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Head and Neck Cancer

Molecular Targets in Squamous Cell Carcinoma of the Head and Neck

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Opinion statement

Worldwide more than a half million people develop Head and Neck cancer annually. Despite a significant decrease in smoking, about 40,000 new patients are diagnosed with carcinoma of the head and neck annually in the United States, and 11,000 of them succumb to their disease. More than 90% of these cancers are squamous cell carcinoma. The survival rates of patients with squamous cell carcinoma of the head and neck (SCCHN) have not improved significantly despite multimodality therapy including surgery, radiation therapy, and chemotherapy. Recently, molecular targeted agents have shown significant improvement in clinical outcomes in chronic myelogeneous leukemia with imatinib, breast cancer with trastuzumab, colon cancer with bevacizumab and cetuximab, and renal cell cancer with sorafenib and sunitinib. In SCCHN the epidermal growth factor receptor (EGFR) antibody cetuximab has shown promising results in a phase III trial in combination with radiation. How best to integrate these agents with the traditional treatment modalities of surgery, radiotherapy, and cytotoxic chemotherapy is of vital importance but has yet to be determined. This article will discuss the biology of molecular targeted agents as well as current clinical trials and future directions of these agents in SCCHN.

Introduction

With the recent significant progress in molecular biology, several mechanisms of carcinogenesis have been elucidated, including both the activation of oncogenes and the inactivation of tumor suppressor genes [1]. A wide variety of carcinogenesis signaling pathways have also been recognized, such as the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF) signaling pathways [2••].

The epidermal growth factor receptor (EGFR) is a member of the ErbB family of receptors. The EGFR family of receptor tyrosine kinases is comprised of EGFR (ErbB1), ErbB2/HER2/neu, ErbB3/HER3, and ErbB4/HER4 [3•, 4]. EGFR is composed of extracellular domains including a ligand-binding domain, a hydrophobic transmembrane region, and a tyrosine kinase-containing cytoplasmic region. Stimulation of the EGFR by endogenous ligands, such as EGF or

transforming growth factor-alpha (TGF-alpha), results in a conformational change in the receptors into either homo or hetero dimerization. Dimerization results in tyrosine kinase activation. Subsequent protein phosphorylation and stimulation of various cell-signaling pathways mediate gene transcription, cell cycle progression, and growth. The EGF signal is terminated primarily through endocytosis of the receptor-ligand complex (down regulation). The EGFR is expressed on normal human cells, but higher levels of expression have been correlated with various malignant diseases including SCCHN.

In cancer cells, signaling through the EGFR leads to increased cell proliferation, inhibition of apoptosis, cell migration, invasion, angiogenesis, and metastasis. In the early 1980s an antibody that targeted EGFR was found to inhibit cancer cell growth both in vivo and in vitro [5]. Subsequent research efforts have focused on multiple aspects of this signaling pathway.

EGFR antibody (Table 1)

- Cetuximab is currently one of the most widely used EGFR antibodies [3•]. It was first approved for the treatment of colon cancer. In February 2006, cetuximab became the first drug approved for Head and Neck cancer in 40 years. Cetuximab is a recombinant human/mouse chimeric IgG1 monoclonal antibody that binds EGFR and inhibits activation of the receptor tyrosine kinase (RTK) and stimulates receptor internalization and down regulation from the cell surface. Cetuximab also induces antibody-dependent cellular cytotoxicity (ADCC), which may be an explanation for some of cetuximab's antineoplastic activity. Cetuximab was approved by the FDA for head and neck cancer in conjunction with radiation after the success of a landmark trial in which Bonner *et al.* demonstrated not only an increase in the duration of loco-regional control from 14.9 months with radiotherapy alone to 24.4 months with cetuximab + radiotherapy, but also an increase in median survival from 29.3 to 49.0 months in patients with locally advanced head and neck cancer [6•].
- This trial did not, however, compare the current standard treatment in this setting, i.e., platinum + radiotherapy, as a control arm. Cetuximab is known to enhance the effect of chemotherapy and radiotherapy in vitro and in vivo. As yet, no phase III study has shown a statistically significant benefit in overall survival with cetuximab combined with chemoradiotherapy over chemoradiotherapy alone. To address this issue, the phase III trial RTOG 0522 (Radiation Therapy and Cisplatin With or Without Cetuximab in Treating Patients With Stage III or Stage IV Head and Neck Cancer) was recently initiated. One of the touted benefits of the cetuximab + radiation regimen is that it is well tolerated in terms of mucositis, dysphagia, and the need for a feeding tube [6•]. Some investigators are concerned that this benefit may be lost if chemotherapy is added to the regimen, as suggested by a recent phase II trial by Pfister *et al.* that combined cetuximab, cisplatin, and radiation [7]. This trial showed promising results: a 3-year overall survival (OS) rate of 76%, a progression-free survival rate of 56%, and a loco-regional control rate of 71%, but it was closed early due to significant toxicities.
- Several other recent trials have addressed whether cetuximab has additive or synergistic effects when used in combination with cytotoxic chemotherapy and radiation. Among 23 evaluable patients in primary platinum resistant recurrent SCCHN, the addition of cetuximab to paclitaxel and carboplatin showed a promising response rate (RR) of 56% in a report by Buentzel *et al.* [8]. No radiotherapy was given in this study. The RR in this study is much higher than in previous studies in platinum pretreated patients with recurrent SCCHN.

- Kies *et al.* presented promising phase II trial data for the addition of cetuximab to neoadjuvant paclitaxel and carboplatin [9]. Although the total number of patients was limited, there was a 98% overall response (OR) which included a 26% complete response (CR) rate. The primary site of cancer in this study was the oropharynx (89%), and 70% had early disease, T0–T2. These promising results in the neoadjuvant setting suggested that there are cytotoxic effects of cetuximab distinct from its radiation sensitizing effects.
- Also in the neoadjuvant setting, two studies were reported at ASCO 2007. ECOG 2303, a phase II trial for stage III/IV operable SCCHN, showed that induction cetuximab + paclitaxel and carboplatin followed by cetuximab + chemoradiation (paclitaxel + carboplatin) resulted in a pathologic CR at the primary site as proven by restaging biopsy for 65% of sampled patients with induction alone and for 100% of sampled patients after chemoradiotherapy [10]. Progression and survival data have not yet matured. Another neoadjuvant phase II trial for locally advanced SCCHN by Argiris *et al.* [11] showed preliminary data from 16 evaluable patients. The overall RR to induction cetuximab + docetaxel and cisplatin was 94% (15/16, CR: 2, partial response (PR): 13, stable disease (SD): 1). All of 10 patients who completed radiotherapy with cetuximab and paclitaxel remain progression free.
- Preliminary results from an Italian phase II study for loco-regional advanced SCCHN by Merlano *et al.* showed a 100% RR (CR: 11, PR: 5) with cisplatin 20 mg/m^2 daily × 5 days + 5 FU 200 mg/m^2 daily × 5 days repeated on days 1, 22, and 43 [12]. At a maximum follow-up of 15 months, 16/20 patients are alive and 16/20 patients are progression free. In this study all patients but one (oropharyngeal) had hypopharyngeal cancer.
- For metastatic or recurrent SCCHN, preliminary but impressive data was presented by Vermorken *et al.* [13] at the recent ASCO 2007. In this international phase III study (EXTREME) of first line therapy, 440 patients were randomized to either cisplatin or carboplatin + 5 FU or cisplatin or carboplatin + 5 FU + cetuximab followed by maintenance cetuximab. Preliminary data showed a prolonged OS of 10.1 months vs. 7.4 months with the addition of cetuximab to traditional platinum based chemotherapy. A 1-year overall survival (OS) rate was 39 vs. 31%, respectively. Prior to this study there was only one phase III study by Burtness *et al.*, which showed an improved response rate (RR) but not a statistically significant benefit in survival [14]. The Spanish Head and Neck Cancer Group phase II study with cetuximab + weekly paclitaxel showed an overall response rate (OR) of 71% and a disease control rate of 88% among 35 evaluable patients (CR: 7, PR: 18, SD: 6) [15] (Table 1).
- The role of molecular targeted agents in adjuvant or maintenance treatment is unclear, but several studies have been designed to address this question. In this setting, erlotinib, a small molecule tyrosine kinase inhibitor, and lapatinib, a dual tyrosine kinase inhibitor of EGFR (ErbB1) and HER2/neu (ErbB2), are now under investigation [16, 17].

. Definitive Therapy Locoregional Advanced

	Phase	N	Regimen	Results
Bonner	III	424	RT ± **cetuximab**	**median survival 29.3mo vs 49mo(p=0.02)**
RTOG 0522	III	ongoing	**cetuximab** ± cisplatin (q3week) + RT	**ongoing**
Pfister	II	22	**cetuximab** + cisplatin (q3week) + RT	a 3yr overall survival rate 76% a 3yr progression free survival rate 56% a 3yr locoregional control rate 71%
Neoadjuvant				
Merlano	II	45	**cetuximab** + cisplatin(daily) + 5FU (daily) + RT	100% RR (CR:11 PR:5)
Kies	II	47	**cetuximab** + paclitaxel + carboplatin → **cetuximab** + paclitaxel + carboplatin + RT	primary 100% RR (CR:7 PR:34,41/41) node 97%RR (CR:12 PR:31,43/44)
Wanebo(ECOG2303)	II	67	**cetuximab** + paclitaxel + carboplatin → **cetuximab** + paclitaxel + carboplatin + RT	65% pCR (26/40) after induction 100% pCR (28/28) after induction+CRT
Argiris	II	21	**cetuximab** + docetaxel + cisplatin → **cetuximab** + cisplatin + RT	94% RR (CR:2 PR:13 SD:1,15/16) after induction+CRT

. Recurrent and/or Metastatic

	Phase	N	Regimen	Results
First-line				
Vermorken	III	440	cisplatin/carboplatin(q3week) + 5FU(daily) ± **cetuximab**	**median survival 10.1mo vs 7.4mo(p=0.036)** a 1yr overall survival rate 39% vs. 31%
Burtness	III	116	Cisplatin (q4week) ± **cetuximab**	RR 26.3% vs. 9.8% median survival 9.2mo vs 8.0mo (p=0.21 no statistical significance)
platinum refractory				
Buentzel	II	23	**cetuximab** + paclitaxel+carboplatin(q3week)	56% RR (CR:1 PR:7 minor R:5,13/23)
Hitt	II	35	**cetuximab** + paclitaxel (weekly)	71% RR (CR:7 PR:18) 88% DCR (SD:6)
Herbst	II	130	**cetuximab** + cisplatin (q3week)	13% RR (CR:2 PR:13 SD:1)
Baselga	II	96	**cetuximab** + cisplatin/carboplatin(q3week)	10% RR 53% DCR
Vermorken	II	103	**cetuximab only**	12.8% RR 46% DCR

RR: response rate, CR: complete response, pCR: pathological complete response, PR: partial response, SD: stable desease
DCR: disease control rate, RT: radiotherapy, CRT: chemoradiotherapy

Prediction of response

- Despite intense efforts, we do not yet have a reliable way to predict response to EGFR targeted antibodies. High levels of EGFR tumor expression have been associated with poor prognosis [18], but the level of expression with immunohistochemistry itself does not correlate with tumor response to EGFR-targeted therapy, as was demonstrated by Kies *et al.* [19]. A better way to predict response to these agents is needed not only from a therapeutic standpoint but also from an economic one. These agents can be a significant economic challenge both for individual patients and for the healthcare system. If a reliable predictor was available, patients whose tumors are not likely to respond to cetuximab could be spared unnecessary expense. In an attempt to find such an indicator, a host of different approaches have been studied including tumor analysis by immunohistochemistry or FISH, determination of the level of EGFR mRNA, EGFR gene amplification, and an assessment of mutation status and genomic/proteonomic signatures. At present no clear indicators have been found. The acne-like rash seen with cetuximab is the only surrogate marker that has been correlated to any extent with tumor response [20].
- A rash has been reported in more than 80% of patients treated with EGFR targeted agents and has been described as acne or acne-like, although strictly speaking, histologically, it is not acne, but a mixture of follicular and intrafollicular pustules without comedones [21•]. The rash caused by cetuximab is histologically similar to the rash caused by the tyrosine kinases inhibitors (TKI) erlotinib and gefitinib. It usually occurs after 1 week of treatment and reaches maximum intensity after 2–3 weeks. Although the precise etiology of the rash has not been elucidated, it is known that HER1/EGFR is expressed by normal keratinocytes, skin fibroblasts, and the outer root sheath of hair follicles. Multiple studies with patients with SCCHN and also with patients with other tumor types have shown a consistent relationship between rash and response, and some have shown one between the presence of rash and survival. In the report of the EVEREST trial in the setting of colorectal cancer, Van Custem *et al.* noted that better treatment outcomes might be achieved by increasing the dose of cetuximab to the level to provoke a rash [22].

Site-specific difference?

- In the key study by Bonner *et al.*, which led to FDA approval of cetuximab for SCCHN, the subset of patients who gained the most benefit was the subset of patients with oropharyngeal cancer [6•]. Site-specific median OS rates were, for oropharynx, 30.3 months vs. >66 months; for larynx, 31.6 months vs. 32.8 months; and for hypopharynx, 13.5 months vs. 13.7 months for RT only vs. RT + cetuximab respectively. The median duration of loco-regional control showed a similar trend: for oropharynx, 23 months vs. 49 months; for larynx, 11.9 months vs. 12.9 months; and for hypopharynx, 10.3 months vs. 12.5 months for RT only vs. RT + cetuximab respectively. Of note, the number of patients with laryngeal and hypopharyngeal cancer is relatively small compared to the number of patients with oropharyngeal cancer in this study. A larger sample size is required to answer the question of whether or not there is a site-specific difference in outcome.

Less toxic?

- Molecular targeted agents are thought to be less toxic compared to traditional chemotherapeutic agents. The recent study with cetuximab and radiation by Bonner *et al.* was promising both in terms of response and observed side effects [6•]. In particular, the frequency and level of mucositis seen in the cetuximab arm were not different from what was seen in the radiation only control arm. Cetuximab appears to be a tumor specific radiosensitizer. The median time from initiation of treatment to resolution of mucositis was 2.5 months for patients receiving radiotherapy alone vs. 2.6 months for those receiving the cetuximab-radiation combination. The onset and the resolution of dysphagia were also equivalent in both arms. However long-term follow up is necessary to see if cetuximab contributes to organ preservation and better functional outcome.
- These agents can be administered to elderly or frail patients who may not tolerate traditional cytotoxic therapies. However, significant side effects that are different from those of traditional cytotoxic chemotherapy have been reported. Cetuximab can cause an acne-like rash, hypomagnesemia, and a rare but potentially fatal infusion reaction [23••]. Interestingly a geographical difference in incidence rates of infusion reactions has been reported. The regions that report high rates of infusion reactions with cetuximab appear to be some areas of North Carolina, South Carolina, Kentucky, and Tennessee. Panitumumab is a fully humanized EGFR monoclonal antibody. The incidence of infusion reaction with panitumumab is less than 1%. Bevacizumab, an antibody directed against VEGF, can cause hypertension, proteinuria, bleeding, and thrombosis. Cardiac dysfunction is a known side effect of trastuzumab, a Her2-neu antibody. Hypothyroidism has been reported with sorafenib, a multi-kinase inhibitor. Fatal interstitial pneumonitis was reported with gefitinib, a tyrosine kinase inhibitor in the EGFR pathway. Clearly, surveillance for long-term side effects with these new biologic agents is essential.

How to combine agents, "vertically" or "horizontally"?

- The response to single small molecule tyrosine kinase inhibitors such as gefitinib and erlotinib in recurrent or metastatic SCCHN is less than that of lung adenocarcinomas with EGFR mutations. To overcome this low level of activity, the concept of "vertical" targeting has been proposed. For example, in the EGFR signaling pathway, EGFR monoclonal antibodies and tyrosine kinase inhibitors act at different points in different ways, the former against extracellular receptors and the latter in the intracellular domain. Using a combination of these agents, synergistic activity has been observed in preclinical settings [24, 25].
- Another engaging concept is "horizontal" blockade. Blocking different pathways such as the EGFR, VEGF, and platelet-derived growth factor receptor (PDGFR) pathways at the same time may lead to a better response. Concurrent VEGF and EGFR blockade could be synergistic and improve the effectiveness of concurrent chemoradiation for SCCHN because of the interruption of the cross talk among these pathways. Although no solid data are available yet, several studies pursuing this concept are actively accruing patients, including a randomized study of erlotinib and bevacizumab in SCCHN [26, 27] and a phase II trial of cetuximab and bevacizumab in patients with recurrent or metastatic SCCHN [28]. Hopefully the recent advances

gained in our understanding of this wide variety of molecular networks will lead to the development of more effective and tolerable treatment strategies for head and neck cancer patients.

New targeting agents and current clinical trials

Small molecule tyrosine kinase inhibitor

- Small molecule tyrosine kinase inhibitors (TKI) target the signaling cascade downstream. Several phase II trials with small molecule EGFR TKI's have been conducted with mixed results. In SCCHN, neither gefitinib nor erlotinib was associated with promising clinical activity as a single agent. EGFR mutations seen in lung adenocarcinoma have not been found yet in SCCHN. Phase II trials with gefitinib showed an OR of 1.4–10.6% with a DCR of 34–53% [29, 30]. Erlotinib monotherapy showed an OR of 4.3% with a DCR of 38.3% [31]. Small molecule TKI monotherapy might not provide an adequate response, but a phase II study of gefitinib in combination with chemoradiotherapy showed an 89% CR (49/55) and a 9% PR (5/55) for a 98% OR in the setting of locally advanced disease [32]. A phase II study with erlotinib in combination with cisplatin and radiotherapy by Herchenhorn *et al.* in locally advanced SCCHN showed an 84% RR (pathological CR: 21) among 25 patients who completed treatment [33]. Another phase II study with erlotinib by Kim *et al.* also showed an OR of 66% and a DCR of 91% in combination with cisplatin, docetaxel, and radiation in recurrent or metastatic settings [34]. Glisson *et al.* showed enhanced cytotoxicity in human SCCHN cell lines when docetaxel was given more than 10 hour prior to erlotinib [35]. The question of what is the optimal sequence of targeted agents and chemotheraphy remains to be answered.

Emerging EGFR antibody

- Panitumumab is a fully humanized anti-EGFR antibody (IgG2 isotype) that has recently been approved for the treatment of colon cancer. It has a lower incidence of infusion reaction than cetuximab, <1% vs. 4–5%. Since it is an IgG2 isotype, it does not induce ADCC. Matuzumab and zalutumumab are also newer humanized EGFR-targeting monoclonal antibodies under clinical trials as monotherapy or in combination with chemoradiation [36, 37].

Antiangiogenic agents

- Angiogenesis, the growth of new blood vessels, is a targeted mechanism of interest for several types of solid tumors, including head and neck cancer [38]. Vascular endothelial growth factor (VEGF) is an important signaling protein involved in both vasculogenesis (the de novo formation of the embryonic circulatory system) and angiogenesis (the growth of blood vessels from pre-existing vasculature) [39••]. VEGF also enhances microvascular permeability. The FDA has approved bevacizumab, a humanized recombinant monoclonal antibody to the VEGF, for the treatment of metastatic colon and lung cancer. Elevated VEGF expression correlates with increased progression and poor prognosis of SCCHN [40]. The mechanism of action of bevacizumab is thought to be not only antiangiogenesis but also the facillitation of an

increase of delivery of chemotherapeutic agents by decreasing microvascular permeability and decreasing intratumor pressure [39••]. The latter mechanism may explain why bevacizumab works synergsistically with chemotherapy. Bevacizumab is currently under investigation in combination with other cytotoxic agents including fluorouracil, hydroxyurea, docetaxel, and pemetrexed in SCCHN. Preliminary data of these studies were presented at ASCO 2007. In combination with 5-fluorouracil, hydroxyurea, and radiation, bevacizumab did not increase bleeding complications [41]. In combination with pemetrexed in recurrent or metastatic SCCHN, bevacizumab showed a 45% OR (CR: 2, PR: 3, SD: 6, PD: 0) among 11 evaluable patients [42]. In this study 5 out of 14 patients evaluable for toxicity had hemorrhagic complications. This phase II study is still under accrual. In a trial with bevacizumab, docetaxel, and radiation in locally advanced SCCHN, 10 patients completed concurrent chemoradiation [43]. Among these 10 patients, 9 patients remain in CR, and 1 patient developed metastatic disease after a median follow-up of 9 months (range: 0–13). Six out of ten patients underwent a planned neck dissection, and they each had a pathologic CR. Six out of nine patients are currently receiving adjuvant bevacizumab.

Multitargeted inhibitors

- The multitargeted inhibitor sunitinib is an oral, small molecule, multikinase inhibitor that targets several receptor tyrosine kinases, including platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), stem cell factor receptor (KIT) and Flt 3. Preclinical data suggest that sunitinib has antitumor activity by way of antiangiogenesis and antiproliferative effects. Sorafenib is an oral multikinase inhibitor that targets serine/threonine Raf-1 kinase and various receptor tyrosine kinases, including VEGFR, PDGFR, KIT, and Flt3. It has been associated with tumor growth inhibition and reduced angiogenesis in several in vitro and animal models. The FDA approved sorafenib in December 2005 for advanced renal cell cancer. The results of a Southwest Oncology Group (SWOG) phase II trial of sorafenib in patients with recurrent and/or metastatic SCCHN were presented at ASCO 2007 [44]. The estimated confirmed RR was only 3% (95% CI: 0–13%) among 34 patients who were evaluated with 9 months median follow-up. Median progression-free survival was 4 months (95% CI: 3–4 months), and median OS was 8 months (95% CI: 7–11 months).
- Lapatinib is an oral, dual tyrosine kinase inhibitor of EGFR (ErbB1) and HER2/neu (ErbB2). Lapatinib monotherapy failed to show response (0% OR) but did show SD in 37% of patients who were TKI naïve and in 20% of patients who had received a TKI in the past [45]. In combination with chemoradiation, it has been reported to show encouraging clinical activity [46]. Vandetanib (ZD6474), an orally active selective inhibitor of VEGFR, EGFR, and rearranged during transfection (RET) tyrosine kinases is also being tested in SCCHN as monotherapy and also in combination with chemotherapy [47].

Other promising agents

Bortezomib

- Bortezomib is a proteasome inhibitor that is mainly used in the treatment of multiple myeloma. Preclinical studies have demonstrated that bortezomib decreases tumor growth, angiogenesis, and metastasis

and increases tumor apoptosis and cell death [48]. Bortezomib inhibits activation of the transcription factor nuclear factor κB (NF-κB) and sensitizes these cells to chemotherapy, radiation, or immunotherapy without added toxicities. Based on these preclinical data, several clinical trials are ongoing including a phase II trial of bortezomib in combination with irinotecan or bortezomib alone for patients with recurrent or metastatic SCCHN, a phase II trial of combination weekly bortezomib and docetaxel in recurrent or metastatic SCCHN [49], and a phase I study of concomitant bortezomib and radiation therapy in recurrent or metastatic SCCHN [50].

mTOR inhibitor

- The mammalian target of rapamycin, commonly known as mTOR, is a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription [51]. Clinically mTOR inhibitors are used commonly for immunosuppression. They are also known to induce G1 cell cycle arrest and apoptosis. In renal cell cancer and lymphoma, mTOR inhibitors have shown promising antitumor effects. In preclinical models mTOR inhibitors have shown the ability to radiosensitize and also to restore sensitivity to chemotherapy including cisplatin. Based on these data, there is a clinical trial with cisplatin and everolimus (RAD-001) in SCCHN [52].

HSP90 inhibitor

- Heat shock protein 90 (Hsp90) is a molecular chaperone that promotes the conformational maturation of numerous client proteins. Hsp90 participates in many key processes in carcinogenesis such as self-sufficiency in growth signals, stabilization of mutant proteins, angiogenesis, and metastasis. Preclinical data have shown antitumor activity in SCCHN cell lines with an ansamycin-based Hsp90 inhibitor [53].

VB4-845 (Proxinium)

- Proxinium is a recombinant fusion protein that binds to the epithelial cell adhesion molecule (Ep-CAM), which is highly expressed on SCCHN. Administered via intratumoural injection, VB4-845 has been tested in a variety of preclinical studies and has demonstrated therapeutic potential in various cellular and animal models of cancer, including animal models of lung cancer and head and neck cancer. A phase I study in SCCHN showed safety and tolerability with VB4-845 [54]. In this study VB4-845 therapy yielded an objective RR of 43% and a tumor growth control rate of 71% in patients whose tumors expressed the Ep-CAM antigen.

Histone deacetylase (HDAC) inhibitor

- Histone deacetylase (HDAC) inhibitors are emerging therapeutic agents that may have the ability to disrupt critical cellular processes in cancer cells. Transcriptional regulation, differentiation, cell cycle

arrest, radiation sensitization, and apoptosis have been observed in response to exposure to HDAC inhibitors. G1 arrest and inhibition of DNA synthesis are the underlining mechanisms of these agents [55].
- A number of other potential agents employing novel targeting approaches including insulin-like growth factor receptor blockade [56] and farnesyl transferase inhibition are also under active investigation.

The role of human papillomavirus (HPV) in SCCHN

- Squamous Cell Carcinoma of the Head and Neck, especially oropharyngeal cancer, has a strong correlation with HPV. A case control study by D'Souza *et al.* proved that the presence of an oral HPV-16 infection was strongly associated with oropharyngeal cancer (odds ratio, 14.6; 95% CI, 6.3–36.6), as was oral infection with any of 37 HPV types (odds ratio, 12.3; 95% CI, 5.4–26.4) [57]. Interestingly in their study, no evidence of synergy was found between HPV exposure and heavy tobacco and alcohol use. The investigators speculated there might be two distinct pathways of oropharyngeal carcinogenesis, one tobacco/alcohol related and another HPV-induced. Several reports in ASCO 2007 addressed the prognostic difference between HPV-related and HPV-unrelated SCCHN. According to these reports, HPV-related SCCHN tend to respond better to chemoradiotherapy [58]. HPV-related SCCHN are more common in oropharyngeal cancer. This may explain the aforementioned site-specific differences in response to radiotherapy with cetuximab. In cases of HPV-positive SCCHN, more than 90% of cases are related to HPV-16. Through the analysis of SEER data (1973–2003), Chaturvedi *et al.* reported that the proportion of HPV-related SCCHN is increasing as opposed to that of HPV-unrelated SCCHN [59]. The role of the recently approved HPV infection preventive vaccine for cervical cancer needs to be explored in the setting of SCCHN. A trial with MAGE-A3/HPV 16 vaccines is addressing this issue [60]. Cancer prevention as well as treatment of early cancerous lesions with a vaccine therapy may be on the horizon.

Conclusion: how to choose the right drug for the right patients in the right settings?

- Existing standard therapies for SCCHN are inadequate, and more research needs to be done. Due to its lower incidence rate compared to breast, colon, and lung cancers, large studies are difficult to perform. Many clinically relevant questions have yet to be answered such as: how best should these agents be combined with chemotherapy and radiation therapy or with each other; how much of the effect of these molecular agents is achieved by radiation sensitization vs. cytotoxicity; at what point in treatment should they be introduced; how can patients who are most likely to have maximal responses be selected to minimize toxicity and cost; what are the late toxicities; and how much will these agents ultimately contribute to loco-regional control, organ preservation, decrease of metastasis, and improved survival? The gaining of a fuller understanding of how to use these novel agents, which may emerge in light of future discoveries about biomarkers, holds great potential to help us further decrease morbidity and mortality from this disease. Although much remains to be elucidated, promising early phase data in preclinical and clinical settings suggest the possibility that ongoing and future investigations will translate into a major positive improvement on survival for patients with head and neck cancer.

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