Chapter 19
Principles of Systemic Chemotherapy for Squamous Cell Head and Neck Cancer

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Abstract Head and neck squamous cell carcinomas are a group of malignancies that are sensitive to systemic therapy, in part due to the complexity of the molecular aberrations in these malignancies that impair DNA repair mechanisms. Administration of chemotherapy in the treatment of head and neck cancers is guided by treatment goals and patient factors unique to this patient population. The known radiation sensitizing properties of chemotherapy and its ability to impact rates of distant failure have established concurrent chemoradiation as a standard definitive and adjuvant therapy for locally advanced disease. Although known to produce tumor responses, chemotherapy given in the metastatic setting has not been consistently demonstrated to improve overall survival. The combination of chemotherapy with targeted monoclonal antibodies has shown promising results. Future investigation of the role of nonoperative treatments in this disease will likely focus on efforts to decrease late treatment-induced morbidity, exploration of reirradiation with concurrent chemotherapy as a salvage therapy, and further integration of chemotherapy, radiation and targeted therapies in both definitive and palliative management.

Keywords Systemic chemotherapy • Multimodality therapy • Concurrent chemoradiation • Palliative chemotherapy

Introduction

Historically, the use of systemic treatments in squamous cell head and neck cancer has required an entirely different approach that taken by the radiation therapist and surgeon. For the medical oncologist, the anatomic distinctions so critical for locoregional disease management are of considerably less importance than the commonalities that head and neck cancers share. These include the common risk factors of tobacco and alcohol abuse, and the associated comorbidity. In addition, these tumors are histologically similar and tend to be locoregionally aggressive with only a limited metastatic potential. The most important similarity, however, has been the relatively uniform response of head and neck cancers to systemic chemotherapy. Indeed, previously untreated squamous cell head and neck cancer is remarkably sensitive to systemic treatments, particularly when compared to most other common solid tumors [1].

Oncogenesis and the Progression from Benign to Malignant Epithelium

The complex process that transforms normal epithelium to invasive squamous cell carcinoma is incompletely understood, and the intense scientific inquiry focused on these events has paved the way for development of effective systemic agents for this disease. Malignant transformation is a multistep process that is thought to involve an accumulation of genetic defects and interplay between carcinogen exposure, genetic predisposition, and more recently, viral infection.

Tobacco and alcohol are well-established risk factors for head and neck cancer. "Field cancerization" is used to describe the predisposition to malignant transformation along the entire upper aerodigestive tract epithelium as a result of carcinogen exposure [2]. Molecular abnormalities known to occur early in oncogenesis are often observed not only in the premalignant lesions themselves, but the surrounding normal epithelium. Synchronous premalignant and malignant lesions in different areas of the aerodigestive tract have been noted to harbor similar molecular abnormalities. This process is felt to be responsible for the clinical observation of second or third primary upper aerodigestive tract malignancies in patients with heavy alcohol and tobacco exposure successfully treated for their index head and neck squamous cell cancer [3].

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The stepwise progression to malignancy is somewhat similar to the colon cancer model of carcinogenesis. One of the first observations supporting this was the reproducible cytogenetic abnormalities identified in hyperplasia, dysplasia, carcinoma in situ, and invasive malignancy [4, 5]. For instance, loss of heterozygosity at the 3p and 9p loci have been frequently observed in early premalignant hyperplastic head and neck mucosal lesions. The transition from hyperplastic to dysplastic epithelium is often characterized by loss of heterozygosity at 17p, and gains in the 11q23 region. With more sophisticated molecular techniques, these chromosomal changes have been found to correspond to genes that play critical roles in cell cycle regulation, specifically the tumor suppressor genes p53, Rb, p16, and cyclin D1.

It is becoming increasingly apparent that neoplastic transformation is mediated by a far more complex interaction of factors than genetic mutations in proteins regulating the cell cycle. Gene silencing through epigenetic phenomena, such as hypermethylation of promoter regions of tumor suppressor genes, has been observed [6]. The role of overexpressed cell surface receptors such as EGFR and its downstream signaling cascade mediating cellular immortalization and invasion has been recognized [7]. The influence of genes and proteins responsible for cellular adhesion, such as E-cadherin [8], and matrix metalloproteinases [9], has also been implicated. These more recently identified pathways represent therapeutic targets and avenues for drug development [10].

The role of viral infection in carcinogenesis in head and neck cancer was first recognized in nasopharyngeal cancer. Virtually all cases of endemic undifferentiated nasopharyngeal carcinoma are found to harbor the Epstein–Barr virus. The viral proteins LMP1 and LMP2a are thought to exert transforming effects through intracellular signaling cascades promoting cellular immortalization [11]. These cancers behave differently from head and neck cancer of other subsites, with a predilection for early distant spread but otherwise superior treatment outcomes after therapy for local disease.

There has also been increasing recent awareness of a distinct patient population with oropharyngeal cancer harboring high-risk human papillomavirus (HPV) subtypes [12]. These patients may not have a prior exposure to tobacco and alcohol, an observation that has challenged the applicability of the field cancerization theory and the multistep carcinogenesis model to all head and neck cancers. These HPV-associated tumors often contain wild-type p53 and Rb, which are functionally inactivated by viral proteins [13]. Not only are these HPV-positive tumors molecularly distinct, but they also appear to have clinically distinct behavior, and a significantly better prognosis after treatment. Investigation into the optimal therapeutic approach for this unique subset is ongoing.

Treatment Goals and Efficacy Endpoints

When defining the management for any patient with cancer, it is critical that a clear treatment goal be identified. If the treatment goal is cure, considerable short- and long-term treatment-induced morbidity may be considered acceptable. Aggressive treatment approaches may still be justified when survival prolongation is possible, even if the disease cannot be cured. When the patient can only be palliated, however, considerable discretion must be exercised in the choice of treatment, and the toxicity considered acceptable. Thus the risk/benefit ratio varies considerably depending on the goal of the treatment and the anticipated outcome. What might be considered to be acceptable risk and toxicity for a potentially curable patient may be entirely unacceptable for a patient treated with palliative intent.

Multiple efficacy endpoints are used in assessing the success of any cancer treatment [14]. The gold standard endpoint, and the endpoint which is easiest to measure in a clinical trial, has always been overall survival. In patients with head and neck cancer, however, survival is not only impacted by the disease itself, but by the frequent underlining cardiopulmonary comorbidity, and by the significant incidence of second primary malignancy.

In patients with advanced disease, an improvement in survival may be difficult to demonstrate, and may not be a prerequisite for symptomatic palliation. Tumor response, i.e., a measurable shrinkage in tumor volume, has always been considered to be an accurate reflection of antineoplastic activity [14]. Clear definitions of what actually constitutes a meaningful response are critically important in determining which chemotherapeutic agents might be of value in drug combinations, or in definitive multimodality treatment. These definitions have evolved over time but have been recently standardized as the Response Evaluation Criteria in Solid Tumors (RECIST) [15]. Although these criteria are important in allowing investigators to assess the efficacy of chemotherapy drugs and combinations, it should also be recognized that achievement of a formal response may not be necessary for a patient to achieve symptomatic benefit.

There has been recent discussion about the value of "stable disease" as an endpoint of palliative systemic therapy [16]. Historically, if a chemotherapeutic drug was unable to produce actual tumor shrinkage, it was considered inactive, and the toxicity produced was not felt to be justified. With the recent proliferation of newer and better tolerated targeted therapies this has been called into question [17]. Many patients treated with these agents achieve disease stability without significant tumor shrinkage; and appear to benefit from continued treatment with a possible impact on survival. Thus the concept of "clinical benefit" (i.e., disease response and disease stability after treatment) has been legitimized as a meaningful endpoint in palliative management.

For patients being treated with curative intent, additional, more sophisticated endpoints are often chosen, including progression-free survival, disease-free survival, event-free survival, or disease-specific survival [18, 19]. Although these functions may be more reflective of the effect of treatment than the overall survival, they are often variably defined and difficult to interpret. Standard definitions have been proposed. When reporting the efficacy of local or regional treatment modalities, investigators have often chosen such endpoints as local or locoregional control [19]. While somewhat reflective of overall outcome, such assessments ignore the relationship between local, regional and distant disease, and do not fully address the overall impact of the disease on the patient. When measuring the effect of a systemic treatment, distant disease control is also a common endpoint. Once again, however, this function is not independent of locoregional control. Furthermore, distant metastases are a relatively infrequent cause of treatment failure in head and neck cancer.

Even these endpoints may not be the most important outcome from the patient's perspective. Cancers in the head and neck and their treatments may significantly compromise several major human functions including speech, swallowing, and nonstomal breathing. Preservation of these functions may be more important to a patient than survival. While organ preservation, i.e., the avoidance of surgical resection of the organ, is easy to measure, it is only a crude estimate of functional preservation, a more difficult endpoint to assess, particularly for any given patient [20].

Moreover, the acceptability of functional compromise will vary between patients, and functional restoration is often possible even after organ removal. Nonlaryngeal speech with preservation of swallowing, may or may not be a preferable outcome to speech preservation with feeding tube dependence for any given patient.

List and colleagues from the University of Chicago have explored these kinds of patient-defined goals after head and neck cancer treatment in some detail [21]. When patients were asked to rank the relative importance of several treatment outcomes, cure and longer survival were consistently most important. There was considerable variability in the relative importance of other functional and cosmetic treatment priorities, including those goals related to pain, energy, voice, swallowing, and appearance. This is a message that we, as physicians, must remember when discussing treatments with our patients.

A number of validated quality of life instruments have also been developed in an attempt to better assess the impact of treatment and disease from the patient's perspective. Several of these tools have been widely employed including the Performance Status Scale for Head and Neck Cancer [22], the Functional Assessment of Cancer Therapy (FACT) scale [23], the EORTC quality of life questionnaire [24], and the University of Washington scale [25]. Thus far, however, the results and importance of these measurements are not entirely clear.

When using chemotherapy as palliative treatment in patients with incurable disease, the acceptability of the acute toxicities is the major determinant of the risk/benefit ratio of the treatment. However, when chemotherapy is being used as part of a curative multimodality treatment approach, the acute toxicities, while important, are of less concern than any late or long-term morbidity. Fortunately, except for a small risk of sterility or of a second malignancy, late morbidity from chemotherapy is uncommon. It is clear, however, that the combination of chemotherapy and radiation increases the likelihood and severity of the long-term morbidities commonly associated with radiation, an interaction which must also be considered when choosing treatments [26].

General Considerations in the Use of Chemotherapy

Most drugs used for systemic therapy in malignant disease exploit cancer cells' innate inability to repair genetic damage. Because normal cells in various tissues are vulnerable to these drug effects, chemotherapeutic agents are a class with a narrow therapeutic window. Preclinical models have demonstrated the steep dose–response curves after the administration of chemotherapy [27]. With any dose reduction of therapy, there is a consequent significant decrement in the degree of cancer cell kill and a resultant compromise in the ability to eliminate the malignant clone. The challenge in the delivery of chemotherapy is remaining within the therapeutic window, that is, being able to administer maximal drug doses while avoiding lethal injury to normal tissues.

Chemotherapy is usually administered intermittently, but at regular time intervals so as to allow normal tissue (usually bone marrow) recovery from drug-related toxicity, and enable administration of adequate drug dose over time. As many chemotherapeutic agents are cell cycle specific, at any given time, a certain proportion of cancer cells are not in the chemotherapy-sensitive phase of the cell cycle. Apart from limiting toxicity, repeated drug exposure over time allows for surviving cancer cells to enter the specific cell cycle phase during which an agent exerts its antitumor effects.

Due to consequences of the lifestyle that predisposes to head and neck cancer, cardiac, pulmonary and renal comorbidity, in addition to suboptimal compliance, complicate treatment planning in this subset of patients. Tailoring the choice of drug and treatment modality to patient factors is critical to optimizing treatment outcomes. The considerable acute toxicity of chemotherapy can result in significant

morbidity and even mortality in patients who are poor candidates for aggressive therapy.

Pharmacokinetic considerations for this patient population also have to be taken into account when selecting the appropriate chemotherapeutic regimen. The oral route is often compromised in patients with advanced tumors of the head and neck, and the delivery and absorption of active orally administered drugs such as hydroxyurea may be impaired. Most chemotherapeutic drugs active in this disease are metabolized in the liver, and excreted through the biliary or renal route. Renal dysfunction, hepatic impairment, preexisting cardiovascular disease, and the frequency of considerable alcohol exposure, are all important considerations in the choice of chemotherapy.

It is well recognized that previously untreated malignancies are more responsive to therapy than is persistent or recurrent local, regional, or distant disease after initial therapy. Certain molecular characteristics have been reported to predict for relapse after chemotherapy and radiation [28–30]. In addition to intrinsic variations in gene expression, persistent or recurrent head and neck cancers often acquire molecular aberrations from prior exposure to pharmacologic agents that render them more resistant to chemotherapy compared to treatment-naïve tumors [31, 32]. Changes in tumor vasculature from previous surgery or radiation, and increased expression of genes that promote hypoxic tumor growth are thought to contribute to radiation insensitivity [33]. These, in addition to the significant symptom burden of recurrent disease and prior therapy, magnify the difficulty of administering effective systemic therapy in this compromised patient population.

Single Agents: Mechanisms of Action, Toxicities, Metabolism

The most frequently used agents in the treatment of both locally advanced and metastatic squamous cell head and neck cancer have been the platinum compounds, methotrexate, 5-fluorouracil, and the taxanes. All four drug classes have single agent activity, have differing mechanisms of action and toxicity, and can be administered concurrent with radiation as radiation sensitizers. Although many other antineoplastic drugs have known activity, the following section will focus on these four classes (Table 19.1).

Cisplatin was the first platinum compound noted to have antitumor activity in head and neck cancer [34]. The mechanism of action is believed to be drug incorporation into DNA, forming DNA adducts which distort the normal DNA helical structure. This triggers cellular recognition of DNA damage and subsequent apoptosis. Increased intracellular cisplatin doses are noted when the drug is given with radiation. The systemic toxicity of cisplatin can be significant and involves multiple organ systems. It is highly emetogenic compound, which can cause both early and delayed chemotherapy-induced nausea and vomiting, now more easily controlled with modern effective antiemetic regimens. Nephrotoxicity through glomerular and renal tubular damage with resultant salt wasting can be a consequence of treatment. This can often be prevented and ameliorated by aggressive hydration. Peripheral neuropathy and irreversible ototoxicity (in the form of high frequency hearing loss) can also result from cumulative drug exposure. Carboplatin is an analogue of cisplatin, whose properties render it less nephro- and neurotoxic, but more myelotoxic than cisplatin. The chemical structure of carboplatin results in delayed drug conversion and excretion, resulting in a longer half-life than cisplatin. Both of these drugs are excreted primarily through the kidney [35].

The antifolates, like methotrexate, exert antitumor effects by impairing the cancer cell's ability to generate precursors for DNA synthesis [36]. Methotrexate was approved for head and squamous cell cancer treatment in 1953. This drug inhibits dihydrofolate reductase, which maintains the intracellular supply of reduced folate essential for purine synthesis. Methotrexate has a wide range of systemic side effects, the most commonly observed are myelosuppression and gastrointestinal toxicity. Interstitial pneumonitis, hepatic transaminase elevation, and renal dysfunction from drug precipitation

Table 19.1 Commonly used chemotherapeutic agents in the management of head and neck cancer

Class	Agents	Mechanism of action	Clearance	Toxicity
Platinum agents	Cisplatin Carboplatin	DNA adduct formation	Renal	Nausea Nephro- and neurotoxicity Myelosuppression
Antifolates	Methotrexate	Depletes precursors for purine synthesis	Renal	Myelosuppression Gastrointestinal toxicity
Antimetabolites	5-Fluorouracil	Depletion of precursors for DNA synthesis Incorporation into RNA	Renal (inactive drug)	Gastrointestinal toxicity Myelosuppression
Taxanes	Paclitaxel Docetaxel	Mitotic arrest by microtubule stabilization	Hepatobiliary	Hypersensitivity Myelosuppression Peripheral neuropathy

in the renal tubules are also recognized side effects. The majority of this drug is eliminated through the kidneys, with a small proportion, about 10%, excreted through the bile.

5-Fluorouracil is a uracil analog that impairs both DNA and RNA synthesis [37]. It is intracellularly converted to its active form, 5FdUMP, which inhibits the enzyme thymidylate synthetase, depleting thymidylate and arresting DNA synthesis. The drug can also be intracellularly converted into 5FUTP which, when incorporated into RNA, results in cell death. The drug has a short half-life lasting minutes, and can be administered as a bolus or infusion. Like methotrexate, 5-fluorouracil results in myelosuppression and gastrointestinal toxicity. Nausea, stomatitis, mucositis, and diarrhea are common manifestations. Coronary vasospasm resulting in myocardial infarction is a rare but reported side effect. This drug is degraded by the enzyme dihydropyrimidine dehydrogenase, which is present in most tissues. The inactive metabolites are excreted in the urine [38].

The taxanes, paclitaxel and docetaxel, are pharmacologic class of agents that induce cell death by stabilizing microtubule formation [39]. Subsequent metaphase arrest results in apoptosis. Both paclitaxel and docetaxel are primarily metabolized by the liver and excreted in the bile, thus appropriate dosage adjustments may be necessary in the setting of hepatic dysfunction [40]. Hypersensitivity reactions to paclitaxel are the most common acute toxicity, myalgias and arthralgias after drug administration are also common. Peripheral neuropathy is a cumulative side effect of both drugs. Docetaxel can result in fluid retention or skin toxicity.

Combination Chemotherapy: Rationale and Principles

When single agents prove active in the management of a malignancy, the next step has always been an attempt to use these drugs in combination. The use of combination chemotherapy, however, is based on several clear principles [41] (Table 19.2).

The first is that for a drug to be useful in a combination chemotherapy regimen, it must have single agent antineoplastic activity. It makes little sense to include an ineffective chemotherapeutic agent in a drug combination, with the hope that it will suddenly prove to kill cancer cells. It should be noted, however, that recent experience using some of the targeted agents, most notably bevacizumab, has suggested that this caveat does not always hold true. Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor is a relatively ineffective antineoplastic agent when used alone. When used in combination with other chemotherapeutic drugs, however, it has a demonstrated benefit in several disease sites [42, 43]. The second general principle in the use of combination chemotherapy is the importance of using drugs in full therapeutic doses. There has been general recognition of a dose–response curve for most systemic chemotherapeutic agents. Larger doses tend to produce larger, if not exponentially larger, responses, and suboptimal dosing of multiple agents would be unlikely to produce a better result than the full therapeutic dose of a single drug.

Table 19.2 Principles of combination chemotherapy

1. Drugs used in combination should have single agent activity
2. Drugs used in combination should be used in full therapeutic doses
3. Drugs used in combination should have nonoverlapping mechanisms of action
4. Drugs used in combination should have nonoverlapping toxicities

Third, drugs used in combination should have nonoverlapping mechanisms of action. There are a number of defined classes of chemotherapeutic agents, often with several different, but similar members. Rarely has the use of two drugs from the same class (e.g., two alkylating agents or two vinca alkaloids) been of any benefit. Finally, drugs, when used in combination should not have overlapping toxicities. In view of the steep dose–response curve for most chemotherapeutic agents, the optimal dosing for each drug is usually defined by its dose-limiting toxicity. Two drugs, with the same dose-limiting toxicity (e.g., myelosuppression), if used at their maximally tolerated dose, will undoubtedly produce significant and perhaps intolerable toxicity and would be a poor combination.

Despite the soundness of the rationale for combining chemotherapeutic agents, many of the common drug combinations used in this disease and others, violate one or several of these principles. Thus careful phase I and II testing for both toxicity and efficacy is important before widespread adoption of any chemotherapy combination.

Systemic Chemotherapy in Palliative Management

Patients with persistent or recurrent disease not amenable to local therapy such as radiation or salvage surgery, or patients who develop or present with systemic metastasis are incurable. The prognosis for patients in this situation is dismal and there is little evidence suggesting that chemotherapy is superior to best supportive care. Survival in this patient group, even when palliative chemotherapy is administered, uniformly ranges from 6 to 9 months. In this situation, when cure and survival prolongation are not possible, the treatment goal is to palliate symptoms and improve quality of life.

Quality of life can be adversely impacted by the local effects of tumors at both the primary site and the sites of metastasis. Local effects of the primary site tumor include

pain, and impairment or loss of important functions such speech, swallowing, smell, hearing, and even vision. Cosmetic deformity in addition to functional compromise can cause significant body image issues and depression. Distant disease most often involves the lung, and less commonly bone. This can result in cough, hemoptysis, painful bone lesions, pathologic fractures, and nerve or spinal cord impingement. Palliative care to address these symptoms should be carried out by a multidisciplinary team. Modalities such as radiation therapy to painful sites, and adequate pain control contribute to palliation in the metastatic setting.

Systemic chemotherapy is a widely used tool for reducing tumor burden, with the assumption that this leads to alleviation of tumor-related symptoms [44]. Active chemotherapy drugs when given as single agents often result in modest response rates ranging from 10 to 30% depending on previous treatment [45–47]. Several well-designed clinical trials have been done to compare various single and multiple drug regimens [48–50]. Although multiagent chemotherapy does produce a consistent increase in response rates, with only one exception, no significant prolongation of median survival has been observed. One of the more important observations has been the reproducible increase in treatment-related toxicity that accompanies combination drug therapy.

This observation introduces a significant conflict with the palliative goals of care in a patient population with incurable disease and significant comorbidity. Certainly, the toxicity of chemotherapy would only be acceptable if it ultimately resulted in some alleviation of tumor-related symptoms. With little convincing evidence of a survival advantage with chemotherapy combinations, great care must be taken to appropriately select patients who are good candidates for combination treatment. In a patient with a compromised performance status, for example, combination chemotherapy may adversely impact quality of life rather than palliate symptoms.

Phase III clinical trials using chemotherapy for patients with incurable disease carried out in the last two decades have focused on examining the endpoints of toxicity, survival and response rates. Little has been done to incorporate validated measurements of quality of life in these studies. The recognition that response rates may not accurately translate to improved symptom control, along with the introduction of a new class of "targeted agents" believed to have a more tolerable side effect profile, have led to the integration of more accurate quality of life measurements in the design of clinical trials.

In general, among most solid tumors, the integration of new pharmacologic agents into curative intent therapy is initiated by observed drug activity in patients with recurrent, pretreated or metastatic disease. Some examples of these emerging drugs showing antitumor effects in the metastatic setting are newer generation nucleoside analogs, antifolates, and topoisomerase inhibitors. Gemcitabine is a novel synthetic pyrimidine analog which is activated through intracellular phosphorylation. In its activated form, it is incorporated into DNA and RNA and arrests their synthesis, it also inhibits its own inactivating enzyme, increasing intracellular concentrations [51]. The new generation antifolate pemetrexed inhibits several enzymes involved in the maintenance of reduced folate pools essential for the production of DNA precursors. Its property of rapid entry into the cellular environment through several transport mechanisms is known to overcome cellular resistance that often hampers the efficacy of older generation antifolates [52]. Irinotecan is a partly synthetic camptothecin, which inhibits topoisomerase I, causing supercoiling of DNA during replication and growth arrest [53]. These drugs have been shown to possess radation-sensitizing properties and their assimilation into curative treatment strategies awaits further investigation.

The epidermal growth factor receptor and its demonstrated synergistic activity with both chemotherapy and radiation resulted in studies using the EGFr inhibitors in the metastatic setting. When compared to single agent methotrexate, EGFr inhibitors used alone have had disappointing response rates and no demonstrable impact on survival [54]. However, recently published data on the combination of platinum-based chemotherapy and EGFr inhibition has shown an unprecedented albeit modest improvement in survival [55]. The combination of chemotherapy with targeted agents has demonstrated a similar survival advantage in other epithelial malignancies and may represent the future paradigm for investigating and treating metastatic disease.

Systemic Chemotherapy in Definitive Management

In the curative management of solid tumors, single modality chemotherapy is rarely sufficient. For most neoplasms, and in particular head and neck cancers, chemotherapy is only effective when used in combination with definitive radiation therapy and/or surgery. Chemotherapy must be considered adjunctive not curative, and its use in multimodality treatment regimens must not compromise the delivery of the definitive locoregional treatment. While considerable morbidity may be acceptable from aggressive curative treatment regimens, the toxicity produced by the addition of chemotherapy cannot be allowed to interfere with the required radiation or surgery.

A number of multimodality treatment approaches have been explored (Table 19.3). All have been based on the recognized chemosensitivity of head and neck cancer. Previously untreated patients with squamous cell head and neck cancer can be expected to respond to systemic

Table 19.3 Multimodality treatment approaches using chemotherapy

Induction chemotherapy	The use of chemotherapy prior to definitive locoregional management
Adjuvant chemotherapy	The use of chemotherapy after definitive locoregional management
Concurrent chemoradiotherapy	
Definitive chemoradiotherapy	The use of concomitant chemotherapy and radiation as definitive management
Adjuvant chemoradiotherapy	The use of concomitant chemotherapy and radiation after definitive locoregional management
Sequential treatment	The use of induction chemotherapy followed by definitive concomitant chemotherapy and radiation

combination chemotherapy up to 90% of the time, with complete responses described in between 30 and 50% of patients. These excellent responses are rarely durable, however, and disease regrowth is the rule. The question then becomes how best to exploit this antineoplastic activity in conjunction with definitive radiation and surgery.

Induction chemotherapy was the first treatment strategy developed. The rationale for induction chemotherapy was that given the increased chemotherapy responsiveness in the previously untreated patient, the optimal time to use chemotherapy would be prior to any locoregional intervention. It was reasoned that if significant tumor shrinkage could be achieved, there might, as well, be an improvement in locoregional control, a decrease in distant metastasis, and an overall survival improvement. The potential for surgical modification or organ preservation after chemotherapy-induced tumor shrinkage was also suggested.

An alternative strategy is the use of adjuvant, or postoperative chemotherapy. Adjuvant chemotherapy strategies are meant to address concern about disease recurrence, and are optimal for those patients likely to develop distant metastasis even after achieving locoregional control. Thus a patient identified as being at high risk for distant disease recurrence after definitive surgery and or radiation might be appropriate for further systemic chemotherapy. Not surprisingly, given the limited risk for distant metastases in this disease, single modality adjuvant chemotherapy has not been of major benefit.

Several observations emerged from these kinds of sequential treatment approaches, however. The first was the recognition that chemotherapy responsiveness was predictive for responsiveness to radiation therapy [56]. This suggested the potential that chemotherapy might serve as a selection tool to identify those patients most likely to benefit from radiotherapeutic (i.e., nonoperative) intervention [57]. Chemotherapy was also found to decrease the risk of distant metastases, an achievement with a limited survival impact in a disease with such a small risk for distant disease [58–60]. Unfortunately, it was also recognized that treatment compliance could be compromised by successful induction chemotherapy. The dramatic response to systemic chemotherapy often experienced by these patients on occasion led to a motivational interference with completion of definitive treatment.

The observation was also made that those patients who respond to systemic chemotherapy live longer than those patients who do not. This has been suggested by some as a justification for the use of systemic chemotherapy. It must be recognized however, that a response to chemotherapy is more common in those patients with a better performance status and smaller disease burden. These are also the patients with a better prognosis irrespective of the treatment utilized [61].

An alternative to the sequential use of single treatment modalities has been the concurrent use of chemotherapy and radiation. The rationale for this approach has been the recognition that both chemotherapy and radiation therapy are independently active treatment modalities and that chemotherapy may potentiate radiation, improve locoregional control, and decrease the impact of distant micrometastatic disease. In addition, the use of these two treatment modalities together, rather than sequentially, will shorten the overall treatment duration and in theory improve compliance. Preclinical data support a synergistic role of chemotherapy and radiation therapy through various postulated mechanisms. The enhanced cell kill from simultaneous exposure to systemic chemotherapy and radiation has been attributed to increased cellular cytotoxic drug uptake during radiation, chemotherapy-induced impairment of DNA repair mechanisms in response to radiation-induced damage, and chemotherapy-induced cell cycle shift resulting in increased radiation sensitivity.

There are also several disadvantages to the concomitant use of chemotherapy and radiation. Clearly, the concurrent use of two treatment modalities will produce greater toxicity than the use of either treatment modality alone. This toxicity may then result in a compromise of dose intensity and efficacy, such as single agent rather than combination chemotherapy, split rather than continuous course radiation, or a reduction of the chemotherapy doses used. Nonetheless, the concurrent use of chemotherapy and radiation has been intensively explored in this disease both as definitive management, and as a postoperative adjuvant. Both locoregional control and survival have been improved with this approach although the treatment has been associated with significant acute and late toxicity [62].

Along with this improvement in locoregional control has been the recognition of a relative increase in the frequency of distant metastases, a change in the natural history of this disease [63, 64]. Given the apparent benefit achieved by induction chemotherapy in reducing the risk of distant metastasis, it has been recently suggested that a sequential treatment approach of induction chemotherapy followed by concurrent chemoradiotherapy might be advantageous [65].

The induction chemotherapy would address the risk of distant metastasis and the concurrent chemoradiotherapy would deal with the locoregional disease. Randomized studies of this treatment schedule are currently underway.

Critical to the use of systemic chemotherapy, both with and without radiation, has been the integration with surgery. Optimal management of the primary site and of the neck requires the definition of careful treatment algorithms. Patients with persistent or recurrent primary site disease after chemoradiotherapy will require some kind of surgical salvage. Patients presenting with large neck nodes at diagnosis, or with neck nodes that only incompletely respond to nonoperative intervention, will require subsequent neck dissection with curative intent [66]. Given the potential for cure after such surgical salvage, it would seem important that we be able to identify those patients likely to fail in the neck or at the primary site after nonoperative intervention.

The development of organ preservation strategies has been somewhat unique to this field. The rationale for organ preservation is the hope that the substitution of radiation, with or without chemotherapy, for surgery might not compromise survival and yet preserve organ integrity and function. The goal of treatment is no longer one of an improved survival. Instead, it is the hope that survival will not be compromised, but that there will be more organ (usually larynx) preservation. Again it is important to point out the difference between organ preservation and organ function preservation [20]. Preservation of a nonfunctional larynx is of little benefit to a patient despite maintenance of its anatomic integrity. Studies of both induction and concurrent chemotherapy and radiation schedules have been conducted with some success. However, recent data has raised the possibility that current organ preservation practices may have compromised overall survival in larynx cancer [67]. Thus, for any given patient, the debate about the relative importance of organ preservation vs. survival continues.

Emerging Issues

Increasing understanding of the molecular processes underlying head and neck squamous cell cancers, the discovery of new therapeutic targets, and the changing disease epidemiology has had a great impact on current scientific inquiry into the role of chemotherapy in improving patient outcomes.

The decreasing popularity of tobacco use has resulted in a plateau and decline of most tobacco-related malignancies of the upper aerodigestive tract [68]. Among head and neck cancers, a distinct clinical entity of high-risk HPV-positive oropharyngeal head and neck cancers in a patient population without exposure to tobacco or alcohol has surfaced. These tumors have a different molecular profile and have improved prognosis compared to non-HPV-related squamous cell malignancies of the head and neck [69]. These patients are younger with less comorbid conditions, and respond to definitive therapy with excellent local and distant control rates. The applicability of previously established therapies for head and neck cancer to this previously unrecognized clinical entity has been called into question, and a reduction of the intensity of therapy to spare patients from the attendant toxicity of chemotherapy and radiation combinations has been proposed for this patient population. Contemporary clinical studies are now moving toward studying HPV-positive and negative head and neck cancers separately, to further define the appropriate therapy for these two distinct subsets of patients.

Since the discovery that inhibiting the bcr-abl tyrosine kinase results in dramatic responses in patients with CML, numerous molecular markers have been identified as therapeutic targets in head and neck cancer. Inhibiting the epidermal growth factor receptor has been shown to result in synergistic cell kill when used with radiation and chemotherapy [70]. The combination of the monoclonal antibody cetuximab with definitive radiation in locally advanced head and neck squamous cell carcinomas have been shown to be superior to radiation alone in a large phase III clinical trial, with no significant increase in treatment-related toxicity [71]. Another phase III trial comparing combination chemotherapy to the same chemotherapy with cetuximab in patients with recurrent metastatic head and neck cancer demonstrated a modest survival advantage; an observation never before made in clinical trials using chemotherapy combinations alone [55]. The generally more favorable toxicity profile of these agents make them attractive prospects for integration into definitive and palliative therapy, and they are currently under study.

Another emerging role for systemic therapy is in salvage treatment for recurrent or persistent disease. Historically, when a patient experiences locoregional failure after definitive chemotherapy and radiation, surgery, when possible, was the only potentially curative option for salvage therapy. With the advent of more sophisticated radiation therapy techniques, reirradiation has been shown to be a feasible and successful in a highly select group of patients. Because of the dose and field limitations imposed by prior radiation therapy, reirradiation with the addition of systemic therapy for radiation sensitization is an attractive prospect. Several phase II studies have demonstrated the tolerability and efficacy of this approach [72, 73].

Sensitivity to chemotherapy is generally thought to identify disease with a more favorable disease biology. Complete responses to systemic therapy in most solid tumor malignancies are almost always associated with improved outcomes. Because the acute and long-term toxicities of surgery and chemoradiation are substantial, the possibility of using chemotherapy alone

to select and cure local disease is being investigated. Single institution clinical studies have explored the use of chemotherapy alone for nonmetastatic laryngeal carcinoma and demonstrated long-term disease remission in a subset of patients [74, 75]. Results of further studies are awaited before this strategy becomes applicable to clinical practice.

Conclusion

The current role of chemotherapy in the definitive management of head and neck cancer has been established by extensive scientific investigation over many decades. The benefits and toxicities of these agents have been well defined. The identification of molecular therapeutic targets, the development of novel active agents, and the changing epidemiology and treatment failure patterns of head and neck cancer are providing avenues for expanding the application of systemic therapy to improve outcomes in both local and metastatic disease.

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