Review Article

Neoadjuvant chemotherapy or chemoradiotherapy in head and neck cancer

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Abstract

The multidisciplinary approach to treating squamous cell carcinoma of the head and neck is complex and evolving. Chemotherapy is increasingly being incorporated into the treatment of squamous cell carcinoma of the head and neck. Previously, radiotherapy following surgery was the standard approach to the treatment of loco regionally advanced resectable disease. Data from randomized trials have confirmed the benefits of concurrent chemo radiotherapy in the adjuvant setting. Chemo radiotherapy is also the recommended approach for unresectable disease. Advanced loco regional disease is the most frequent clinical situation in Head and Neck cancer. The standard of care for most clinicians is a multidisciplinary treatment with concomitant chemotherapy plus radiotherapy (CRT). However, retrospective studies have shown that in patients treated with CRT there was a relative increase in systemic relapse due to a lack of systemic control. For this reason a renewed interest has appeared for the incorporation of induction chemotherapy in the treatment of locally advanced Head and Neck Cancer. Furthermore new combination regimens with taxanes have shown to be more active than the classical cisplatin and 5-fluorouracil induction regimen. Novel targeted agents, such as epidermal growth factor receptor antagonists, are showing promise in the treatment of patients with both loco regionally advanced and recurrent/metastatic squamous cell carcinoma of the head and neck.

Key words: Chemo radiation, head and neck cancers, induction chemotherapy

Introduction

Squamous cell carcinoma of the head and neck (SCCHN) has been considered the sixth most common cancer in the world. Presentation with distant metastases occurs in about 10% of newly diagnosed patients with SCCHN. In a similar way, more than 50% of newly diagnosed patients with SCCHN will relapse locally or at a distant site and patients with recurrent and/or metastatic SCCHN have a poor prognosis with a median survival time of less than a year.

Advanced loco regional disease, defined as either non metastatic stage III or stage IV, is the most frequent clinical situation appearing in 60% of the diagnosed patients. It is well-known that advanced loco regional disease has a poor prognosis. It is estimated that approximately 50-60% of patients have local disease recurrence within 2 years, and 20-30% of patients develop metastatic disease. For the loco regional disease, an acceptable option is a local treatment based on surgery and/or radiotherapy (RT). On the other hand, in the treatment of unresectable loco regionally advanced SCCHN the principal treatment in most institutions is the combined-modality treatment with chemo radiotherapy (CRT) if the patient is medically fit. During the last years, this last approach has become the standard treatment for most clinicians.[1]

The Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) demonstrated that adding chemotherapy to radiotherapy in both definitive and adjuvant postoperative settings resulted in a 12% reduction in the risk of death from SCCHN, corresponding to an absolute improvement of 4% in 5 years survival.[2] A recent update has shown a 19% reduction in the risk of death and an overall 8% improvement in 5-year survival compared with treatment with RT alone. These findings were a result of the use of concurrent chemotherapy.

Although concomitant treatment with chemotherapy

and radiotherapy is the standard of treatment, several questions are still pending. For instance, retrospective studies have shown that in patients treated with CRT there was an increase in systemic relapse due to a lack of systemic control. To this regard, a renewed interest has appeared for the use of induction chemotherapy (IC). It is considered that IC has failed to demonstrate any survival benefit. Several meta-analyses have failed to reveal any significant improvement in survival using induction chemotherapy. The largest one, as mentioned before, is ''The Meta Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC)'' which analyzed individual patient data for more than 5200 patients. A non significant 2% improvement in overall survival at 5-year was observed.[2] However, significant survival benefits were identified in the 15 trials that employed an induction regimen using fluorouracil and platin compounds (hazard ratio 0.88; 95% CI, 0.79-0.97). If we consider only individual trials, only two studies have shown a survival benefit in inoperable patients with oropharynx cancer.

On the other hand, the incorporation of taxanes to the classical cisplatin and 5-fluorouracil regimen has shown an increase in response rates and therefore clinical trials are incorporating a three-drug arm with taxanes.

Currently, three multimodality treatment approaches are used. The first approach is surgery followed by adjuvant concurrent chemo radiotherapy, which enables precise pathologic staging and identification of high-risk features that influence the choice of adjuvant treatment. This approach can have limitations, such as poor organ preservation, depending on the anatomic location (e.g. larynx) and the majority of loco regionally advanced tumors are unresectable, especially if organ preservation is the goal.

The second approach is definitive concurrent chemo radiotherapy with surgery as an optional salvage or completion treatment. Although no pathologic information is obtained with this approach, it has the advantage of improved organ preservation. This benefit is most clearly established for laryngeal cancer but is increasingly recognized for other anatomic locations; however, this approach remains controversial for oral cavity tumors.

The third approach is the use of induction chemotherapy followed by definitive local therapy. Advantages include the potential to decrease the risk of distant failure and a rapid reduction in tumor bulk in responders. A response to induction appears to predict responsiveness to chemo radiotherapy. Nonetheless, this can result in prolonged treatment and additional chemotherapy-related toxic effects from systemic doses. This approach remains controversial, but data from recent clinical trials seem to support its use. The role of this approach in the context of concomitant chemo radiotherapy is currently being investigated in several large, multicenter, randomized trials.

Definitive Chemo Radiotherapy for Locally Advanced-SCCHN

Conventional, once-daily, fractionation radiotherapy in 2 Gy fractions up to a total of 66 to 70 Gy over 7 weeks has been used as definitive therapy in unresectable SCCHN and sometimes in resectable tumors instead of surgery. This results in high loco regional relapse rates (50% to 60% at 2-year) and overall survival of approximately 40% at 3-year.[3,4] Efforts to improve the loco regional control of SCCHN by altering the fractionation of radiotherapy have only been marginally successful. In an attempt to improve local control and survival, chemotherapy has been investigated as an adjunct to loco regional treatment.

Various schedules of chemotherapy and radiotherapy have been investigated: Induction chemotherapy (chemotherapy given before radiotherapy), adjuvant or sequential chemotherapy (chemotherapy given after radiotherapy), and concurrent or concomitant chemotherapy (chemotherapy given at the same time as radiotherapy). Theoretical benefits of delivering concurrent chemo radiotherapy are twofold: (1) local antitumor activity of radiotherapy is enhanced by the simultaneous use of chemotherapy as radio sensitizers and (2) the systemic activity of chemotherapy may eradicate possible micro metastases outside the irradiated field and improve survival. Meta-analyses have shown that concurrent chemo radiotherapy is superior to other sequences of chemotherapy and radiotherapy.[5,6]

A systematic review by Browman *et al*,[6] pooled analyses of 18 RCTs and detected a reduction in mortality for concomitant chemo radiotherapy compared with radiotherapy alone. The MACH-NC group reviewed 63 randomized trials conducted between 1965 and 1993 comparing combinations of loco regional treatment and chemotherapy versus loco regional treatment alone. The magnitude of the survival benefit associated with the addition of concomitant chemo radiotherapy was 8% at 5 years. This survival benefit was mainly due to an improvement in the loco regional control and only had a marginal effect on distant metastases.

The use of concomitant chemo radiotherapy for loco regionally advanced unresectable SCCHN is further supported by several recent RCTs. Adelstein *et al*, Olmi

et al and Calais *et al* reported randomized trials[4,7,8] comparing conventional doses of radiotherapy with or without concomitant chemotherapy. Regardless of the specific chemotherapy regimens used, the trials demonstrated a significant and consistent benefit in local control rates, translating into improvement in disease-free survival by a magnitude of 15% to 20%.

Toxicities Associated with Chemo Radiotherapy

Radiotherapy to the head and neck is commonly associated with acute and late toxicities.

Commonly observed acute toxicities are mucositis, stomatitis, and dermatitis, while depending on the site of irradiation, late toxic effects may include chronic xerostomia, dysgeusia, dysphagia, skin fibrosis, trismus, feeding-tube dependence, aspiration, and thyroid dysfunction. In general, the acute toxicities of radiotherapy are increased with the addition of concurrent chemotherapy.

The duration of acute toxicities also tends to be longer in patients receiving chemo radiotherapy. Furthermore, chemotherapy-specific toxicities such as nausea, vomiting, neuropathy, nephropathy, and ototoxicity occur with the use of systemic doses of chemotherapy. Acute hematologic and nonhematologic toxicity rates are consistently higher in the chemo radiotherapy arm across the clinical trials.

Patient selection for chemo radiotherapy and adequate supportive care during therapy are crucial. Co morbidities play an important role in determination of therapy. One important long-term quality-of-life outcome after chemo radiotherapy to the head and neck is swallowing function.

Biologic Agents in Frontline Therapy

An important step forward in the field of concomitant chemo radiotherapy was made with the advent of molecularly targeted therapies. It has been observed that the epidermal growth factor receptor (EGFR) is over expressed in almost all SCCHN tumors, and over expression of EGFR is associated with higher disease stage, lymph node metastasis, and poorer survival. EGFR expression increases progressively with increasing degrees of dysplasia and becomes markedly elevated in carcinomas, suggesting that EGFR up regulation is an early event in SCCHN oncogenesis. Since EGFR plays a significant role in SCCHN, a randomized trial comparing radiotherapy with or without cetuximab (anti-EGFR monoclonal antibody) was performed in patients with LA-SCCHN. The 2-year loco regional control rates increased from 48% to 56% with concurrent cetuximab radiotherapy. Major toxicities were dermatitis, mucositis, dysphagia, and acneiform rash (in the cetuximab arm). The toxicity rates in both arms were similar, except for rash in the cetuximab arm. This trial provides an important proof of principle that modulating the biology of SCCHN in combination with a physically targeted agent can impact on therapeutic outcome. This increases the armamentarium of drugs that are active with radiotherapy.[9,10]

Future Challenges

It is sufficient to state that concurrent chemo radiotherapy with a platinum agent is the current standard of care when a chemo radiation regimen is selected for therapy of LASCCHN; however, this remains a moving target as more effective chemotherapies and biologics are investigated. As the use of concurrent chemo radiotherapy increases in SCCHN, patient selection for primary surgery or definitive concurrent chemo radiotherapy becomes more complex. There has been no prospective randomized trial comparing outcomes of primary surgery versus definitive concurrent chemo radiotherapy to guide us. Therefore, a multidisciplinary approach coupled with close communication among the medical oncologist, radiation oncologist, radiologist, and surgeon is crucial to develop the best treatment plan for a particular patient.

Postoperative Chemo Radiotherapy for LA-SCCHN

Although surgery alone may be adequate treatment for early-stage SCCHN, additional therapy is required to prevent disease recurrence, even after an apparently complete resection for LA-SCCHN (Locally Advanced Squamous Cell Carcinoma of Head and Neck). A number of pathologic poor risk factors have been associated with higher recurrence rates after surgery, including positive margins of resection, extra capsular extension of disease from a lymph node, oral cavity primary, involvement of lymph nodes at levels 4 or 5 from carcinomas arising in the oral cavity or oropharynx, perineural extension, and vascular tumor emboli.

Data from 2 large randomized trials have substantiated that microscopically involved resection margins and/or extra capsular spread of tumor from lymph nodes are the most significant adverse prognostic factors. Retrospective studies have shown that adjuvant radiotherapy significantly reduces the recurrence rate of LA-SCCHN, especially for poor-risk patients. Despite adjuvant radiotherapy achieving good local control rates, distant metastasis occurred in almost one-third of

patients with poor-risk factors. Therefore, investigators have combined radiotherapy with radio sensitizing doses of chemotherapy.

This strategy utilizing cisplatin weekly with radiotherapy resulted in improvement in overall and disease free survivals over radiotherapy alone (5-year overall survival 36% versus 13%). However, distant disease control rates were similar. This implies that although good local control is achievable with radio sensitizing chemo radiotherapy, distant micro metastases are not obliterated with low doses of chemotherapy. The loco regional control rate and disease-free survival in the adjuvant chemo radiotherapy arm were significantly better than radiation alone.

Taken together, these trials provide new evidence that adjuvant chemo radiotherapy with a cisplatin-based regimen improves loco regional control rates and DFS, and improvement in OS appears very likely. Adjuvant concurrent chemo radiotherapy is associated with higher incidences of severe acute toxicities. In order to improve overall survival, the gain in loco regional control from the radio sensitizing effect of the chemotherapy needs to be integrated with therapy that decreases the risk of distant metastases. Adequate control of distant failure still has not been achieved, with approximately 20% to 30% of patients failing as a result of metastatic disease. One possible hypothesis is the chemotherapy used in these trials is ineffective in eradicating micro metastasis. Therefore, the incorporation of additional effective drugs should be investigated in the adjuvant setting.[11,12]

Update of Induction Chemotherapy: New Roles

The rationale underlying the use of an induction treatment plan is based on two hypotheses. One involves the better delivery of the drug in untreated, well-vascularized tumors and the second involves the eradication of the micrometastatic disease with systematically active doses of chemotherapy. In addition, the patient who is treatment-naïve is possibly more tolerant of the adverse effects of the chemotherapy treatment than the patient who has been irradiated. As mentioned a renewed interest has recently appeared for the use of IC.

Several phase II trials have explored the role of three-drug combination chemotherapy regimens with the administration of fluorouracil, cisplatin, and a taxane. In these studies, response rates higher than 90% were observed with complete responses in more than 50% of patients. Results from several large randomized trials have compared induction fluorouracil and cisplatin with fluorouracil, cisplatin and a taxane.[13-15] In the phase III trial reported by Vermorken *et al*, (TAX 323)[13] presented at ASCO 2004, 358 patients with unresectable disease were treated with docetaxel, cisplatin and 5-Fu (DPF) or cisplatin and 5- FU (PF), followed by radiotherapy. This study was updated and recently published with a median follow up of 32.5 months. The DPF regimen resulted in a significantly higher PFS (11.0 months vs. 8.2 months) and OS (18.8 months vs. 14.5 months). This study showed the superiority of DPF in terms of not only survival, but also quality of life. Another randomized phase III trial conducted by Calais *et al*,[16] presented at ASCO 2006 showed significant improvement in the response rate with the addition of a taxane. Patients with locally advanced cancer of the larynx or hypo pharynx were treated with cisplatin and 5-Fu with or without docetaxel, followed by radiotherapy alone for responders or total laryngectomy with neck dissection and postoperative radiotherapy for non responders. The overall response rate was significantly higher with DPF (82% vs. 60%) and more patients with DPF were able to avoid undergoing laryngectomy compared with patients receiving PF (73% vs. 63%).[16]

On the other hand, different studies have observed that chemo radiotherapy treatment have improved the loco regional control but have relative increased the risk of distant metastases. In these studies, distant metastases were developed in 15-20% of patients, irrespective of whether concurrent chemotherapy was utilized in the definitive management. The last consideration for this renewed interest is the observation that a response to chemotherapy could predict a response to subsequent irradiation. The discovery of biomarkers of response is an important issue when selecting patients in order to avoid toxicities. Ongoing clinical trials are incorporating this approach to select patients.

Sequential Therapy

Sequential therapy refers to the combination of induction chemotherapy followed by concurrent administration of chemo radiotherapy. Both approaches have advantages and disadvantages. For instance, classical IC advantages include the treatment of distant and loco regional disease. For the distant disease, IC treatment is administered with the intention of eradicate the microscopic disease. For the loco regional disease, the objective of IC treatment is to reduce the tumor before the start of radiotherapy. Toxicity with IC is usually transient, but IC does require a longer course of therapy.

On the other hand, CRT increases loco regional dose intensity in order to increase loco regional control.

However, this is an ineffective systemic therapy and is associated with significant local and systemic toxicity. In the same way, there is no method to assess prognosis and adjust intensity once CRT has started. For all these reasons combining IC with CRT as sequential therapy has a strong biologic rationale[17] and for thus, ongoing clinical trials are testing this approach.

The study performed by Machtay *et al*. included two cycles of carboplatin (area under the curve formula equal to 6) and paclitaxel 200 mg/m^2, followed by re-evaluation. Patients with major response continued to receive definitive radiotherapy (70 Gy over seven weeks) plus concurrent once-weekly paclitaxel (30 mg/m2/wk). In another study reported by Vokes *et al*, the sequential approach consisted of six weekly cycles of intensive carboplatin and paclitaxel (CP) chemotherapy followed by chemo radiotherapy with paclitaxel, hydroxyurea, 5-FU, and radiotherapy twice a day every other week. With a median follow-up of 28 months, the 3-year overall survival rate and progression free survival was 70% and 80%, respectively. The study conducted by Cmelak A used paclitaxel and carboplatin as an induction chemotherapy followed by CRT with carboplatin and paclitaxel. The 1 and 2-year-event free survival was 72% and 57%, respectively ($p = 0.02$).

Investigators from the Minnie Pearl Cancer Research Network Trial performed a study of high-dose carboplatin and paclitaxel (CP) for two cycles with 6-week continuous infusion of 5-FU. This induction regimen was followed by CP weekly with radiotherapy. There was a 51% 3-year survival rate in this group of patients with advanced disease. In a phase III study conducted by Hitt *et al*,[18] 383 patients were randomized to receive three cycles of paclitaxel and cisplatin and 5-FU (TPF) in one arm, or cisplatin and 5-FU (PF) in the other arm, followed by cisplatinum-based CRT. Resectable and unresectable patients were included (66% resectable vs. 33% unresectable). The primary objective was objective response. CR was observed in 33% in the TPF arm compared with 14% in the PF arm ($p < 0.001$). Patients with CR or PR of greater than 80% in primary tumor received cisplatinum based CRT. Patients with a partial response of less than 80% or stable disease in the neck lymph nodes after induction were referred to surgery before the administration of cisplatinum based CRT. Patients with no response in the primary tumor or progressive disease were taken off study and treated according to the investigator's discretion. An increase in TTP was observed for unresectable tumors in the TPF group (17.7 vs. 21.7). TPF patients had a trend to longer survival. Contrary to what might be expected, toxicity with paclitaxel plus cisplatin and 5-FU was less than that observed in those in the cisplatin and 5-FU arm.

The phase III trial, TAX 324,[19] recently published and conducted by Posner *et al*, evaluated more than 501 patients with loco regionally advanced SCCHN (both, non resectable and organ preservation candidates) in a sequential therapy plan of induction chemotherapy with cisplatin and 5-Fu with or without docetaxel followed by chemo radiation with carboplatin and surgical resection in patients with locally advanced head and neck cancer. The ORR after induction chemotherapy trended toward an improvement with DPF (72% vs. 64%). The 3-year survival data, including 69% of patients who have been followed for more than 3 years, demonstrated a significant advantage for DPF (62% vs. 48%). The median overall survival was 71 months and 30 months, respectively. There was better loco regional control in DPF arm than in the PF arm, but the incidence of distant metastases in the two arms did not differ significantly.

Although these studies have shown that the sequential approach is feasible and active, to our knowledge, there are no published data from phase III trials comparing the standard treatment of CRT versus an induction chemotherapy treatment followed by CRT. A phase II trial conducted by Paccagnella *et al*, presented at ASCO 2006 randomized patients with unresectable tumors to CRT (two cycles of cisplatin 20 mg/m2 d1-4 and 5-FU 800 mg/m2 I.C 96 h) versus three cycles of neoadjuvant DPF followed by the same CRT. The sequential approach was feasible and did not compromise the subsequent concomitant CRT. Radiological complete response was 20% in the arm of CRT versus 64% in the arm of sequential therapy. This difference justifies the starting of a phase III study.

To better address this issue investigators from the Spanish Head and Neck Cancer Study Group are conducting a phase III trial in which patients are randomized to cisplatin and 5-FU (PF) or cisplatin and 5-FU with docetaxel (TPF) followed by CRT or CRT alone. Although both schedule of induction chemotherapy were similar in terms of efficacy, induction chemotherapy plus CRT was feasible and more active than CRT alone. When TTP was considered, the sequential approach was superior to CRT alone.

Other studies are ongoing, for instance, in North America three clinical trials are testing a fluorouracil/cisplatin/docetaxel induction regimen followed by definitive chemo radiotherapy, compared with chemo radiotherapy alone. It is of interest to consider that two of these studies are using chemotherapy response as a predictor for the success of subsequent chemotherapy. In

one of those studies for patients not responders a more aggressive chemo radiation approach is administered, and in another one, surgical resection is the choice. It is important to consider that these phase III studies compare a three-drug induction regimen followed by definitive chemo radiotherapy, with chemo radiotherapy alone in a high-risk patient population with the intention of detecting difference in overall survival. The final results of these studies will have the potential to changing patterns of treatment improving the standard approach in the treatment of advanced SCCHN.

Integration of Novel Agents in the Sequential Approach

According to recent findings, agents that target the epidermal growth factor receptor such as cetuximab have shown to be active in combination with platinum compounds in metastatic SCCHN, and in combination with radiotherapy in locally advanced head and neck cancer. A recent phase III trial[9] randomized 424 patients with loco regionally advanced SCCHN to receive high-dose radiotherapy alone or high-dose radiotherapy plus weekly cetuximab. The median duration of loco regional control was 24.4 months among patients treated with radiotherapy plus cetuximab, and 14.9 months among those treated with radiotherapy alone but the cumulative rates of incidence of distant metastases at one and two years were similar in the two groups. There was a significant increase in the median duration of overall survival, 49.0 months among patients treated with combined therapy, compared to 29.3 months among those treated with radiotherapy alone.

One aspect to consider with this approach is the manner in which these new drugs are incorporated into the sequential treatment of locally advanced Head and Neck Cancer. For instance, the Eastern Cooperative Oncology Group is conducting a phase II trial in which cetuximab is administered in combination with weekly paclitaxel and carboplatin as induction chemotherapy followed by CRT in operable patients. This phase II trial was recently presented in ASCO 2007. This schedule of induction chemotherapy with cetuximab elicited a complete pathologic response at the primary site by restaging biopsy of 65% with induction alone, and 100% among sampled patients after chemo radiotherapy. These results suggest a high response with acceptable toxicity, included acneiform rash. The new toxicity profile of these combination regimens with new agents should be taken into consideration.

Conclusion

Like most tumors, SCCHN can be considered a systemic disease and for thus, an active systemic treatment should be administered. However, loco regional control of the disease is a main goal especially in locally advanced head and neck cancer. If we take these premises into consideration, the sequential treatment covers both necessities, and for thus, fit the biology of this disease in a better manner. Related to induction chemotherapy, it seems that taxanes could increase the response rates compared with the classical cisplatin and fluorouracil infusion regimen, although the best schedule has yet to be defined. In the same way, the toxicity profile of these combinations has not been clearly studied. In a similar manner, the study reported by Hitt *et al*, clearly demonstrated that the induction with paclitaxel could increase the response rates without increasing the toxicity. Although CRT is the standard approach in the treatment of unresectable locally advanced head and neck cancer, several questions are unclear.

Which is the Best Chemotherapy and Schedule to Administer with Radiotherapy?

At this point controversy still exists regarding the composition of the standard regimen. It is clear that no randomized trial has demonstrated that a taxane alone or in combination with other drugs is more effective than platinum monotherapy in combination with radiotherapy. At this moment it is important to consider that the role of chemotherapy is to sensitize local and regional disease to the effects of radiotherapy. In a similar way, the future role of CRT in combination with cetuximab should be defined.

The major goal of these studies is to better determine if sequential treatment with induction chemotherapy followed by CRT is a better option than CRT alone in terms of overall survival. This sequential approach has a strong biologic rationale. It is considered that the immediate period after completion of IC may be a biologically critical time. Considering the theoretical Gompertzian kinetics model, when the tumor volume is low the proliferation of cancer cells is more rapid. This is exactly what could happen after the administration of IC. With this model in mind, the addition of a non-cross-resistant therapy with minimal delay, as is the case of CRT after IC, should improve loco regional control. Most of the studies carry a CRT arm alone as a control arm to which the sequential approach should be compared. In conclusion, although CRT is considered by some authors as the standard treatment in locally advanced Head and Neck Cancer, sequential regimens are promising and data suggest that this approach could be superior to CRT.

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