Current Treatment Options in Oncology (2012) 13:35–46
DOI 10.1007/s11864-011-0176-y

Head and Neck Cancer (T Day, Section Editor)

Current Treatment Options for Metastatic Head and Neck Cancer

Katharine A. R. Price, MD[1]
Ezra E. Cohen, MD[*,2]

Address
[1]Division of Medical Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
Email: price.katharine@mayo.edu
[*,2]Medical Oncology, University of Chicago, Chicago, IL, USA
Email: ecohen@medicine.bsd.uchicago.edu

Published online: 18 January 2012
© Springer Science+Business Media, LLC 2012

Keywords Head and neck cancer · Metastatic · Chemotherapy · Targeted therapy

Opinion statement

Head and neck squamous cell carcinoma is now the 8th most common cancer affecting men in the United States largely due to a rising epidemic of oropharynx cancer (tonsil and tongue base) associated with the human papillomavirus (HPV). The median overall survival for recurrent or metastatic head and neck cancer (R/M HNSCC) remains less than 1 year despite modern chemotherapy and targeted agents. Palliative chemotherapy and the epidermal growth factor receptor inhibitor, cetuximab, constitute the backbone of treatment for patients with R/M HNSCC. Platinum doublets studied in phase III trials include cisplatin/5-FU, cisplatin/paclitaxel, and cisplatin/pemetrexed. Platinum chemotherapy in combination with 5-fluorouracil and cetuximab has resulted in the longest median overall survival. Combination platinum regimens increase response rates and toxicity but not survival and should be reserved for patients who are symptomatic from their disease for whom the benefit of a partial response may be worth the cost of increased treatment-related side effects. For many patients who are asymptomatic with a low disease burden, single agent regimens are appropriate to balance treatment with side effects. Drugs commonly used as single agents in the treatment of R/M HNSCC include docetaxel, paclitaxel, cetuximab, capecitabine, pemetrexed, and methotrexate. Best supportive care alone is often appropriate for poor performance status patients. Palliative radiation therapy is beneficial for treating symptomatic metastatic sites. Aggressive symptom management is imperative for all patients and often should include referral to experts in palliative care and pain management. New therapies currently under investigation include mTOR inhibitors, anti-angiogenic agents, and IGF1R inhibitors. Given the poor prognosis for most patients with R/M HNSCC, enrollment in clinical trials investigating novel approaches to therapy should be encouraged.

Introduction

Pathogenesis and epidemiology

Historically the major risk factors for the development of head and neck squamous cell carcinoma (HNSCC) were alcohol and tobacco use. The most notable discovery in the field of head and neck oncology in recent years is that the human papillomavirus (HPV)—predominantly HPV 16—is the causative agent in the majority of cases of oropharynx cancers (tongue base and tonsil) [1, 2]. As the rates of tobacco use have declined so has the incidence of HPV-negative HNSCC. In contrast, the incidence of HPV-positive HNSCC has been rising for the past three decades and now is the eighth most common cancer among men in the United States [3, 4]. The HPV virus is ubiquitous and is sexually transmitted. Most infections are asymptomatic and are cleared by the host immune system. However, some individuals become chronic carriers and a percentage of carriers go on to develop an HPV-associated cancer. Unlike HPV-negative HNSCC that is driven by the stepwise accumulation of mutations in the squamous epithelium, notably mutations in the p53 tumor suppressor gene, [5] HPV-positive HNSCC is caused by two viral oncogenes encoding for early viral proteins, E6 and E7, that bind and inactivate the tumor suppressor genes p53 and pRb leading to malignant transformation of the squamous epithelium. Thus, HPV-negative and HPV-positive cancers truly represent two different diseases each with a distinct biology, clinical presentation, and prognosis.

Presentation

Initial presentation

Classic presenting symptoms of head and neck squamous cell carcinoma include pain, dysphagia, odynophagia, dysphonia, otalgia, hoarseness, and citrus intolerance. HPV oropharynx cancer is characterized by smaller primaries (T1 and T2) with early cervical lymph node metastases and therefore typically presents with a painless neck mass. Patients with HPV oropharynx cancer are typically 5–10 years younger than patients with HPV-negative HNSCC. Often patients –particularly never smokers - will have been treated with multiple courses of antibiotics as primary providers may have a low level of suspicion for cancer. HPV-positive HNSCC often has cystic cervical lymph node metastases, so an initial fine needle aspiration (FNA) may be non-diagnostic. Pathologically, HPV oropharynx cancer is likely to be poorly differentiated and to have basaloid features.

Presentation of recurrent or metastatic disease

Loco-regionally recurrent head and neck cancer is often evident clinically (physical exam or nasopharyngoscopy), and in most cases is heralded by new patient-reported symptoms, most commonly pain [6]. Asymptomatic metastatic disease is often found on routine imaging, or on imaging prompted by new symptoms such as pain or cough or by laboratory abnormalities such as elevation of calcium, alkaline phosphatase, or liver function tests. The most common sites of distant disease include lung, lymph nodes, bone, and liver.

Diagnosis

Initial diagnosis of head and neck cancer is usually made by obtaining a tissue biopsy of an enlarged cervical lymph node—most often by ultrasound-guided FNA—or by biopsying the primary tumor either in the office or the operating room. A diagnosis of R/M HNSCC is often heralded by patient reported symptoms such as new pain in the head and neck, odynophagia, or dysphagia, or by the discovery of new lymphadenopathy or a mucosal lesion on physical exam or nasopharyngoscopy. Imaging is important, however, in the evaluation of a suspected recurrence to clarify the extent of disease in order to identify a subset of patients with disease localized to the head and neck who may be a candidate for salvage surgery or re-irradiation. CT or MRI are the primary imaging modalities used to evaluate the extent of disease in the head and neck and PET is a useful adjunct to evaluate for distant disease. A biopsy is often indicated to confirm recurrence, particularly distant sites, as many patients with head and neck cancer are also at risk for other smoking-related primary malignancies such as lung cancer.

Prognosis

Despite advances in systemic therapies, the median overall survival for patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) remains less than 1 year. The prognosis of locally advanced HPV-positive HNSCC is significantly

better than HPV-negative HNSCC [7, 8••] but it has not yet been shown that the prognosis of patients with R/M HPV-positive HNSCC differs from HPV-negative R/M HNSCC. There is some preliminary evidence that HPV-positive R/M oropharynx cancer has a more favorable outcome than HPV-negative R/M oropharynx cancer when treated with chemotherapy, [9•] but additional trials need to be done to determine optimal therapy for these two patient populations.

Treatment

- The backbone of treatment for R/M HNSCC is palliative systemic therapy with standard chemotherapeutic agents and inhibitors of the epidermal growth factor receptor (EGFR). Despite the use of third generation chemotherapeutic agents and targeted therapy, the median overall survival for patients with metastatic or recurrent head and neck cancer remains less than 1 year. Novel therapeutic approaches are needed, and enrollment in clinical trials should be encouraged.

Cytotoxic chemotherapy

- Platinum-based chemotherapy has been the cornerstone of treatment for R/M HNSCC since the 1980s when single agent cisplatin was shown to improve survival over supportive care alone [10] and to be superior to single agent methotrexate [11]. In 1984 a phase II study of cisplatin and infusional 5-fluoruracil (5-FU) reported a response rate of 70% and a complete response rate of 27% prompting enthusiasm over combination chemotherapy regimens for this patient population [12].
- Unfortunately, multi-agent platinum-based chemotherapy regimens have never been shown to improve survival over single agent regimens in randomized phase III trials. Jacobs et al reported a phase III study of 249 patients with R/M HNSCC who were randomized to cisplatin alone (100 mg/m^2), infusional 5-FU (1,000 mg/m^2), or the combination once every three weeks [13]. Although the overall response rate improved with the combination (32% versus 17% for cisplatin and 13% for 5-FU), the median survival remained 5.7 months for all groups. Leukopenia and infectious complications were greater in the combination arm. The same year the Southwest Oncology Group (SWOG) published a randomized phase III study comparing cisplatin (100 mg/m^2 IV on day 1) and 5-FU (1,000 mg/m^2 daily IV days 1–4) every 21 days, carboplatin (300 mg/m^2 IV on day 1) and 5-FU (1,000 mg/m^2 daily IV days 1–4) every 28 days, and single agent methotrexate (40 mg/m^2 IV weekly) [14]. The response rate of cisplatin and 5-FU was superior to methotrexate (32% versus 10%, $p<0.001$) and was improved but not statistically significant for carboplatin and 5-FU versus methotrexate (21% versus 10%, $p=0.05$). The median overall survival was equivalent for all three arms

(cisplatin and 5-FU 6.6 months, carboplatin and 5-FU 5.0 months, methotrexate 5.6 months), but there was significantly more grade 3 toxicity seen in patients receiving cisplatin and 5-FU ($p<0.001$).

- No specific platinum chemotherapy regimen is clearly superior in the treatment of R/M HNSCC [15•].Cisplatin doublets using third generation agents have not shown a survival benefit in randomized phase III trials [9•, 16]. The Eastern Cooperative Oncology Group (ECOG) compared the historical chemotherapy backbone of cisplatin and 5-FU to cisplatin and paclitaxel in 218 patients with R/M HNSCC who had not received prior therapy and found no difference in overall survival or response rate [16]. Although the trial did not demonstrate superiority of the cisplatin/paclitaxel combination, it does provide evidence for using platinum and taxane doublets as first-line therapy which offers advantages in terms of ease of administration and schedule and obviates the need for an indwelling catheter or port. At the 2010 meeting of the European Society for Medical Oncology (ESMO), phase III trial results were presented that did not show any benefit of cisplatin and pemetrexed compared with cisplatin alone for an unselected patient population of R/M HNSCC [9•]. The trial enrolled 795 patients and randomized them to receive cisplatin (75 mg/m^2) plus either placebo ($n=397$) or pemetrexed (500 mg/m^2, $n=398$) once every three weeks. Primary endpoint was overall survival (OS) with secondary endpoints including progression free survival (PFS) and response rate (RR). Median survival for the whole population was 7.3 months in the cisplatin/pemetrexed arm versus 6.3 months in the cisplatin/placebo arm (HR=0.87, 95% CI 0.75–1.02, $p=0.082$). Neither PFS nor RR were significantly improved with the addition of pemetrexed. Of note, however, preplanned subset analyses of patients with oropharynx cancer ($n=192$) and patients with a good performance status (ECOG 0 or 1, $n=690$) did have superior OS and PFS with the addition of pemetrexed compared with cisplatin alone (oropharynx subset, OS 9.9 versus 6.1 months, HR=0.59, $p=0.002$ and PFS 4.0 versus 3.4 months, HR=0.73, $p=0.047$; PS 0-1 subset, OS 8.4 versus 6.7 months, HR=0.83, $p=0.026$ and PFS 4.0 versus 3.0 months, HR=0.85, $p=0.44$)).
- Chemotherapy drugs with single agent activity in phase II trials of R/M HNSCC include the following: paclitaxel [17, 18], docetaxel [19–21], gemcitabine [22, 23], ifosfamide [24–27], vinorelbine [28–30], pemetrexed [31], capecitabine [32], irinotecan [33], and ixabepilone [34] (see Table 1). Most of the single agents were tested in the first line metastatic setting. The most promising single agents on the basis of phase II data are docetaxel, paclitaxel, and pemetrexed. The only agents to have been tested beyond the first line setting (ifosfamide, irinotecan, vinorelbine) have shown minimal activity.

- Non-platinum doublets have shown activity but have no proven benefit over single agent therapy and should not be used routinely outside of a clinical trial.
- The optimal treatment of elderly patients with R/M HNSCC is not known as many older patients will have confounding issues of medical co-morbidities, poor performance status, and lack of social support. Argiris et al reported on the experience of fit elderly patients (≥70 years) treated on two phase III ECOG trials of cisplatin-based palliative chemotherapy [35]. Median overall survival did not differ for elderly and younger patients (5.3 and 8.0 months, respectively; $p=0.17$), but elderly patients did experience more treatment-related toxicity and there was a trend towards a higher rate of treatment-related deaths (13% versus 8%, $p=0.29$). Although select elderly patients may be able to withstand platinum-based therapy, most likely single-agent treatment or best supportive care is appropriate for many elderly patients.
- Currently patients with HPV-positive and HPV-negative R/M HNSCC are treated similarly. Future trials are likely to study these two groups of patients separately and may lead to separate treatment paradigms.

Targeted therapy: EGFR inhibitors

- The epidermal growth factor receptor (EGFR) is commonly expressed in HNSCC and overexpression is associated with a poorer prognosis [36].
- Cetuximab—a monoclonal antibody to the EGFR—is the only targeted therapy to be routinely used in clinical practice in the treatment of R/M HNSCC.
- The main side effects of cetuximab are the classic acneiform skin rash, hypomagnesemia, and a risk for infusion reactions. Although initially the risk of an anaphylactic reaction was reported as 3%, it is now recognized that there is significant geographic variation in the rate of anaphylaxis from <1% in the northeast to as high as 22% in the south. Pre-existing IgE antibodies against cetuximab have been associated with many of the cases of hypersensitivity [37].

Table 1. Phase II trials of single agent chemotherapy in R/M HNSCC

Agent	Response Rates	Overall Survival (months)
Pemetrexed	26%	7.3
Docetaxel	20–42%	6.7
Paclitaxel	36–40%	9.2
Gemcitabine	0–13%	6
Ifosfamide[a]	4–42%	4–11
Capecitabine	24%	7.3
Irinotecan[a]	14%	
Vinorelbine[a]	6–16%	5–8
Ixabepilone	16%[b]	7.2

[a]Ifosfamide, vinorelbine, irinotecan minimal activity in previously treated patients
[b]Responses only in taxane-naïve patients

- Cetuximab has shown benefit in both the first-line recurrent setting in combination with chemotherapy and as a single agent in patients with platinum resistant disease.
- The landmark EXTREME study investigated the benefit of adding cetuximab to chemotherapy and was the first phase III trial in R/M HNSCC to show a significant improvement in overall survival since the introduction of cisplatin. The study enrolled 442 patients with newly diagnosed R/M HNSCC and randomized them to chemotherapy with either cisplatin (100 mg/m^2 on day 1) or carboplatin (AUC 5 on day 1) plus 5-FU (1,000 mg/m^2/day x 4 days) every 3 weeks with or without cetuximab (400 mg/m^2 loading dose then 250 mg/m^2 weekly) [38]. Chemotherapy was given for a maximum of six cycles in both arms. Patients randomized to the cetuximab arm continued to receive weekly cetuximab until disease progression or unacceptable side effects. The primary endpoint was OS with secondary endpoints of PFS, best overall response, disease control (complete response+partial response+stable disease), time to treatment failure, duration of response, and safety. The most common primary site in both arms was oropharynx (36% in cetuximab arm, 31% in chemotherapy alone arm). The addition of cetuximab to chemotherapy significantly improved OS—the primary study endpoint—from 7.4 months with chemotherapy alone to 10.1 months with chemotherapy plus cetuximab (p=0.04, hazard ratio for death, 0.80; 95% CI, 0.64–0.99). Progression free survival was also improved from 3.3 months to 5.6 months (p<0.001, hazard ratio for progression, 0.54, 95% CI 0.43–0.67). The addition of cetuximab improved the response rate from 20% with chemotherapy alone to 36% with chemotherapy plus cetuximab (p<0.001), although the duration of response did not differ significantly (4.7 months in chemotherapy arm, 5.6 months with cetuximab). Patients in the cetuximab arm had significantly more grade 3 skin toxicity (p<0.001), hypomagnesemia (p=0.05) and sepsis (p=0.02). Six patients in the cetuximab arm had grade 3 or 4 infusion reactions compared with none in the chemotherapy alone group. There were 10 treatment-related deaths, 3 on the cetuximab are and seven in the chemotherapy alone arm [38].
- ECOG 5397 was a randomized phase III trial of 117 patients with newly diagnosed R/M HNSCC who were randomized to receive either cisplatin (100 mg/m^2 on day 1 every 4 weeks) plus placebo (weekly) or the same dose of cisplatin plus cetuximab (200 mL/m^2 on day 1 x 1 cycle, then 125 mL/m^2/week) [39]. The addition of cetuximab to cisplatin improved the overall response rate from 10% to 26% (p=0.03) but did not significantly improve either PFS or OS.
- Single agent cetuximab has modest activity in patients with platinum-refractory R/M HNSCC. Vermorken et al reported a phase II study that treated 103 patients with disease progression on platinum-based che-

motherapy with single agent cetuximab platinum-based chemotherapy [40]. Patients were allowed to receive platinum plus cetuximab as salvage treatment upon disease progression. The best overall response rate—the primary endpoint of the trial—was 13% (95%CI, 7%–21%) with no complete responses seen. The disease control rate (CR+PR+SD) was 46% with a median time-to-progression of 70 days. Of the 53 patients (51%) who received platinum plus cetuximab at progression, no responses were seen.

- Panitumumab is a fully human IgG2 monoclonal antibody to the EGFR currently approved for use in colorectal cancer. It was studied in a randomized phase III trial identical to the study design of the EXTREME study where patients were randomized to platinum and 5-FU with or without panitumumab [41•]. The addition of panitumumab to chemotherapy had clinical activity with an increase in PFS and response rate, but failed to demonstrate a survival benefit. It is not currently approved for use in R/M HNSCC.
- Zalutumumab is a novel IgG1κ monoclonal antibody that blocks EGFR signaling and triggers Fc-mediated antibody-dependent cellular toxicity. A recent open-label, phase III study randomized 286 patients with platinum-refractory R/M HNSCC in a 2:1 fashion to zalutumumab or best supportive care [42•]. Zalutumumab was dose-escalated to achieve a grade 2 rash. Patients in the best supportive care arm had the option to receive weekly methotrexate up to 50 mg/m^2/week. Eligible patients were allowed up to two prior chemotherapy regimens in addition to treatment with platinum. Forty and 45% of patients in the zalutumumab and control arm, respectively, had received two prior lines of chemotherapy. Zalutumumab significantly prolonged PFS from 8.4 weeks in the control group to 9.9 weeks (HR for progression or death 0.63, 95% CI 0.47–0.84, p=0.0012). Response rate for zalutumumab was 6% including two complete responses. The toxicity profile of zalutumumab was similar to that of other EGFR monoclonal antibodies. Quality-of-life (QOL) data was reported by 84% of the patients and notably did not show a difference between the treatment arms. Although there was no survival benefit with zalutumumab, it did have clinical activity in a pretreated, platinum-refractory patient population without adversely affecting QOL [42•].
- The non-platinum regimen of cetuximab in combination with paclitaxel for patients with newly diagnosed R/M HNSCC after failure of definitive therapy has shown promising results. In a phase II trial of 46 patients, the overall response rate to weekly cetuximab (400 mg/m^2 loading dose, 250 mg/m^2 subsequent doses) and paclitaxel (80 mg/m^2/week) was 54% (95% CI, 39%–69%) with a complete response rate of 22% (95% CI 11%–36%). The median PFS was 4.2 months (95% CI 2.9–5.5 months) and the median overall survival was 8.1 months (95% CI 6.6–9.6 months), comparable

with historic controls [43]. Sixteen patients (35%) had received prior platinum therapy as part of their definitive treatment. Of note, 61% of the patients had a Karnofsky performance status of 70–80% suggesting that this may be a valuable regimen for patients who are not fit enough to receive platinum therapy. Further evaluation of this regimen is indicated in a larger patient population.

- The tyrosine kinase inhibitors gefitinib and erlotinib have shown only modest single agent activity in R/M HNSCC and are not routinely used in clinical practice. The initial phase II trial of gefitinib reported a response rate of 11% and an overall survival of 8.1 months [44] but in a phase III trial where 486 patients were randomized to gefitinib 250 mg/day, gefitinib 500 mg/day, or methotrexate 40 mg/m^2 IV weekly, neither dose of gefitinib was superior to single agent methotrexate in either response or survival [45•]. Response rates were 3%, 8%, and 4%, respectively, and median overall survival was 5.6, 6.0, and 6.7 months. The addition of gefitinib to weekly docetaxel in a previously treated patient population with R/M HNSCC failed to improve overall survival, PFS, or response rate but showed a modest improvement in time-to-progression from 2 months with docetaxel/placebo to 3.5 months with docetaxel/gefitinib (p=0.03) [46•].

Emerging therapies & clinical trials in progress

- Bevacizumab has shown promise in R/M HNSCC in phase II trials in combination with cytotoxic chemotherapy [47]. ECOG 1305 is a phase III trial in progress investigating the benefit of adding bevacizumab to platinum chemotherapy as first line therapy for patients with R/M HNSCC. Patients will receive either cisplatin and docetaxel or cisplatin and 5-FU with or without bevacizumab.
- The PI3K/AKT/mTOR pathway is a target for current research in R/M HNSCC. *MET* is an established oncogene in HNSCC [48] and is upstream to the PI3K/AKT pathway. Pre-clinical data is showing MET to be a promising target for HNSCC [48, 49] and trials of c-MET inhibitors in R/M HNSCC are anticipated. The mammalian target of rapamycin (mTOR) is a serine/threonine kinase downstream of PI3K/AKT, and the mTOR inhibitors—temsirolimus and everolimus—are currently under investigation alone and in combination with other agents.
- The insulin-like growth factor 1 (IGF1R) inhibitors have shown no single agent activity in R/M HNSCC [50] but continue to be an area of active investigation for R/M HNSCC in combination with chemotherapy or targeted agents.
- Other areas of research interest for R/M HNSCC include viral therapy and immunotherapy.

Palliative radiation therapy

- Palliative radiation therapy to distant metastatic sites can be effective for symptomatic relief. Select patients with recurrent disease confined to the head and neck may be candidates for re-irradiation which can result in long-term disease control in 10–20% of patients.

Supportive care

- Patients with R/M HNSCC have a high symptom burden at the end of life, predominantly pain. Aggressive palliation is indicated in most patients and often requires referral to palliative care and pain specialists.

Suggested treatment algorithm (see Fig. 1)

- Fit patients who are symptomatic from their recurrent or metastatic disease should be considered for platinum-based, multi-agent regimens that combine cytotoxic chemotherapy with cetuximab [15•].
- Single agent chemotherapy regimens are appropriate for many asymptomatic patients with a low burden of disease [15•].
- Patients with platinum-resistant R/M HNSCC should be treated with a cetuximab-based regimen, either cetuximab alone or cetuximab plus paclitaxel.
- Given the modest benefit of palliative chemotherapy in R/M HNSCC, best supportive care alone is often appropriate for patients with a poor performance status [15•].
- Aggressive symptom management is imperative for all patients given the significant morbidity of R/M HNSCC .

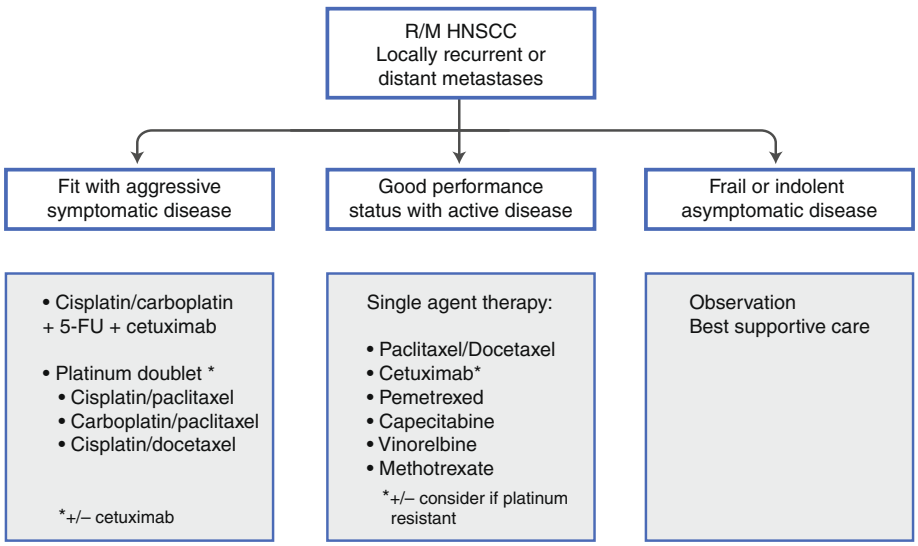

Figure 1. Treatment algorithm for choosing appropriate chemotherapy regimen for patients with recurrent or metastatic head and neck squamous cell carcinoma.

Diet and lifestyle

- Patient with HNSCC who continue to smoke should be counseled on the importance of smoking cessation. No specific diet has been shown to impact outcomes of patients with recurrent or metastatic HNSCC.

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med. 2007;356(19):1944.
2. Gillison ML, Lowy DR. A causal role for human papillomavirus in head and neck cancer. Lancet. 2004;363(9420):1488.
3. Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer. 2007;110(7):1429–35.
4. Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011. CA: Clin Lung Canc. 2011;61(4):212–36.
5. Gasco M, Crook T. The p53 network in head and neck cancer. Oral Oncol. 2003;39:222–31.
6. Smit M, Balm A, Hilgers F, et al. Pain as sign of recurrent disease in head and neck squamous cell carcinoma. Head & Neck. 2001;23:372–5.
7. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008;100:261–9.
8. •• Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival in patients with oropharyngeal cancer. N Engl J Med. 2010;363:24–35.

This paper demonstrates that tumor HPV status is a strong and independent prognostic factor for survival in patients with oropharynx cancer. It also defines three risk groups based on HPV status and smoking history that may be useful in designing future clinical trials.

9. • Urba S, van Herpen CM, Sahoo TP, et al. Phase III study of pemetrexed in combination with cisplatin (pem/cis) versus placebo plus cisplatin (cis) in patients with recurrent or metastatic squamous cell head and neck cancer (HNC). Ann Oncol. 2010;21 suppl 8:viii314.

This recently presented abstract reports the results of a randomized phase III trial that did not show a benefit of adding pemetrexed to cisplatin in an unselected patient population. Interestingly, subset analysis did show a benefit with the combination of cisplatin and pemetrexed over cisplatin alone in patients with oropharynx cancer or a good performance status.

10. Morton RP, Rugman F, Dorman EB, et al. Cisplatinum and bleomycin for advanced or recurrent squamous cell carcinoma of the head and neck: a randomized factorial phase III controlled trial. Canc Chemother Pharmacol. 1985;15:283–9.
11. The Liverpool Head and Neck Oncology Group. A phase III randomized trial of cisplatinum, methotrexate, cisplatinum+methotrexate and cisplatinum+5-FU in end stage squamous cell carcinoma of the head and neck. Br J Cancer. 1990;61:311–5.
12. Kish MS, Weaver A, Jacobs J, et al. Cisplatinum and 5-fluorouracil infusion in patients with recurrent and disseminated epidermoid cancer of the head and neck. Cancer. 1984;53:1819.
13. Jacobs C, Lyman G, Velez-Garcia 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(2):257–63.
14. 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(8):1245–51.

15.• Fury MG, Pfister DG. Current recommendations for systemic therapy of recurrent and/or metastatic head and neck squamous cell cancer. JNCCN. 2011;9:681–90.

This article is an excellent summary of the use of chemotherapy in R/M HNSCC with practical advice for the clinician on how to approach patients with R/M HNSCC.

16. Gibson MK, Li Y, Murphy B, et al. 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;23:3562–7.

17. Forastiere AA, Shank D, Neuberg D, et al. Final report of a phase II evaluation of paclitaxel in patients with advanced squamous cell carcinoma of the head and neck. Cancer. 1998;82:2270–4.

18. Smith RE, Thornton DE, Allen J. A phase II trial of paclitaxel in squamous cell carcinoma of the head and neck with correlative laboratory studies. Semin Oncol. 1995;22(3 suppl 6):41–6.

19. 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;14:1672–8.

20. Couteau C, Chouaki N, Leyvraz S, et al. A phase II study of docetaxel in patients with squamous cell carcinoma of the head and neck. Br J Cancer. 1999;81(3):457–62.

21. Catimel G, Verweij J, Mattijssen V, et al. Docetaxel (Taxotere): an active drug for the treatment of patients with advanced squamous cell carcinoma of the head and neck. EORTC Early Clinical Trials Group. Ann Oncol. 1994;5(6):533–7.

22. Catimel G, Vermorken JB, Clavel M, et al. A phase II study of gemcitabine (LY 188011) in patients with advanced squamous cell carcinoma of the head and neck. EORTC Early Clinical Trials Group. Ann Oncol. 1994;5:543–7.

23. Samlowski WE, Gundacker H, Kuebler JP, et al. Evaluation of gemcitabine in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: a Southwest Oncology Group phase II study. Invest New Drugs. 2001;19:311–5.

24. Sandler A, Saxman S, Bandealy M, et al. Ifosfamide in the treatment of advanced or recurrent squamous cell carcinoma of the head and neck: a phase II Hoosier Oncology Group trial. Am J Clin Oncol. 1998;21 (2):195–7.

25. Cervellino JC, Araujo CE, Pirisi C, et al. Ifosfamide and mesna for the treatment of advanced squamous cell head and neck cancer. A GETLAC study. Oncology. 1991;4892:89–92.

26. Huber M, Lippman S, Benner S, et al. A phase II study of ifosfamide in recurrent squamous cell carcinoma of the head and neck. Am Journal Clin Oncol. 1996;19(4):379–83.

27. Martin M, Diaz-Rubio E, Gonzalez Larriba JL, et al. Ifosfamide in advanced epidermoid head and neck cancer. Canc Chemother Pharmacol. 1993;31 (4):340–2.

28. Degardin M, Oliveira J, Geoffrois J, et al. An EORTC-ECSG phase II study of vinorelbine in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol. 1998;9:1103–7.

29. Saxman S, Mann B, Canfield V, et al. A phase II trial of vinorelbine in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. Am J Clin Oncol. 1998;21(4):398–400.

30. Testolin A, Recher G, Cristoferi V, et al. Vinorelbine in pre-treated advanced head & neck squamous cell carcinoma. A phase II study. Investig New Drugs. 1994;12(3):231–4.

31. 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;85:649–55.

32. Martinez-Trufero J, Isla D, Adansa JC, et al. Phase II study of capecitabine as palliative treatment for patients with recurrent and metastatic squamous head and neck cancer after previous platinum-based treatment. Br J Cancer. 2010;102:1687–91.

33. Murphy BA. Topoisomerases in the treatment of metastatic or recurrent squamous carcinoma of the head and neck. Expert Opin Pharmacother. 2005;6 (1):85–92.

34. Burtness BA, Manola J, Axelrod R, et al. A randomized phase II study of ixabepilone (BMS-247550) given daily x 5 days every 3 weeks or weekly in patients with metastatic or recurrent squamous cell carcinoma of the head and neck: an Eastern Cooperative Oncology Group study. Annals Oncol. 2008;19:977–83.

35. Argiris A, Li Y, Murphy BA, et al. Outcome of elderly patients with recurrent or metastatic head and neck cancer treated with cisplatin-based chemotherapy. J Clin Oncol. 2004;22:262–8.

36. Ang KK, Berkey BA, Tu X, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer Res. 2002;62:7350–6.

37. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-α-1,3-galactose. N Engl J Med. 2008;358:1109–17.

38. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359:1116–27.

39. Burtness B, Goldwasser MA, Flood W, et al. 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;23:8646–54.

40. 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;25:2171–7.

41.• Vermorken JB, Stohlmacher J, Davidenko I, et al: Primary efficacy and safety results of SPECTRUM, a phase 3 trial in patients (pts) with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) receiving chemotherapy with or without panitumumab (pmab). *ESMO* 2010.

This abstract reports clinical activity but no survival benefit with the addition of panitumumab to chemotherapy in patients with R/M HNSCC.

42.• Machiels J, Subramanian S, Ruzsa A, et al. Zalutumumab plus best supportive care versus best supportive care alone in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck after failure of platinum-based chemotherapy: an open-label, randomized phase 3 trial. Lancet Oncol. 2011;12:333–43.

This thought-provoking abstract reports clinical activity, but no survival benefit, for zalutumumab in a heavily pre-treated, platinum-refractory population without adversely affecting quality of life.

43. Hitt R, Irigoyen A, Cortes-Funes H, et al: Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. *Annals Oncology* 2011, August 23, epub ahead of print.

44. Cohen EE, Rosen F, Stadler WM, et al. Phase II trial of ZD 1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. J Clin Oncol. 2003;21:1980–7.

45.• Stewart JWS, Cohen EEW, Licitra L, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck. J Clin Oncol. 2009;27:1864–71.

This paper reports a phase III trial demonstrating very modest activity of gefitinib and no improvement over single agent methotrexate in patients with R/M HNSCC. The use of EGFR tyrosine kinase inhibitors would not be recommended in routine clinical practice.

46.• Argiris A, Ghebremichael M, Gilbert J, et al. A phase III randomized, placebo-controlled trial of docetaxel (D) with or without gefitinib (G) in recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): A trial of the Eastern Cooperative Oncology Group (ECOG). J Clin Oncol. 2009;27:15s. suppl; abstr 6011.

This abstract reports a phase III trial of docetaxel with or without gefitinib showing only modest improvement in time-to-progression with the addition of gefitinib but no impact on response rate, overall survival, or progression-free survival.

47. Argiris A, Karamouzis MV, Gooding WE, et al. Phase II trial of pemetrexed and bevacizumab in patients with recurrent or metastatic head and neck cancer. J Clin Oncol. 2011;29:1140–5.

48. Seiwert TY, Jagadeeswaran R, Faoro L, et al. The MET receptor tyrosine kinase is a potential novel therapeutic target for head and neck squamous cell carcinoma. Cancer Res. 2009;69:3021–31.

49. Knowles LM, Stabile LP, Egloff AM, et al. HGF and c-Met participate in paracrine tumorigenic pathways in head and neck squamous cell cancer. Clin Cancer Res. 2009;15:3740–50.

50. Schmitz S, Kaminsky-Forrett M, Henry S, et al. Phase II study of figitumumab in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: GORTEC 2008-02. J Clin Oncol. 2010;28(suppl):5500.