Combined-Modality Therapy for Head and Neck Cancer

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Chemotherapy, when combined with radiotherapy and/or surgery in the treatment of patients with head and neck cancer, appears to be most efficacious if it is given concurrently with radiotherapy. Concurrent chemotherapy and

Introduction

Chemotherapy has often been combined with radiotherapy and/or surgery in the treatment of patients with advanced head and neck cancer in an attempt to improve locoregional control, decrease distant metastasis, and increase survival. Recently, induction chemotherapy has been used in the selection of patients with advanced resectable carcinoma of the larynx and hypopharynx for organ preservation.[1,2] Patients who achieve complete or partial responses to chemotherapy are candidates for organ preservation with subsequent radiotherapy.

The rationale for combining chemotherapy and radiotherapy has been reviewed previously.[3] Chemotherapy may sterilize micrometastases outside of the radiation field, sensitize tumor cells to radiation, inhibit repair of sublethal and potentially lethal radiation damage, and decrease tumor mass, thus increasing tumor reoxygenation and radiosensitivity.[4] Chemotherapy may also perturb cell kinetics, increasing the proportion of cells in the sensitive cell-cycle phase and proliferative state. Some drugs, such as mitomycin (Mutamycin), may preferentially kill hypoxic cells, which are more resistant to radiotherapy. Chemotherapy may also inhibit tumor repopulation during fractionated radiotherapy.

On the other hand, radiotherapy may decrease tumor mass, leading to improved blood supply and improved drug delivery and uptake. Decreased tumor mass may also lead to increased tumor proliferation and chemosensitivity. In addition, radiotherapy may inhibit the repair of drug damage. Finally, both chemotherapy and radiotherapy can induce apoptosis. It is possible that chemotherapy may enhance radiation-induced apoptosis and that radiation may enhance chemotherapy-induced apoptosis.[5]

When chemotherapy is combined with radiotherapy and/or surgery, it has been given as: (1) induction or neoadjuvant chemotherapy before surgery and/or radiotherapy, (2) a radiation enhancer concurrent with or alternating with radiotherapy, or (3) adjuvant therapy following primary surgery and/or radiotherapy. This paper presents an overview of the results of randomized trials of combined-modality therapy for advanced head and neck cancer.

Induction Chemotherapy

Induction chemotherapy has been used prior to locoregional treatment for both operable and inoperable head and neck cancer. At least 10 randomized trials of induction chemotherapy for advanced operable head and neck cancer have been conducted (Table 1). [1,2,6-14] In most of these trials, the chemotherapeutic regimen consisted of a combination of drugs, such as cis-platin (Platinol), fluorouracil (5-FU), bleomycin (Blenoxane), methotrexate, and vincristine. The combination of infusional 5-FU and cisplatin or carboplatin (Paraplatin) has been the most common regimen used in recent trials.

Response rates to induction chemotherapy ranged from 37% to 98%, and complete response rates varied from 5% to 54%, depending on the drug regimen and the number of cycles of drugs administered. Despite high response rates to induction chemotherapy, no significant improvements in locoregional control or survival were observed.

There have been at least 14 randomized trials in which induction chemotherapy was used in patients with operable and/or inoperable head and neck cancer, including nasopharyngeal carcinoma.[15-28] Response rates to induction chemotherapy varied from 21% to 91%, with complete response rates ranging from 0% to 46%. Although response to induction chemotherapy appeared to predict the efficacy of subsequent radiotherapy, there was no demonstrable benefit in locoregional control or
survival with induction chemotherapy.[23]

None of the trials showed a significant difference in survival between the standard-treatment and induction-chemotherapy groups. Although one trial showed an improved 5-year survival in patients who received intra-arterial methotrexate prior to radiotherapy compared to radiotherapy alone, subset analysis showed that the difference was statistically significant only for those with stage II oral cavity tumors.[15]

Another trial by Paccagnella et al included patients with operable or inoperable disease. Although there were fewer distant metastases in the induction-chemotherapy group than in the control group, who received surgery and/or radiotherapy, there was no difference in locoregional failure, disease-free survival, or overall survival.[24] Subset analysis showed that induction chemotherapy improved local control and overall survival in patients with inoperable disease but not those with operable disease. However, the overall 2-year survival rate was poor in both treatment arms for patients with inoperable disease (10% in the control arm and 24% in the induction-chemotherapy arm).

The results of the combined-treatment arm in this trial are no better than those with radiotherapy alone reported in the literature. Thus, based on this trial, one cannot conclude that induction chemotherapy improves the survival of patients with inoperable head and neck cancer.

Some of the induction chemotherapy trials have been criticized on a number of grounds. These include: (1) small number of patients, (2) patient and tumor heterogeneity, (3) use of ineffective drugs and drug combinations, (4) suboptimal drug dose and/or schedule, (5) variable standard treatment in the control arm, (6) delay of standard treatment in nonresponders, and (7) poor patient compliance. Also, the high incidence of intercurrent deaths and second cancers in this patient population makes it difficult to demonstrate a survival benefit, if any exists.

**Selection of Patients for Organ Preservation**

Although induction chemotherapy does not improve survival, it may be useful in the selection of patients who can undergo organ preservation with subsequent radiotherapy.[1,2,11] This treatment strategy was studied in a trial conducted by the Veterans Affairs Laryngeal Cancer Study Group (VALCS), which included patients with operable stage III or IV laryngeal cancer,[1,11] and a European Organization for Research and Treatment of Cancer (EORTC) trial, which included patients with operable stage T2-4, N0-2b squamous cell carcinoma of the pyriform sinus and aryepiglottic fold.[2]

The study design of the two trials was similar: Eligible patients were randomized to receive either surgery followed by postoperative radiotherapy or induction chemotherapy with cisplatin and 5-FU infusion. In the VALCS trial, after two cycles of induction chemotherapy, the partial or complete responders received an additional cycle of chemotherapy followed by definitive radiotherapy. Those with residual or recurrent disease after completion of radiotherapy underwent surgery for salvage.

Patients who showed no response or whose disease progressed after two cycles of induction chemotherapy were treated with salvage surgery and postoperative radiotherapy. The EORTC trial differed from the VALCS trial in that only patients who had a complete response in the primary tumor after three cycles of induction chemotherapy were treated with radiotherapy; the remaining patients underwent surgery.

Neither trial showed a significant difference in overall survival between the induction-chemotherapy and standard-treatment arms. Disease-free survival was lower in the induction-chemotherapy arm in the VALCS trial but not in the EORTC trial. Distant metastasis was significantly reduced in the induction-chemotherapy group in the EORTC trial. In the VALCS trial, although distant metastasis as a first site of relapse was reduced in the induction-chemotherapy arm, the overall incidence of distant metastasis was similar in both arms.[11]

The percentages of patients in the induction-chemotherapy arm who underwent laryngectomy because of lack of response or for salvage after radiotherapy were 38% at 4 years in the VALCS trial and 43% in the EORTC trial. In the VALCS trial, 31% of the 166 patients in the induction-chemotherapy arm were alive with a functioning larynx at 4 years. In the EORTC trial, for the 100 patients randomized to the induction-chemotherapy arm, estimated rates of survival with a functioning larynx were 28% at 3 years and 17% at 5 years. No increase in morbidity or complications of surgery or radiotherapy was observed following induction chemotherapy in either trial.

The results of these two trials suggest that induction chemotherapy followed by definitive radiotherapy in chemotherapy responders is an alternative treatment option for patients with locally advanced, resectable squamous cell carcinoma of the larynx or hypopharynx who desire organ function preservation.

**Ongoing Intergroup Phase III Trial of Larynx Preservation**
However, induction chemotherapy can be toxic and costly, and it is not known whether similar or better results can be achieved with concurrent chemotherapy and radiotherapy or radiotherapy alone. To address this issue, the Head and Neck Intergroup is conducting a phase III trial in which patients with operable T2, T3, or early T4 squamous cell carcinoma of the glottis or supraglottic larynx are randomized to receive: (1) induction chemotherapy followed by radiotherapy in the responders or salvage surgery and radiotherapy in the nonresponders, (2) radiotherapy and concurrent cisplatin chemotherapy, or (3) radiotherapy alone.[29] The induction chemotherapy regimen is the same as that used in the VALCS trial. In the concurrent radiotherapy and chemotherapy arm, cisplatin is given at a dose of 100 mg/m$^2$ every 3 weeks during radiotherapy. The radiotherapy regimen is the same in all three arms: 70 Gy in 35 fractions over 7 weeks. This ongoing trial is targeted to accrue 546 patients. In addition to survival with preservation of the larynx, quality of life will also be prospectively assessed as a treatment end point. Results of this trial should determine the relative efficacy of induction vs concurrent chemotherapy and radiotherapy vs radiotherapy alone for larynx preservation in patients with advanced, operable carcinoma of the larynx.

**Concurrent Chemotherapy and Radiotherapy**

Chemotherapeutic agents, either singly or in multidrug combinations, have been used with concurrent radiotherapy mainly in the treatment of advanced, inoperable head and neck cancer. Single-agent chemotherapy with such drugs as 5-FU, bleomycin, methotrexate, cisplatin, and mitomycin has been employed in the past. Combination chemotherapy, usually consisting of a 5-FU infusion and cisplatin, has been used more commonly in recent trials. Results of most of the randomized trials of concurrent chemotherapy and radiotherapy have been negative. However, at least 14 randomized trials have demonstrated positive results (Table 2).[30-43] In 10 of these trials, locoregional control was significantly better with concurrent radiotherapy plus chemotherapy (5-FU, bleomycin, methotrexate, mitomycin, cisplatin, carboplatin, or cisplatin plus infusional 5-FU) than with radiotherapy alone.[30-34,36,40,42,43] A significant improvement in disease-free survival was shown in 11 trials.[32,34-43] Overall survival was significantly better with concurrent radiotherapy and 5-FU, bleomycin, cisplatin, or carboplatin in six trials.[30,31,35,40,41,43] A trial from France also showed a significant improvement in disease-specific survival in patients given cisplatin during postoperative radiotherapy.[36]

Although the combination of concurrent low-dose cisplatin (20 mg/m$^2$/wk) and radiotherapy was no better than radiotherapy alone, high-dose cisplatin (50 mg/wk or 100 mg/m$^2$ every 3 weeks) may be more effective.[36,43] The efficacy of concurrent high-dose cisplatin and radiotherapy is being evaluated in three ongoing phase III trials conducted by the Head and Neck Intergroup. In the larynx preservation trial mentioned above, the combination of concurrent cisplatin (100 mg/m$^2$ on days 1, 22, and 43) and radiotherapy is being compared to induction chemotherapy followed by radiotherapy and to radiotherapy alone.[29] A trial for high-risk patients with operable disease coordinated by the Radiation Therapy Oncology Group (RTOG) is comparing concurrent cisplatin and postoperative radiotherapy to postoperative radiotherapy alone.[29] In another three-arm trial coordinated by the Eastern Cooperative Oncology Group (ECOG), patients with unresectable squamous cell carcinoma of the head and neck are being randomized to: (1) standard fractionated radiotherapy alone, (2) concurrent cisplatin and standard fractionated radiotherapy, (3) split-course radiotherapy and concurrent cisplatin and 5-FU.

**Mucositis**

With concurrent administration of chemotherapy and radiotherapy, there is usually a significant increase in acute mucositis, especially when more than one drug is given or when accelerated or hyperfractionated radiotherapy is used. For example, in a trial from the Cleveland Clinic, compared with radiotherapy alone, concurrent 5-FU, cisplatin, and radiotherapy resulted in a significant increase in the incidence of acute mucositis (30% vs 58%) and weight loss.[39] In a trial conducted at Duke University that combined hyperfractionated radiotherapy with concurrent chemotherapy, 45% of the patients in the combined-treatment arm required tube feeding, as opposed to 28% in the radiotherapy-alone arm.[42] However, most studies showed no significant increase in late normal tissue toxicity.

**Alternating Chemotherapy and Radiotherapy**

More recently, multidrug chemotherapy using a variety of regimens and approaches has been tested with concurrent radiotherapy. In general, when more than one chemotherapeutic agent is used with
concurrent radiotherapy, acute mucositis is markedly increased, necessitating the use of split-course radiotherapy or alternating chemotherapy and radiotherapy.

To date, at least six randomized trials have compared sequential chemotherapy and radiotherapy to simultaneous or alternating chemotherapy and split-course radiotherapy in advanced head and neck cancer.[44-49] As shown in Table 3, the complete response rate was better with the concurrent or alternating chemotherapy and radiotherapy regimen than with the sequential regimen. Three trials showed a significantly improved disease-free survival with the concurrent or alternating chemotherapy and radiotherapy regimen, as compared with the sequential regimen.[44-46] In one trial from Milan, overall survival also was significantly better in patients treated with alternating chemotherapy and radiotherapy than in those given sequential chemotherapy and radiotherapy.[46] It should be noted that none of these trials had a radiotherapy-alone control arm. As a matter of fact, in the trial by the Southeast Cooperative Oncology Group (SECOG) from England, results of synchronous chemotherapy and radiotherapy were no better than historical data of radiotherapy alone.[44] As a result, a third arm of radiotherapy alone was added to the trial.

**Alternating Chemotherapy and Radiotherapy vs Radiotherapy Alone**

Thus far, only one randomized trial has compared alternating chemotherapy and radiotherapy to radiotherapy alone.[50] Updated results showed a significantly better complete response rate in the alternating chemotherapy-radiotherapy group than in the radiotherapy-alone group (43% vs 22%; \( P = .037 \)), as well as significantly higher rates of locoregional control (28.8% vs 7.8%; \( P = .028 \)), 5-year locoregional relapse-free survival (64% vs 32%; \( P = .038 \)), progression-free survival (21% vs 9%; \( P = .008 \)), and overall survival (24% vs 10%; \( P = .01 \)). However, there was no significant difference between the two groups with respect to the incidence of distant metastases (7.5% vs 6.5%) or toxicity (19% vs 18% grade 3 to 4 mucositis).[51]

Several aspects of this trial may be problematic. First, early closure of the trial limits the statistical significance of the observed differences between the two treatment groups.

Second, the difference in survival was due largely to the poor locoregional control in the radiotherapy-alone group. The complete response rate in the radiotherapy-alone group was 22%, the locoregional control rate was 7.8%, and the 5-year overall survival rate was 10%.[50,51] The poor locoregional control rate with radiotherapy alone could have been due to the suboptimal delivery of radiotherapy.[50] Although the protocol called for a dose of 70 Gy in 7 weeks in the radiotherapy-alone group, the median dose actually delivered was only 62 Gy.

Treatment delays were also more frequent in the radiotherapy-alone group. Treatment delays of 1, 2, and greater than 2 weeks occurred in 32%, 11%, and 14%, of patients in this group, respectively. It has been shown that treatment interruptions have an adverse effect on the outcome of patients irradiated for head and neck cancer.[52]

In view of these deficiencies in treatment delivery and the poor results in the radiotherapy-alone arm, the results of this trial should be regarded as inconclusive and in need of further confirmation.

**Adjuvant Chemotherapy**

The use of adjuvant chemotherapy following standard therapy has been evaluated in at least 10 randomized trials (Table 4).[6,7,17,19,32,43,53-56] The most frequently used drugs include methotrexate, bleomycin, 5-FU, and cisplatin. Except for the recently closed Head and Neck Intergroup trial (INT 0099) of nasopharyngeal carcinoma, none of these trials demonstrated a significant improvement in overall survival with adjuvant chemotherapy. However, in this Intergroup trial, patients in the combined-treatment group also received concurrent cisplatin during radiotherapy. Thus, the relative contributions of adjuvant vs concurrent chemotherapy to the improved survival in the combined-treatment group are unclear.

One of the major limitations of adjuvant chemotherapy trials has been poor patient compliance. Patient refusal of adjuvant chemotherapy after intensive locoregional treatment has been common. In the Head and Neck Contracts Program (HNCP) trial, only 13 (9%) of the 151 patients randomized to receive maintenance chemotherapy completed all six cycles of chemotherapy.[6] In the Northern California Oncology Group (NCOG) trial, only 10 (22%) of the 45 patients in the combined-treatment arm received 50% or more of the dose of maintenance chemotherapy and none received the full dose.[32]

Another limitation is the lack of effective chemotherapy regimens. It is unlikely that adjuvant chemotherapy using existing drug regimens will have a significant impact on the prognosis of advanced head and neck cancer.
Chemotherapy Plus Radiotherapy for Nasopharyngeal Cancer

Of all the squamous cell carcinomas of the head and neck, nasopharyngeal carcinoma has the highest incidence of distant metastasis. It is also the most chemo-sensitive.

**Induction Chemotherapy**

Three randomized trials have evaluated the efficacy of induction chemotherapy in patients with nasopharyngeal carcinoma.[26,27,57] Preliminary results of the International Nasopharynx Cancer Study Group (INCSG) trial were first presented at the 1994 annual meeting of the American Society of Clinical Oncology (ASCO) and were recently published.[27] Patients with World Health Organization (WHO) type 2 or 3 nasopharyngeal cancer and stage N2-3, M0 disease were randomized to receive: (1) induction chemotherapy with three cycles of bleomycin, epirubicin, and cisplatin (BEC) plus radiotherapy or (2) radiotherapy alone. This study showed a significantly better disease-free survival with induction chemotherapy. However, there was no significant difference between the groups with regard to overall survival. There was an 8% incidence of treatment-related mortality in the chemotherapy arm and major toxicity was also significantly more frequent.

In another trial from the Chinese University of Hong Kong, patients with WHO type 3 nasopharyngeal cancer and Ho’s stage N3 disease or lymph nodes greater than 4 cm were randomized to receive: (1) two cycles of induction chemotherapy with cisplatin and 5-FU followed by radiotherapy and four additional cycles of chemotherapy and radiotherapy or (2) radiotherapy alone.[26] There were no significant difference between the two groups with respect to disease-free or overall survival. However, not all patients received the induction chemotherapy regimen as prescribed, the complete response rate to induction chemotherapy was low (only 5.4%), and patient compliance to post-radiotherapy chemotherapy was poor.

**Adjuvant Chemotherapy**

In addition to these trials of induction chemotherapy, the role of adjuvant chemotherapy was evaluated in a randomized trial conducted at the Cancer Institute in Milan.[55] Patients who achieved a complete response after radiotherapy were randomized to receive six cycles of adjuvant chemotherapy consisting of vincristine, cyclophosphamide (Cytoxan, Neosar), and doxorubicin or no further treatment. The two groups did not differ significantly with regard to relapse-free or overall survival or the incidence of distant metastasis. However, the drug combination used was probably suboptimal by current standards.

The only positive trial to date is the recently completed Intergroup trial.[43] This trial differs from all other trials for nasopharyngeal carcinoma in that chemotherapy was given during as well as after radiotherapy. Patients with stage III or IV squamous cell carcinoma of the nasopharynx were randomized to receive radiotherapy alone or radiotherapy plus concurrent as well as adjuvant chemotherapy. Chemotherapy consisted of cisplatin (100 mg/m²) every 3 weeks beginning the first day of radiotherapy followed by three cycles of cisplatin (80 mg/m²) and infusional 5-FU (1,000 mg/m²/d) on days 1 to 4 every 3 weeks after the completion of radiotherapy. Compared with patients receiving radiotherapy alone, patients given concurrent plus adjuvant chemotherapy had significantly higher rates of progression-free survival (24% vs 69% at 3 years; P < .001) and overall survival (47% vs 78% at 3 years; P = .002).[43] These results suggest that patients with locally advanced stage III or IV nasopharyngeal carcinoma can benefit from concurrent and adjuvant chemotherapy combined with radiotherapy.

**Impact of Induction or Adjuvant Chemotherapy on Distant Metastasis**

Although there has been no improvement in survival with the use of induction or adjuvant chemotherapy, there have been at least six randomized trials in which the incidence of distant metastasis was significantly decreased in the induction- or adjuvant-chemotherapy group. These include trials by the HNCP,[58] Southwest Oncology Group,[8] and Head and Neck Intergroup (INT 0034),[56] a trial from the Institute Curie,[23] an induction chemotherapy trial from Padua, Italy,[24] and an EORTC trial in pyriform sinus cancer.[2] In addition, a decrease in distant metastasis was observed with concurrent chemotherapy and radiotherapy in a Cleveland Clinic trial[39] and with concurrent and adjuvant chemotherapy in an Intergroup trial of nasopharyngeal carcinoma.[43] However, with the exception of the Intergroup trial of nasopharyngeal carcinoma, the decreased incidence of distant metastasis did not lead to increased overall survival. One of the possible explanations could be the high incidence of death due to locoregional failure, second cancers, or intercurrent disease.

Locoregional control has a significant impact on the incidence of distant metastasis as well as
survival. Data from the RTOG head and neck cancer database showed that the 5-year survival rate was 49% for patients who achieved locoregional control, as compared with 18% for patients who experienced locoregional failure.[59] Rates of 5-year time-adjusted distant metastasis-free survival in these two groups were 79% and 62%, respectively. Furthermore, locoregional control may also have a significant impact on quality of life after treatment. Thus, at present, improvement of locoregional control remains the top priority of clinical trials in head and neck cancer.

**Future Directions**

In the future, in order to integrate chemotherapy and radiotherapy more successfully, we need to establish the optimal drug regimen, radiation dose, and treatment schedules. Evidence thus far would favor a concurrent or alternating schedule for radiotherapy and chemotherapy administration. However, there is no consensus as to the optimal drug or drug combinations for use in combined-modality therapy, or the optimal drug and radiation dose schedule. If the ongoing randomized trials demonstrate an advantage for hyperfractionated and/or accelerated fractionated radiotherapy over standard fractionated radiotherapy, further improvement may be gained by integrating chemotherapy into an altered fractionation radiotherapy regimen. A potential complication to such an approach would be increased acute toxicity. Thus, to improve the therapeutic ratio further, we need to develop agents that can increase the efficacy and/or decrease the toxicity of radiotherapy and chemotherapy. Radioprotective agents, growth factors, and cytokines that can minimize the toxicity of radiotherapy and chemotherapy may play an important role in future combined-modality therapy.[29] Agents that can potentially decrease the acute and/or late effects of radiotherapy and chemotherapy, including amifostine (Ethyol), the prostaglandin E analog misoprostol (Cytotec), pentoxifylline (Trental), and pilocarpine (Salagen), are under clinical investigation.[29] To decrease the risk of distant metastasis and improve survival, we need to continue to search for more effective drugs or drug combinations. The efficacy of a number of new chemotherapeutic drugs, such as paclitaxel (Taxol) and gemcitabine (Gemzar), alone or combined with other chemotherapeutic agents and radiotherapy, needs further investigation in controlled clinical trials. Because tumor response to radiotherapy and chemotherapy is heterogeneous, reliable clinical and biologic predictors are needed to identify patients who may benefit from combined-modality therapy. Recently, a number of biomarkers of tumor proliferation or angiogenesis, such as p53 overexpression, p53 mutation, p105 antigen density, Ki 67/MIB-1 and c-erbB2 expression, and tumor microvessel density have been shown to have prognostic significance in head and neck cancer.[29,60-62] The role of these biomarkers as prognostic indicators is currently being evaluated in prospective clinical trials.[29] In the future, these predictive assays may be useful in the selection of patients for organ preservation with combined chemotherapy and radiotherapy. Patients with advanced, resectable, radioresistant tumors are best managed with immediate surgery. Cellular ability to repair DNA damage due to radiation and chemotherapy may be a determinant of cellular response to radiotherapy and chemotherapy. Research on the molecular basis of radiation and drug resistance and the cellular repair of radiation and drug damage, as well as the development of agents that may modulate the genetic regulation of radiation and drug resistance and DNA repair, may lead to improved efficacy of combined-modality treatment. Finally, the outcome of combined-modality therapy may best be assessed by evaluating patients’ quality of life after treatment. Quality of life should be an important end point for all future clinical trials of combined-modality therapy.

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