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Promising Newer Molecular-Targeted Therapies in Head and Neck Cancer

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Abstract

Head and neck cancer (HNC) is the fifth most common cancer in the world. In the US alone, HNC accounts for 3–5% of all malignancies annually. Squamous cell carcinoma arising from the mucosa of the upper aerodigestive tract is the most common type of HNC and accounts for 90% of HNC diagnoses. Despite continued advances in the therapeutic options, the disease-free survival, functional outcome, toxicity of therapy and overall survival have remained less than optimal for patients with locally advanced, recurrent or metastatic disease. Therefore, new approaches for the treatment of patients with HNC, particularly patients with advanced stage, are clearly needed. Among the new therapies, molecular-targeted and biological therapies have gained special attention. While clinical trial data support the use of epidermal growth factor receptor (EGFR) inhibition in metastatic and locally advanced HNC, numerous trials are seeking to establish a clear role for new therapies targeting EGFR, the receptor for the type I insulin-like growth factor, as well as anti-angiogenesis agents.

Head and neck cancer (HNC) is the fifth most common cancer in the world.[1,2] In the US, HNC accounts for 3–5% of all malignancies annually, with an estimated 45 660 new cases diagnosed in 2006 and 11 210 deaths attributed to this disease in 2006, representing approximately 2% of all cancer deaths that year.[3] Squamous cell carcinoma of the head and neck (HNSCC) represents the majority of HNC and arises from the mucosa of the upper aerodigestive tract, including cancers of the oral cavities, the pharynx (naso-, oro- and hypopharynx), the larynx and the paranasal sinuses. While treatment of HNSCC is complex, some general principles apply, including single modality treatment with surgery or radiation therapy (RT) alone for patients who present with early-stage (stage I or stage II) disease. Although treatment for these patients confers a remarkable cure rate, the majority of patients present with locally advanced disease (stage III or stage IV) at diagnosis.[4] Despite continued advances in the therapeutic options in the last 20 years, the disease-free survival, functional outcome, toxicity of therapy and overall survival have remained less than optimal.[5] Long-term survival varies from 10% to 50%, depending upon the factors such as tumour site, stage and resectability. Furthermore, patients with recurrent or metastatic cancers will have a worse prognosis, with a median survival time of 6 to 9 months.[6,7] Therefore, new approaches for the treatment of patients with HNC, particularly patients with advanced stage, are clearly needed.

In the global treatment of patients with malignancies, new therapeutic approaches are constantly evolving. Among them, molecular-targeted therapies have gained special attention. As the process of cancer evolution is better understood to be derived

from alternations in genetic and epigenetic processes, molecularly-targeted agents offer a promising scenario by restoring normal control of oncogenic processes.[2] Recently, a number of new targets have been identified in HNSCC as playing key roles in tumour pathogenesis. Epidermal growth factor receptor (EGFR) is one of the most attractive targets. Expression of EGFR in HNSCC is frequent and an elevated level of EGFR protein carries a poor prognosis.[8,9] Treatments targeting the function of this receptor have resulted in clinical improvement in HNSCC.[10] Cetuximab is approved by the US FDA for use in patients with platinum-refractory recurrent or metastatic HNSCC, and also in patients with locally advanced HNSCC to use concurrently with RT.[11] The vascular endothelial growth factor (VEGF) is another explored target. Tumour growth and metastasis rely on angiogenesis. VEGF, an angiogenic stimulator, is one of the key regulators of tumour angiogenesis.[12] Anti-VEGF agents have been shown to be an effective therapy in colorectal cancer, non-small cell lung cancer and renal cell carcinoma, and are actively being explored in HNSCC for activity.[13-15]

This article focuses on key aspects of EGFR biology and the role of anti-EGFR agents in HNSCC. It also summarizes emerging data on alternative pathways and targets, including angiogenesis and the insulin-like growth factor (IGF) type I receptor (IGF-1R). Only the two FDA-approved indications for targeted therapy in HNC are discussed.

1. Epidermal Growth Factor Receptor (EGFR)-Targeted Therapy

1.1 EGFR Structure and Signalling

EGFR is a member of the ErbB/Her family of ligand-activated receptor tyrosine kinases (RTKs). This receptor family includes four related receptors: EGFR/ErbB1, human epidermal growth factor receptor 2 (HER2)/neu (ErbB2), ErbB3 and ErbB4.[16] EGFR and its family members play an important role in cell proliferation, survival and migration.[17] Aberrant EGFR activity is strongly associated with tumour progression. Therefore, it has been recognized as a rational therapeutic target.[18]

The EGFR is a highly glycosylated transmembrane RTK, consisting of a single 170 kDa polypeptide chain of 1186 amino acids.[19] Like all RTKs, EGFR is composed of an extracellular ligand-binding domain, a hydrophobic transmembrane segment, which is involved in interactions between receptors within the cell membrane, and a cytoplasmic domain with tyrosine kinase activity.[20] Multiple ligands are reported to bind EGFR, including epidermal growth factor (EGF), transforming growth factor (TGF)-α, heparin-binding EGF-like growth factor, amphiregulin, betacellulin and epiregulin.[17] Prior to ligand binding, EGFR exists as monomers on the cell surface. Upon the ligand binding to the extracellular domain, EGFR undergoes homodimerization or heterodimerization with other ErbB family members, which leads to autophosphorylation of a range of key tyrosine residues in the cytoplasmic domain.[21] These phosphorylated tyrosine residues then serve as attachment sites of cellular docking proteins, activating a variety of downstream signalling pathways. The following three downstream signalling cascades have been characterized: (i) Ras-Raf-mitogen-activated protein kinase (MEK)-extracellular-signal-regulated kinase (ERK); (ii) the phosphatidylinositol-3′kinase (PI3K)-protein kinase B (AKT); and (iii) Janus kinase 2/signal transducers and activators of transcription 3 pathway (STAT3). Activation of these pathways eventually leads to cell proliferation, tumour invasion and metastasis, angiogenesis, and tumour resistance to chemotherapy (figure 1).[22-25] Inactivation of the EGFR can be mediated by either receptor dephosphorylation or receptor downregulation.[26]

Several mechanisms can produce dysregulated EGFR activity in human cancers, including (i) increased ligand production; (ii) over-expression of EGFR protein from autoactivation by ligand-independent receptor dimerization; (iii) EGFR mutations leading to constitutively active variants; (iv) dysfunction in EGFR downregulation; and (v) heterodimerization and EGFR crosstalk.[27,28]

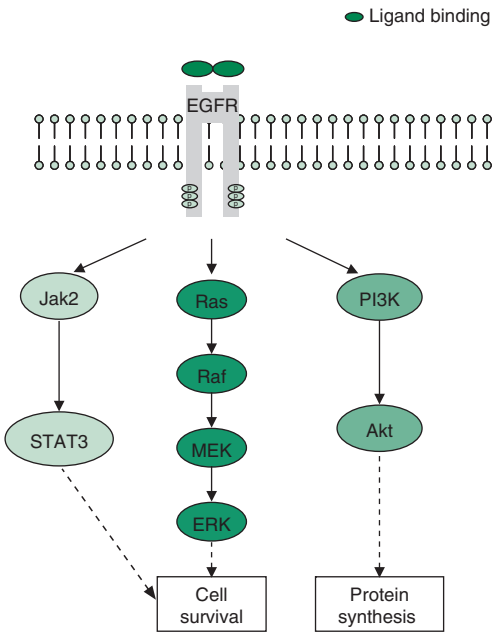

Fig. 1. A simplified model illustrating epidermal growth factor receptor (EGFR) signalling. Binding of a ligand to the EGFR causes receptor dimerization, autophosphorylation and activation of several intracellular downstream signalling pathways, which eventually lead to protein synthesis and cell survival. Targeting the ligand binding, receptor dimerization, phosphorylation and activation, as well as signalling pathways may provide intervention sites for biologically targeted therapies for squamous cell carcinoma of the head and neck. **Akt** = protein kinase B; **ERK** = extracellular-signal-regulated kinase; **Jak2** = Janus kinase 2; **MEK** = mitogen-activated protein kinase; **PI3K** = the phosphatidylinositol-3′kinase; **STAT3** = signal transducers and activators of transcription 3.

1.2 Rationale and Methods of EGFR-Targeted Therapies

EGFR is frequently expressed in HNSCC and has been implicated in its pathogenesis, such that elevated EGFR expression is strongly linked to a poor prognosis. Therefore, targeting EGFR has gained special attention.[8,9]

Several therapies targeting EGFR have been developed, two of which (monoclonal antibodies and small tyrosine kinase inhibitors [TKIs]) appear to be the most successful in the clinic. Monoclonal antibodies targeting EGFR directly interfere with the ligand-receptor binding. The small TKIs block the activation and phosphorylation of EGFR. Although EGFR signalling inhibition can be accomplished by either method of inhibition, several important distinctions exist. Monoclonal antibodies are large proteins and susceptible to degradation in the gastrointestinal tract, so must be given by intravenous injection. However, monoclonal antibodies also have relatively long half-lives, thus weekly infusion is the preferred method of delivery. In contrast, the small TKIs are small molecules that can be absorbed effectively across the gastrointestinal tract and are given orally. TKIs are given daily because of their shorter half-lives.[29]

1.3 Monoclonal Antibodies Against the EGFR

1.3.1 Cetuximab

Cetuximab is a human-murine chimeric anti-EGFR IgG_1 monoclonal antibody. It is the most widely studied anti-EGFR monoclonal antibody. Cetuximab is highly specific because it interacts only with the EGFR and not with other ErbB receptors.[30] Currently, cetuximab is approved by the FDA for the treatment of locoregionally advanced HNSCC (in combination with RT) or metastatic HNSCC (as a single agent).

Multidisciplinary treatment involving the use of RT and chemotherapy has been a standard modality in patients with locally advanced, unresectable HNSCC. In preclinical models, cetuximab was synergistic with RT,[31,32] and cetuximab in combination with RT was well tolerated with promising activity in a phase I study.[33] It is the first targeted agent to demonstrate a survival advantage in combination with RT in HNSCC; in 2006, Bonner et al.[34] reported a phase III clinical trial involving 424 patients with stage III/IV SCC of the oropharynx, hypopharynx or larynx who had no prior therapy. Patients were randomized to receive RT alone (213 patients) or RT plus weekly cetuximab (211 patients). The addition of cetuximab to high-dose RT resulted in significant improvement of the median duration of the locoregional control (24.4 vs 14.9 months), median overall survival (49 vs 29 months) and a 26% reduction in the risk of mortality ($p = 0.03$). With the exception of infusion-related reactions, interstitial lung disease, acneform rash and hypomagnesaemia,

the regimen was well tolerated. The incidence of grade 3 or 4 toxicity was similar between the two groups.

In mouse models, cetuximab potentiated the antitumoural activity of several chemotherapeutic agents such as cisplatin, paclitaxel and fluorouracil (5-FU). Clinically, cetuximab has been studied in combination with chemotherapy and RT. One study by Pfister and colleagues[35] using a combination of RT, cisplatin and cetuximab was encouraging; however, the study was closed as a result of an excess of severe toxicity including deaths (10%) and myocardial infarction (5%). To overcome the excessive toxicities, a second phase II study investigated cetuximab in combination with alternating chemotherapy and RT. Chemotherapy with cisplatin, 5-FU was given on days 1–5, 22–26 and 43–47, and RT was given in the pauses between and after the chemotherapy courses. Preliminary data revealed encouraging activity with a tolerable toxicity profile.[36] Another phase II trial studying cetuximab, paclitaxel, carboplatin and RT after induction therapy is currently ongoing and preliminary results suggested a high pathological complete response rate after the therapy.[37]

Cetuximab has also been studied in combination with chemotherapy in patients with recurrent and/or metastatic HNSCC, and is also currently undergoing trials in induction therapy. A phase III trial was performed by the Eastern Cooperative Oncology Group in which 117 patients with recurrent/metastatic HNSCC were randomly assigned to receive cisplatin with or without cetuximab. The primary endpoint of progression-free survival did not meet statistical difference for the cisplatin-cetuximab group (4.2 vs 2.7 months; $p = 0.09$), neither did overall survival (9.2 vs 8 months; $p = 0.21$). However, objective response rate in patients treated with cetuximab was superior to the placebo group (26% vs 10%; $p = 0.03$). Correlation analysis between clinical endpoints and skin toxicity revealed a survival advantage in the subpopulation developing skin rash with an hazard ratio of 0.42 (95% CI 0.21, 0.86) for survival in the cetuximab group.[38] The benefit of cetuximab in addition to first-line platinum-based chemotherapy was reported in a randomized phase III study. A total of 442 patients with recurrent or metastatic HNSCC were randomized in the trial; 222 patients received cetuximab plus cisplatin or carboplatin plus 5-FU, and 220 patients received cisplatin or carboplatin plus 5-FU. Medium survival was 10.1 months in the cetuximab group versus 7.4 months in the chemotherapy only group ($p = 0.036$).[39]

The role of cetuximab in platinum-refractory disease has been established and approved by the FDA after several phase II trials. Vermorken et al.[40] tested cetuximab alone in 103 patients who progressed after a platinum-based regimen. An overall response of 13%, with a disease control rate (complete response/partial response/stable disease) of 46% and a medium survival of 178 days was reported. Two phase II studies examined cetuximab in combination with platinum after patients had progressed through platinum therapy. These studies found an overall response rate of 10%, and suggested the activity in these trials can be contributed mostly to cetuximab and that cetuximab as a single agent may achieve similar results.[41,42]

Several ongoing phase II trials are studying the efficacy of adding cetuximab to induction chemotherapy. Kies et al.[43] added cetuximab to induction chemotherapy with paclitaxel and carboplatin in 41 patients. All patients had a major objective response with 83% of these patients having a complete response and another 17% a partial response. Toxicity was generally acceptable with leukopenia, folliculitis and hypersensitivity reactions. The results suggest that inclusion of cetuximab in induction chemotherapy is feasible and additional confirmatory studies are needed to optimize the dose administration schedule.

1.3.2 Panitumumab

Panitumumab is a fully humanized IgG_2 anti-EGFR monoclonal antibody that binds EGFR with a high affinity, preventing the binding of endogenous ligands, such as EGF and TGF-α, to EGFR.[44] Panitumumab leads to cell cycle arrest and inhibits tumour colony formation *in vitro*.[45] Panitumumab has been FDA approved for chemotherapy-refrac-

tory metastatic colorectal cancer. Currently, the drug is undergoing several early clinical trials in patients with HNSCC.

1.3.3 Other Monoclonal Antibodies

Other antibodies against the ligand-binding domain of the EGFR are in clinical development. Matuzumab (EMD 72000) is a selective humanized monoclonal antibody.[46] This drug has been recently evaluated in patients with HNSCC, showing a good toxicity profile. The main adverse reaction was related to cutaneous reactions.[47]

Nimotuzumab (H-R3) is another monoclonal antibody that has been evaluated in a phase I trial in combination with RT. It demonstrated promising activity. The major toxicity was related to infusion reactions, in contrast with cutaneous rashes associated with other anti-EGFR therapy.[48] Phase II studies with or without RT are still ongoing.[49]

1.4 EGFR Tyrosine Kinase Inhibitors (TKIs)

1.4.1 Erlotinib

Erlotinib is an orally available low-molecular weight TKI of EGFR that competes with the adenosine triphosphate (ATP)-binding site.

Soulieres et al.[50] conducted a multicentre phase II study using erlotinib as a single agent in patients with refractory, recurrent and/or metastatic HNSCC. Among 115 patients enrolled, the overall objective response rate was 4.3% with 38.3% disease stabilization. The median progression-free survival was 9.6 weeks; median overall survival was 6.0 months. No difference was detected with EGFR expression; however, in patients with at least grade 2 skin rash, the subgroup analysis revealed improved overall survival compared with the cohort who experienced less than grade 2 skin rash. The combination of erlotinib with cisplatin has shown additive antitumour activity without increased toxicity *in vivo*.[51] Based on the above observation, a phase I/II study was conducted to test erlotinib and cisplatin as a first-line therapy in patients with recurrent or metastatic HNSCC. Siu et al.[52] reported an objective response of 21% in 44 patients with a median survival of 7.9 months. The combination was well tolerated.

Identifying biomarkers for HNSCC patients who may benefit from targeted studies is a pressing issue. Agulnik et al.[53] conducted pharmacodynamic tissue studies on the phase I/II trial of erlotinib and cisplatin.[52] The investigators tested levels of EGFR, downstream signalling intermediates before and after treatment. The study found that high EGFR gene copy in tumour specimens may predict an increased likelihood of response to erlotinib and decreased phosphorylated EGFR level in skin biopsies during treatment may represent a potential surrogate marker for improved clinical outcome. Further studies on larger prospective trials are warranted.

Erlotinib in combination with chemotherapy has also been evaluated in other trials. A phase II trial reported encouraging preliminary data by adding erlotinib to cisplatin and docetaxel doublet.[54]

1.4.2 Gefitinib

Like erlotinib, gefitinib is also inhibits tyrosine kinase by competing with ATP binding. Preclinical studies have demonstrated the antitumour activity of gefitinib in a variety of cultured tumour cell lines and in human tumour xenografts. Phase I studies found administration of gefitinib up to 800 mg/day to be generally safe, with a pharmacokinetic profile demonstrating dose-dependent exposure.[55,56]

One phase I trial was conducted using gefitinib in combination with RT or chemotherapy (with weekly cisplatin) plus RT in locally advanced HNSCC, and found that gefitinib was well tolerated with either combination.[57] In a phase II trial of gefitinib monotherapy (500 mg/day) for recurrent or metastatic HNSCC, Cohen et al.[58] reported overall response rate of 10.6%, with 53% disease control and a median survival of 8 months. However, another phase II trial using gefitinib 250 mg/day had only one partial response with 1.4% overall response rate,[59] suggesting a dose-response relationship may exist in HNSCC.

The efficacy of gefitinib as a monotherapy in recurrent HNSCC was confirmed in a third study, whereby a clinical benefit of 45% was observed.

However, no association between rash and clinical response was detected.[60]

Recently, a phase II study evaluated the combination of gefitinib with cisplatin and docetaxel doublet in patients with metastatic and recurrent HNSCC. An overall response rate of 62.5% (37.5% complete response and 25% partial response) was reported with median progression-free survival of 5.1 months.[61]

1.4.3 Lapatinib

Lapatinib is an orally available dual TKI that selectively blocks the activation of both EGFR/ErbB1 and ErbB2.[29] Signalling mediated by these receptors is believed to play complementary roles in tumour progression, invasion and metastases, thereby providing the rationale of a dual-targeting therapy. Currently, lapatinib is FDA approved for the treatment of metastatic breast cancer in combination with capecitabine.

Lapatinib was studied in a phase II trial of 40 patients with progressive metastatic or recurrent EGFR and/or HER2-overexpressing salivary gland tumour. There were no objective responses; however, stable disease was achieved in 15 of 19 patients (79%) with adenoid cystic carcinoma (ACC) and 8 of 17 (47%) with the non-ACC patients.[62] Abidoye et al.[63] conducted a phase II trial in 42 patients with recurrent or metastatic HNSCC (27 patients with and 15 patients without prior EGFR inhibitor therapy). Although no objective responses were observed, stable disease was reported in 37% of patients without prior EGFR inhibitor and in 20% of patients with prior exposure.

The exploration of lapatinib in combination with chemotherapy plus RT has revealed more encouraging results. A phase I trial of lapatinib with concurrent cisplatin and RT in 19 patients with locally advanced HNSCC revealed 74% complete response and 26% partial response.[64] At the moment, studies are ongoing to examine the synergy of lapatinib and chemoradiotherapy.[65]

2. Receptor for the Type 1 Insulin-Like Growth Factor (IGF-1R)-Targeted Therapy

2.1 IGF-1R and its Signalling

IGF-1R belongs to the insulin receptor subfamily of RTKs.[66] IGF-1R is a tetramic transmembrane RTK that is widely expressed in human tissues.[67] Binding of endogenous ligands, such as IGF-I or -II, initiates conformational changes and autophosphorylation, subsequently leading to the activation of downstream signalling cascades including Ras-Raf-MEK and PI3K/AKT pathways. IGF-1R has been demonstrated to mediate a variety of cellular events including cell proliferation, differentiation, motility and resistance to apoptosis.[68]

2.2 Targeting IGF-1R

Targeting the IGF signalling pathway is a new promising therapy in cancer. In both preclinical and clinical studies, IGF-1R and its ligands (IGF-I and IGF-II) have been shown to play a key role in the development and progression of numerous human cancers.[69-71] Increases in systemic IGF-I levels and elevated tissue IGF-1R expression are associated with increased risk of a number of cancer types, more rapid disease progression and tumour metastatic potential.[69] Barnes et al.[68] reported recently that IGF-1R was over-expressed in HNC cell lines, and IGF-1R signalling was associated with the proliferation, motility and tumourigenecity of human HNC cell lines. In addition, EGFR and IGF-1R has been shown to form functional heterodimers in HNC. These findings suggest targeting IGF-1R for therapeutic intervention in HNC and also provide a basis for simultaneously targeting IGF-1R and EGFR. Phase I clinical trials are ongoing to test antibodies for IGF-1R.[72]

3. Anti-Vascular Endothelial Growth Factor (VEGF) and VEGF Receptor (VEGFR) Therapy

3.1 VEGF, VEGFR and Anti-Angiogenesis Therapy

Human tumours rely on angiogenesis for growth, progression and metastatic dissemination. VEGF is a one of the most essential angiogenic cytokines implicated in tumour vasculogenesis.[73] It has four isoforms including VEGF-A, -B, -C and -D. VEGF-A is a key component among the VEGF family, and binds and activates VEGF-1 and VEGF-2 tyrosine kinase receptors.[74] VEGF receptor (VEGFR)-1 is mainly involved in the early inflammation process, while VEGFR-2 plays a pivotal role in tumour angiogenesis development and haematopoiesis.[75] VEGFR-3 is an important receptor for proliferation and survival of lymphovascular cells. Hence, much effort has been devoted to discovering an inhibitor of VEGFR-2/-3 tyrosine kinases as antitumour agents.[74]

Like most other cancer types, HNSCC requires a blood supply for tumour growth. VEGF expression has been associated with a worse prognosis in patients with HNSCC. The expression of VEGF and VERFR-2 has also been associated with a higher proliferation index and a worse survival in HNSCC patients.[76,77] Therefore, the VEGF pathway may represent a target for the HNC therapy.

3.2 Anti-VEGR Monoclonal Antibodies

Bevacizumab is an anti-angiogenic monoclonal antibody directed against VEGF. It is FDA approved for the treatment of metastatic colon and non-small cell lung cancer. Unlike cetuximab, bevacizumab is currently not FDA approved for use in HNC. Furthermore, its safety and activity in HNC are still under investigation.

Preclinical data support the theory that inhibition of VEGF improves radiosensitivity, which provides the rationale of integrating bevacizumab with RT. Recently, a phase II trial studied the role of bevacizumab in combination with concurrent chemotherapy (5-FU and hydroxyurea) and RT. A total of 21 patients with stage II–IV HNC were enrolled, pathological complete response rates were observed in 92% and 100% in bevacizumab and control arms, respectively. Adverse effects are tolerable in both arms.[78] Preliminary data from another phase II study of bevacizumab in combination with docetaxel plus RT in locally advanced HNSCC are encouraging. Of ten patients who have completed concurrent bevacizumab with chemoradiation, nine patients remain in complete remission, and six of ten patients who received neck dissection were found to be in pathological complete response.[79]

Bevacizumab has also been evaluated in combination with chemotherapy. A phase II trial of pemetrexed plus bevacizumab in patients with recurrent or metastatic HNSCC is ongoing. An interim analysis revealed a 45% overall response rate for the combination among 11 patients evaluated.[80]

EGFR activation upregulates VEGF expression, which has been correlated with resistance to anti-EGFR agents. Several studies are exploring the combination of anti-VEGF and anti-EGFR therapies. A phase I/II study on erlotinib plus bevacizumab in 51 patients with recurrent or metastatic HNSCC showed median overall survival to be 7.3 months and progression-free survival to be 3.9 months.[81]

3.3 Anti-Angiogenic Receptor TKIs

3.3.1 Sorafenib

Sorafenib is a multiple TKI, targeting VEGR-2, VEGFR-3, Raf and platelet-derived growth factor receptor (PDGFR)-β.

A phase II Southwest Oncology Group trial studied the role of sorafenib as a single agent in 44 patients with metastatic or recurrent HNSCC and who were chemotherapy naive. One patient had partial response (3%) and 14 patients (45%) had stable disease. Overall survival was 8 months. Sorafenib was well tolerated in the study; the most common adverse effects included fatigue, nausea, mucositis, rash, hand-foot syndrome and hypertension.[82] Sorafenib monotherapy has also been evaluated in another phase II trial by Elser et al.[83] in which

28 patients with metastatic or recurrent HNSCC or nasopharyngeal carcinoma were enrolled. Of the patients eligible for evaluation, one patient had partial response (4%) and ten patients (37%) had stable disease. Overall survival was 4 months. The difference between the two studies is likely to be a result of the prior chemotherapy exposure of most patients in the latter trial.

These trials suggest that sorafenib may not be suitable as a single agent because of an overall poor response rate. However, its role in combination with chemotherapy needs to be explored.

3.3.2 Other VEGFR TKIs

Other anti-angiogenic TKIs are also undergoing active pre-clinical or clinical investigations.

Cediranib (AZD2171) is a highly potent VEGFR-1, -2 and -3 inhibitor, and inhibits the PDGFR family.[74] In a recent French study, the combination of cediranib, gefitinib and RT led to greater tumour inhibition in a nude mice xenograft model of HNC cells.[84] Currently, cediranib is being studied in a phase I trial in combination with gefitinib in HNSCC and non-small cell lung cancer.[85]

Vandetanib (ZD6474) is another VEGFR-2 and -3 TKI that also has activity against the EGFR tyrosine kinase.[86] Vandetanib has demonstrated antitumour activity in nude mice with xenograft of HNC cell lines.[87]

The results on semaxanib (SU5416), a synthetic small molecule inhibitor of the tyrosine kinase domain of VEGFR-2, were disappointing. Only one partial response was observed in 31 patients evaluated, with median survival being 6.25 months in a phase II study in patients with advanced or recurrent HNC.[14]

4. Conclusions

Treatment of HNC remains challenging, especially in patients with recurrent or metastatic disease. While conventional chemotherapies continue to play a vital role in treating HNC, it is evident that many patients become chemo-resistant and/or develop intolerable adverse effects necessitating new treatment approaches. The molecular-targeted therapies represent the most promising new treatments for HNC. Numerous studies involving molecular-targeted therapies are being conducted to investigate new biological targets. While the molecular profiles of malignancies are complex, molecular-targeted therapies need to be complex as well. It is unlikely that targeting one receptor will provide meaningful benefits to patients and, as such, new agents that target multiple receptors or combination therapy are likely to provide the most therapeutic benefit for patients with HNSCC. These agents should certainly be further explored in an integrated approach with chemotherapy, RT and the combination of both. Furthermore, the combination of different targeted therapies for improving efficacy and/or overcoming drug resistance may provide additional advance for the treatment of HNC. Targeted therapies already belong to the treatment and management of patients with HNSCC, and new targeted agents and combination therapies will certainly emerge as the standard of care in the near future.

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References

1. Chin D, Boyle GM, Porceddu S, et al. Head and neck cancer: past, present and future. Expert Rev Anticancer Ther 2006; 6: 1111-8
2. Agulnik M. Malignancies of the head and neck: the role for molecular targeted agents. Expert Opin Ther Targets 2007; 11: 207-17
3. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. CA Cancer J Clin 2007; 57: 43-66
4. Monnerat C, Faivre S, Temam S, et al. End points for new agents in induction chemotherapy for locally advanced head and neck cancers. Ann Oncol 2002; 13: 995-1006
5. Carvalho AL, Nishimoto IN, Califano JA, et al. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. Int J Cancer 2005; 114: 806-16
6. Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2006; 24: 2644-52
7. Cohen EE, Lingen MW, Vokes EE. The expanding role of systemic therapy in head and neck cancer. J Clin Oncol 2004; 22: 1743-52
8. Nicholson RI, Gee JM, Harper ME. EGFR and cancer prognosis. Eur J Cancer 2001; 37 Suppl. 4: S9-15
9. Zimmermann M, Zouhair A, Azria D, et al. The epidermal growth factor receptor (EGFR) in head and neck cancer: its role and treatment implications. Radiat Oncol 2006; 1: 11

10. Astsaturov I, Cohen RB, Harari P. EGFR-targeting monoclonal antibodies in head and neck cancer. Curr Cancer Drug Targets 2007; 7: 650-65
11. Blick SK, Scott LJ. Cetuximab: a review of its use in squamous cell carcinoma of the head and neck and metastatic colorectal cancer. Drugs 2007; 67: 2585-607
12. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med 1995; 1: 27-31
13. Ranieri G, Patruno R, Ruggieri E, et al. Vascular endothelial growth factor (VEGF) as a target of bevacizumab in cancer: from the biology to the clinic. Curr Med Chem 2006; 13: 1845-57
14. Fury MG, Zahalsky A, Wong R, et al. A Phase II study of SU5416 in patients with advanced or recurrent head and neck cancers. Invest New Drugs 2007; 25: 165-72
15. Saba NF, Shin DM, Khuri FR. Targeting angiogenesis in head and neck cancer. Curr Cancer Drug Targets 2007; 7: 643-9
16. Holbro T, Civenni G, Hynes NE. The ErbB receptors and their role in cancer progression. Exp Cell Res 2003; 284: 99-110
17. Hynes NE, Horsch K, Olayioye MA, et al. The ErbB receptor tyrosine family as signal integrators. Endocr Relat Cancer 2001; 8: 151-9
18. Rocha-Lima CM, Soares HP, Raez LE, et al. EGFR targeting of solid tumors. Cancer Control 2007; 14: 295-304
19. Ogiso H, Ishitani R, Nureki O, et al. Crystal structure of the complex of human epidermal growth factor and receptor extracellular domains. Cell 2002; 110: 775-87
20. Schlessinger J. Ligand-induced, receptor-mediated dimerization and activation of EGF receptor. Cell 2002; 110: 669-72
21. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2001; 2: 127-37
22. Kruger JS, Reddy KB. Distinct mechanisms mediate the initial and sustained phases of cell migration in epidermal growth factor receptor-overexpressing cells. Mol Cancer Res 2003; 1: 801-9
23. Masuda M, Toh S, Koike K, et al. The roles of JNK1 and Stat3 in the response of head and neck cancer cell lines to combined treatment with all-trans-retinoic acid and 5-fluorouracil. Jpn J Cancer Res 2002; 93: 329-39
24. Vivanco I, Sawyers CL. The phosphatidylinositol 3-Kinase AKT pathway in human cancer. Nat Rev Cancer 2002; 2: 489-501
25. Ellerbroek SM, Halbleib JM, Benavidez M, et al. Phosphatidylinositol 3-kinase activity in epidermal growth factor-stimulated matrix metalloproteinase-9 production and cell surface association. Cancer Res 2001; 61: 1855-61
26. Shtiegman K, Yarden Y. The role of ubiquitylation in signaling by growth factors: implications to cancer. Semin Cancer Biol 2003; 13: 29-40
27. Arteaga CL. Epidermal growth factor receptor dependence in human tumors: more than just expression? Oncologist 2002; 7 Suppl. 4: 31-9
28. Cruz JJ, Ocana A, Del Barco E, et al. Targeting receptor tyrosine kinases and their signal transduction routes in head and neck cancer. Ann Oncol 2007; 18: 421-30
29. Harari PM, Allen GW, Bonner JA. Biology of interactions: antiepidermal growth factor receptor agents. J Clin Oncol 2007; 25: 4057-65
30. Masui H, Kawamoto T, Sato JD, et al. Growth inhibition of human tumor cells in athymic mice by anti-epidermal growth factor receptor monoclonal antibodies. Cancer Res 1984; 44: 1002-7
31. Harari PM, Huang SM. Head and neck cancer as a clinical model for molecular targeting of therapy: combining EGFR blockade with radiation. Int J Radiat Oncol Biol Phys 2001; 49: 427-33
32. Milas L, Mason K, Hunter N, et al. In vivo enhancement of tumor radioresponse by C225 antiepidermal growth factor receptor antibody. Clin Cancer Res 2000; 6: 701-8
33. Baselga J, Pfister D, Cooper MR, et al. Phase I studies of antiepidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin. J Clin Oncol 2000; 18: 904-14
34. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006; 354: 567-78
35. Pfister DG, Su YB, Kraus DH, et al. Concurrent cetuximab, cisplatin, and concomitant boost radiotherapy for locoregionally advanced, squamous cell head and neck cancer: a pilot phase II study of a new combined-modality paradigm. J Clin Oncol 2006; 24: 1072-8
36. Merlano MC, Numico G, Russi EG, et al. Cetuximab (C-mab) and chemo-radiation (CT-RT) for loco-regional advanced squamous cell carcinoma of the head and neck (HNC): a phase II study [abstract]. J Clin Oncol 2007; 25: 6043
37. Wanebo HJ, Ghebremichael M, Burtness B, et al. Phase II evaluation of cetuximab (C225) combined with induction paclitaxel and carboplatin followed by C225, paclitaxel, carboplatin, and radiation for stage III/IV operable squamous cancer of the head and neck (ECOG, E2303) [abstract]. J Clin Oncol 2007; 25: 6015
38. Burtness B, Goldwasser MA, Flood W, et al. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol 2005; 23: 8646-54
39. Vermorken J, Mesia R, Vega V, et al. Cetuximab extends survival of patients with recurrent or metastatic SCCHN when added to first line platinum based therapy: results of a randomized phase III (Extreme) study [abstract]. J Clin Oncol 2007; 25: 6091
40. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 2007; 25: 2171-7
41. Baselga J, Trigo JM, Bourhis J, et al. Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2005; 23: 5568-77
42. Herbst RS, Arquette M, Shin DM, et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. J Clin Oncol 2005; 23: 5578-87
43. Kies MS, Garden AS, Holsinger C, et al. Induction chemotherapy (CT) with weekly paclitaxel, carboplatin, and cetuximab for squamous cell carcinoma of the head and neck (HN) [abstract]. J Clin Oncol 2006; 24: 5520
44. Yang XD, Jia XC, Corvalan JR, et al. Development of ABX-EGF, a fully human anti-EGF receptor monoclonal antibody, for cancer therapy. Crit Rev Oncol Hematol 2001; 38: 17-23

45. Foon KA, Yang XD, Weiner LM, et al. Preclinical and clinical evaluations of ABX-EGF, a fully human anti-epidermal growth factor receptor antibody. Int J Radiat Oncol Biol Phys 2004; 58: 984-90
46. Kettleborough CA, Saldanha J, Heath VJ, et al. Humanization of a mouse monoclonal antibody by CDR-grafting: the importance of framework residues on loop conformation. Protein Eng 1991; 4: 773-83
47. Hoffend J, Mohammed A, Eisenhut M, et al. Uptake of the anti-epidermal growth factor receptor (EGFR) antibody EMD 72000 in tumors of subjects with head and neck squamous cell carcinoma (HNSCC) [abstract]. J Clin Oncol 2004; 22: 3043
48. Crombet T, Osorio M, Cruz T, et al. Use of the humanized anti-epidermal growth factor receptor monoclonal antibody h-R3 in combination with radiotherapy in the treatment of locally advanced head and neck cancer patients. J Clin Oncol 2004; 22: 1646-54
49. ClinicalTrials.gov. Phase II study of nimotuzumab and cisplatin/radiotherapy for locally advanced head and neck squamous cell cancer [online]. Available from URL: http://www.clinicaltrials.gov/ct2/show/NCT00702481 [Accessed 2008 Jul 10]
50. Soulieres D, Senzer NN, Vokes EE, et al. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. J Clin Oncol 2004; 22: 77-85
51. Pollack VA, Savage DM, Baker DA, et al. Inhibition of epidermal growth factor receptor-associated tyrosine phosphorylation in human carcinomas with CP-358,774: dynamics of receptor inhibition in situ and antitumor effects in athymic mice. J Pharmacol Exp Ther 1999; 291: 739-48
52. Siu LL, Soulieres D, Chen EX, et al. Phase I/II trial of erlotinib and cisplatin in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: a Princess Margaret Hospital phase II consortium and National Cancer Institute of Canada Clinical Trials Group Study. J Clin Oncol 2007; 25: 2178-83
53. Agulnik M, da Cunha Santos G, Hedley D, et al. Predictive and pharmacodynamic biomarker studies in tumor and skin tissue samples of patients with recurrent or metastatic squamous cell carcinoma of the head and neck treated with erlotinib. J Clin Oncol 2007; 25: 2184-90
54. Kim ES, Kies MS, Glisson BS, et al. Final results of a phase II study of erlotinib, docetaxel and cisplatin in patients with recurrent/metastatic head and neck cancer [abstract]. J Clin Onc 2007; 25: 6013
55. Goss G, Hirte H, Miller Jr WH, et al. A phase I study of oral ZD 1839 given daily in patients with solid tumors: IND.122, a study of the Investigational New Drug Program of the National Cancer Institute of Canada Clinical Trials Group. Invest New Drugs 2005; 23: 147-55
56. Wolf M, Swaisland H, Averbuch S. Development of the novel biologically targeted anticancer agent gefitinib: determining the optimum dose for clinical efficacy. Clin Cancer Res 2004; 10: 4607-13
57. Chen C, Kane M, Song J, et al. Phase I trial of gefitinib in combination with radiation or chemoradiation for patients with locally advanced squamous cell head and neck cancer. J Clin Oncol 2007; 25: 4880-6
58. Cohen EE, Rosen F, Stadler WM, et al. Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. J Clin Oncol 2003; 21: 1980-7
59. Cohen EE, Kane MA, List MA, et al. Phase II trial of gefitinib 250mg daily in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Clin Cancer Res 2005; 11: 8418-24
60. Wheeler RH, Jones D, Sharma P, et al. Clinical and molecular phase II study of gefitinib in patients (pts) with recurrent squamous cell cancer of the head and neck (H&N Ca) [abstract]. J Clin Oncol 2005; 23: 5531
61. Belón J, Irigoyen A, Rodríguez I, et al. Preliminary results of a phase II study to evaluate gefitinib combined with docetaxel and cisplatin in patients with recurrent and/or metastatic squamous-cell carcinoma of the head and neck [abstract]. J Clin Oncol 2005; 23: 5563
62. Agulnik M, Cohen EW, Cohen RB, et al. Phase II study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non adenoid cystic carcinoma malignant tumors of the salivary glands. J Clin Oncol 2007; 25: 3978-84
63. Abidoye OO, Cohen EE, Wong SJ, et al. A phase II study of lapatinib (GW572016) in recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) [abstract]. J Clin Oncol 2006; 24: 5568
64. Bourhis J, Harrington K, Rosine D, et al. A phase I, open label study (EGF 100262) of lapatinib plus chemoradiation in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) [abstract]. Ann Oncol 2006; 17 (9s): 180
65. ClinicalTrials.gov. Lapatinib versus placebo given concurrently with cisplatin and radiotherapy in patients with head and neck cancer [online]. Available from URL: http://www.clinicaltrials.gov/ct2/show/NCT00387127 [Accessed 2008 Jul 10]
66. Bahr C, Groner B. The IGF-1 receptor and its contributions to metastatic tumor growth-novel approaches to the inhibition of IGF-1R function. Growth Factors 2005; 23: 1-14
67. Adams TE, Epa VC, Garrett TP, et al. Structure and function of the type 1 insulin-like growth factor receptor. Cell Mol Life Sci 2000; 57: 1050-93
68. Barnes CJ, Ohshiro K, Rayala SK, et al. Insulin-like growth factor receptor as a therapeutic target in head and neck cancer. Clin Cancer Res 2007; 13: 4291-9
69. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. Nat Rev Cancer 2004; 4: 505-18
70. Mitsiades CS, Mitsiades N. Treatment of hematologic malignancies and solid tumors by inhibiting IGF receptor signaling. Expert Rev Anticancer Ther 2005; 5: 487-99
71. Larsson O, Girnita A, Girnita L. Role of insulin-like growth factor 1 receptor signalling in cancer. Br J Cancer 2007; 96 Suppl.: R2-6
72. ClinicalTrials.gov. Phase 1 study of BIIB022 (anti-IGF-1R monoclonal antibody) in relapsed/refractory solid tumors [online]. Available from URL: http://www.clinicaltrials.gov/ct2/show/NCT00555724 [Accessed 2008 Jul 10]
73. Folkman J. What is the evidence that tumors are angiogenesis dependent? J Natl Cancer Inst 1990; 82: 4-6
74. Zhong H, Bowen JP. Molecular design and clinical development of VEGFR kinase inhibitors. Curr Top Med Chem 2007; 7: 1379-93
75. Shalaby F, Rossant J, Yamaguchi TP, et al. Failure of blood-island formation and vasculogenesis in Flk-1-deficient mice. Nature 1995; 376: 62-6
76. Kyzas PA, Cunha IW, Ioannidis JP. Prognostic significance of vascular endothelial growth factor immunohistochemical expression in head and neck squamous cell carcinoma: a meta-analysis. Clin Cancer Res 2005; 11: 1434-40

77. Kyzas PA, Stefanou D, Batistatou A, et al. Potential autocrine function of vascular endothelial growth factor in head and neck cancer via vascular endothelial growth factor receptor-2. Mod Pathol 2005; 18: 485-94
78. Choong NW, Haraf DJ, Cohen EE, et al. Randomized phase II study of concomitant chemoradiotherapy with 5-fluorouracil-hydroxyurea (FHX) compared to FHX and bevazicumab (BFHX) in intermediate stage head and neck cancer (HNC) [abstract]. J Clin Oncol 2007; 25: 6043
79. Savvides P, Greskovich J, Bokar J, et al. Phase II study of bevacizumab in combination with docetaxel and radiation in locally advanced squamous cell cancer of the head and neck (SCCHN) [abstract]. J Clin Oncol 2007; 25: 6068
80. Karamouzis MV, Friedland D, Johnson R, et al. Phase II trial of pemetrexed (P) and bevacizumab (B) in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC): an interim analysis [abstract]. J Clin Oncol 2007; 25: 6049
81. Seiwert TY, Davis DW, Yan D, et al. pKDR/KDR ratio predicts response in a phase I/II pharmacodynamic study of erlotinib and bevacizumab for recurrent or metastatic head and neck cancer (HNC) [abstract]. J Clin Oncol 2007; 25: 6021
82. Williamson SK, Moon J, Huang CH, et al. A phase II trial of sorafenib in patients with recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC): a Southwest Oncology Group (SWOG) trial [abstract]. J Clin Oncol 2007; 25: 6044
83. Elser C, Siu LL, Winquist E, et al. Phase II trial of sorafenib in patients with recurrent or metastatic squamous cell carcinoma of the head and neck or nasopharyngeal carcinoma. J Clin Oncol 2007; 25: 3766-73
84. Bozec A, Formento P, Lassalle S, et al. Dual inhibition of EGFR and VEGFR pathways in combination with irradiation: antitumour supra-additive effects on human head and neck cancer xenografts. Br J Cancer 2007; 97: 65-72
85. ClinicalTrials.gov. The effects of AZD2171 & gefitinib in patients with non-small cell lung cancer or head & neck cancer [online]. Available from URL: http://www.clinicaltrials.gov/ct2/show/NCT00243347 [Accessed 2008 Jul 10]
86. Bianco C, Giovannetti E, Ciardiello F, et al. Synergistic antitumor activity of ZD6474, an inhibitor of vascular endothelial growth factor receptor and epidermal growth factor receptor signaling, with gemcitabine and ionizing radiation against pancreatic cancer. Clin Cancer Res 2006; 12: 7099-107
87. Sano D, Kawakami M, Fujita K, et al. Antitumor effects of ZD6474 on head and neck squamous cell carcinoma. Oncol Rep 2007; 17: 289-95

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