiously limited to conserve laryngeal, tongue, and mandibular function (Taylor et al, 1985b) or entire

preservation of the larynx was made possible (Pfister et al, 1986). However, survival advantage over radiation therapy plus surgery alone remains to be shown.

In summary, the combination of chemotherapy and radiation therapy may improve local or regional disease control; however, toxicity and costs are likewise increased. At present, the selectivity of these combinations and sensitivity to each modality leave much to be desired. In certain situations owing to the anatomic location of the tumor, there may be a profound advantage conferred by the use of combined therapies, resulting in a cancer cure. Methods of chemically increasing the selectivity of radiation during combined therapy are not well established and need to be investigated further.

Biologic Therapy

Delayed hypersensitivity to various antigens, including recall antigens and dinitrochlorobenzene (DNCB), was found to be depressed in patients with advanced head and neck cancer. Total lymphocytes and peripheral blood T-cells, especially T-helper cells, were decreased (Hong and Bromer, 1983; Kies et al, 1985). Elevated serum levels of immunoglobulins, antiviral antibodies, acute phase proteins, and immune complexes have been reported in patients with head and neck cancer, which may explain the nonspecific immunosuppressive effects of patient's sera on in vitro immune function. The biologic function of these serum components is not clear, but it has been proposed that they may function as blocking factors in the immune mechanism (Wolf, 1984). Tumors may also escape immune rejection by virtue of their cellular heterogeneity or through mechanisms involving the release of factors that bind to antitumor effector cells and subvert their action. Of these factors, prostaglandins may be of particular importance in head and neck cancer patients (Gemsa et al, 1986). Correlation of alteration of in vivo and in vitro immunoreactivity with tumor extent and prognosis suggests that clinical use of agents that modify the immune response by enhancing or restoring immunologic homeostasis may result in objective benefits in terms of prolonged survival or an increased disease-free interval. However, the development of appropriate and effective clinical approaches to immunotherapy for patients with head and neck cancer has been limited despite the identification of a large number of agents capable of modifying in vitro immunoreactivity (Hersh, 1986).

Biologic response modifiers have been defined as agents that alter the interactions between tumor and host through a modification of the biologic response of the host to the tumor. Of the large number of studies of immunotherapy in humans, few have been prospective randomized trials and very few of those have been conducted in patients with head and neck cancer. Nonspecific immunostimulants, including bacillus Calmette-Guerin (BCG), or *Corynebacterium parvum*, thymosin, and levamisole, were used following surgery or radiation therapy. The results of these trials have generally been disappointing (Wolf, 1984).

Cytokines such alpha-interferon and beta-interferon are effective in the treatment of some human malignancies. Other cytokines such as gamma-interferon, interleukin-2, and tumor-necrosis factor are under study, but no results are readily available for head and neck cancer patients. Predominantly, antigen-dependent effects are those caused by immunomodulating natural and synthetic drugs, perhaps by the interferons, by some lymphokines, by certain anti-T-cell monoclonal antibodies (MOAB), and by thymic factors

restoring T-cell functions. The antitumor effects of adoptively transferred T-cells, both the classical T cytotoxic effector cells, and possibly the recently discovered lymphokine-activated killer cells, and those of passively transferred antitumor MOAB, both by themselves and as delivery vectors, are dependent on the presence and accessibility of tumor-associated antigens (Mihich, 1986).

MOABs may be used to precisely dissect the surface antigenic display of tumor cells with a real possibility of yielding powerful forms of serotherapy and immunotoxin therapy.

MOABs have been demonstrated to localize efficiently in solid tumors in vivo. Limited therapeutic activity of MOABs alone has been seen in melanoma, along with solid tumors. Promising work is under way with drug-, isotope-, and toxin-coupled monoclonal antibodies (Hersh, 1986; Zenner, 1981).

Therapeutic problems with MOAB therapy include antigenic modulation (changes in the antigenic pattern), release of free antigen, immune reaction to anti-mouse antibodies, tumor heterogeneity, lack of *in vivo* cytotoxicity of the antibody alone, and neoplastic cells not accessible to blood supply. Some of these problems can be theoretically solved by carefully choosing MOABs that do not cause antigenic modulation, by plasmapheresis, or by the use of multiple MOABs and appropriate conjugates (drugs, toxins, or radionuclides)(Morgan and Foon, 1986).

It is conceivable that certain biologic response modifiers may have greater usefulness as agents restoring or augmenting host defenses against opportunistic infections in cancer patients than as antitumor agents (Oldham, 1985).

Indiscriminate use of biologic response modifiers without the necessary insight into the effects of this type of therapy and the effects of conventional and immune therapy of immune reactivity and lymphocyte subpopulations has led and will continue to lead to therapeutic failure. Disturbance of immune functions can even enhance tumor growth. Many nonspecific immunotherapy approaches using BCG, *C. parvum*, thymic hormones, or levamisole have produced conflicting results and were aborted (Wolf, 1984). The prospect of the immunotherapy of cancer may brighten again with a new understanding of tumor cell-immune cell actions and an explosive development of new technologies. Recombinant DNA technologies can deliver large quantities of cytokines with powerful immunomodulatory effects (Berlinger, 1986). In addition, new approaches of interfering with tumor invasion and the metastatic seeding (collagenase-inhibitors, laminin receptor antibodies, cyclo-oxygenase-inhibitors, heparin) should be pursued (Mihich, 1986). The timing of biologic interventions relative to one another and to the circadian timing of the patient is obviously critical to effective manipulation of the immune system.

As multimodality treatment including chemotherapy, radiation, and surgery may prove to be superior for certain stages of head and neck cancer, this concept may be expanded to incorporate immune response modifiers, once their effectiveness has been established.

Retinoids

In animals, vitamin A and retinoids delay tumor formation or protect against tumor induction by various carcinogens. Retinoids modify both cell proliferation and differentiation (Mahrle, 1985). Meyskens and co-workers (1982) studied the effect of oral isotretinoin in patients with various tumors. Of 24 patients with squamous cell carcinoma, including a few of head and neck origin, 25 per cent improved. However, the therapeutic use of retinoids is not established.

Discussion

The Role of Chemotherapy as a Single-Treatment Modality

We do not presently have the means to cure either recurrent or metastatic squamous head and neck cancer with chemotherapy. The goal of the chemotherapy in these patients is palliation. The benefits of chemotherapy must be continually weighed against the toxicities that are encountered. In most patients with metastatic head and neck cancer or with recurrent tumor that is not potentially curable with surgery and radiation therapy, a trial of chemotherapy is indicated. A decision for a palliative attempt must take into consideration the various contraindications to chemotherapy, such as severe malnutrition, renal or hepatic failure, unresolved infection, and inability of the patient to comply with the regimen. Almost all currently used chemotherapy programs for squamous cell head and neck include MTX, CP, or both. Although many clinical trials have investigated the effect of combination chemotherapy, there are few prospective randomized studies that have compared combination chemotherapy with single-agent therapy.

Especially for far-advanced cancers, it must be kept in mind that tumor growth follows gompertzian kinetics, so that the initial exponential growth is gradually replaced by an exponential retardation of growth as the overall tumor burden increases. This principle is consistent with the concept that sensitivity to chemotherapy varies inversely with tumor burden. In order to improve response rates and to delay the emergence of resistance, many combined active drug regimens have been developed. Theoretically, the use of multiple active drugs in a single treatment regimen should attack different malignant cell components at different phases of cell replication cycles. It is hoped that this approach will eventually counter the problems imposed by tumor heterogeneity, when multiple cell populations within a given carcinoma have varying sensitivity profiles to chemotherapeutic agents.

Although some sites of tumor involvement of the head and neck are relatively easy to measure in a quantitative fashion, other tumors are more difficult to quantitate, especially if the tumor is ulcerated and associated with significant inflammation, edema, or bone destruction. In such cases, efforts should be made to document tumor size by using photography, CT scanning, and measurements made by multiple observers. Since these lesions are easily accessible for repeated biopsies, documentation of malignancy should be obtained when patients are to be treated and again when a complete response to chemotherapy is obtained.

It is possible to achieve response rates (complete plus partial response rates)(Miller et al, 1981) of 40 to 60 per cent in patients with recurrent disease (but no prior

chemotherapy). Previously untreated patients with advanced regional disease have 70 to 90 per cent response rates with the same regimens. Although results of pilot studies are often encouraging, the regimens must ultimately be tested against less toxic single-agent therapies in randomized prospective trials before they can be accepted as clearly superior.

In patients with metastatic disease, chemotherapy has not been able to improve survival significantly, despite the achievement of high response rates. It is possible that symptomatic treatment of the patients and maintenance of adequate nutrition and attempts to control the local complications of infection and hemorrhage can also lead to similar survival rates without drug toxicity. The use of cytotoxic drugs alone or in combination in such a heterogeneous disease has led to highly variable results. Nevertheless, despite few controlled studies, some encouraging results with drug combinations have been reported that should allow the eventual development of effective combined modality treatment. It should be noted that there is an extensive variety not only in the type of drugs used in combination but also in doses, modes, sequences, and time schedules of drug administration. Obviously, much more attention must be given to drug timing and sequencing, as well as to optimal combination with biologic treatment, surgery, and irradiation. Complex combinations can be given automatically by programmable infusion pumps at precise circadian stages. This process will help standardize treatment schedules and will result in improved therapeutic index by optimal timing of drug delivery. The first such system, the Intelliject four-chamber automatic drug pump, has become commercially available from Intelligent Medicine of Englewood, Colorado.

There is no hard evidence that multidrug regimens are superior to standard single agents when remission duration and overall survival are compared. In the minority of patients who actually achieve a complete response, life is probably also prolonged. The use of aggressive combination chemotherapy may produce serious toxicity. If palliation is the major goal, however, it is hard to justify settling for a 20 per cent response rate compared with 60 to 80 per cent yielded through the use of complex combinations.

Chemotherapy in Combination with Radiation Therapy and/or Surgery

The Present Role of Chemotherapy

A large number of single-armed uncontrolled studies have reported the results of adding chemotherapy to surgery or radiation, or both, in the treatment of patients with locally advanced squamous cell carcinoma of the head and neck. Cigarette smoking and alcohol use are powerful risk factors for this group of diseases, so that many of the patients who develop the disease have a poor performance status and some of them are unfit for combined modality treatment. Thus, clinical studies of adjunctive chemotherapy invariably enroll selected patients. Obviously, single-armed studies give no indication of survival benefit as compared with an identical group that does not receive chemotherapy as one of the modalities. Based upon their experience and a thorough literature review, Tannock and Browman (1986) have recently drawn the following conclusions: (1) Chemotherapy, when administered concurrently with radiation therapy, usually increases the toxicity of the two modalities. (2) A variety of drug regimens leads to high and rapid rates of tumor shrinkage when the disease is reassessed at the time of surgery or at initiation of radiation therapy. (3) Those patients who respond to chemotherapy have a better prognosis and are more comfortable than those who do not. This might imply that patients who are inclined to have a better prognosis are more likely to

respond to chemotherapy. (4) High rates of response to initial treatment with chemotherapy do not necessarily translate into marked improvement of the length of disease-free survival as compared with historical controls. Whenever an improvement in the length of survival is claimed, one has to analyze the patient selection and prognostic parameters carefully. (5) A major goal of single-armed studies should be to test feasibility of a new treatment program before it is introduced into randomized, controlled trials.

Most large, randomized controlled studies that have compared radiation therapy plus concurrent or sequential chemotherapy with radiation therapy alone are inconclusive in terms of revealing a survival advantage in either regimen. The failure of combined modality treatment to improve survival in spite of impressive response rates might be due to limited cell killing and the presence of drug-resistant subpopulations, explaining the short duration of response. Another possibility is the rapid progression of tumors to a drug-resistant state. A limited cell kill from chemotherapy makes it likely that only the smallest of micrometastases are sterilized. The majority of patients have a relapse in the primary site or the neck nodes. Chemotherapy does not sterilize any anatomic region that is visibly involved with tumor at the start of treatment. Thus, chemotherapy does not render an inoperable patient operable for cure. One might expect an added capacity for cell kill from a combination of chemotherapy and radiation therapy. The failure to meaningfully increase cure rates may indicate that both radiation and drugs are selective for the same subpopulation of cells, and are, therefore, subadditive in their combined effects. Possible reasons include tumor fractions of hypoxic cells resistant to radiotherapy and poor penetration of chemotherapy in tissue.

Combined treatment modalities in operable patients bear definite risks. If chemotherapy or radiation therapy is applied first, surgical debulking is often delayed, which can conceivably lead to an increased incidence of distant metastases, especially in patients who respond only partially or do not respond to initial chemotherapy or radiation therapy, or both. Furthermore, circulating tumor cells may have a higher probability of forming metastases in drug- or radiation-damaged organs. However, if surgery is performed as the initial treatment in operable patients, tumor manipulation might theoretically lead to the seeding of visible tumor cells into the circulation.

The value of chemotherapy before and after radiation therapy or surgery, or both, has not been determined. Studies of postsurgical or postradiation adjuvant chemotherapy have been disappointing. Presurgical or preradiation therapy for advanced lesions is currently an area of intensive investigation but cannot be recommended as routine procedure. Presurgical or postsurgical adjuvant chemotherapy should be considered for patients with locally advanced stage III and IV tumors and perhaps for patients with lower stage tumors of special sites known to carry a higher risk of relapse or metastasis like T2 cancers arising in the hypopharynx.

In summary, combined modality treatment with induction chemotherapy, surgery, and radiation therapy can improve treatment results locally in selected patients but may not reduce the incidence of distant metastases significantly (Hong et al, 1985).

Risk Factors for Survival

Performance status, nutritional status, age, and concurrent nonmalignant diseases are among the most important factors determining the individual patient's longevity.

Among the factors that positively influence survival is greater tumor differentiation (Ensley et al, 1986; Hill et al, 1986). Grade of tumor differentiation does not, however, allow prediction of the likelihood of response to chemotherapy. The single most important prognostic factor is tumor stage. The nearness of the primary tumor to vital structures is also of critical importance. The presence of necrotic areas, abscess formation, and ulcerations often triggers fatal infections in these frequently immunosuppressed patients.

The slower the growth of these tumors, the better the prognosis. If it takes a longer time to induce complete remission, the remission duration is usually shorter (Hong et al, 1985).

Risk factors for early relapse after complete remission include persistently high serum ferritin levels (Maxim and Veltri, 1986) and certain anatomic sites of the primary tumor. Patients with oral cavity lesions are more likely to experience local treatment failure, whereas hypopharyngeal cancers bear a higher risk of distant metastases; treatment of oropharyngeal lesions is more prone to fail both locally and distally.

Biologic Response Modifiers

The place of biologic therapy and combined cytotoxic and immunotherapy still needs to be defined. Nonspecific immunostimulation with BCG, *C. parvum,* and other substances has been largely abandoned.

There is presently no established role for the use of ad hoc chemotherapy or immunotherapy in the treatment of primary head and neck cancer, but there is a definite need to include these treatment modalities in controlled studies.

Chemotherapy can definitely palliate patients with a good performance status. The value of diminishing or delaying the severe local symptoms that always accompany these dreaded diseases must not be denigrated.