

Current status of experimental therapeutics for head and neck cancer

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Abstract

As with many cancers, early detection of head and neck cancer increases a patient's survival rate. If diagnosed early, its five-year survival nears 90% with standard therapy alone. Unfortunately, the average survival rate for head and neck cancer is low due to the difficulty in early detection and achieving a sustainable response. Conventional treatments are not adequate for the majority of advanced or recurrent head and neck cancer patients because of the remarkable resistance of tumors to chemotherapy and radiation, and the situation is especially devastating for the first time treatment failure. The major limitations of these treatments are the lack of specificity for the tumor cell and unacceptable toxicity to the patient. As a result, current research in therapeutics for advanced, chemotherapy-resistant or recurrent head and neck cancer patients has focused on new treatment modalities that exploit biological differences between tumor and normal cells. These therapies include monoclonal antibodies, molecular inhibitors, gene therapy and photodynamic therapy. This article reviews the current preclinical and clinical evidence of these experimental therapeutics as they relate to head and neck cancer.

Keywords: head and neck cancer, monoclonal antibodies, molecular inhibitors, gene therapy, photodynamic therapy

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Introduction

Head and neck cancers, 90% of which are overwhelmingly squamous cell carcinomas, include cancers of the oral cavity, oropharynx, hypopharynx, larynx, and, to a lesser degree, the nose and paranasal sinuses. Treatment for squamous cell carcinomas of the head and neck (SCCHN) has mainly consisted of a combination of surgery and radiation, or combined radiation and chemotherapy. Unfortunately, these standard therapies are not adequate, as demonstrated by the high incidence of locoregional failure and a poor overall survival rate (around 50%) for patients with SCCHN.¹ The lack of success for conventional treatment modalities is in part due to the remarkable resistance of tumors to chemotherapy. Attempts to overcome resistance with higher doses of chemotherapeutics inevitably result in an unacceptable degree of toxicity and bystander damage to normal tissues.¹ Combinations of currently available treatment modalities have been moderately successful; however, these combination therapies often cause unacceptably high toxicity without survival advantage.^{1,2} The major limitations of all these treatments and their combinations are

the lack of specificity for the tumor cell and the unacceptable toxicity to the patient.

Recent advances in molecular biology have documented significant genetic differences between cancer cells and normal cells, leading to the development of potential new therapeutics that exploit these disparities.³ These new therapies include monoclonal antibodies, molecular antagonists, gene therapy and photodynamic therapy (PDT).^{1,3} This article reviews the mechanisms of action of these developments and examines their clinical trial status as they relate to head and neck cancer.

Molecular biology of head and neck squamous cell carcinoma

A number of specific genetic events have been identified in the malignant progression of SCCHN. These genetic events include amplification and/or overexpression of oncogenes and mutations and deletions leading to inactivation of tumor suppressor gene.⁴ The identification of these molecular alterations has allowed the development of new

therapeutic approaches targeting specific differences between normal and malignant cells. Among the most important targets for new therapeutic strategies in SCCHN are the epidermal growth factor receptor (EGFR) oncogene and the p53 tumor suppressor gene.

Epidermal growth factor receptor

The EGFR (or *erbB1*) is a member of the family of tyrosine kinase membrane receptors which is made up of four distinct, but structurally similar, receptors encoded by the proto-oncogenes *EGFR*, *HER2*, *c-ERBB3/HER3* and *c-ERBB4/HER4*. The binding of the ligands (EGF and transforming growth factor- α [TGF- α]) to the receptor's extracellular domain induces EGFR dimerization, resulting in activation of the receptor tyrosine kinase activity and EGFR autophosphorylation on specific tyrosine residues.³ These phosphorylated tyrosines recruit signal transducers or adaptors that initiate various intracellular signaling pathways such as Ras/Raf/MEK/MAPK, which control cellular proliferation, migration and differentiation.

Overexpression of EGFR has been reported in 80–90% of SCCHN and shows a significant association with EGFR gene amplification but not with EGFR mutations.^{1,4} EGFR has been found to be overexpressed in dysplastic lesions and histologically normal mucosa from SCCHN patients, indicating that EGFR upregulation represents an early event in carcinogenesis.⁴ Furthermore, EGFR overexpression correlates with more aggressive disease, resistance to both chemotherapy and radiotherapy, and a poor prognosis (Figure 1).^{4–6}

p53

Genetic alterations, leading to inactivation of tumor suppressor genes such as *p16* and *p53*, are frequently observed, and chromosomes 3p, 9p and 17p are regions with the highest loss of heterozygosity in SCCHN and are associated with the development and progression of the disease.⁷ Mutations of *p53* are found in 40–70% of SCCHN with 20% in premalignant lesions.⁸ A higher incidence of mutations have been detected in invasive carcinomas than in non-invasive cancers.⁹ Tumors with *p53* overexpression have been reported to be more aggressive and associated with higher tumor stage, increased incidence of lymph node metastasis and shortened survival.¹⁰ In addition, it has been shown that detection of clonal-specific *p53* mutations at tumor margins in SCCHN is a predictor of local recurrence.^{6,11}

The tumor suppressor gene *p53* encodes a M_r 53,000 transcription factor that activates the transcription of at least six or seven genes known to be involved in cell-cycle control and the induction of programmed cell death, apoptosis.¹² Normally, the concentration of p53 protein is low or even undetectable in the cell because protease activity causes a short protein half-life (about 20 min). When DNA damage occurs in the normal cell, the concentration of active p53 protein is increased because of its lengthened half-life and increased expression, together with post-translational activation of the protein.¹² Increased levels of active p53 may

induce either G₁ cell-cycle arrest or apoptosis in the cell. The p53-mediated cell-cycle arrest is evidently due to transcriptional activation and increased expression of the tumor suppressor gene *p21*.^{3,12}

Several *in vitro* studies have shown that introduction of wild-type (wt) *p53* in human cancer cells that lack functional *p53* induces apoptosis in the cells.^{12–15} Cell-cycle arrest and apoptosis both serve to suppress tumorigenesis. When the cell lacks functional *p53*, the probability of DNA damage accumulation leading to cell transformation is therefore increased. The fact that *p53* contains mutations in more than 50% of all human cancers¹⁶ has caused wt *p53* to become the center of most studies in which the therapeutic potential of restoring a tumor suppressor gene in cancer cells has been examined.

EGFR inhibitors

A number of agents have been designed to target EGFR with different mechanisms including monoclonal antibodies, tyrosine kinase-specific inhibitors, ligand-linked immunotoxins and antisenses, and are currently being studied in clinical field; several of them have been successful enough to be approved by the United States Food and Drug Administration (FDA) as secondary drugs for different types of cancers.¹⁷ The furthest in development are cetuximab (Erbix, IMC-C225), trastuzumab (Herceptin), gefitinib (Iressa, ZD1839) and erlotinib (Tarceva, OSI-774). Gefitinib and erlotinib are orally active molecular inhibitors for EGFR inhibitors, while cetuximab and trastuzumab are anti-EGFR monoclonal antibodies.^{17,18} Presently, only cetuximab has been approved by the FDA for two indications in the head and neck cancer population.

Cetuximab

Cetuximab (IMC-C225), a chimeric humanized version of the murine monoclonal antibody, M225, was generated to avoid the host's immune response. It competitively binds and induces the downregulation of the EGFR, preventing further receptor binding and activation of the ligands. Preclinical studies show that cetuximab inhibits the proliferation of cell lines expressing EGFR, and increases the cytotoxic effects of chemotherapy and radiation.^{17–19}

Clinical trials

In several phase I trials, antitumor responses were observed in patients with various cancers, including head and neck, when treated with cetuximab alone and in combination with chemotherapy. When treated with cetuximab alone, a majority of patients (18/28, 64%) experienced stable disease (SD) (Table 1, trial 1).²⁰ When treated with cetuximab and cisplatin, 11/19 patients (58%) had SD.²⁰ Two patients with head and neck tumors exhibited a partial response. There were a few grade 3 or 4 toxicities, and one patient developed antibodies against cetuximab. When used in combination with radiation therapy (RT), a dose-escalation study found that 15 patients with advanced SCCHN achieved an objective response; 13 patients had

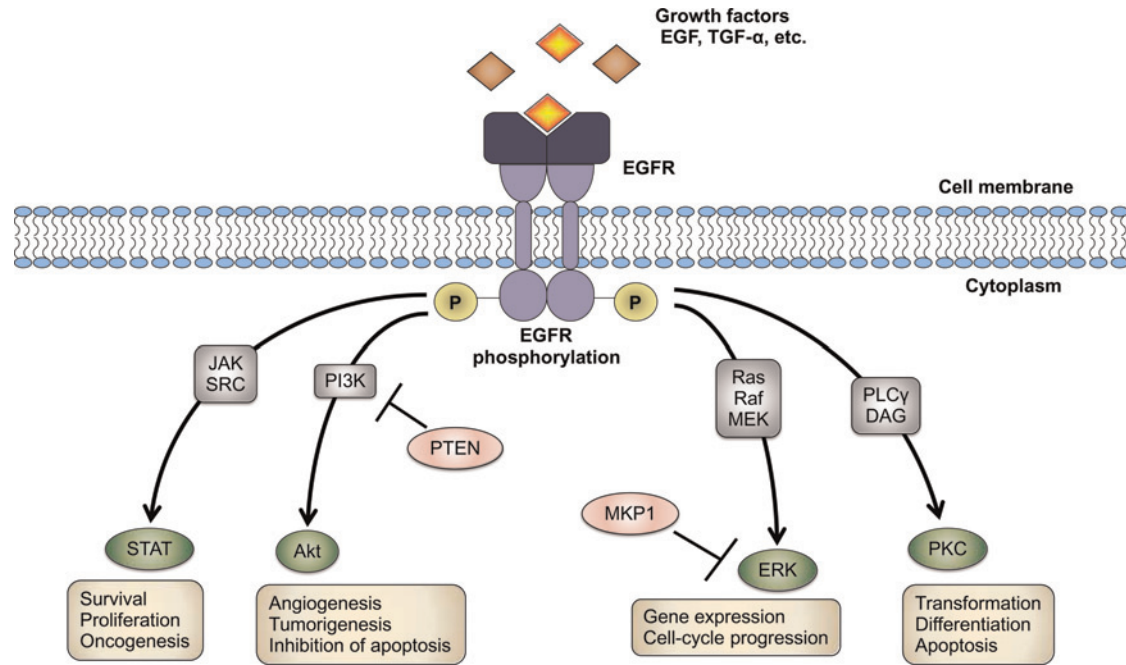


Figure 1 The EGFR signaling pathway. The figure shows signaling pathways that are activated by EGFR. Important signaling pathways regulated by EGFR are represented with important functions highlighted in colored boxes. The signaling cascade does not include all the known components of a given pathway, and cross-talk is not shown for clarity. Examples of inhibitory signals are also shown, such as PTEN (phosphatase and tensin homologue), which can dephosphorylate PI3K, and MKP1 (MAPK phosphatase 1), which can dephosphorylate ERK1/2 signaling pathways (A color version of this figure is available in the online journal)

complete remissions while two patients experienced a partial response (Table 1, trial 2).²¹ Most adverse events were grade 1 or 2.

One phase II trial has studied cetuximab in combination with cisplatin.²² Of 78 evaluable patients with recurrent or metastatic SCCHN, nine (11.5%) achieved a partial response while 13 (16.7%) experienced disease stabilization (Table 1, trial 3). Toxicities were consistent with the known safety profiles of the study drugs. In another phase II trial of

cetuximab in combination with cisplatin or carboplatin, 96 patients have been evaluated for response, including two (2.1%) complete responses and 12 (12.5%) partial responses, with an overall response rate of 14.6% (CI 8.3–23.1%) (Table 1, trial 4).²³ Thirty-eight patients (39.6%) had SD or minor responses lasting for at least six weeks.

A multinational landmark phase III trial has recently provided the results of cetuximab in combination with radiotherapy (Table 1, trial 5).²⁴ Over 400 patients with locoregionally

Table 1 Clinical trials for cetuximab

Tumor type	Phase	Vector name	Delivery mode	No. of patients evaluable	No. and type of responses	Adverse reactions	Reference
Bladder, breast, head and neck, kidney, lung, ovary, prostate	I	Cetuximab	IV	28	18 stable disease; 10 progressive	Asthenia, chills, fever, nausea, skin toxicities, transaminase elevation	20
Head and neck	I	Cetuximab	IV plus radiation therapy	15	13 complete response; 2 partial response	Asthenia, fever, nausea, skin toxicities, transaminase elevation	21
Head and neck	II	Cetuximab	IV plus cisplatin	78	9 partial response; 13 stable disease	Anemia, nausea, rash	22
Head and neck	II	Cetuximab	IV plus cisplatin or carboplatin	96	2 complete response; 12 partial response; 38 stable disease	Anemia, asthenia, rash	23
Head and neck	III	Cetuximab	IV plus radiation therapy	424	Overall response: 74% (+cetuximab) versus 64% (–cetuximab)	Rash	24
Head and neck	III	Cetuximab	IV plus cisplatin	112	Objective response = 10% (–cetuximab), 26% (+cetuximab)	Hypersensitivity, neutropenia, rash	25
Head and neck	III	Cetuximab	IV plus platinum-based chemotherapy	442	Overall response: 36% (+cetuximab) versus 20% (–cetuximab)	Rash	26

advanced SCCHN received high-dose RT either alone or together with cetuximab (initial dose 400 mg/m², followed by weekly doses of 250 mg/m²), with the initial dose administered one week prior to radiotherapy. The study met both its primary endpoint of locoregional control and its secondary endpoint of overall survival, both of which were statistically significant. The median duration of locoregional control was significantly improved among cetuximab plus radiotherapy group compared with radiotherapy alone group (24.4 versus 14.9 months, $P = 0.005$). Cetuximab plus radiotherapy also demonstrated a significant improvement in the median overall survival. With a median follow-up of 54 months, the median survival with cetuximab plus radiotherapy was 49 months compared with 29.3 months for patients receiving radiotherapy alone ($P = 0.03$).²⁴ It is notable that the increase in survival achieved with no worsening of radiation-induced adverse effects. However, it has the limitation that the trial did not compare the cetuximab combination with a platinum-based chemoradiotherapy (CRT) treatment, which is currently the standard of care for patients with SCCHN. Also, the trial did not administer the same radiation regimens to all patients, which complicates how the results should be interpreted.^{17,24}

A pilot phase II demonstrated the preliminary efficacy of combining cetuximab with CRT in locally advanced SCCHN.²⁷ Twenty-two patients received concomitant boost radiotherapy, cisplatin (100 mg/m² intravenously weeks 1 and 4) and cetuximab (400 mg/m² intravenously week 1, followed by 250 mg/m² weeks 2–10). With a median follow-up of 52 months, the three-year overall survival rate is 76%, the three-year progression-free survival (PFS) rate is 56%, and the three-year locoregional control rate is 71%. However, the study was closed for significant adverse events, including grade 3/4 adverse events (myocardial infarction, bacteremia and atrial fibrillation) and two deaths (one from pneumonia and one of unknown cause). Currently, a randomized phase III study is being conducted to further investigate the use of cisplatin and accelerated fractionated radiotherapy with or without cetuximab in locally advanced SCCHN.

In a phase III randomized trial conducted by the Eastern Cooperative Oncology Group (ECOG) to determine the effect of the addition of cetuximab on the recurrent and/or metastatic SCCHN, patients were assigned to receive cisplatin every four weeks, with weekly cetuximab or placebo (Table 1, trial 6).²⁵ Among 117 evaluable patients treated, the addition of cetuximab to cisplatin significantly improved the response rate compared with placebo (26% versus 10%; $P = 0.03$). However, PFS and overall survival were not significantly improved by the addition of cetuximab. The development of skin toxicity was significantly associated with a reduction in the risk of death; the hazard ratio for survival by skin toxicity in cetuximab-treated patients was 0.42.

A multicenter European phase III trial (EXTREME) randomized 442 patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) to receive either platinum-5-FU with placebo (PF) or platinum-5-FU with cetuximab (PF-C).²⁶ Patients enrolled in this trial were required to be chemotherapy-naïve unless

chemotherapy was used for definitive treatment and given more than six months previously. The only difference in grade 3/4 toxicities was a higher incidence in the cetuximab arm of sepsis ($P = 0.02$), hypomagnesemia ($P = 0.05$) and skin rash ($P < 0.001$), as well as four cases of infusion-related reactions. All three efficacy parameters favored the cetuximab-containing therapy; specifically, patients receiving that therapy had a higher response rate (36% versus 20%; $P < 0.001$), better PFS ($P < 0.001$) and better overall survival ($P = 0.04$). Moreover, both the PFS and overall survival benefit was seen across most of the subgroups analyzed. The EXTREME trial is therefore the first phase III study in metastatic or recurrent HNSCC to show a survival benefit over platinum doublet combination regimens.

Recent data from an open-label multicenter study of cetuximab as a single agent in patients with recurrent and/or metastatic SCCHN showed that cetuximab achieved response rates that are comparable to that seen with cetuximab plus platinum combination regimens in the same setting.²⁸ One hundred and three patients with disease progression on two to six cycles of platinum therapy received cetuximab monotherapy (initial dose 400 mg/m², followed by 250 mg/m² > or = 6 weeks) (single-agent phase). Patients who experienced disease progression ($n = 53$) received salvage therapy with cetuximab plus platinum (combination-therapy phase). In the single-agent phase, response rate was 13%, disease control rate (complete response/partial response/SD) was 46% and median time to progression was 70 d, compared with 0%, 26% and 50 d, respectively, in the combination-therapy phase. Based on a statistically significant improvement in overall survival for RT plus cetuximab²⁴ and the durable objective tumor responses with cetuximab as a single-agent in second- or third-line treatment of advanced SCCHN,²⁸ the US FDA granted approval to cetuximab for use in combination with RT for the treatment of locally or regionally advanced SCCHN or as a single agent for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed.

Other monoclonal antibodies

Herceptin (trastuzumab) is a humanized anti-HER2 monoclonal antibody. It induces HER2 receptor downmodulation and, as a result, inhibits critical signaling pathways and blocks cell-cycle progression. In cancer cell lines, herceptin has been found to induce apoptosis and enhances the cytolytic activity of T lymphocytes against HER2-overexpressing tumor cells.^{29,30} In addition, it has been found to enhance the antitumor activity of standard chemotherapies both in cancer cell lines and in tumor xenografts, including in those of SCCHN. It has been approved by the FDA for the treatment of metastatic breast cancer.

One phase II trial has reported the use of herceptin in monotherapy for patients with advanced or metastatic salivary gland carcinomas (Table 2, trial 1).³¹ Response to treatment could be assessed in 13 patients. Treatment was well tolerated overall with none of the patients discontinuing therapy due to toxicity. One patient had a partial response with disappearance of some bony lesions and stabilization

Table 2 Other novel therapeutics

Tumor type	Phase	Vector name	Delivery mode	No. of patients evaluable	No. and type of responses	Adverse reactions	Reference
Head and neck	II	Herceptin	IV	13	1 partial response; 12 progressive	No significant toxicity	31
Head and neck	I	Panitumumab	IV plus carboplatin and radiation	15	13 complete response	Dysphagia, mucositis, acneiform rash	32
Head and neck	II	Iressa	Oral dose	47	1 complete response; 4 partial response; 20 stable disease; 22 progressive	Acne-like rash, diarrhea	33
Head and neck	III	Iressa	Oral dose	486	Median overall survival = 5.6 months (gefitinib 250 mg/d), 6.0 months (gefitinib 500 mg/d), 6.7 months (methotrexate)	Acne-like rash, diarrhea	34
Various cancers	I	Erlotinib	Oral dose	39	1 complete response; 1 partial response; 2 stable disease	Acne-like rash, diarrhea	35
Head and neck	II	Erlotinib	Oral dose	78	10 partial response; 23 stable disease; 45 progressive	Acne-like rash, diarrhea, fatigue, headache, nausea, and vomiting	36

of others; no new lesions have been identified. His performance status remained excellent throughout his treatment. All the other patients have progressed. Median time to progression was 4.2 months. Other phase II trials are ongoing to examine the role of herceptin in combination with paclitaxel/cisplatin for metastatic or recurrent SCCHN.

Panitumumab is a fully human monoclonal antibody that binds to the extracellular ligand-binding domain of the EGFR. By blocking binding of natural ligands to the EGFR, panitumumab inhibits the function of the receptor, resulting in blockade of EGFR-mediated signaling pathways, causing G1/G0 cell-cycle arrest, growth inhibition and apoptosis.³⁷ It has been approved by the US FDA as a single agent for the treatment of metastatic colorectal cancer. Interestingly, in metastatic colorectal cancer, panitumumab activity was found to be limited to patients whose tumors expressed wt *KRAS*; the response rate was 17% versus 0% in patients with tumors with *KRAS* mutations.^{38,39} The PFS was longer for patients with wt *KRAS* tumors treated with panitumumab. Whether the presence of wt *KRAS* is also associated with response to panitumumab in patients with SCCHN tumors is unknown. Overexpression of *HRAS* appears to be fairly common in SCCHN tumors, although *KRAS* mutations are infrequent.⁴⁰

Panitumumab has shown efficacy in clinical trials for patients with advanced SCCHN. An initial phase I study of this agent was conducted in 19 treatment-naïve patients with stage III/IV disease (Table 2, trial 2).³² Panitumumab (2.5 mg/kg) was administered with weekly carboplatin plus radiotherapy. Of the 15 patients evaluable for response, 13 (87%) had a complete response. The most common adverse events included dysphagia, mucositis and acneiform rash. These preliminary results suggest that panitumumab, in combination with carboplatin and RT, may potentially be effective for treatment of patients with advanced SCCHN.

Currently, there are a number of phase II trials of panitumumab in SCCHN. PRISM is a non-randomized, open-label, multicenter phase II study designed to evaluate

single-agent panitumumab as second-line therapy in patients with platinum-refractory recurrent or metastatic SCCHN. In this trial, all patients will receive panitumumab and treatment will be continued until disease progression, as measured by tumor assessment, or unacceptable toxicity, study withdrawal, death or end of the study.

Another phase II study (PARTNER) is a randomized, multicenter, open-label trial designed to evaluate the addition of panitumumab to a combination of docetaxel and cisplatin for first-line treatment of metastatic or recurrent SCCHN. The study allows for the crossover to panitumumab monotherapy for patients with disease progression on docetaxel/cisplatin alone. Patients eligible for the PARTNER trial must have histologically or cytologically confirmed metastatic and/or recurrent SCCHN not curable by surgery and/or RT. The primary study endpoint for this trial is PFS. Secondary endpoints include overall response rate, time to response, duration of response, rate of disease control and safety. Currently, however, this study has been suspended for safety analysis.

There are also two phase II trials studying panitumumab in the treatment of locally advanced SCCHN. One trial examines the difference in local-regional control rate at two years in subjects receiving CRT or panitumumab plus radiotherapy as first-line treatment for locally advanced SCCHN. The second trial seeks to evaluate the PFS of locoregionally advanced (stages III/IV) SCCHN patients undergoing postoperative CRT with panitumumab. Notably, this study will also attempt to correlate efficacy parameters with a number of biomarkers, including EGFR and downstream pathway activation. Currently, there is one phase III trial examining panitumumab in SCCHN. This study seeks to compare the PFS of patients with locally advanced SCCHN treated with radiotherapy and high-dose cisplatin versus radiotherapy and panitumumab.

Matuzumab is another humanized monoclonal antibody of the immunoglobulin G₁ (IgG₁) subclass that binds selectively to the EGFR, competing with both EGF and TGF- α

for binding. In contrast to the chimeric antibody cetuximab, the humanized antibody has prolonged half-life, approximately 6–7 d, allowing for a less frequent administration schedule. Currently, matuzumab is in clinical studies for treatment of various solid tumors known to overexpress the EGFR including SCCHN.^{41–43}

hR3 is a humanized murine monoclonal antibody to EGFR. hR3 was tested for safety and efficacy in combination with RT in patients with stage III/IV SCCHN not amenable to surgery in a phase Ib/IIa trial. hR3 was generally well tolerated without significant hypersensitivity. The most common side-effects were nausea/vomiting, headache and fatigue. Seven complete responses and one progressive disease have been observed in eight evaluable patients at week 12 or 24 assessment.⁴⁴

Gefitinib

Gefitinib (Iressa) is an oral EGFR-specific anilinoquinazoline, which reversibly inhibits autophosphorylation. Preclinical studies show that it inhibits proliferation of cell lines expressing even low levels of EGFR and inhibited the growth of tumor xenografts in nude mice. In addition, it is the first drug of its class to be approved by the FDA as third-line treatment for patients with advanced NSCLC.

Clinical trials

One phase II trial has evaluated gefitinib at the level of 500 mg/d as first- or second-line monotherapy in 52 patients with recurrent or metastatic SCCHN, most of whom had previously received combination chemotherapy or radiotherapy (Table 1, trial 3).³³ Of 47 patients who were evaluable for tumour response, 10.6% (one complete response) demonstrated objective responses and 53% of patients showed disease control rate. The response rates and survival times of patients who received gefitinib as first-line therapy were not significantly different from those of patients who had received prior chemotherapy. Overall, the median times to progression and death were 3.4 and 8.1 months, respectively, with an estimated one-year survival of 29%. These results are more favourable than those achieved with chemotherapy in this setting, but with the additional benefit of reduced treatment-related toxicity.

Thus far, only one phase III trial of gefitinib has been completed in head and neck cancer. This study compared the survival in patients with recurrent or metastatic SCCHN treated with gefitinib or methotrexate (Table 2, trial 4).³⁴ Four hundred and eighty-six patients with recurrent SCCHN were randomly assigned to oral gefitinib 250 mg/d, gefitinib 500 mg/d or methotrexate 40 mg/m² intravenously weekly. Neither dose of gefitinib improved overall survival compared with methotrexate.

Erlotinib

Erlotinib (Tarceva, OSI-774) is another anilinoquinazoline derivative and orally active EGFR inhibitor that can induce both G1 cell-cycle arrest and apoptosis. It inhibits EGFR autophosphorylation and has a selectivity more than 1000 times greater than other tyrosine kinase

inhibitors.^{3,17} It reduced EGFR-associated phosphorylation by about 70%, 24 h after a single 100 mg/kg dose. In mouse xenograft models, concurrent erlotinib and cisplatin chemotherapy produced increased antitumor activity over that of cisplatin alone, without any increased toxicity.

Clinical trials

Phase I studies for advanced solid malignancies including head and neck cancer patients showed that diarrhea, rash, nausea, headache, emesis and fatigue were the most frequent side-effects. At doses of 200 mg/d, diarrhea was dose-limiting but manageable. The 150 mg/d dose was selected for subsequent studies because of its safety and tolerability profile (Table 2, trial 5).³⁵ One phase II trial of erlotinib in recurrent or metastatic squamous cell carcinoma of the head and neck has been reported (Table 1, trial 6).³⁶ Response data from 78 patients include 10 patients (13%) with partial responses, 23 (29%) with SD and 45 (58%) with progressive disease.

In addition to the monotherapeutic approach, several studies are ongoing evaluating erlotinib in combination with chemotherapeutics patients with various solid tumors including SCCHN. A phase I/II trial of a combination of erlotinib with cisplatin in recurrent or metastatic SCCHN was conducted to determine the recommended phase II dose of this combination and evaluate the efficacy and toxicity of this combination in this population.⁴⁵ Patients with no prior chemotherapy and measurable disease were treated in three escalating-dose cohorts of daily continuous oral erlotinib and intermittent intravenous cisplatin given every 21 d. The recommended phase II dose was identified as erlotinib 100 mg orally daily and cisplatin 75 mg/m² intravenous every 21 d. Objective tumor responses were seen in nine of 39 assessable patients, which included one complete and eight partial responses.

Two additional patients had unconfirmed partial responses that were counted as SD. Median PFS was 3.3 months and median overall survival was 7.9 months. The combination was well tolerated, with minimal grade 3 or higher toxicity. Subgroup analysis suggested that patients who developed higher grade skin rashes during cycle 1 had better survival outcomes.

Other notable inhibitors

Antiangiogenic treatment is becoming a fundamental strategy in solid tumor oncology. Inhibitors of vascular endothelial growth factor (VEGF) and its receptor, VEGFR, have proven efficacy in non-small-cell lung cancer (NSCLC) and in colorectal cancer, breast cancer and renal cell carcinoma. However, early trials in NSCLC demonstrated that antiangiogenic agents had the potential to cause fatal pulmonary hemoptysis in patients with squamous cell carcinoma. Nevertheless, the VEGFR inhibitor bevacizumab has been approved for use in chemotherapy-naïve NSCLC patients who do not have squamous cell carcinoma histology.

Given the concerns about potential life-threatening bleeding, antiangiogenic agents have not been extensively studied in SCCHN. Nonetheless, preliminary results of

five clinical trials using VEGF and VEGFR inhibitors were presented at the 2008 and 2009 meetings of the American Society of Clinical Oncology (ASCO). These early results with small numbers of patients show an elevated rate of bleeding toxicity, although one trial of 18 patients did not report any bleeding complications.

The first trial, by Kies *et al.*,⁴⁶ tested dual inhibition of VEGF and EGFR with the combination of bevacizumab and cetuximab in patients with SCCHN who had been previously treated ($n = 15$ evaluable). This trial found a 27% partial response rate and a 53% rate of SD. Although the patient numbers were small, the initial response rate was higher than that seen with cetuximab monotherapy in patients with SCCHN treated on a salvage basis. In a separate, ongoing trial, bevacizumab combined with erlotinib for metastatic SCCHN is under investigation. It remains to be seen whether this trial will show a benefit in SCCHN, because in the pretreated NSCLC population, a large phase III trial of bevacizumab-erlotinib (BETA Lung) found that the combination improved the PFS but not the overall survival.

Another trial combined bevacizumab with pemetrexed (Alimta) in chemotherapy-naïve patients with SCCHN.⁴⁷ Pemetrexed targets the enzymes thymidylate synthase, glycylamide ribonucleotide formyltransferase and dihydrofolate reductase. This study reported a 16% rate of bleeding complications, including one fatality, in the initial 25 patients. The preliminary efficacy results reported were a 36% response rate, a 59% rate of SD and a median time to disease progression of seven months. Although the patients studied had not received any chemotherapy, these results were surprisingly good, as in the NSCLC arena, pemetrexed had recently been shown in large clinical trials not to be as efficacious in the subset of patients with squamous cell carcinoma. The proposed explanation is that squamous cell cancers produce such high levels of thymidylate synthase that it counteracts the effect of pemetrexed and is an intrinsic mechanism of resistance. It is possible that bevacizumab may confer substantial benefit when added to chemotherapy in patients with SCCHN.

Two salvage clinical trials have evaluated sunitinib, an inhibitor of VEGFR-1, -2 and -3; the platelet-derived growth factor receptor α/β ; RET; Kit and Flt-3. In one trial, sunitinib was given orally at 50 mg daily for four weeks followed by a two-week break, for a total cycle length of six weeks.⁴⁸ All patients had been pretreated with two or fewer prior therapies. They were divided into two cohorts: cohort A, for patients with an ECOG performance status score of 0 or 1, and cohort B, for patients with an ECOG performance status score of 2. There were eight total cases of bleeding among the first 22 patients. In cohort A, the response rate was 8% and the rate of SD was 25%; in cohort B, there were no responses, although 29% of patients had SD. The median overall survival duration was 19 weeks, and the time to disease progression was 10 weeks. As cohort A did not meet its primary endpoint, the trial was closed to accrual.

In the second trial, sunitinib was administered to patients who had failed to respond to prior platinum therapy. Thirty-eight patients were evaluable for efficacy and only

one patient had a confirmed partial response.⁴⁹ The median PFS was 60 d, and median overall survival was 102 d. There was a significant amount of grade 3/4 toxicity as well as a reported 16% grade 3–5 bleeding toxicity.

As these studies had small sample sizes, conclusions cannot be drawn on the benefit of antiangiogenic treatment in SCCHN. However, these early trials suggest that there may be an increased risk of bleeding toxicity. Further evaluation and vigilance regarding the toxicities are required to ascertain whether the benefit is worth the risk.

Gene therapy

Gene therapy involves the introduction of new genetic material into cancer cells that will selectively kill the cancer cells with no toxicity to the surrounding non-malignant cells. These approaches include replacing or compensating for tumor suppressor genes that were lost or altered, inserting genes into the tumor that produce catabolic substances, or modulating the immune system to destroy the tumor. Gene therapy is especially attractive for head and neck cancer, because of the anatomic accessibility of head and neck cancers for direct injection of gene therapy agents and the crucial function of normal tissues around the tumor that would be preserved.

In head and neck cancer, a multitude of genetic mutations related to cell-cycle regulation has been described, including mutations of p53, the retinoblastoma gene, p16, p21 and many other genetic sites. These frequently mutated genes are targeted for cancer gene therapy and has shown efficacy in animal models. As gene therapy using p53 has been most advanced in terms of clinical development, we will focus on p53-based gene therapy. Based on types of vectors carrying p53, there are three gene therapy approaches using p53, Adp53 (also named as Ad5CMV-p53), ONYX-015 and rAdp53.

Adp53 (also named as Ad5CMV-p53) is a replication-deficient type 5 adenovirus in which the viral *E1* gene was replaced with a wt p53 expression cassette driven by cytomegalovirus (CMV) promoter. Onyx-015 is an adenovirus from which the E1B region has been deleted, which was designed to selectively replicate in tumor cells. rAdp53 is a replication-deficient type 5 adenovirus in which the viral *E1* gene was replaced with a wt p53 expression cassette driven by Rous sarcoma virus (RSV) promoter with a bovine growth hormone (BGH) poly(A) tail.

Adp53 (Ad5CMV-p53) replacement gene therapy: Advexin

Mutations in the tumor suppressor gene p53 are frequent in head and neck cancer, occurring in 40–70%, with 20% in premalignant lesions.⁸ Because of the relatively high prevalence of p53 mutations in head and neck malignancies, the gene therapies studied for SCCHN have concentrated on the introduction of wt-p53 into tumors.⁵⁰ A replication-deficient type 5 adenovirus (Adp53) in which the viral *E1* gene was replaced with a wt p53 expression cassette driven by a CMV promoter has been extensively used as

they transduce both dividing and non-dividing cells, achieve higher expression levels, and can be produced with high titers and in a large scale. Preclinical studies have demonstrated that the introduction of Adp53 into SCCHN cells produced higher levels of exogenous p53 mRNA and proteins than in cells treated with vector only.⁵¹ *In vitro* growth assays revealed growth arrest following Adp53 infection as well as cell morphological changes consistent with apoptosis. *In vivo* studies in nude mice with established subcutaneous squamous carcinoma nodules demonstrated significantly reduced tumor volumes when treated with p53-adenovirus. In addition, responses were more marked in tumors with mutated p53 rather than normal, wt p53.^{50–53} Preclinical trials have also examined the introduction of wt p53 in combination with conventional RT and chemotherapy, both *in vitro* and *in vivo*. These studies demonstrated an increased sensitization to these conventional treatments after wt p53 was introduced into SCCHN cell lines and tumor xenografts.⁵⁴

Clinical trials

Advexin is an Adp53 produced from Introgen Therapeutics, Inc (Austin, TX, USA) and in a phase I study of 33 patients with bulk SCCHN, Advexin was found to be safe with little toxicity, and significant clinical response was observed in nine out of 18 clinically evaluable patients (Table 3, trial 1).⁵⁵ Interestingly, systemic Adp53 DNA was present transiently for <48 h and was demonstrated in blood, urine and sputum.

Three phase II trials have been conducted to evaluate the safety and efficacy of Advexin on recurrent or advanced SCCHN patients. One of these evaluated two different schedules of administration during a 28-d cycle (3 versus 6 injections per month, up to 12 cycles per patient, at doses of 5×10^{11} – 2.5×10^{12} virus particles [vp]). Of 105 evaluable patients, 6% exhibited complete response or

partial response, and there was no significant difference between the three- and six-injection schedules. A second concurrent trial using the same entry criteria and patient population was conducted using a 50-fold lower dose of Advexin in 58 patients. This low-dose trial showed only a 2% response rate, indicating a dose–response relationship to Advexin clinical activity. The percentage of patients with objective response or durable SD (>3 months) was 20% for high-dose patients, compared with 14% for the low-dose group. Substantial differences in median survival (6.0 versus 3.5 months) and mortality rate at 150 d (60% versus 40%) were observed between patients treated with high and low doses of Advexin, respectively. The results indicate a dose-related effect. Both univariate and multivariate analyses were performed to identify prognostic factors for response rate and tumor growth control. A minimal set of parameters has been identified to define the population of patients most likely to benefit from intratumoral Advexin therapy. Applying these prognostic parameters to define a patient population, an objective response rate of 20–30% can be obtained.⁵⁶ Overall, >200 SCCHN patients have been treated with Advexin in phase II studies. Data from patients with both recurrent and refractory SCCHN show objective clinical activity and prolonged inhibition of tumour growth.⁵⁶ These results warranted further investigation in phase III trials.

There are two phase III trials to compare the safety, efficacy and overall survival of treatment with Advexin as monotherapy or in combination with chemotherapy in patients with head and neck cancer. In one of these trials (T-301), 123 patients with local or regional recurrent refractory SCCHN who have failed RT and chemotherapy with platinum-containing drugs or taxanes are randomized to either intratumoral Advexin or intravenous methotrexate; the study evaluates overall survival as the primary endpoint. Preliminary results have demonstrated that this trial

Table 3 Gene therapy for squamous cell carcinomas of the head and neck in the USA

Tumor type	Phase	Vector name	Delivery mode	No. of patients evaluable	Summary of responses	Adverse reactions	Reference
Head and neck	I	Adp53 (adeno)	Intratumoral	18	1 complete response; 2 regressed > 50%; 6 stable up to 3.5 months; 9 progressive	Flu-like, injection site pains	55
Head and neck	II (T201/T202)	Adp53 (adeno)	Intratumoral	160	T1 (high dose, 108) showed improved response as compared with T2 (low dose, 58)	Flu-like, injection site pains	56
Head and neck	III (T301)	Adp53 (adeno)	Intratumoral	123	Similar overall survival with methotrexate arm, improved survival in p53 favorable group (7.2 months vs 2.7 months)	Flu-like, injection site pain, lymphopenia, neutropenia: overall, better side-effects profile compared with methotrexate arm	57
Head and neck	II	Onyx-015	Intratumoral	36	4 regressed > 50%; 12 stable disease; 13 progressive	Flu-like, injection site pains	58
Head and neck	II	Onyx-015	Intratumoral plus cisplatin and 5-FU	30	8 complete response; 11 partial response	Flu-like, injection site pains, leukopenia, lymphopenia	59
Head and neck	II	Onyx-015	Intratumoral plus IL-2	5	2 stable disease; 3 progressive	Injection site pain, fatigue, chills, fever, anemia, leukopenia	60

is the first phase III gene therapy cancer trial in the USA to meet its study objectives successfully. Advexin significantly increased survival in patients with p53 favorable biomarker profiles compared with patients with p53 unfavorable profiles (7.2 versus 2.7 months; $P < 0.0001$). In contrast, methotrexate patients with p53 profiles favorable for Advexin treatment had a median survival of only 4.3 months. Methotrexate improved survival in a different group of patients with the complementary p53 biomarker profiles unfavorable for Advexin efficacy (median survival 5.9 versus 2.7 months; $P = 0.0112$).

Favorable p53 biomarkers were also associated with a statistically significant increase in tumor responses to Advexin. Among Advexin-treated patients in the pivotal phase II and III trials (T201, T301), tumor response was 78.4% in patients with p53 favorable profiles compared with 26.8% of patients with p53 unfavorable profiles ($P = 0.014$). In contrast, the reverse associations were seen in methotrexate-treated patients and a higher proportion of responders were observed in patients with p53 unfavorable profiles (83.3%) compared with patients with p53 favorable profiles (52.4%). Advexin also had a superior safety profile compared with methotrexate. There was a significant decrease in the number of patients with lymphopenia, stomatitis, leucopenia, neutropenia and pneumonia in the group treated with advexin compared with that treated with methotrexate. Thus far, the overall safety data of advexin demonstrate that it is well tolerated with localized or self-limiting events (fever, chills and injection site discomfort) seen most often. Typically, these side-effects were effectively treated with over-the-counter medication (i.e. acetaminophen). It should be noted, however, that there was no statistical difference in survival between Advexin and methotrexate in the intent-to-treat population, which included both p53 favorable and unfavorable patients in both study arms (median survival 6.1 versus 4.4 months; $P = 0.236$).

In the second study (T302), patients with local or regional recurrent SCCHN are treated with a combination of intratumoral Advexin, cisplatin and 5-fluorouracil (5-FU), and compared with patients treated with the same regimen of cisplatin/5-FU. The primary endpoint is time to progression and it is expected that a total of 288 patients will be recruited.

These favorable clinical trial results have allowed Advexin to be granted designation as a Fast Track Drug Product development program by the FDA for prolonging survival and delaying time to disease progression in patients with recurrent, unresectable squamous cell carcinoma of the head and neck. Previously, Advexin had also received orphan drug designation from the FDA for head and neck cancer. While Advexin has not received US FDA approval yet, it is important to note that this is the most advanced gene therapy program in the USA.

Onyx-015

Onyx-015 is an adenovirus from which the E1B region has been deleted. The E1B region of the virus normally binds to and inactivates p53 tumor suppressor protein and is essential to viral replication in normal cells. The Onyx-015, which lacks

E1B, therefore can only infect cells that lack functional p53, leaving normal cells unaffected. *In vivo* and *in vitro* studies showed that ONYX-015 infected and replicated efficiently within tumors following either intravenous or intratumoral administration.⁵⁰ Yet, subsequent *in vitro* studies have demonstrated that specificity of Onyx-015 is independent of p53 status, questioning the selectivity of this virus.^{61,62} Although Onyx-015 can replicate in both p53 wt and mutant cells *in vitro*, the virus demonstrates significantly greater antitumor activity against mutant p53 tumors *in vivo*.⁶³ In addition, pre-clinical studies have demonstrated that Onyx-015 viral therapy can be combined with radiation or chemotherapy to improve its antitumor activity.⁶³⁻⁶⁵

Clinical trials

Phase I study of Onyx-015 intratumoral injection to total of 22 patients with recurrent head and neck cancer showed that intratumoral administration of Onyx-015 is feasible, well-tolerated and associated with biological activity, with the main toxicity being grade 1/2 flu-like symptoms.⁶⁶

Phase II clinical testing of intratumoral and peritumoral Onyx-015 injection in 37 patients with recurrent head and neck carcinoma documented selective Onyx-015 presence and/or replication in the tumor tissue in post-treatment biopsies (Table 2, trial 2).⁵⁸ Tissue destruction was also highly selective. p53-mutant tumors were significantly more likely to undergo Onyx-015-induced necrosis (7 of 12) than p53-wt tumors (0 of 7). Significant tumor regression (>50%) occurred in 21% of evaluable patients, and there was no toxicity to injected normal peritumoral tissues.

A phase II trial treated 40 patients with recurrent or relapsed SCCHN using either a standard dosage schedule (5 consecutive days) or a hyperfractionated schedule (twice daily for 2 consecutive weeks).⁶⁷ While standard treatment resulted in a greater antitumor response than hyperfractionated treatment (14% versus 10%, respectively), patients on hyperfractionated treatment experienced a greater rate of SD (62% versus 41%, respectively). The most common treatment-related toxicities included mild to moderate fever and injection site pain.

Although Onyx-015 and chemotherapy have demonstrated antitumoral activity in patients with recurrent head and neck cancer, disease recurs rapidly with either therapy alone. For that reason, a phase II study of intratumoral Onyx-015 injection in combination with chemotherapeutics, cisplatin and 5-FU, was designed (Table 2, trial 3).⁵⁹ This therapeutic modality showed tumor-selective viral replication and necrosis induction on tumor biopsies with acceptable toxicities. There were substantial objective responses. Of 30 evaluable patients, complete clinical response was seen in eight patients (27%) while a partial response was seen in 11 patients (36%). In addition, by six months, none of the responding tumors had progressed while all tumors treated with chemotherapy alone did.

A pilot trial has studied Onyx-015 in combination with irinotecan and 5-FU and in combination with interleukin-2 (IL-2) (Table 2, trials 4 and 5).⁶⁰ Toxicity attributable to Onyx-015 was limited to transient fever. The results suggest that Onyx-015 can be administered safely in combination with irinotecan and 5-FU or low-dose IL-2, and is

able to access malignant tissue following intravenous infusion. Of the four evaluable patients treated with Onyx-015 in combination with chemotherapy, two achieved SD. Of the five evaluable patients treated with Onyx-015 in combination with IL-2, two experienced SD.

While these results seemed quite promising, it has now been demonstrated that ONYX-015 did not kill cells based on p53 status of cells.⁵⁰ Rather, it was shown that other functions of E1B55kDa were more important for tumor selectivity. Presently, clinical trials in the USA using ONYX-015 has been stopped and therefore its role in the treatment of SCCHN remains unclear.

rAdp53replacement gene therapy: Gendicine

Gendicine is a modified Adp53 developed by Shenzhen SiBiono GeneTech (SiBiono, Shenzhen, China). While Adp53 is a recombinant human serotype 5 adenovirus in which the E1 region is replaced by a human wt p53 expression cassette driven by a CMV promoter, in Gendicine, the p53 gene is driven by a RSV promoter with a BGH poly(A) tail, and this makes differences from Adp53, which is driven from a CMV promoter. The recombinant adenovirus is produced in human embryonic kidney 293 cells grown in a bioreactor. Virus produced from the bioreactor is further processed and chromatographically purified to produce the recombinant human Adp53 injection product.

Clinical trial

In phase I clinical trial, Gendicine was used for the treatment of 12 patients with advanced laryngeal cancer, with an average clinical course of 41 months.⁶⁸ Seven of the 12 patients had not received any treatment before Gendicine administration and five of the 12 patients had one or multi-recurrent history. The patients were divided into three groups receiving escalating doses of Gendicine. Intratumoral injection was administered at a dose of 1×10^{10} , 1×10^{11} and 1×10^{12} VP every other day for a total of 10 injections. In the subsequent 36- to 42-month follow-up no patient relapsed. In addition, there was still no patient relapse more than five years after Gendicine treatment. In comparison, the three-year relapse rate for patients with advanced laryngeal cancer receiving surgery alone is generally about 30%.

In phase II/III clinical trials, a multicenter, concurrently controlled, randomized clinical trial was conducted in which Gendicine was administered to 135 patients with HNSCC and basically demonstrated significant synergistic effects for the combination of Gendicine with radiotherapy.⁶⁸ Of the enrolled patients, 77% had late stage III-IV cancer and had failed in either radio- or chemotherapy or were not eligible for surgery. Like the phase I trial, the majority (85%) of the patients had nasopharyngeal cancer. The patients were divided randomly into two groups: one group received gene therapy in combination with radiotherapy (GTRT) and the other group received radiotherapy alone (RT). Radiotherapy was used at doses of 70 Gy administered in 35 fractions over 7-8 weeks for the RT group. For the GTRT group, Gendicine was given each week at a dose of 1×10^{12} VP three days before radiotherapy, for a total of

eight weeks with the same radiotherapy as that used in the RT group. In the GTRT group, there were 93% overall response, with 64% showing complete regression (CR) and 29% partial regression (PR). The response rate in the RT group was 79%, with 19% of the patients showing CR and 60% PR. There is a significant difference ($P = 0.01$) between the two groups in terms of both the CR rate and the PR rate and 65% of patients showing PR were observed in the GTRT group, whereas 40% of those with PR and 57% SD were in the RT group. Based on this result, in China, a new multicenter, concurrently controlled, randomized phase IV clinical trial including 300 patients with SCCHN has been initiated.

Laboratory testing of patient blood samples showed an elevated level of serum antibodies against adenovirus 2-3 weeks after Gendicine injection, reflecting the development of a specific immune response against Gendicine.⁶⁸ From specimens of tumor tissues derived from 11 patients with squamous or adenocarcinoma, there is no significant correlation between the effects of Gendicine and the status of the p53 gene in tumor cells.

After extensive multiyear and multicenter clinical studies, Gendicine was approved by the State Food and Drug Administration of China on October 16, 2003 for the treatment of HNSCC, and was formally launched in April 2004. Gendicine became the world's first gene therapy product approved by a governmental agency for the treatment of cancer.

Photodynamic therapy

Photodynamic treatment (PDT) is a form of treatment that combines a photosensitizing agent with exposure to laser light in order to elicit phototoxic reactions that destroy tumor cells.⁶⁹ In PDT, light is used to activate a photosensitizer (Photofrin, HPD, ALA or Foscan) in the presence of oxygen, generating free radicals that may induce cell death and an immune response.^{69,70} Therefore, PDT works through non-thermal chemical pathways to damage cancer cells. The cancer cells are destroyed by a process that might take up to several weeks and the treated area heals with normal mucosa advancing from adjacent tissue much like radiation treatment.^{69,70} The therapeutic response of PDT depends on a complex combination of parameters that includes drug dose, drug-light interval, tissue oxygenation, light dose and light intensity.^{69,70} Overall, the side-effects from PDT are much less frequent and severe compared with chemotherapy. Sunlight exposure have shown that photosensitivity is not a real burden for these patients and only limited adverse events were related to this problem.^{69,70}

Application in head and neck cancer

So far, over 1500 patients have been treated with PDT for head and neck cancers.^{69,71} One of the earliest studies was reported by a group in China based on 137 patients with nasopharyngeal cancer (NPC). One hundred and thirty-seven NPC patients underwent a series of hematoporphyrin

derivative (HpD)-mediated PDT. Forty-eight and 72 h after intravenous administration of 3–5 mg/kg HpD, laser treatment with either argon (57 patients) or dye laser (80 patients) was carried out.⁷¹ While it is rather unclear whether the patients had recurrent NPC or PDT is delivered as primary first-choice treatment, the results were impressive (complete response 76 cases [55.47%], marked response 47 cases [34.31%], with an overall marked response rate of 89.78% [123/137]). Rigual *et al.*⁷² reported on 26 patients with dysplasia, carcinoma *in situ* and T1 carcinoma of the oral cavity and larynx. A complete response was observed in 24 (92%) patients, of whom three patients with oral dysplasia experienced recurrence, for which salvage treatment was performed. A more important study was recently reported by Lorenz *et al.*⁷³ In this report, among 35 patients with recurrent or second primary head and neck tumors and unsuitable for other treatments, local control was achieved by PDT in 21 (60%) patients without serious complications. In these patients, tumors had a maximum thickness of 10 mm.⁴⁷ In deeper-seated tumors, interstitial PDT was used as an option. This study shows that PDT is an important treatment option for patients who present with recurrent or second primary head and neck tumors and reconfirms the conclusion from prior studies.^{69,70,73,74}

In 2004, D'Cruz *et al.*⁷⁴ reported a multicenter clinical trial result based on 128 patients who were treated with mTHPC followed by illumination of the tumor surface with 652-nm laser light. In this study, 38% of evaluable patients achieved an overall tumor response, and 16% achieved a complete tumor response.⁷⁴ Forty-three percent of assessable lesions achieved 100% tumor mass reduction, and 58% achieved 50% or greater tumor mass reduction. Of note, 61% demonstrated significant clinical quality-of-life benefit. Median survival was significantly better in responders. No major toxicities were detected. This study had clearly demonstrated that PDT can improve response rate, quality of life without a major toxicity in recurrent or refractory head and neck cancer patients and stimulated subsequent studies. Most recently, another study based on ultrasound-guided interstitial PDT reconfirmed that PDT can be a potential alternative for recurrent or refractory SCCHN. In this prospective study, 68 patients with different disorders (49% carcinomas) underwent ultrasound-guided interstitial PDT and demonstrated some radiological response in 75% of patients.⁷⁵ While a significant response (> 50% reduction) was observed only in 16% of the patients, patients with SCCHN responded quite favorably. Overall, the authors concluded that in selected patients, PDT can be an effective treatment options for patients with recurrent, residual or second primary SCCHN based on its favorable long-term morbidity, particularly as it does not compromise future treatment options.⁷⁵ While PDT becomes one of promising tools for recurrent or refractory SCCHN patients, delivery of laser light to oropharyngeal or nasopharyngeal cavity can be challenging, since access to certain parts of these areas can be difficult due to their complex and irregular geometry.⁷⁶ Furthermore, depending on each patient, the cavity varies significantly in size and geometry. For example, the complex shape of the nasopharyngeal cavity

sometimes makes it impossible to produce a homogenous field of illumination and in order to deliver a sufficient light distribution throughout the nasopharyngeal cavity overexposure often at times cannot be avoided. Therefore, a dedicated light delivery applicator that ensures proper light delivery to the target area and enables for proper shielding of the risk areas are under development.^{77,78}

Conclusions and future directions

Each year in the last five years in the USA, more than 55,000 new cases of head and neck cancer have been diagnosed, and 13,000 die from the disease. In 2002, the World Health Organization (WHO) estimated that there were 600,000 new cases of head and neck cancer and 300,000 deaths each year worldwide, with the most common sites being the oral cavity (389,000 cases a year), the larynx (160,000) and the pharynx (65,000).⁷⁹ The male-to-female ratio reported by large-scale epidemiological studies and national cancer registries varies from 2:1 to 15:1 depending on the site of disease.⁷⁹ The incidence of cancers of the head and neck increases with age. In Europe, 98% and 50% of patients diagnosed are over 40 and 60 years of age, respectively.⁷⁹

A high incidence of head and neck cancer is seen in the Indian subcontinent, Australia, France, Brazil and Southern Africa. Nasopharyngeal cancer is largely restricted to southern China.^{79,80} The incidence of oral, laryngeal and other smoking-related cancers is declining in North America and Western Europe, primarily because of decreased exposure to carcinogens, especially tobacco, while other various carcinogen exposure has been postulated as potential carcinogens.^{79,80} WHO projections estimate worldwide mortality figures from mouth and oropharyngeal cancer in 2008 to be 371,000. This is projected to rise to 595,000 in 2030 because of a predicted rise in mortality in South East Asia (182,000 in 2008 to 324,000 in 2030). Modest rises are predicted in Africa, the Americas and the Middle East, whereas mortality in Europe is expected to remain stable.^{79,80}

Recent advances in molecular biology, however, have led to a better understanding of tumor physiology and the differences between tumor and normal cells. As a result, many drugs have been developed to exploit these differences to increase specificity for the tumor cell and avoid damage to normal tissues. Initially, the two therapies that have shown the most promise are the EGFR monoclonal antibody cetuximab and the p53-based gene therapy Advexin. Cetuximab has been approved by the FDA for use in combination with radiation for the treatment of locally or regionally advanced SCCHN and as a single agent for the treatment of patients with platinum-refractory recurrent or metastatic SCCHN. Advexin has been fast tracked by the FDA and demonstrated significant objective response rates although such approval is not granted yet.

EGFR and p53, however, are not the only targets for SCCHN therapies. A number of other pathways have been explored as possible strategies of treatment, including angiogenesis inhibitors. Inhibitors of VEGF and its receptor,

VEGFR, have proven effective in NSCLC and in colorectal cancer, breast cancer and renal carcinoma. However, given the concerns about potential life-threatening bleeding, anti-angiogenic agents have not been studied extensively in SCCHN. Nonetheless, preliminary trials have begun to examine these inhibitors in SCCHN. Early trials have demonstrated that antiangiogenesis inhibitors have efficacy in SCCHN and phase II trials of these drugs have begun. As expected, though, these trials have also shown that there may be an increased risk of bleeding toxicity.

EGFR downstream signaling pathways and other molecular pathways, other than EGFR and VEGFR, underlying the development and progression of SCCHN are also becoming an area of great interest. For example, Ras and TOR, both of which are downstream of EGFR, become the target of farnesyltransferase inhibitors and mammalian target of rapamycin inhibitors.⁸¹ Likewise, cyclooxygenase-2 (COX-2) is overexpressed in premalignant lesions (oral leukoplakia) and in squamous cell carcinoma of the head and neck. EGFR and COX-2 signaling pathways form a positive feedback loop. As their toxicity profiles are non-overlapping, combination of COX-2 inhibitors and EGFR-targeted therapies looks attractive.⁸² Other kinase inhibitors such as aurora kinase inhibitors, insulin-like growth factor inhibitors and histone acetylase inhibitors, have recently gained interest as potential new promising ways of tackling tumors including SCCHN.⁸³

While we expect to see the era of targeted therapy in the management of SCCHN, predicting which patients will benefit from these various targeted therapies may be as important as identifying novel agents. For example, in the case of cetuximab, acneiform rash is a common side-effect and may be important in indicating the patients who are benefiting the most from cetuximab.¹⁷ Recently, more subset analyses of clinical trials involving EGFR targeting have provided certain molecular insights. For example, in NSCLC, EGFR gene mutations and copy number were shown to be associated with gefitinib sensitivity. Response rates were found to be higher in patients with EGFR gene mutations or increased copy numbers.^{3,83,84} Furthermore, cell line data suggest a similar case in SCCHN for both gefitinib and cetuximab.⁸⁴ Overall, we expect that future targeted therapy in SCCHN will be individualized to the biology of each patient's tumor, not just to the tumor type itself. PDT has the potential to be a very effective local treatment modality for head and neck cancer including NPC, without the severe side-effects seen with radiotherapy. While several advantages of PDT for management of head and neck cancer have been proposed, the most important advantage is its repeatability even for recurrent disease after chemoradiation or postoperative RT. While continued applications of this technology in more community settings and accumulated experience from diverse clinical trials are warranted in the future, due to its minimal side-effect and reasonable local control, we expect to see that PDT will play an important role in the management of recurrent or refractory head and neck cancer. The results from current clinical trials suggest that inhibition of one aberrant pathway or replacing one targeted gene is not sufficient enough to control tumors and improve survival, due to

multiple genetic mutations and multilevel stimulation of pathways. A greater understanding of cancer biology, adequate design of clinical evaluations and optimal application of drugs, is required in the development of new strategies to combine new drugs with conventional therapy and in the selection of best tumor types to be targeted, in order to overcome the current limitations, and to benefit the head and neck patients with improved quality of life and extended survival.

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