The Role of Chemotherapy in the Management of Patients with Head and Neck Cancer

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ABSTRACT

Recent advances in the management of patients with head and neck cancer point to an expanding role of chemotherapy, resulting in an increased involvement of the medical oncologist in the multidisciplinary care of these patients. This review focuses on patients with squamous cell carcinoma of the oral cavity, pharynx, and larynx. A comprehensive review of the clinical trial data that have defined new standards of care and a detailed presentation of widely used chemotherapeutic regimens, including both cytotoxic and molecularly targeted agents, are presented. Information on human papilloma virus-associated squamous cell cancer of the head and neck is presented, and implications in the clinical management of this subgroup of patients based on the epidemiologic and pathologic characteristics are discussed.

KEYWORDS: Cancer of the head and neck, chemotherapy, squamous cell carcinoma

Approximately 48,000 new cases of head and neck cancer were expected in the United States in 2009 alone,¹ and more than 600,000 new cases will be diagnosed worldwide. Head and neck cancer accounts for 3 to 4% of all cancer diagnoses in Western countries,^{2,3} and its incidence is higher in southeast Asia and in Africa where it accounts for 8 to 10% of all cancers.⁴ Overall, head and neck cancer represents the eighth most common cause of cancer death.

Historically, treatment of patients with squamous cell carcinoma of the head and neck (SSCHN) has primarily been driven by surgical interventions and continued advances in radiation therapy (RT) treatment planning and delivery. In this setting of complex treatment algorithms, recent advances in the management of

patients with head and neck cancer point to an expanding role of chemotherapy and therefore an increased involvement of the medical oncologist in the multidisciplinary care of these patients.

The scope of this review is to provide a comprehensive description of expanding chemotherapeutic options, including both cytotoxic and molecularly targeted agents, that are applicable to patients diagnosed with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx. Data on patients diagnosed with cancer of the nasopharynx will be presented separately because of its distinct etiology, pathology, and response to treatment modalities.

Chemotherapy alone does not have curative potential. As a result, it does not have a defined role

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in the management of patients with early-stage disease (stages I and II) where single modality (surgery or RT) offers high cure rates, with 5-year overall survival (OS) rates around 85% for stage I SCCHN and around 70% for stage II disease.⁵⁻⁸ The remaining part of the review will therefore focus on describing the role of chemotherapy in the locally advanced (LA SCCHN) recurrent and metastatic settings.

Although the importance of site-specific characteristics in selecting the most appropriate combination modalities should not be underestimated, we purposely chose a concept-based approach to better address the continuity and evolution of treatment concepts (Fig. 1).

ROLE OF CHEMOTHERAPY IN LA SCCHN

Chemotherapy with Concurrent RT in the Postsurgical Setting

In patients with LA SCCHN undergoing definitive surgery (stages III, IVa), local and regional recurrence rates remain significant (up to 50% at 2 years), distant metastases develop (up to 20% at 2 years), and 5-year survival rates are poor.⁹ Postoperative adjuvant RT in this setting has been used in patients with pathologic findings associated with high risk for locoregional recurrence.

In an attempt to further improve outcomes, the role of concurrent administration of cytotoxic chemotherapy during RT has been investigated in two phase III clinical trials where high-dose cisplatin (100 mg/m²)

administered on days 1, 22, and 43 of concurrent RT was evaluated.^{10,11}

In both trials, patients with LA SCCHN of the oral cavity, oropharynx, larynx, or hypopharynx were included. In the first trial conducted in Europe, an improvement in both OS as well as improved locoregional control was observed, favoring the addition of chemotherapy to concurrent RT treatment. In the trial conducted in the United States and coordinated by the Radiation Therapy Oncology Group (RTOG), an improvement in disease-free survival was documented, but it did not result in a statistically significant improvement in OS. Based on these findings, concurrent chemoradiation therapy (CRT) has become the new standard of care for patients with surgically resected tumors demonstrating high-risk features.

Precise definition of high-risk features remains a research question, as definitions were not identical in the two trials. More specifically, in the European trial, high-risk features included pathologically defined advanced primary tumors (pT3 or pT4) and any nodal stage (N), except T3N0 of the larynx with negative resection margins, or an early primary tumor (pT1 or pT2) with an advanced nodal stage (N2 or N3) and no distant metastasis (M0). Patients with early-stage primary tumor (pT1 or pT2) and nodal stage (N0 or N1) who had unfavorable pathology findings (extranodal spread, positive resection margins, perineural involvement, or vascular tumor embolism) were also eligible, as were patients with oral cavity or oropharyngeal primary tumors with involved lymph nodes at level IV or V. In the

Figure 1 Treatment options involving chemotherapy for locally advanced squamous cell carcinoma of the head and neck.

RTOG trial, the presence of any or all of the following features allowed patients to meet eligibility criteria: histologic evidence of invasion of two or more regional lymph nodes, extracapsular extension of nodal disease, and microscopically involved mucosal margins of resection.

In an attempt to identify the subgroup of patients most likely to benefit from concurrent CRT, a retrospective pooled analysis of data of individual patients was undertaken,¹² which revealed that positive margins and/or extracapsular spread of tumor from involved lymph nodes were the most significant prognostic factors for poor outcome. As a result, consensus recommendations, currently endorsed by the National Comprehensive Cancer Network (NCCN) Head and Neck Committee, identifies this subgroup of patients at high risk for recurrence, and addition of chemotherapy to adjuvant RT represents the current standard of care. Additional high-risk features included in the eligibility criteria of these trials as well as retrospective analyses undertaken using other data sets (pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism)^{13–15} can still be considered on a case by case basis in making adjuvant RT versus concurrent chemotherapy and RT recommendations.

Induction Chemotherapy in the Management of Patients with LA SCCHN

As early clinical trials in the metastatic setting established that SCCHN is a chemosensitive disease, attempts were initiated to evaluate the additional benefit in improved locoregional control and decreased incidence of metastatic disease by the addition of chemotherapy prior to surgery or RT. In theory, induction chemotherapy offers several advantages, including decreasing the size of the primary tumor and nodal metastases allowing improved efficacy and potentially less local toxicity after the subsequent use of either surgery or RT and reducing/eliminating potential sites of distant micrometastases.^{16–18}

The landmark trial that validated induction chemotherapy is the Department of Veterans Affairs Laryngeal Cancer Study Group trial,¹⁹ which compared total laryngectomy to organ preservation with induction chemotherapy followed by RT. This study also established the use of the cisplatin and 5-fluorouracil (5-FU) combination regimen, which remained the standard of care regimen for induction chemotherapy until improved induction chemotherapy outcomes were demonstrated with the addition of a taxane to the cisplatin and 5-FU backbone.

The efficacy of induction chemotherapy followed by RT compared with that of RT alone was evaluated in a meta-analysis that documented that there was no survival benefit of adding induction chemotherapy to

RT alone when all induction regimens were included in the meta-analysis; however, a statistically significant benefit could be established (hazard ratio = 0.88, 95% CI, 0.79 to 0.97) when only platinum and 5-FU combination regimens were examined.²⁰

More recently, multiple trials have shown that the addition of a taxane to the cisplatin and 5-FU backbone results in improved outcomes. Docetaxel has been added to cisplatin and 5-FU (TPF regimen) both as an organ preservation study as well as in patients with LA unresectable SCCHN.^{21,22} In the setting of an organ preservation strategy, the addition of docetaxel resulted in a statistically significant 3-year laryngeal preservation rate (70% vs. 58%), and in the unresectable SCCHN setting the addition of docetaxel resulted in an improvement in both progression-free survival (PFS) as well as OS (11 vs. 8.2 months, and 18.8 vs. 14.5 months, respectively). Paclitaxel-containing induction regimens have also been evaluated and have demonstrated improved outcomes.^{23,24}

Finally, induction chemotherapy has been used as a tool to guide subsequent modality selection. In this setting, a cycle of induction chemotherapy is administered followed by administration of definitive concurrent CRT to responders, whereas nonresponders undergo surgery. This approach has been successful in patients with LA SCC of the larynx,²⁵ but the same strategy has not been successful in patients with oropharyngeal²⁶ and oral cavity²⁷ primary tumors. Given mixed results, this approach remains investigational and should not be used outside of a clinical trial setting.²⁸

Concurrent CRT

The Department of Veterans Affairs laryngeal trial established that an organ preservation strategy using induction chemotherapy followed by definitive RT results in an OS survival comparable with that of primary surgical resection.¹⁹

Subsequent clinical research, including the landmark intergroup RTOG study 91–11, attempted to define the most effective organ preservation strategy. This three-arm study in patients with LA SCC of the larynx compared RT alone to concurrent CRT and to induction chemotherapy followed by definitive RT.^{29,30} A total of 547 patients were included in the study, and, after a median follow-up period of 3.8 years, RT with concurrent administration of cisplatin was found to be superior to induction chemotherapy followed by RT or RT alone for laryngeal preservation (88% vs. 75% vs. 70%, respectively) and locoregional control (78% vs. 61% vs. 56%, respectively).

The chemotherapeutic agent is high-dose cisplatin (100 mg/m²), administered concurrently with RT on days 1, 22, and 43. However, cisplatin administration is associated with significant toxicities (Table 1). Therefore,

Table 1 Commonly Used Chemotherapeutic Regimens

Chemotherapy	Dose, Frequency, Number of Cycles	Selected Adverse Events	References
Cisplatin (P)	(Every 3 weeks, RT days 1, 22, 43) P: 100 mg/m ² on day 1	(Grade 3–5 increased frequencies, compared with control arm, occurring in more than 10% of patients) Nausea/vomiting (12–40%) Neutropenia (13%) Infection (12%) Peripheral neuropathy (10%) Nausea/vomiting (12–40%) Neutropenia (13%) Infection (12%) Peripheral neuropathy (10%)	10, 11, 29
Cetuximab	Loading dose: 400 mg/m ² (4–10 days prior to RT) Maintenance: 250 mg/m ² (weekly during RT)	(Grade 3–5 increased frequencies) Infusion reactions (3%) Acneiform rash (17%) Hypomagnesemia	32, 44, 60, 78
TPF (TAX 324)	(Every 3 weeks for 3 cycles)	(Grade 3 or 4 frequencies)	33
Docetaxel (T)	T: 75 mg/m ² on day 1	Neutropenia (33%)	
Cisplatin (P)	P: 100 mg/m ² on day 1	Infection (7%)	
5-FU (F)	F: 1000 mg/m ² CI days 1–4	Febrile neutropenia (5%)	
TPF (European)	(Every 3 weeks for 4 cycles)	(Grade 3 or 4 frequencies)	21
Docetaxel (T)	T: 75 mg/m ² on day 1	Neutropenia (77%)	
Cisplatin (P)	P: 75 mg/m ² on day 1	Alopecia (12%)	
5-FU (F)	F: 750 mg/m ² by CI days 1–5	Infection (7%) Febrile neutropenia (5%)	
Cisplatin (P)	P: 100 mg/m ² on day 1	Nausea/vomiting (7–14%)	19, 21, 33, 87
5-FU (F)	F: 1000 mg/m ² by CI days 1–5	Hematologic (52–56%) Infection (5–6%) Peripheral neuropathy (1–4%)	

CI, continuous infusion; 5-FU, 5-fluorouracil; RT, radiation therapy.

alternative cytotoxic chemotherapy regimens have been tried in select patient populations, including weekly cisplatin protocols, substitution with carboplatin, and combination cisplatin/carboplatin with a taxane of 5-FU, supported by limited clinical trial data and included in the NCCN Head and Neck Committee guidelines.

Meta-analyses have compared the efficacy of concurrent CRT to RT alone and have consistently demonstrated improved efficacy for the concurrent CRT approach. For platinum including chemoradiation protocols, an improved OS of 8 to 11% has been demonstrated in both surgically resectable patients and unresectable patients.³¹ Based on these findings, concurrent CRT is considered the standard of care.

Cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor (EGFR), is currently approved for use with RT in patients with LA SCCHN, based on phase III clinical trial data comparing RT alone to concurrent RT and cetuximab, which documented a statistically significant improvement in OS for the combination arm.³² This is analyzed in detail in the later section “Molecularly Targeted

Agents in LA SCCHN.” No direct comparisons of a cytotoxic agent to a targeted agent when administered concurrently with RT have been reported, as clinical research efforts are currently directed to evaluating the effectiveness and safety of cytotoxic and targeted combination chemotherapy regimens administered concurrently with RT.

Sequential Treatment

Sequential therapy, that is, the combination of induction chemotherapy followed by concurrent CRT, represents the most recently developed treatment paradigm in the management of patients with LA SCCHN. It is an attempt to combine the gains observed with both induction chemotherapy (resulting in decreased distant metastases) and concurrent CRT (resulting in improved locoregional control).^{33,34} It remains unclear at this point if sequential treatment will provide a survival advantage over concurrent CRT; randomized trials addressing this question are currently being conducted.^{35,36}

The most recent attempt at optimizing the induction regimen in a sequential treatment approach has been the TAX 324 study,³³ which is a phase III registration trial comparing two induction regimens, TPF (docetaxel, cisplatin, 5-FU) and PF (cisplatin, 5-FU), each followed by concurrent CRT with carboplatin (administered weekly at an area under the concentration-time curve of 1.5). After a median follow-up of 42 months, the TPF arm demonstrated statistically significant improvement in both median PFS (36 vs. 13 months) as well as OS (62% vs. 48%) compared with the PF arm.

However, improved outcomes were achieved at a cost because sequential therapy regimens have been associated with significant acute toxicities. The TPF regimen has been associated with increased incidence of neutropenia and febrile neutropenia despite prophylactic antibiotic use. Interestingly, not all toxicities occurred more frequently in the three-drug combination regimen TPF, as mucositis and treatment delays were more frequent in the two-drug combination regimen PF.

Therefore, selection of the appropriate patients appears to be critical. Sequential therapy protocols should be preferentially offered to younger patients, patients with a good performance status (ECOG performance status 0 or 1), normal end-organ function, and no significant comorbidities. Patients with T4 primary tumors, as well as extensive lymphadenopathy (N2 and N3), may benefit the most from a sequential therapy regimen, as it might control better the risk for metastases.

Further optimization of the chemotherapy regimens used in the sequential treatment protocols will be accomplished once the proper incorporation of molecularly targeted therapies, such as the monoclonal anti-EGFR antibody cetuximab, has been defined. Currently, the addition of cetuximab to cytotoxic regimens both in induction as well as with concurrent chemoradiation appears feasible, but confirmatory results from large clinical trials are still lacking.

MOLECULARLY TARGETED AGENTS IN LA SCCHN

EGFR has been shown to be overexpressed in SCCHN and has been associated with worse prognosis.^{37,38} Activation of EGFR promotes angiogenesis and proliferation therefore facilitating tumor growth and metastasis.³⁹

It is not surprising therefore that EGFR inhibition in patients with SCCHN has been an early target for drug development. The monoclonal anti-EGFR antibody binds to the receptor and prevents phosphorylation and activation of downstream kinases.

Cetuximab was evaluated in a phase III clinical trial comparing RT alone to RT with cetuximab in patients with LA SCCHN. The addition of cetuximab

resulted in statistically significant improvement in both locoregional control (24 vs. 15 months) and rates of PFS (42% vs. 31%) and OS (55% vs. 45%). Overall, cetuximab was well tolerated. Compared with RT alone, cetuximab was associated with rare infusion reactions, hypomagnesemia, and the development of acneiform rash in the majority of exposed patients. Although not observed in the initial trial, subsequent data point to increased rates and severity of radiation dermatitis and mucositis in patients treated with concurrent cetuximab and RT.

It remains unclear how cetuximab compares with cytotoxic radiosensitizing chemotherapy, as direct comparisons have not been reported and current research efforts are focused on how best to combine cytotoxic chemotherapy and cetuximab with concurrent RT, and many clinical trials are currently attempting to optimize combination regimens.

It also remains unclear in which subgroup of patients with LA SCCHN cetuximab should be the radiosensitizing agent of choice. For patients who are not old, with an excellent performance status, no compromise of their end-organ functions, and no significant comorbidities, cisplatin radiosensitizing chemotherapy represents the widely accepted standard of care. For patients who are not eligible for cytotoxic chemotherapy, representing a significant proportion of newly diagnosed LA SCCHN patients, cetuximab should be always considered.

ROLE OF CHEMOTHERAPY IN RECURRENT DISEASE

For patients who develop locally recurrent disease or a second primary within the radiation field, salvage surgery represents the best option for improving survival, if technically feasible.

Administration of induction chemotherapy prior to surgery and re-irradiation has been studied. For example, a small clinical trial using an induction regimen of pemetrexed and gemcitabine and carboplatin and pemetrexed as radiosensitizers reported an encouraging 42% 1-year survival in an early abstract,⁴⁰ but it is impossible to compare this with other published reports using different approaches because outcomes appear to be primarily driven by patient selection.

For patients not eligible for surgical resection or who deny surgery, palliative chemotherapy still represents the standard of care, but re-irradiation is increasingly being used. In this setting, concurrent administration of chemotherapy as a way to overcome radioresistance is conceptually well justified but has not been optimized. Outside of a clinical trial, administration of a platinum compound either alone or in combination with a taxane of 5-FU is used. Decisions are driven by patient characteristics, including age, performance status, comorbidities,

and expected toxicities.^{41,42} In all re-irradiation clinical research attempts, acute toxicities have been a serious concern, as reported outcomes from phase II clinical trials conducted by RTOG show 8 to 11% treatment-related fatalities.

Given poor outcomes and significant toxicities, novel agents are urgently needed. Unfortunately, most of these trials are single-institution, small phase I/II trials, which are more useful in early identification of potential safety issues rather than evaluation of efficacy given inevitable patient selection bias. Current efforts evaluating various anti-EGFR molecules alone or in combination with anti-angiogenesis agents are under way.

CHEMOTHERAPY IN METASTATIC DISEASE

Overall prognosis of patients diagnosed with metastatic disease is poor, with a median survival of 6 to 9 months. Survival and quality of life vary widely based on patient and disease parameters. The role of systemic palliative chemotherapy versus best supportive care has been studied, and an improved median survival by 2.5 months over best supportive care with the use of a cisplatin-containing regimen was demonstrated.⁴³

Depending on patient's age, performance status, and comorbidities, palliative chemotherapy recommendations may include single-agent or combination cytotoxic chemotherapy or molecularly targeted agents either alone or in combination with cytotoxic chemotherapy.^{44,45} Numerous chemotherapeutic agents have shown single-agent activity including, but not limited to, cisplatin,^{46,47} taxanes,^{48,49} 5-FU,^{50,51} gemcitabine,^{52,53} pemetrexed,⁵⁴ etoposide,⁵⁵ irinotecan,^{56,57} and methotrexate.^{58,59}

Observed response rates for single-agent cytotoxic chemotherapy range from 15 to 30% with responses lasting 3 to 5 months on average. Molecularly targeted agents show lower response rates, ranging from 10 to 13% for the monoclonal anti-EGFR antibody cetuximab⁶⁰ to 1 to 11% for the tyrosine kinase inhibitors erlotinib⁶¹ and gefitinib.^{62–66}

For patients with excellent performance status, normal end-organ function, and no significant comorbidities, combination chemotherapy regimens are recommended. Most frequently used are two-drug combination regimens (cisplatin + 5-FU,^{67,68} cisplatin + paclitaxel,^{69,70} cisplatin + docetaxel,^{71–74} carboplatin + taxane^{75–77}) and are associated with improved response rates compared with single agent, but they are also associated with increased toxicity and no statistically significant survival benefit.

Cetuximab has a modest single-agent activity, and its addition to cisplatin compared with cisplatin alone has led to an improvement in response rate (26%

vs. 10%) but with no improvement in PFS or OS.⁷⁸ However, the addition of cetuximab to the two cytotoxic drug combination of cisplatin and 5-FU (PF) resulted in a statistically significant improvement in both the PFS (5.6 vs. 3.3 months) as well as the OS (10.1 vs. 7.4 months) when compared with cisplatin and 5-FU alone in a phase III European trial⁴⁴ and could become a new standard of care for first-line treatment of metastatic SCCHN.

ROLE OF CHEMOTHERAPY IN HUMAN PAPILLOMA VIRUS-ASSOCIATED HEAD AND NECK CANCER

Recent epidemiologic and molecular studies have provided evidence of a causal association between (human papilloma virus) HPV and a subset of head and neck cancers. The overall prevalence of HPV-associated head and neck cancer appears to be around 26%.^{79–81} HPV prevalence is higher in oropharyngeal SCC and lower in oral and laryngeal SCC.^{82,83}

Specific highly oncogenic HPV types are involved; HPV 16 accounts for the majority of cases followed by HPV 18. HPV 16 appears to be responsible for the majority of HPV-positive oropharyngeal SCCs, pointing to specific virus–tissue interactions. Oncogenic HPVs, other than HPV 16 and HPV 18, including HPV 31, 33, and 35, have rarely been associated with SCCHN.

Interestingly, the annual incidence rates of potentially HPV-associated cancers of the tonsil and base of tongue both increased significantly from 1998 through 2003 with an annual percentage change equal to 3.0, whereas the incidence rates of cancer at the comparison sites generally decreased. Incidence rates for these sites were highest among blacks and higher among non-Hispanics and men than among Hispanics and women.^{84,85}

HPV-associated SCCHN tends to have distinct characteristics. Clinically, patients diagnosed with HPV-associated SCCHN demonstrate improved disease-specific survival. Morphologically, HPV-associated SCCHN tends to have a characteristic basaloid morphology and molecularly is less likely to have TP53 mutations.

HPV-associated SCCHN was independently associated with several measures of sexual behavior and exposure to marijuana, but not with tobacco smoking, alcohol drinking, or poor oral hygiene. Associations increased in strength with increasing number of oral sex partners and with increasing intensity (joints per month), duration, and cumulative joint-years of marijuana use. By contrast, non-HPV-associated SCCHN was associated with measures of tobacco smoking, alcohol drinking, and poor oral hygiene but not with any measure of sexual behavior or marijuana use. Associations increased in

strength with increasing intensity (cigarettes per day), duration, and cumulative pack-years of tobacco smoking, increasing years of heavy alcohol drinking, and increasing number of lost teeth.⁸⁶

In conclusion, accumulating evidence confirms that HPV-associated SCCHN comprises a distinct molecular, clinical, and pathologic disease entity that has an improved prognosis. Current treatment algorithms do not take into account HPV tumor status for management recommendations, but clinical trial concepts specific for HPV-positive or HPV-negative SCCHN are currently under development.

ROLE OF CHEMOTHERAPY IN THE MANAGEMENT OF NASOPHARYNGEAL CARCINOMA

Nasopharyngeal carcinoma (NPC) is a unique cancer of the head and neck with distinct epidemiology, pathology, and natural history.

Role of Chemotherapy in the Management of Locally Advanced NPC

The currently employed standard of care regimen for locally advanced NPC is the regimen evaluated in the Intergroup Study 0099, a phase III randomized trial of RT versus concurrent CRT followed by adjuvant chemotherapy, which showed a statistically significant improvement in 5-year survival rates from 37% on the RT-alone arm to 67% in the chemotherapy and radiation arm. The chemotherapy regimen used in this trial included high-dose cisplatin (100 mg/m²) administered on days 1, 22, and 43 of concurrent RT, followed by three cycles of cisplatin and 5-FU (PF) adjuvant chemotherapy.⁸⁷

Observed clinically and statistically improved outcomes occurred at the cost of increased toxicities. In the Intergroup 0099 study, only 55% of patients in the CRT arm completed all three planned cycles of adjuvant chemotherapy. It still remains unclear if adjuvant chemotherapy after CRT contributes (and to what degree) to improved outcomes. Outcomes remain comparable when trials including adjuvant chemotherapy after CRT are compared with trials with CRT alone.⁸⁸⁻⁹³ Furthermore, meta-analyses evaluating the role of adjuvant chemotherapy after CRT have not been able to demonstrate improved outcomes such as improved locoregional control, decreased risk of distant metastases, or improved OS with the addition of adjuvant chemotherapy.^{94,95}

However, given the lack of randomized data, recommendations on administration of adjuvant chemotherapy after CRT should be individualized based on the characteristics and preferences of individual patients.

Role of Chemotherapy in the Management of Recurrent NPC

Salvage surgery if technically feasible represents the best option for possible cure but is associated with significant surgical complications including death, deformities, and functional deficits. In the setting of disease that is not surgically resectable, re-irradiation protocols with administration of concurrent chemotherapy represents an effective option if the patient is a re-irradiation candidate. In this setting, a platin and taxane chemotherapeutic combination is frequently used. As is the case in recurrent SCC of other primary sites, re-irradiation protocols in the recurrent NPC setting are associated with significant toxicities, including treatment-related death rates of up to 17%.

Role of Chemotherapy in the Management of Metastatic Disease

Chemotherapy has a palliative role in this setting. Participation in clinical trials is encouraged in cases where the patient's age, performance status, comorbidities, and end-organ function meet eligibility criteria. Palliative chemotherapy regimens evaluating single-agent or combination cytotoxic chemotherapy with or without molecularly targeted agents, addressing anti-EGFR and/or anti-angiogenic strategies, are being evaluated.

CONCLUSION

Over the past two decades, major advances in head and neck oncology have occurred. In this setting of continuously evolving multimodality management algorithms, chemotherapy plays an increasing role in all stages of SCCHN. Further improvements in clinical outcomes are needed, and optimized incorporation of new molecularly targeted agents represents the biggest hope and challenge for head and neck medical oncology.

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225-249
2. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007;18:581-592
3. Edwards BK, Brown ML, Wingo PA, et al. Annual report to the nation on the status of cancer, 1975-2002, featuring population-based trends in cancer treatment. *J Natl Cancer Inst* 2005;97:1407-1427
4. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006;24:2137-2150

5. Spector JG, Sessions DG, Chao KS, Hanson JM, Simpson JR, Perez CA. Management of stage II (T2N0M0) glottic carcinoma by radiotherapy and conservation surgery. *Head Neck* 1999;21:116-123
6. Spector JG, Sessions DG, Chao KS, et al. Stage I (T1 N0 M0) squamous cell carcinoma of the laryngeal glottis: therapeutic results and voice preservation. *Head Neck* 1999; 21:707-717
7. Sessions DG, Lenox J, Spector GJ. Supraglottic laryngeal cancer: analysis of treatment results. *Laryngoscope* 2005;115: 1402-1410
8. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;349:2091-2098
9. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001;51:571-578
10. Bernier J, Dometge C, Ozsahin M, et al; European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350:1945-1952
11. Cooper JS, Pajak TF, Forastiere AA, et al; Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004;350:1937-1944
12. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck* 2005;27:843-850
13. Cooper JS, Pajak TF, Forastiere AA, et al. Precisely defining high-risk operable head and neck tumors based on RTOG #85-03 and #88-24: targets for postoperative radiochemotherapy? *Head Neck* 1998;20:588-594
14. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001;51:571-578
15. Rosenthal DI, Liu L, Lee JH, et al. Importance of the treatment package time in surgery and postoperative radiation therapy for squamous carcinoma of the head and neck. *Head Neck* 2002;24:115-126
16. Vokes EE, Weichselbaum RR, Lippman SN, Itong WK. Head and neck cancer. *NEJM* 1993;328:184-194
17. Ensley JF, Jacobs JR, Weaver A, et al. Correlation between response to cisplatin-combination chemotherapy and subsequent radiotherapy in previously untreated patients with advanced squamous cell cancers of the head and neck. *Cancer* 1984;54:811-814
18. Rosenthal DI, Pistenmaa DA, Glatstein E. A review of neoadjuvant chemotherapy for head and neck cancer: partially shrunken tumors may be both leaner and meaner. *Int J Radiat Oncol Biol Phys* 1994;28:315-320
19. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991;324:1685-1690
20. Pignon JP, Bourhis J, Dometge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet* 2000;355:949-955
21. Vermorken JB, Remenar E, van Herpen C, et al; EORTC 24971/TAX 323 Study Group. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med* 2007;357:1695-1704
22. Schrijvers D, Van Herpen C, Kerger J, et al. Docetaxel, cisplatin and 5-fluorouracil in patients with locally advanced unresectable head and neck cancer: a phase I-II feasibility study. *Ann Oncol* 2004;15:638-645
23. Dunphy FR, Dunleavy TL, Harrison BR, et al. Induction paclitaxel and carboplatin for patients with head and neck carcinoma. Analysis of 62 patients treated between 1994 and 1999. *Cancer* 2001;91:940-948
24. Dietz A, Rudat V, Dreyhaupt J, et al. Induction chemotherapy with paclitaxel and cisplatin followed by radiotherapy for larynx organ preservation in advanced laryngeal and hypopharyngeal cancer offers moderate late toxicity outcome (DeLOS-I-trial). *Eur Arch Otorhinolaryngol* 2009;266: 1291-1300
25. Urba S, Wolf G, Eisbruch A, et al. Single-cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: a new treatment paradigm. *J Clin Oncol* 2006;24:593-598
26. Worden FP, Kumar B, Lee JS, et al. Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV16 copy number. *J Clin Oncol* 2008;26:3138-3146
27. Urba S, Worden F, Carey T, et al. One cycle of induction chemotherapy (IC) to select for organ preservation for patients (PTS) with advanced squamous carcinoma of the oral cavity (SCCOC) [abstract]. *J Clin Oncol* 2005; 23:513s
28. Adelstein DJ. Redefining the role of induction chemotherapy in head and neck cancer. *J Clin Oncol* 2008;26:3117-3119
29. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;349:2091-2098
30. Forastiere AA, Maor M, Weber RS, et al. Long-term results of Intergroup RTOG 91-11: a phase III trial to preserve the larynx-induction cisplatin/5-FU and radiation therapy versus concurrent cisplatin and radiation therapy versus radiation therapy [abstract]. *J Clin Oncol* 2006;24:284s
31. Pignon JP, le Maitre A, Maillard E, Bourhis JP; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009;92:4-14
32. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354:567-578
33. Posner MR, Herschock DM, Blajman CR, et al; TAX 324 Study Group. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med* 2007; 357:1705-1715
34. Hitt R, López-Pousa A, Martínez-Trufero J, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol* 2005;23:8636-8645

35. Paccagnella A, Buffoli A, Koussis H, et al. Concomitant chemoradiotherapy versus neoadjuvant chemotherapy with docetaxel, cisplatin, 5-fluorouracil (TPF) followed by chemoradiotherapy in locally advanced head and neck cancer [abstract]. *J Clin Oncol* 2008;26:6000
36. Hitt R, Grau JJ, Lopez-Pousa A, et al. Randomized phase II/III clinical trial of induction chemotherapy (ICT) with either cisplatin/5-fluorouracil (PF) or docetaxel/cisplatin/5-fluorouracil (TPF) followed by chemoradiotherapy (CRT) vs. CRT alone for patients (pts) with unresectable locally advanced head and neck cancer (LAHNC) [abstract]. *J Clin Oncol* 2006;24:5515
37. Grandis JR, Twardy DJ. Elevated levels of transforming growth factor alpha and epidermal growth factor receptor messenger RNA are early markers of carcinogenesis in head and neck cancer. *Cancer Res* 1993;53:3579–3584
38. Dassonville O, Formento JL, Francoual M, et al. Expression of epidermal growth factor receptor and survival in upper aerodigestive tract cancer. *J Clin Oncol* 1993;11:1873–1878
39. Woodburn JR. The epidermal growth factor receptor and its inhibition in cancer therapy. *Pharmacol Ther* 1999;82:241–250
40. Villaflor VM, Cohen EE, Haraf D, et al. Phase II trial pemetrexed-based induction chemotherapy followed by concomitant chemoradiotherapy in previously irradiated head and neck cancer patients [abstract]. *J Clin Oncol* 2008;26(Suppl):323s
41. Spencer SA, Harris J, Wheeler RH, et al. Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck. *Head Neck* 2008;30:281–288
42. Langer CJ, Harris J, Horwitz EM, et al. Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. *J Clin Oncol* 2007;25:4800–4805
43. Constenla DO, Hill ME, A'Hern RP, et al. Chemotherapy for symptom control in recurrent squamous cell carcinoma of the head and neck. *Ann Oncol* 1997;8:445–449
44. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359:1116–1127
45. Specenier PM, Vermorken JB. Current concepts for the management of head and neck cancer: chemotherapy. *Oral Oncol* 2009;45:409–415
46. Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol* 1999;17:409–422
47. Jacobs C, Lyman G, Velez-García E, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. *J Clin Oncol* 1992;10:257–263
48. Catimel G, Verweij J, Mattijssen V, et al; EORTC Early Clinical Trials Group. Docetaxel (Taxotere): an active drug for the treatment of patients with advanced squamous cell carcinoma of the head and neck. *Ann Oncol* 1994;5:533–537
49. Dreyfuss AI, Clark JR, Norris CM, et al. Docetaxel: an active drug for squamous cell carcinoma of the head and neck. *J Clin Oncol* 1996;14:1672–1678
50. Jacobs C, Lyman G, Velez-García E, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. *J Clin Oncol* 1992;10:257–263
51. Tapazoglou E, Kish J, Ensley J, Al-Sarraf M. The activity of a single-agent 5-fluorouracil infusion in advanced and recurrent head and neck cancer. *Cancer* 1986;57:1105–1109
52. Raguse JD, Gath HJ, Bier J, Riess H, Oettle H. Gemcitabine in the treatment of advanced head and neck cancer. *Clin Oncol (R Coll Radiol)* 2005;17:425–429
53. Catimel G, Vermorken JB, Clavel M, et al; EORTC Early Clinical Trials Group. A phase II study of gemcitabine (LY 188011) in patients with advanced squamous cell carcinoma of the head and neck. *Ann Oncol* 1994;5:543–547
54. Pivot X, Raymond E, Laguerre B, et al. Pemetrexed disodium in recurrent locally advanced or metastatic squamous cell carcinoma of the head and neck. *Br J Cancer* 2001;85:649–655
55. Gedlicka C, Kornfehl J, Turhani D, Burian M, Formanek M. Salvage therapy with oral etoposide in recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Cancer Invest* 2006;24:242–245
56. Murphy BA, Cmelak A, Burkey B, et al. Topoisomerase I inhibitors in the treatment of head and neck cancer. *Oncology (Williston Park)* 2001;15(7, Suppl 8):47–52
57. Murphy BA. Topoisomerases in the treatment of metastatic or recurrent squamous carcinoma of the head and neck. *Expert Opin Pharmacother* 2005;6:85–92
58. Williams SD, Velez-Garcia E, Essessee I, Ratkin G, Birch R, Einhorn LH. Chemotherapy for head and neck cancer. Comparison of cisplatin + vinblastine + bleomycin versus methotrexate. *Cancer* 1986;57:18–23
59. Eisenberger M, Krasnow S, Ellenberg S, et al. A comparison of carboplatin plus methotrexate versus methotrexate alone in patients with recurrent and metastatic head and neck cancer. *J Clin Oncol* 1989;7:1341–1345
60. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol* 2007;25:2171–2177
61. Soulieres D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol* 2004;22:77–85
62. Cohen EE, Kane MA, List MA, et al. Phase II trial of gefitinib 250 mg daily in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Clin Cancer Res* 2005;11:8418–8424
63. Kirby AM, A'Hern RP, D'Ambrosio C, et al. Gefitinib (ZD1839, Iressa) as palliative treatment in recurrent or metastatic head and neck cancer. *Br J Cancer* 2006;94:631–636
64. Stewart JS, Cohen EE, Licitra L, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. *J Clin Oncol* 2009;27:1864–1871
65. Lorch JH, Posner MR, Wirth LJ, Haddad RI. Seeking alternative biological therapies: the future of targeted molecular treatment. *Oral Oncol* 2009;45:447–453

66. Le Tourneau C, Chen EX. Molecularly targeted agents in the treatment of recurrent or metastatic squamous cell carcinomas of the head and neck. *Hematol Oncol Clin North Am* 2008;22:1209–1220; ix
67. Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. *J Clin Oncol* 1992;10:1245–1251
68. Clavel M, Vermorken JB, Cognetti F, et al. Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. *Ann Oncol* 1994;5:521–526
69. Forastiere AA, Leong T, Rowinsky E, et al. Phase III comparison of high-dose paclitaxel + cisplatin + granulocyte colony-stimulating factor versus low-dose paclitaxel + cisplatin in advanced head and neck cancer: Eastern Cooperative Oncology Group Study E1393. *J Clin Oncol* 2001;19:1088–1095
70. Gibson MK, Li Y, Murphy B, et al; Eastern Cooperative Oncology Group. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2005;23:3562–3567
71. Glisson BS, Murphy BA, Frenette G, Khuri FR, Forastiere AA. Phase II trial of docetaxel and cisplatin combination chemotherapy in patients with squamous cell carcinoma of the head and neck. *J Clin Oncol* 2002;20:1593–1599
72. Specht L, Larsen SK, Hansen HS. Phase II study of docetaxel and cisplatin in patients with recurrent or disseminated squamous-cell carcinoma of the head and neck. *Ann Oncol* 2000;11:845–849
73. Baur M, Kienzer HR, Schweiger J, et al. Docetaxel/cisplatin as first-line chemotherapy in patients with head and neck carcinoma: a phase II trial. *Cancer* 2002;94:2953–2958
74. Guntinas-Lichius O, Appenrodt S, Veelken F, Krug B. Phase II study of weekly docetaxel and cisplatin in patients with advanced recurrent and metastatic head and neck cancer. *Laryngoscope* 2006;116:613–618
75. Stathopoulos GP, Rigatos S, Papakostas P, Fountzilas G. Effectiveness of paclitaxel and carboplatin combination in heavily pretreated patients with head and neck cancers. *Eur J Cancer* 1997;33:1780–1783
76. Clark JI, Hofmeister C, Choudhury A, et al. Phase II evaluation of paclitaxel in combination with carboplatin in advanced head and neck carcinoma. *Cancer* 2001;92:2334–2340
77. Samlowski WE, Moon J, Kuebler JP, et al. Evaluation of the combination of docetaxel/carboplatin in patients with metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN): a Southwest Oncology Group Phase II study. *Cancer Invest* 2007;25:182–188
78. Burtneß B, Goldwasser MA, Flood W, Mattar B, Forastiere AA; Eastern Cooperative Oncology Group. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 2005;23:8646–8654
79. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst* 2000;92:709–720
80. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med* 2007;356:1944–1956
81. Gillison ML, Lowy DR. A causal role for human papillomavirus in head and neck cancer. *Lancet* 2004;363:1488–1489
82. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2005;14:467–475
83. Ryerson AB, Peters ES, Coughlin SS, et al. Burden of potentially human papillomavirus-associated cancers of the oropharynx and oral cavity in the US, 1998–2003. *Cancer* 2008;113(10, Suppl):2901–2909
84. Dahlstrand H, Näsman A, Romanitan M, Lindquist D, Ramqvist T, Dalianis T. Human papillomavirus accounts both for increased incidence and better prognosis in tonsillar cancer. *Anticancer Res* 2008;28:1133–1138
85. Näsman A, Attner P, Hammarstedt L, et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma? *Int J Cancer* 2009;125:362–366
86. Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst* 2008;100:407–420
87. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol* 1998;16:1310–1317
88. Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst* 2005;97:536–539
89. Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol* 2005;23:6730–6738
90. Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. *J Clin Oncol* 2003;21:631–637
91. Chan ATC, Teo PML, Ngan RK, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol* 2002;20:2038–2044
92. Lee AW, Lau WH, Tung SY, et al; Hong Kong Nasopharyngeal Cancer Study Group. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. *J Clin Oncol* 2005;23:6966–6975
93. Kwong DL, Sham JS, Au GK, et al. Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. *J Clin Oncol* 2004;22:2643–2653

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94. Baujat B, Audry H, Bourhis J, et al; MAC-NPC Collaborative Group. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys* 2006;64:47–56
 95. Langendijk JA, Leemans CR, Buter J, Berkhof J, Slotman BJ. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. *J Clin Oncol* 2004;22:4604–4612