Targeted Therapy for Squamous Cell Carcinoma of the Head and Neck

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ABSTRACT

Targeted agents have emerged as novel drugs in the oncology field based on our understanding of the biology of individual malignancies, and have had a promising impact in several tumors. Squamous cell carcinoma of the head and neck (SCCHN) is a common disease with little progress made in survival over the past few decades. SCCHN is characterized by overexpression of the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF), both of which appear to have a prognostic value. Hence these receptors and their downstream pathways make attractive therapeutic targets. This review discusses targeted therapies currently being evaluated for their role in squamous cell carcinoma of the head and neck.


INTRODUCTION

Cancers of the head and neck include a wide spectrum of malignant neoplasms that originate from the oral cavity, larynx and pharynx. It is the fifth most common cancer worldwide, accounting for 5% of all malignancies. Ninety percent of head and neck cancers (HNC) are categorized as squamous cell carcinomas. Despite the evolution in cancer therapy, there have not been significant advances in the field of HNC in terms of disease management and improvement in survival over the past three decades [1]. Hence, there is an urgent need for modalities of therapy other than the traditional ones in an attempt to correct this anomaly. The prognosis of the disease relies primarily on the stage of the disease and patient’s performance status at the time of diagnosis [2,3].

Most patients with squamous cell carcinoma of the head and neck (SCCHN) are potentially curable in the absence of distant metastasis. For early stage disease (stage I/II), single modality therapy, either comprehensive radiation therapy of the primary site as well as the regional lymph nodes or definitive surgical resection, can be undertaken. Definitive concurrent chemoradiation is the approach of choice in patients with locally advanced disease (stage III/IV) of the hypopharynx and larynx since it has yielded an equivalent survival benefit to surgery, with the added advantage of preservation of organ function [4,5]. Surgical resection followed by adjuvant concurrent chemoradiotherapy is the current standard of care in locally advanced SCCHN at other sites [6-8]. Recurrent and metastatic (R/M) SCCHN is an aggressive disease with a median overall survival (OS) of 6 to 9 months. Platinum-based chemotherapy has been the standard first line therapy for patients with R/M SCCHN and the median survival is less than 3.5 months in platinum refractory disease [9]. A major problem however is that the majority of these patients have a relatively poor performance status, thereby precluding the use of platinum-based therapy. This has paved the way towards the investigation of targeted, presumably safer, agents in this disease.

The role of targeted agents in squamous cell carcinoma of the head and neck (SCCHN) has been gaining increasing attention since studies...
have shown that the majority of these cancers are distinguished by high expression of epidermal growth factor receptor (EGFR) [10] and vascular endothelial growth factor (VEGF) receptor [11,12], and their overexpression have been linked to inferior outcomes in terms of disease aggressiveness and resistance to treatment [13-17]. The excellent results of combining cetuximab with radiotherapy in locally advanced head and neck cancer has opened the road for more trials to investigate targeting therapies in other disease stages and therapeutic combinations in SCCHN. This manuscript reviews the advances that have been made in utilizing molecular agents in head and neck cancer and explores the new trials and advances.

EGFR:

EGFR is a 170-kd transmembrane glycoprotein with tyrosine kinase (TK) activity belonging to the ErbB/HER family. It is composed of an extracellular ligand-binding domain, a transmembrane-anchoring region, and an intracellular domain that carries the TK activity. Activation of EGFR promotes activation of the intracellular TK and multiple downstream signals which subsequently mediate gene transcription and cell cycle progression [18].

EGFR overexpression is widely seen in human epithelial malignancies and it is considered as a distinctive feature of SCCHN; protein expression is detected in more than 90% of cases [13]. Excess EGFR activation in human malignancies is characterized by increased cell proliferation, angiogenesis, invasion and metastasis, and reduced apoptosis [19]. EGFR overexpression is correlated with more aggressive disease, increase resistance to radio-and chemotherapy, increased metastasis, poor prognosis, and decrease survival rate [13-16]. Moreover, higher numbers of gene copies were found to be correlated with a worse prognosis [20].

Inhibiting EGFR activity can be accomplished through three strategies:

- **Monoclonal antibodies** directed against the extracellular domain of the EGFR. These compete against endogenous ligands and interrupt the signaling cascade.

- **Small molecules TK inhibitors** (TKIs) which have a direct action on the EGFR receptor through binding the intracellular ATP-binding domain.

- **Intra-tumoral EGFR antisense gene therapy**-introducing EGFR antisense-expressing plasmids and blocking EGFR messenger RNA translation.

ANTI-EGFR MONOCLONAL ANTIBODIES:

**Cetuximab:**

Cetuximab is a chimeric, human-murine immunoglobulin G1 (IgG1) monoclonal antibody that binds specifically to the extracellular domain of the human EGFR and competitively blocks endogenous ligand binding site. Cetuximab received FDA approval as a first line therapy in combination with radiotherapy for locally advanced head and neck cancer, and second line therapy as a single agent in platinum resistant metastatic/refractory head and neck cancer [21].

Acneiform rash is a characteristic manifestation of cetuximab as well as the other EGFR targeting agents. It presents as a pustular or maculopapular follicular eruption, and resolves without scarring upon therapy discontinuation. It has been shown that the onset and severity of acneiform rash is a predictive factor of clinical response for these agents [22]. Other reported adverse effects for cetuximab include infusion reaction, malaise, fever, nausea, diarrhea and constipation.

A large randomized, international, phase III clinical trial demonstrated a significant survival benefit associated with combining cetuximab with radiotherapy in locally advanced SCCHN [23]. Four hundred and twenty-four previously untreated patients with locally advanced SCCHN were assigned to radiotherapy alone versus radiotherapy plus weekly cetuximab. Superior outcomes were seen in the combination therapy arm as compared to radiotherapy alone arm in terms of median locoregional control (24.4 versus 14.9 months, \(p=0.005\)) and median OS (49 versus 29.3%, \(p=0.03\)), without worsening radiotherapy-related mucositis. However, the rates of distant metastasis at 1 and 2 years were similar in both groups. Subset analyses showed that the survival benefit was most prominent in patients with oropharyngeal cancer as opposed to hypopharyngeal or laryngeal cancers. However, this study did not compare cetuximab
with cisplatin, which is the chemotherapy agent of choice given concurrently with radiation in this group of patients.

The promising data on cetuximab from the previous trial directed studies to investigate its efficacy in combination with chemoradiotherapy. A phase II trial of combination concurrent chemoradiation (cisplatin) with cetuximab in locally advanced SCCHN reported a 3-year OS and PFS of 76% and 56%, respectively. Unfortunately, the study was terminated early after 2 cases of deaths (case of pneumonia and case of unknown cause) had occurred. The authors concluded that although the preliminary results are encouraging, the search for safer combination with cetuximab is needed [24]. Subsequently, two large randomized clinical trials have been initiated to study the validity of adding cetuximab to concurrent chemoradiotherapy in locally advanced disease. RTOG-0522, a phase III study, randomized patients to concurrent chemoradiotherapy (cisplatin) with or without cetuximab in stage III/IV SCCHN. The second study is RTOG-0234, a phase II randomized trial of surgery followed by chemoradiotherapy and cetuximab in patients with resected stage III/IV SCCHN. The study compares the efficacy and safety of adjuvant docetaxel to cisplatin in association with cetuximab and radiotherapy.

Cetuximab was included in induction regimens with chemotherapy (paclitaxel and carboplatin) in SCCHN. Forty-seven treatment-naïve patients with locally advanced disease were treated with 6 weeks of induction therapy and subsequently underwent risk based local therapy. Response in the primary site was achieved in all evaluable patients enrolled in the study (CR= 83%, PR= 17%), whereas the nodal response was seen in 97% (CR= 27%, PR= 70%) of the evaluable patients [25].

Recurrent and metastatic SCCHN pose a special attention since the disease has devastating outcomes and limited available options. Cetuximab was investigated as a single agent in R/M SCCHN in patients who failed platinum-based therapy in phase II trial. One hundred and three patients with R/M SCCHN with documented disease progression on platinum-based therapy were enrolled. Cetuximab was given as a monotherapy for ≥6 weeks and platinum was added later for patients whose disease progressed on cetuximab. The study reported an overall response rate (ORR) and disease-control rate (DCR) of 13% and 46%, respectively, with median OS of 178 days. The regimen was tolerated, although 49% of patients experienced skin reactions and one case of death secondary to infusion reaction was reported [26]. An analysis of 3 prospective phase II trials investigated the role of cetuximab as a single agent in R/M SCCHN in patients who had failed platinum-based therapy [26-29]. The results were numerically superior, in terms of overall response and disease control rates, to retrospective outcomes from 2 studies that included various other second line chemotherapy and best supportive care [30]. The median OS ranged from 5.2 to 6.1 months compared to 3.4 to 3.6 months in the retrospective studies. Cetuximab was well tolerated and no worsening platinum toxicity was reported [9].

Cetuximab was tested as first line therapy in combination with platinum-based chemotherapy in patients with untreated R/M SCCHN. Four hundred and forty-two patients were randomly assigned to platinum-based chemotherapy plus 5-fluorouracil with or without cetuximab. The addition of cetuximab improved median OS (7.4 vs. 10.1 months, p=0.04), PFS (3.3 vs. 5.6 months, p<0.001), and response rate (20% vs. 36%, p<0.001). Grade III skin reactions and grade III/IV infusion-related reactions were seen in 9% and 3%, respectively, in the cetuximab arm. However, there were no cetuximab-related deaths [31]. Another phase III trial randomized 117 patients with R/M HNC to cisplatin with or without cetuximab. Although the addition of cetuximab improved response rates, there was no effect on OS and PFS [32]. A phase II trial of cetuximab with weekly paclitaxel tested in R/M SCCHN, conducted by the Spanish Head and Neck Cancer Group (TTCC), reported a 71% ORR and 88% disease control rate in 35 evaluable patients [33]. These results would suggest a role for cetuximab in the setting of R/M SCCHN, however more work needs to be performed in order to better identify patients who would respond to this treatment.

SMALL MOLECULE EGFR-tyrosine kinase inhibitors (TKIS):

The role of small molecule tyrosine kinase inhibitors is less well defined than cetuximab. Studies thus far have failed to show a survival benefit with these agents.
**Gefitinib:**

The application of gefitinib produced more than additive anti-tumor effect in combination with radiotherapy in a preclinical study [34]. A phase I/II clinical trial was conducted on 34 patients with locally advanced SCCHN. Patients underwent induction with combination chemotherapy (docetaxel, carboplatin and 5-FU) plus gefitinib followed by concurrent chemoradiation and gefitinib. The study reported CR in 32% (11 patients) and PR in 53% (18 patients). The 1-year PFS and OS were 68% and 86%, respectively [35]. Another phase II trial enrolled 67 previously untreated subjects with locally advanced SCCHN who underwent induction combination chemotherapy (carboplatin and paclitaxel) followed by concurrent chemoradiation (hydroxyurea and 5-FU) and gefitinib, and maintenance gefitinib for 2 years. The study reported 3-year OS and PFS of 73% and 64%, respectively. In 51 evaluable patients, a 91% CR was observed [36].

Gefitinib was investigated as a monotherapy in R/M SCCHN with variable results [35-38]. Despite the encouraging phase II results with gefitinib in patients with R/M SCCHN [39], gefitinib failed to show survival benefit in a phase III trial (IMEX). This study randomized 486 patients with platinum-refractory head and neck cancer to gefitinib at doses of 250mg or 500mg or methotrexate. There was an increased incidence of bleeding within the tumor associated with gefitinib [40]. A combination of docetaxel and gefitinib is being currently evaluated in a phase III trial in patients with R/M SCCHN (Clinicaltrials.gov identifier: NCT00695760).

**Erlotinib:**

Erlotinib is a reversible tyrosine kinase inhibitor. It was studied in combination with chemoradiation in locally advanced SCCHN in small trials. In a phase I dose-escalation study of erlotinib combined with docetaxel and radiation, 23 subjects with locally advanced SCCHN were enrolled. No significant pharmacokinetic interactions between erlotinib and docetaxel were observed and the authors concluded that this regimen was feasible and active [41]. A similar study was conducted using erlotinib plus cisplatin and radiotherapy for locally advanced SCCHN. Of 25 evaluable patients, 21 (84%) experienced a complete pathologic response, and the study reported tolerable adverse effects [42].

In a large multicenter trial, single agent erlotinib achieved partial response rate and disease stabilization in 4% and 38% of the cases, respectively, with a median duration of 16.1 weeks in R/M SCCHN. The median OS was 6 months and the 1-year survival rate was 20%, numbers comparable to those attained by cytotoxic chemotherapy, but with a better side effect profile. There was no survival difference based on EGFR expression. 46% of the enrolled patients required dose reduction or interruption, the most common drug-related toxicities were rash and diarrhea [43].

Preclinical studies suggested that erlotinib had an additive antitumor effect when added to cisplatin without increased toxicity [44]. Erlotinib was studied in combination with cisplatin in phase I/II trial in 51 patients with R/M SCCHN, RR and DS were 21% and 49%, respectively, and the median PFS and OS were 3.3 and 7.9 months, respectively [45]. A phase II study of erlotinib in combination with cisplatin and docetaxel in 47 patients with R/M SCCHN showed ORR and DCR of 67% and 95%, respectively; median OS was 11 months and PFS was 6 months [46].

**DUAL EGFR INHIBITORS:**

**Lapatinib:**

Lapatinib is a small molecule dual EGFR and ERBB2/HER2 tyrosine kinase inhibitor, approved for the treatment of patients with HER2-positive advanced or metastatic breast cancer. The most commonly reported side effects of lapatinib include diarrhea, nausea, vomiting, rash, hand-foot syndrome (swelling and discomfort of hands and feet) and, to a lesser extent, reversible impairment of left heart ejection fraction.

Lapatinib was investigated in combination with chemoradiation (cisplatin) in locally advanced SCCHN; the preliminary results showed encouraging clinical activity with tolerable toxicity [47]. Lapatinib is currently being tested in a phase III international trial as an adjuvant therapy in combination with radiotherapy and cisplatin in patients with locally advanced SCCHN (Clinicaltrials.gov identifier: NCT00424255).
A phase II multicenter trial of monotherapy with lapatinib in 42 patients with R/M SCCHN did not show any objective response. Adverse effects included diarrhea (40%), fatigue (21%), rash (21%), and nausea (14%). One patient had an asymptomatic reduction of the left ventricular ejection fraction that resolved upon discontinuation of lapatinib. Although the study reported a favorable side-effect profile, there does not appear to be any significant activity in this setting [48].

EGFR ANTISENSE THERAPY:

A phase I clinical trial to evaluate the safety and biological effects of intra-tumoral injection of EGFR antisense DNA in 17 patients with R/M SCCHN showed that there was anti-tumor antisense DNA present in the tumor tissue [49]. Five patients achieved a response with 2 CR and 3 PR. Two additional patients had stable disease. Patients who achieved a CR also were noted to have a decrease in EGFR as demonstrated by immunohistochemistry.

ANGIOGENESIS INHIBITORS:

Angiogenesis is a crucial step in normal physiological processes though it is necessary for tumor growth and metastasis [50]. The process is mediated primarily through the vascular endothelial growth factor (VEGF) [51]. VEGF expression has been shown to be up-regulated in SCCHN, and therefore, this represents a promising therapeutic target. Elevated VEGF expression has been correlated with increased tumor progression and inferior prognosis in SCCHN [17].

Bevacizumab:

Bevacizumab is the first recombinant, humanized anti-VEGF monoclonal antibody, it binds and inactivates all isoforms of VEGF and hence inhibits angiogenesis and tumor growth and proliferation [52]. Irradiation was found to induce tumor angiogenesis in preclinical studies and administration of bevacizumab in combination with radiotherapy has resulted in counter-balancing this effect [53]. Reported adverse effects of bevacizumab include hypertension, gastrointestinal tract perforation, delayed wound healing, bleeding, thromboembolic events, proteinuria, and congestive heart failure.

In a phase I study, bevacizumab was administered to patients with poor-prognosis SCCHN, in combination with fluorouracil, hydroxyurea and concomitant radiotherapy [54]. Thirty-four patients completed the treatment course. The addition of bevacizumab did not appear to be associated with a major synergistic toxic effect. Median OS for irradiated patients with recurrent, non-metastatic disease was 10.3 months with a 2-year cumulative incidence of death from disease of 51.7%. Late complications, such as fistula formation and ulceration/tissue necrosis, were seen in 11.6% and 9.3%, respectively, and were attributed to bevacizumab [54].

Bevacizumab was studied in combination with concurrent chemoradiation (docetaxel) in a phase II trial in locally advanced SCCHN. Twenty-three patients completed the scheduled regimen. At a median follow up of 9 months, 17 patients had a CR, 4 patients developed recurrent and/or metastatic disease and 2 patients died. The estimated 1-year OS and PFS were 89 and 78%, respectively. No healing complications were observed after planned neck dissections [55]. Bevacizumab was combined with pemetrexed in patients with R/M SCCHN and demonstrated a 45% overall RR (CR: 2, PR: 3, SD: 6, PD: 0) among 11 evaluable patients. Bleeding occurred in 36% (2 patients with grade III and 3 patients with grade I/II hemorrhagic events) [56]. An interim analysis of an ongoing randomized phase II study of patients with intermediate stage head and neck cancer using concomitant chemoradiotherapy (5-fluouracil and hydroxurea) with or without bevacizumab, reported that the addition of bevacizumab was associated with an increased incidence of leukopenia; however, a similar incidence of bleeding complications was noted in both study arms [57].

DUAL PATHWAY INHIBITION:

SCCHN is characterized by overlapping abnormal activation of both EGFR and VEGF, thereby providing the scientific rationale for targeting more than one pathway. A preclinical study showed supra-additive effects with the combination of bevacizumab and erlotinib with irradiation in SCCHN [53].

In a phase I/II trial of erlotinib and escalating doses of bevacizumab, 51 patients with R/M SCCHN were enrolled. Dose-limiting toxicity
was not observed. Reported toxicities include skin rash, diarrhea, fatigue and grade IV hemorrage in 1 patient. At the time of the interim analysis, ORR in the phase II trial was 14.6%, median PFS and OS were 127 and 226 days, respectively [58]. Preliminary results of another phase II study combining cetuximab and bevacizumab in 18 patients with R/M SCCHN showed a 27% response rate with an additional 53% of patients having stable disease, thereby suggesting that this combination is active [59].

CYCLO-OXYGENASE 2 (COX-2):

High levels of COX-2 expression in head and neck cancer have shown to be correlated with lymph node metastasis, resistance to radiotherapy and overall poor prognosis [60-62]. Furthermore, COX-2 expression was also associated with overexpression of EGFR in SCCHN.

A phase Ib/II trial was conducted to evaluate the toxicity and efficacy of combining celecoxib concurrently with chemoradiotherapy (cisplatin and paclitaxel) for locally advanced SCCHN. Of the 28 patients enrolled, 30% did not complete the scheduled regimen secondary to myelosuppression. Two year OS and local control were 65% and 76%, respectively in the 20 evaluable patients. There was no improvement in survival compared to the existing published data; however, the incidence of febrile neutropenia was higher than previously reported with standard therapy [63].

In a phase I trial in patients with previously treated R/M SCCHN, 19 patients were given celecoxib and gefitinib in 3 different doses. The study reported no dose limiting toxicities of the 18 evaluable patients, 4 had documented partial response [64].

GENE THERAPY:

Gene therapy uses vectors to deliver mutant genes that alter cancer biology and destroy cancer cells. Introduction of the mutant DNA uses either viral or non-viral vectors, though the former technique is more widely used. Adenoviruses make the ideal vector in gene therapy due to their high capability for gene transfer and low pathogenicity in humans.

p53 is a tumor suppressor gene that possesses an essential role in mediating cell-cycle arrest and/or apoptosis in response to DNA damage in normal cells [65, 66]. The p53 gene is either mutated or deleted in more than 50% of all human cancers [66], and its mutation has been correlated with resistance to therapy.

Onyx-015 is a chimeric human group C adenovirus that does not express the 55-kDa product of the E1B gene [68]. E1B is the region of adenovirus that binds and inactivates p53. Therefore, Onyx-015 selectively replicates in and lyses p53-deficient cancer cells. Onyx-015 was studied in SCCHN as 25-77% of the cases were reported to have mutated p53 gene [69,70].

In a phase I trial, Onyx-015 was given as a single agent for 22 patients with recurrent SCCHN. Although there were no objective responses, the study reported biological anti-tumoral activity of Onyx-015 in cancer cells and safety toxicity profile of the agent. The most reported side effect of Onyx-015 was flu-like symptoms. Using in situ hybridization, Onyx-015 was detected in cancerous cells with mutant p53 in contrast to cancerous cells with wild-type p53 and in noncancerous cells where viral replication was absent [71]. In a subsequent phase II study intra-tumoral Onyx-015 in 40 patients with refractory SCCHN showed modest activity, with 5 patients demonstrating a response [72].

In anticipation to enhance response, Onyx-015 was investigated in combination with chemotheraphy (cisplatin and 5-fluourouracil) in a phase II trial. Thirty-seven patients with recurrent HNC were enrolled in the study. Of 30 evaluable patients for response, 63% had ORR (27% CR and 36% PR). The study reported no relation between response and the status p53 gene mutation [73].

CONCLUSIONS:

Targeted agents, especially those inhibiting the EGFR pathway, have been studied extensively in SCCHN. Although initial results are promising with respect to disease control and toxicity profile, larger randomized studies comparing these approaches with standard regimens are warranted to establish their safety and superiority. In addition, searching for the optimal combination with cytotoxic chemotherapy, radiotherapy, and other biological agents is needed.
REFERENCES

10- Grandis JR, Tweardy DJ. Elevated levels of transforming growth factor alpha and epidermal growth factor receptor messenger RNA are early markers of carcino genesis in head and neck cancer. Cancer Res. 1993, 53: 3579-84.


56- Karamouzis MV, Friedland D, Johnson R, Rajasenan K, Branstetter B, Argiris A. Phase II trial of pemetrexed (P) and bevacizumab (B) in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (HNSSC): An interim analysis (Abst). J Clin Oncol. 2007, 25: 18S.


59- Kies MS, Gibson MK, Kim SW, Savvides P, Blumen-schein GR, Jr., Worden F, Chen H, Grandis JR, Argiris AE. Cetuximab (C) and bevacizumab (B) in patients with recurrent or metastatic head and neck squamous cell carcinoma (SCCHN): An interim analysis (Abst). J Clin Oncol. 2005, 24: 501S.


