Update on role of chemotherapy in head and neck squamous cell cancer

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Abstract

Head and neck squamous cell cancer (HNSCC) is most commonly a tobacco-related disease, affecting nearly 600,000 people worldwide each year. For decades, HNSCC has been treated successfully with multimodality treatments including, surgery, radiation, and chemotherapy, though the ‘perfect’ treatment paradigm remains elusive. This review will discuss a number of clinical trials, comparing various combinations of chemotherapy and the settings in which they are most successful. Promising research and recent data on the combination of cytotoxic chemotherapy with new biological agents indicate chemotherapy plays a critical role in treatment of HNSCC and will only continue to improve.

Keywords Head and neck cancer · chemotherapy · chemoradiation · induction chemotherapy · targeted therapy · cetuximab

Introduction

Head and neck Squamous cell cancer (HNSCC) affects approximately 600,000 individuals worldwide yearly,¹ including 45,660 in the USA.² HNSCC was first shown to be a chemosensitive disease in the 1960s and 70s,^{3,4} and since then has been treated successfully with platinum compounds, fluoropyrimidines, taxanes and, more recently, biological agents such as cetuximab. Radical surgery and/or radiation was the standard of care until the late 70s, when a role for chemotherapy in initial curative management began to be defined. In the 1980s, investigators focused on induction chemotherapy (IC) integrated with surgery and/or radiation to improve survival and functional outcomes. However, in the early 1990s, the focus shifted to administering chemotherapy concomitantly with radiation, to take advantage of the radiation enhancing properties of cytotoxics active in HNSCC. Defining the optimal sequence of chemotherapy and radiation became an important goal. More recently, efforts have focused on testing IC followed by concurrent chemora-

diation (CRT) to improve organ preservation rates, reduce locoregional and distant failure and improve overall survival. Importantly, biological therapies have entered into investigational trials and clinical practice for management of both locally advanced and recurrent/metastatic disease, adding a new dimension to treatment of HNSCC.

In the management of potentially curable HNSCC, chemotherapy has been used:

1. As IC with several cycles of a drug combination followed by definitive radiation/surgery.
2. As CRT in patients with resectable disease for organ preservation.
3. As CRT for patients with unresectable disease.
4. As IC alternating with radiation therapy.
5. As adjuvant CRT in patients whose resected tumors have high-risk pathologic features.

In the management of incurable HNSCC, chemotherapy has been used for palliation:

1. As a single agent, as an alternative to best supportive care in patients with poor performance status.

2. As combination chemotherapy in patients with good performance status.
3. As a combination with biological agents.

Role of induction chemotherapy

Chemotherapy administered prior to locoregional treatment reduces the risk of distant failure in patients with locally advanced tumors and particularly advanced neck disease (N2N3). Theoretically, the delivery of chemotherapy through intact tumor vasculature prior to surgery or radiation should improve response. The response to platinum-based IC is predictive of the response to subsequent therapy^{5–7} and would allow for alternative curative treatment for resistant non-responders. However, this approach potentially delays definitive locoregional treatment, and exposes patients to systemic toxicity.

Induction with cis/5FU

Three landmark randomized controlled trials (RCTs) investigated the role of IC and radiation (RT) as an alternative to surgery that included total laryngectomy. In 1985, the Veterans Administration Laryngeal Study Group (VALSG)⁸ conducted a study assigning 332 patients with stage III/IV resectable larynx cancer to 3 cycles of IC with cisplatin/5-fluorouracil (PF) followed by RT, or surgery (total laryngectomy) followed by postoperative RT. After a median follow-up of 33 months, 2-year survival was equivalent in both groups (68%) and the rate of larynx preservation in the IC group was 64%. In 1986, the European Organization for Research and Treatment of Cancer (EORTC) conducted a RCT in patients with respectable stage III/IV hypopharynx cancer, comparing IC with PF followed by RT, or surgery (total laryngectomy with partial pharyngectomy) and postoperative RT.⁹ Five-year survival rates were 38% and 33% for the IC/RT and surgery/RT groups, respectively. Five-year survival with a functional larynx for the IC/RT group was 22%. A third trial, for resectable larynx cancer, demonstrated significantly higher rates of larynx preservation and locoregional control with CRT, compared to IC followed by RT or RT alone.¹⁰

The role of IC was also investigated in patients with unresectable, locally advanced HNSCC. A study by Paccagnella et al.¹¹ that included resectable and unresectable Stage III/IV SCC of the oral cavity, oropharynx, hypopharynx and paranasal sinuses, randomized patients to IC with PF followed by RT, or RT alone. The 3-year disease-free and overall survival (OS) rates for IC/RT (34% and 24%, respectively) were significantly better compared to RT alone (26% and 10%, respectively). A 10-year follow-up revealed improved locoregional control and fewer distant metastases in the IC group compared to RT

alone.¹² A similar RCT by the Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC)¹³ treated 318 inoperable, oropharynx patients with 3 cycles of PF followed by RT, or surgery or locoregional treatment alone. The IC group had better median OS despite the study closing early for slow accrual. However, of over 30 such RCTs conducted worldwide, only in these two did induction cisplatin-based combination chemotherapy improve locoregional control or OS, although an impact was seen on reducing distant metastases in a number of studies. This led investigators to improvise the PF induction regimens over the last decade.

Induction chemotherapy with taxane/cisplatin/5FU (TPF)

To improve upon PF, RCTs of newly diagnosed patients receiving non-surgical curative therapy evaluated the addition of taxane to the standard PF doublet. Three Phase-III trials demonstrated superior efficacy for the 3-drug regimen. The TAX 323 trial randomized 300 patients with inoperable or unresectable HNSCC to 4 cycles of PF followed by RT (control), or 4 cycles of TPF (docetaxel, 75 mg/m²; cisplatin, 75 mg/m²; 5-FU, 750 mg/m²/day continuous IV infusion for 5 days) with growth factor support followed by radiotherapy.¹⁴ The response rate to the induction three-drug regimen was significantly higher compared with the two-drug regimen (68% vs 54%, $P = 0.006$), as was OS (HR = 0.73 (0.57, 0.94); $P = 0.016$). Importantly, less toxicity was exhibited with the three-drug combination.

Similarly, the TAX 324 trial treated 501 patients with unresectable or resectable disease (all sites) with three cycles of standard induction PF or to induction TPF. In both treatment groups, patients achieving at least a partial response subsequently received definitive radiotherapy plus weekly carboplatin.¹⁵ OS significantly improved for patients receiving the three-drug induction therapy.

The third trial, conducted by the European Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC), randomized 220 patients with resectable larynx or hypopharynx cancer requiring total laryngectomy to 3 cycles of induction PF or induction TPF (dosing same as TAX 323).¹⁶ Following IC, responding patients received 70 Gy of RT, while those with inadequate response underwent laryngectomy. The three-drug therapy was shown to be statistically superior for both response to IC (83% vs. 61%) and preservation of a functional larynx at 3 years (63% vs 41%).

The results of these RCTs suggest TPF induction is more effective than PF. However, because all patients received the same sequence of locoregional definitive treatment, the value of IC compared to treatment with CRT alone, the standard of care cannot be assessed. The trials were not uniform in reporting differences in local

control and distant control rates or site specific outcomes. Unfortunately, three RCTs initiated in the US to address this question were terminated early, for failure to accrue or loss of funding. Therefore, it remains unclear whether induction TPF followed by CRT or RT alone has an advantage over standard CRT.

As more intense treatment regimens are explored, it is apparent that a subset of HNSCC is more sensitive to chemotherapy and radiotherapy. The human papilloma virus-16 (HPV-16)-associated base of tongue and tonsillar cancers^{17,18} have a better prognosis than tobacco-related cancers of the oropharynx.^{19,20} Whether HPV-16 is also a predictive biomarker for response to a specific treatment regimen is yet to be demonstrated. The Eastern Cooperative Oncology Group (ECOG) reported the first prospective study of HPV tumor status and treatment outcomes. Patients undergoing non-surgical treatment of resectable larynx and oropharynx cancers received IC carboplatin and paclitaxel followed by CRT with paclitaxel and RT 70 Gy. The HPV-positive oropharynx cancer patients had significantly better response to IC (82% vs 55%, $P = 0.01$), as well as 2-yr progression-free survival (PFS; 85% vs 50%, $P = 0.05$) and OS rates (94% vs 58% $P = 0.004$) when compared to HPV negative patients.²¹ These results have encouraged investigators to explore less intense treatment in HPV-positive patients, without compromising survival outcomes. The ECOG has planned an important follow-up study using cisplatin/paclitaxel/cetuximab IC followed by lower dose RT and concurrent cetuximab in those achieving a complete response to IC, hypothesizing that this de-escalation of RT will reduce acute and late toxicities and improve function outcomes without compromising survival.

Induction chemotherapy with targeted agents

Prompted by favorable survival outcomes in other regimens, investigators are exploring less toxic triplet regimens by combining cetuximab, a monoclonal epidermal growth factor receptor (EGFR) antibody, with platinum and taxane. Cetuximab targets the EGFR, overexpressed in HNSCC, and has demonstrated activity in HNSCC when combined with RT in initial curative treatment and in the metastatic setting. Kies et al.²² conducted a Phase-II trial enrolling 47 patients with locally advanced HNSCC. Treatment consisted of induction paclitaxel (135 mg/m² weekly), carboplatin (AUC 2 weekly), plus Cetuximab (400 mg/m² week 1 then 250 mg/m² weekly) for a total of 6 weeks, followed by locoregional therapy. The complete response rate to IC was 70% for the primary site and 22% for regional nodes. The 3-year OS and PFS rates were 91% and 87%, respectively. A similar IC was tested in ECOG 2303, with 74 patients with locally advanced HNSCC.²³ Biopsy was performed to confirm response and a pathological complete response rate (CR) of 65% was deter-

mined after the induction regimen. Argiris et al.²⁴ conducted a Phase-II trial of IC docetaxel, cisplatin and cetuximab. The preliminary CR rate at the primary site was excellent. These novel induction regimens with cetuximab appear promising, but longer follow-up and RCTs will be needed to fully evaluate survival benefit.

Induction chemotherapy in nasopharyngeal carcinoma

The standard treatment for nasopharyngeal carcinoma (NPC) consists of concomitant cisplatin and radiation followed by adjuvant cisplatin + 5-FU. However, only 55% of patients are able to complete 3 cycles of the adjuvant chemotherapy. The high rate of distant metastases in NPC has led investigators to instead explore the feasibility of IC followed by chemoradiation. Rischin and colleagues²⁵ tested three cycles of induction epirubicin, cisplatin, and 5-FU followed by 60 Gy of radiotherapy and concurrent cisplatin (20 mg/m² daily for 5 days, administered weeks 1 and 6) in 35 patients with stage III/IV NPC. All patients completed the induction phase; 97% completed radiotherapy and cisplatin, note that the total dose of radiotherapy was lower than standard and that two, rather than three, courses of cisplatin were administered concurrently with the radiotherapy. After 4 years, OS was 94% and PFS was 81%. Similarly, Chan and colleagues²⁶ evaluated IC with carboplatin and paclitaxel followed by cisplatin (40 mg/m² per week)/RT in 31 patients with stage III/IV NPC. All patients completed the IC; 71% tolerated at least six weekly doses of cisplatin during RT. After 2 years, OS was 92% and PFS was 78.5%. Importantly, the number of patients in these trials was small, the enrolled population was from endemic areas and the CRT used in the US was not evaluated. However, the results appear promising and this sequential approach warrants further study.

Role of chemotherapy concurrent with radiation for organ preservation

The shift in treatment efforts during the 1990s allowed investigators to take advantage of potential radiosensitization. Cisplatin or carboplatin, 5 FU, paclitaxel, and most recently cetuximab, have been most frequently tested in combination with radiation. CRT is now the standard treatment for locally advanced oropharynx cancer, NPC, larynx and hypopharynx cancers. Site-specific landmark CRT trials that have established the standard of care in HNSCC are highlighted in Table 1.^{27–35}

The GORTEC study³³ included 226 patients with stage III/IV SCC of the oropharynx. Patients received either RT alone or radiation with concomitant bolus doses of carboplatin and 5-FU infusion for 4 days every 21 days.

Table 1. Selected randomized trials of concurrent chemoradiation in locally advanced HNSCC

Reference	Regimen	LRC	OS
Jeremic et al., 1997 5 year estimate ²⁷	Single agent		
	RT		15%
	RT + Cis (6 mg/m ²)		32% ($P = 0.011$)
	RT + Carbo (25 mg/m ²)		29% ($P = 0.019$)
Hugenin et al., 2004 5 year estimate ²⁸	RT	33%	32%
	RT + Cis(20 mg/m ²)	51% ($P = 0.039$)	46% (NS)
Adelstein et al., 2003 3 year estimate ²⁹	RT	NR	23%
	RT + Cis (100 mg/m ²)		37% ($P < 0.001$)
Forastiere et al., 2006 5 year estimate ³⁰	RT + Cis	69%	55%
	RT	51% ($P = 0.0005$)	54% (NS)
	Cis + 5 Fu f/b RT	55% ($P = 0.0018$)	59% (NS)
Bonner et al., 2006 3 year estimate ³¹	RT	41%	45%
	RT + Cetuximab	50% ($P = 0.005$)	50% ($P = 0.005$)
Brizel et al., 1998 3 year estimate ³²	Multiple agents		
	HF-RT	44%	34%
Calais et al., 1999 3 year estimate ³³	HF-RT + Cis + 5 FU	70% ($P = 0.01$)	55% ($P = 0.07$)
Starr et al., 2001 2 year estimate ³⁴	RT	42%	31%
	RT + Carbo + 5 FU	66% ($P = 0.03$)	51% ($P = 0.02$)
Denis et al., 2004 5 year estimate ³⁵	HF-RT	45%	39%
	HF-RT + Carbo + 5 FU	51% (NS)	48% ($P = 0.092$)
	RT	25%	16%
	RT + Carbo + 5 FU	48% ($P = 0.02$)	22% ($P = 0.05$)

Abbr: RT: Radiation, Cis: Cisplatin, Carbo: carboplatin, 5FU: 5 Fluorouracil, HF-RT: hyper fraction radiation, LRC: Locoregional control, OS: overall survival

CRT treatment produced a better 3-year survival rate (51% versus 31%; $P = 0.02$) and disease-free survival (42% vs 20%; $P = 0.04$), along with a greater degree of mucositis, need for a feeding tube, and hematologic toxicity. The improved survival outcomes in a population with typical tobacco history indicated CRT as a standard treatment option. It applies particularly to the management of stage T3 and T4 or N2 and N3 cancers otherwise resulting in substantial impairment of speech or swallowing function if treated with primary resection.

Another landmark trial, Intergroup 91-11 (for patients desiring to preserve their larynx) established concomitant chemoradiation with cisplatin as the standard of care. Surgery is reserved for management of persistent or recurrent disease following treatment completion.^{10,30} This trial addressed two important issues unresolved by the VALCSG trial: the precise contribution of chemotherapy added to radiotherapy, and the optimal sequencing of chemotherapy and radiotherapy (IC followed by

RT or CRT). 547 patients with resectable stage III/IV (T2 to low-volume T4) SCC of the larynx were randomly assigned to the following treatment groups: RT (70 Gy, 35 fractions); CRT with cisplatin (100 mg/m²), administered on days 1, 22 and 43 with the same radiation dose; or IC cisplatin and 5-FU, followed by RT for patients who had a complete or partial response at the primary site. Significant improvement in the 2-year larynx preservation rate and locoregional control was observed for the CRT group (88% and 78%, respectively) over the induction group (75% and 61%, respectively) and the radiation-only group (70% and 56%, respectively). The distant metastases rates were 8%, 9% and 16% for concomitant, induction and radiation-only groups, respectively. Further, disease-free survival was significantly better in both the concomitant (61%) and the induction (52%) arms compared with the radiation-only arm (44%); however, OS did not differ among the three groups. Chemotherapy-related toxicities, i.e. mucositis and hematologic toxic-

ity, were more common with combination treatments than radiation only. After a minimum follow-up of nearly 5 years, no survival differences were observed among the three treatment groups, and confirmed the benefit previously reported for concomitant cisplatin and radiation and establishing CRT as the standard of care for larynx SCC.

Locally advanced NPC has also benefited from the integration of chemotherapy into initial curative management. The results of the US Intergroup nasopharynx study, established a new standard of care.³⁷ Patients with stage III/IV NPC were randomly assigned to receive either radiation alone (70 Gy, 35 fractions for 7 weeks) or concomitant cisplatin (100 mg/m²) administered every 21 days with radiation, followed by three cycles of adjuvant cisplatin (80 mg/m²) and 5-FU (1000 mg/m²/day for 4 days). The OS and PFS after 5 years were significantly higher for patients who received combined-modality therapy (OS: 67% vs. 37%; PFS: 58% vs 29%). Strikingly, only 63% of patients received all three planned cycles of cisplatin during radiation and only 55% received all three cycles of adjuvant cisplatin and 5-FU.

Two meta-analyses have confirmed the benefit of combined chemotherapy and radiation in NPC. Huncharek et al.³⁸ analyzed six RCTs comprising 1500 patients; at 4 years, chemotherapy improved PFS by 34% and OS by 20%. A second report analyzed 8 RCTs (1753 patients) published between 1966 and 2003 using updated individual patient data.³⁹ The OS with combined chemotherapy and radiotherapy was an absolute survival benefit of 6% (56% to 62%; hazard rate [HR] of death) at 5 years. Event-free survival demonstrated an absolute benefit of 10% (42% to 52%; HR of tumor failure [local, regional or distant] or death) at 5 years. A significant interaction between the timing of chemotherapy and OS was observed with the highest benefit resulting from CRT.

Role of targeted therapy in combination with radiation

The epidermal growth factor receptor (EGFR) is highly expressed in HNSCC and is associated with poor prognosis. Thus, HNSCC trials have focused on therapies inhibiting EGFR. Bonner and colleagues³¹ piloted an important proof-of-principle multi-center RCT that led to USFDA approval of cetuximab for treatment of locally advanced HNSCC. 424 patients with locally advanced cancers of the oropharynx, larynx and hypopharynx received radiation with or without cetuximab. Local-regional failure-free survival and OS rates were significantly improved with the addition of cetuximab: the median duration of local-regional failure-free survival was 24.4 months with cetuximab and 14.8 months with RT alone ($P = 0.005$). At a median follow-up of 54 months, the 3-year survival rates were 57% with cetuximab/radiation versus 44%

with radiotherapy alone ($P = 0.02$). Cetuximab had no effect on reducing distant metastases. However, this combination has not been compared to standard chemoradiation; until then, the exact role for cetuximab with radiotherapy remains unclear. In our practice, we utilize cetuximab concomitant with radiation only in the treatment of patients whose age, performance status and/or extent of co-morbid disease would preclude concomitant chemoradiation with cisplatin or carboplatin.

Role of chemotherapy administered concurrently with radiation in the adjuvant setting

The results of two RCT, by the EORTC⁴⁰ and the RTOG,⁴¹ have clarified indications for the addition of cisplatin to adjuvant radiotherapy (Table 2). The experimental arms of both studies consisted of standard fractionation radiation with concurrent cisplatin (100 mg/m²) on days 1, 22 and 43. The 5-year results of the EORTC study indicated significant improvement in PFS (47% versus 36%, $P = 0.04$) and OS (53% versus 40%, $P = 0.02$) for concurrent cisplatin plus radiation. The 2-year results of the RTOG demonstrated a significant advantage with combined-modality adjuvant therapy for PFS, but not for OS (3-year survival: 56% versus 47%; $P = 0.09$). In both studies, toxicity was greater with CRT. With longer follow-up of the RTOG trial, the difference in disease-free survival was no longer significant.⁴² Importantly, a pooled analysis of both trials revealed that the subset of patients that significantly benefitted from adjuvant CRT were those with either positive margins or extracapsular extension of disease in neck nodes.⁴³ The presence of either or both of these risk factors is considered a clear indication for adjuvant CRT.

Impact of chemotherapy on survival in locally advanced HNSCC

The MACH-NC Collaborative group⁴⁴ conducted a meta-analysis of updated patient data to determine the benefit of chemotherapy as induction, adjuvant or concomitant with radiotherapy in the curative management of HNSCC. This meta-analysis initially included 63 RCT published from 1965 to 1993. There was no significant survival benefit from IC (31 trials; 5,269 patients; HR = 0.95; 95% CI: 0.88, 1.01; $P = 0.10$) compared to definitive local therapy alone. Interestingly, however, in a subset analysis of trials of induction PF, a survival benefit was noted, (HR of 0.88, 95% CI 0.79–0.97, $P = 0.05$) along with a decrease in the incidence of distant metastases.

An updated meta-analysis by MACH-NC included studies from 1965 to 2000.⁴⁵ Adding chemotherapy yielded a significant benefit in OS with a 4.5% absolute improvement in 5-year survival. A more pronounced

Table 2. Selected randomized trials of postoperative adjuvant concurrent chemoradiation

Reference	Regimen	OS	LRC
EORTC 22931	S f/b RT	40%	69%
Bernier et al., 2004 5 year estimate ⁴⁰	S f/b RT + Cis*	53% ($P = 0.02$)	82% ($P = 0.007$)
RTOG 9501	S f/b RT	57%	72%
Cooper et al., 2004 2 year estimate ⁴¹	S f/b RT + Cis*	64% ($P = 0.19$)	82% ($P = 0.01$)

Abbr: S: Surgery, RT: Radiation, Cis: Cisplatin, f/b: followed by, OS: Overall survival, LRC: Locoregional control. *Cisplatin 100mg/m² Day1, 22 and 43

Table 3. Meta-analysis of chemotherapy in HNSCC (MACH-NC). An update on 93 trials and 17,346 patients (adapted from Pignon et al.)⁴⁵

Endpoint	Induction CT	Concomittant CT
Locoregional failure	HR 1.03 (0.95–1.13) $P = 0.43$	HR 0.74 (0.70–0.79) $P < 0.0001$
Distant failure	HR 0.73 (0.61–0.88) $P = 0.001$	HR 0.88 (0.77–1.00) $P = 0.04$
Overall survival	HR 0.96 (0.90–1.02)	HR 0.81 (0.78–0.86) $P < 0.0001$

Abbr: HR: Hazard rate

effect of chemotherapy was noted in the concomitant group, but no benefit was observed for chemotherapy in the induction or adjuvant chemotherapy group (HR 1.06 [0.95–1.18] $P = 0.32$). The overall absolute benefit at 5 years for the entire population that received chemotherapy was 4.1% (from 26.8 to 30.9%). Concomitant chemoradiation positively affected OS, event-free survival and loco-regional failure. The magnitude of benefit with concomitant therapy was identical for the trials from 1965 to 1993 and 1994 to 2000. The absolute benefit in survival (6.5%) favored the concomitant approach.

For IC, a non-significant absolute benefit of 2.4% was observed at 5 years.⁴⁵ Further, there was no significant difference in survival by type of chemotherapy. IC also did not have a differential effect on survival related to age, sex, performance status, or tumor site. However, there was a significant reduction in distant metastases with IC compared to CRT (Table 3). Such results support the hypothesis that induction chemotherapy and concomitant chemoradiation are complementary and provide a basis for clinical trials testing IC followed by CRT.

Role of chemotherapy in recurrent or metastatic HNSCC

In patients with unresectable recurrent or metastatic disease, the options for treatment depend on patient performance status and tumor burden and range from combination chemotherapy and combination targeted

therapy plus cytotoxic chemotherapy, to single agent chemotherapy or best supportive care.⁴⁶

Numerous single agents have demonstrated activity in HNSCC, with response rates ranging from 15 to 45%. Among these are cisplatin/carboplatin,⁴⁷ methotrexate,⁴⁸ 5-FU,⁴⁹ taxanes,^{50–52} gemcitabine,⁵³ doxorubicin,⁵⁴ pemetrexed,⁵⁵ cyclophosphamide,⁴⁶ hydroxyurea,⁴⁶ irinotecan⁴⁶ and ifosfamide⁷¹ (Table 4). For example, in a Phase-III trial 259 patients with recurrent head and neck cancer received either cisplatin (100 mg/m²) and 5-FU (1 g/m² × 4), cisplatin alone or 5-FU alone every 3 weeks. The overall response rate to the combination was 32%, better than cisplatin alone (17%) or 5-FU alone (13%).⁴⁹ No significant difference in median OS (5.7 months) was observed among the groups; the median PFS was 2.5 months. More recently biological agents such as cetuximab, erlotinib, gefitinib and lapatinib, have demonstrated a response rate of 10–14% as single agents.⁵⁶ In a Phase-II trial of 52 patients, 500 mg/day of gefitinib resulted in an 11% major response rate.⁵⁷ In a Phase II trial with 115 patients, erlotinib (150 mg/day) resulted in a 4% major response rate.⁵⁸ Among the biological agents, cetuximab is the only molecularly targeted drug to be approved for use in head and neck cancer, specifically for patients considered platinum refractory. Several other EGFR monoclonal antibodies are being developed for HNSCC, including matuzumab, panitumumab, and nimotuzumab.

Phase-III trials comparing combination regimens to single-agent chemotherapy in metastatic/recurrent HNSCC revealed higher response rates and increased toxicity with

Table 4. Selected trials in recurrent/metastatic HNSCC

Reference	Regimen	Overall response rate (%)	Median survival (months)
Hong et al., 1983 ⁴⁸	MTX	23.5%	ND
	Cisplatin	28.6%	
Jacobs et al., 1992 ⁴⁹	Cisplatin	17%	ND
	5 FU	13%	
	Cis/5FU	32%	
Forastiere et al., 1992 ⁵⁹	MTX	10%	ND
	Carbo/5FU	21%	
	Cis/5 FU	32%	
Gibson et al., 2005 ⁶¹	Cis/5 FU	27%	ND
	Cis/Paclitaxel	26%	
Glisson et al., 2002 ⁶²	Docetaxel/Cis	40%	9.6
Bentzen et al., 2007 ⁶⁷	Paclitaxel/capecitabine	42%	8
Hitt et al., 2004 ⁶⁸	Cisplatin/capecitabine	68%	12.6
Worden et al., 2006 ⁶⁹	Paclitaxel/Cis/5 FU	41%	10
Shin et al., 1998 ⁷¹	Paclitaxel/ifosfamide/cisplatin	58%	8.8
Burtneess et al., 2005 ⁷⁶	Cis/Placebo	10%	ND
	Cis/Cetuximab	26% ($P = 0.03$)	7.4
Vermoken et al., 2008 ⁷⁷	Cis/Carbo/5-FU	20%	10.1 ($P = 0.036$)
	Cis/CArbo/5-FU/Cetux	36% ($P < 0.001$)	

Abbr: MTX: methotrexate, Cis: cisplatin, Carbo: Carboplatin, 5-FU: 5 Fluorouracil. ND: No difference

combination regimens, but no improvement in overall survival.^{59–70} In a multi-center RCT comparing cisplatin or carboplatin + 5-FU with methotrexate, a significantly better response was observed rate for the combination arms, though median survival and duration of response were unchanged.⁵⁹ Response rates in studies comparing triple-drug regimens such as cisplatin or carboplatin + ifosfamide + paclitaxel or cisplatin + 5-FU + docetaxel have been as high as 60%, even in pretreated patients, with median of survival of 9–11 months.⁷¹ Another more complex regimen of cisplatin + methotrexate + bleomycin + vincristine compared with cisplatin + 5-FU or with cisplatin alone found similarly improved response rate and greater toxicity for combination regimens, but no survival advantage over single-agent therapy.⁷²

Biological agents with additive effects when combined with active HNSCC cytotoxics are of clinical interest because they add potential new, and successful, treatment options.^{73–76} Burtneess et al. first reported the treatment of 123 patients with recurrent HNSCC with either cisplatin + placebo or cisplatin + cetuximab. There was no significant difference in the median PFS (2.7 months versus 4.2 months, respectively; $P = 0.27$), but the major response rate (complete plus partial) was significantly higher for patients who received cisplatin plus cetuximab (26% vs 10%, respectively; $P = 0.03$).⁷⁶

Importantly, a recent Phase-III trial reported an improvement in OS of patients with recurrent/metastatic HNSCC.⁷⁷ 440 patients with recurrent or metastatic dis-

ease received either first-line therapy with cisplatin + 5-FU + cetuximab or standard PF. After a median follow-up of 19.1 months, the median survival was significantly better in the cisplatin/5-FU + cetuximab treatment group (10.1 vs 7.4 months (HR 0.80; 95% CI, 0.64 to 0.99; $P = 0.04$). The median PFS also improved (5.6 vs 3.3 months (HR 0.54; $P < 0.001$) as did response rate (20% to 36% ($P < 0.001$)).

Trials are ongoing for combination therapy with other biological agents targeting the EGFR pathway, such as vascular endothelial growth factor (VEGF) inhibitor.^{78,79} One phase-II trial of the combination of erlotinib (EGFR TK inhibitor) and bevacizumab (VEGF inhibitor) resulted in a 17% response rate and median survival of 7.5 months in patients previously treated for recurrent disease.⁷⁸ Such biologicals prove promising in improving treatment options for HNSCC.

Conclusion

The role of chemotherapy in the management of HNSCC has evolved over more than two decades of clinical research trials conducted around the globe, defining current standards of care. Cisplatin combined with radiotherapy increases organ preservation, vastly improving quality of life without jeopardizing survival. While standard surgical approaches would substantially impair speech and swallowing function for patients with locally

advanced cancers of the larynx, hypopharynx and oropharynx, recent studies have promoted the use of nonsurgical treatment options. However, the use of concomitant chemoradiation is not without cost, due to the potential for late effects. Advances in our understanding of the biology of HNSCC, along with changes in epidemiology, e.g. the recently discovered association of HPV-16 and

oropharynx cancer, provide new challenges for the clinician and researcher. The addition of biological therapies into the clinic has added an entirely new class of systemic therapeutics that will likely change treatment paradigms. It has become clear that there is no longer only one way to manage HNSCC and that the best care is delivered through a multi-disciplinary team approach.

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