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LEADING ARTICLE

Promising New Molecular Targeted Therapies in Head and Neck Cancer

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Abstract Despite advances in multimodality therapies for the treatment of squamous cell carcinoma of the head and neck (SCCHN), survival rates, functional outcomes and toxicities of therapy remain poor. The recognition of the prognostic value of human papillomavirus (HPV) status, and the advent of biologically targeted therapies with potential for decreased toxicities and increased selectivity, represent significant developments in our understanding of SCCHN. Targeted agents currently approved or under investigation for SCCHN include epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab, panitumumab, zalutumumab, nimotuzumab), EGFR tyrosine kinase inhibitors (gefitinib, erlotinib, lapatinib, afatanib, dacomitinib), vascular endothelial growth factor receptor (VEGFR) inhibitors (bevacizumab, sorafenib, sunitinib, vandetanib) and various inhibitors of other pathways and targets, including phosphatidylinositol 3′ kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), MET and insulin-like growth factor receptor (IGF-1R). On-going clinical trials are evaluating these emerging agents and their combinations in the treatment of SCCHN.

1 Introduction

Head and neck cancers (HNCs) are a diverse group of tumours arising in the oral cavity, oropharynx, larynx and hypopharynx. In 2012, there were an estimated 40,250 new cases of HNC in the USA, and 7,850 patients died from the disease, representing approximately 1.5 % of all cancer deaths that year [1]. Squamous cell carcinoma of the head and neck (SCCHN) represents approximately 90 % of all new cases. SCCHN is the eighth most common cancer worldwide, with approximately 650,000 new cases reported annually [2]. Historically, the major risk factors for SCCHN were alcohol and tobacco use. More recently, high-risk types of human papillomavirus (HPV) have been linked to the development of oropharyngeal cancers [3]. As tobacco use has declined, an increase in the incidence rates of HPV-positive SCCHN has been seen [4]. Unlike HPV-negative SCCHN, which is driven by stepwise mutations in the squamous epithelium, HPV-positive SCCHN is caused by two viral oncogenes that inactivate tumour suppressor genes and lead to malignant transformation of the squamous epithelium [5]. Locally advanced HPV-positive SCCHN has been shown to have a significantly better prognosis than HPV-negative disease [6, 7]. Recognition of the diverging prognoses and distinct biology of SCCHN based on HPV status represents a significant development in our understanding of SCCHN.

While treatment of SCCHN is complex, some general principles apply, including management of early stages with surgery or radiotherapy. Though treatment for these patients confers a remarkable cure rate, the majority of patients present with locally advanced disease at diagnosis, which is treated with a combination of surgery, chemoradiotherapy and/or targeted therapy [8]. Despite continued advances in the therapeutic options in the last 20 years, the disease-free survival, functional outcome, toxicity of therapy and overall survival (OS) have remained less than optimal [9]. Long-term survival varies from 10 to 50 %, depending upon factors such as tumour site, stage and resectability. Furthermore, patients with recurrent or metastatic cancers will have a worse prognosis, with a median

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survival time of 6–9 months [10, 11]. 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, understanding the molecular biology of cancer has driven the search for new therapies. The focus of SCCHN therapy has shifted to the molecular level, with a number of new targets identified as playing key roles in tumour pathogenesis such as the epidermal growth factor receptor (EGFR) pathway. Expression of EGFR in SCCHN is detected in >90 % of all SCCHN tumours, and high levels of protein expression are associated with decreased survival, resistance to radiotherapy, locoregional treatment failure and increased rates of distant metastases [12]. Cetuximab, a recombinant chimeric anti-EGFR monoclonal antibody (mAb), is approved by the US FDA in combination with radiotherapy for use in locally advanced disease and as a single agent or in combination with platinum-based chemotherapy for recurrent or metastatic SCCHN.

This review focuses on key aspects of EGFR biology and the role of anti-EGFR agents (both mAbs and tyrosine kinase inhibitors [TKIs]) in SCCHN (Fig. 1). We also summarize emerging data on alternative pathways and targets, including the vascular endothelial growth factor (VEGF) pathway, the phosphatidylinositol-3′ kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway, the MET receptor and its ligand hepatocyte growth factor (HGF) pathway, and the receptor for the type I insulin-like growth factor (IGF-1R). A comprehensive review of relevant literature was performed using the computerized database PubMed, with search terms including head and neck squamous cell carcinoma and targeted molecular therapy.

2 Epidermal Growth Factor Receptor (EGFR)-Targeted Therapy

2.1 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, HER2/neu (ErbB2), ErbB3 and ErbB4 [13]. EGFR and its family members play an important role in cell proliferation, survival and migration [14]. Aberrant EGFR activity is strongly associated with tumour progression. Therefore, it has been recognized as a rational therapeutic target [15].

The EGFR is a highly glycosylated transmembrane RTK, consisting of a single 170 kDa polypeptide chain of 1,186 amino acids [16]. Like all tyrosine kinase receptors, EGFR is composed of an extracellular ligand-binding domain, a hydrophobic transmembrane segment that is involved in interactions between receptors within the cell membrane, and a cytoplasmic domain with tyrosine kinase activity [17]. Multiple ligands are reported to bind EGFR, including EGF, transforming growth factor (TGF)-α, heparin-binding EGF-like growth factor (HB-EGF), amphiregulin (AR), betacellulin (BTC) and epiregulin (EPR) [14]. 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 [18]. These phosphorylated tyrosine residues then serve as attachment sites of cellular docking proteins, activating a variety of downstream signalling pathways. Three downstream signalling cascades have been characterized, including Ras-RAF-mitogen-activated protein kinase (MEK)-extracellular-signal-regulated kinase (ERK), the PI3K/AKT and Janus kinase 2 (Jak2)/signal transducers and activators of transcription 3 (STAT3) pathway. Activation of these pathways eventually leads to cell proliferation, tumour invasion and metastasis, angiogenesis and tumour resistance to chemotherapy [19–22]. Inactivation of the EGFR can be mediated by either receptor dephosphorylation or receptor downregulation [23].

Several mechanisms can produce dysregulated EGFR activity in human cancers, including (1) increased ligand production, (2) over-expression of EGFR protein, autoactivation by ligand-independent receptor dimerization, (3) EGFR mutations leading to constitutively active variants, (4) dysfunction in EGFR downregulation, and (5) heterodimerization and EGFR crosstalk [24, 25].

EGFR is frequently expressed in SCCHN 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 [26, 27]. Several therapies targeting EGFR have been developed, two of which, mAbs and small TKIs, appear to be most successful.

2.2 Monoclonal Antibodies Against the EGFR

mAbs targeting EGFR directly interfere with the ligand-receptor binding. mAbs are large proteins and susceptible to degradation in the gastrointestinal (GI) tract; therefore, they must be given by intravenous injection. On the other hand, mAbs have relatively long half-lives, thus weekly infusion is the preferred method of delivery. Anti-EGFR mAbs that are discussed include cetuximab, panitumumab, zalutumumab and nimotuzumab.

2.2.1 Cetuximab

Cetuximab is a human-murine chimeric anti-EGFR immunoglobulin G (IgG)-1 mAb. It is the most widely

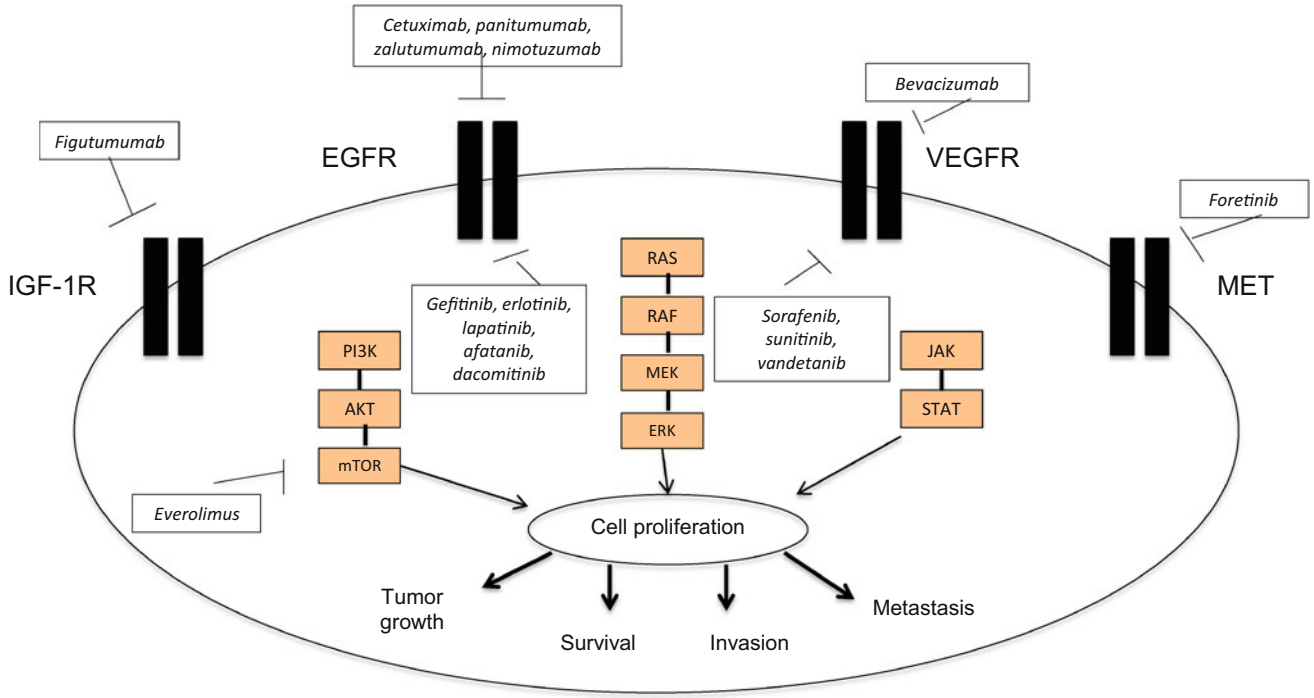

Fig. 1 A simplified model illustrating potential molecular targets for therapy including cell surface receptors and downstream signaling pathways. *AKT* protein kinase B, *EGFR* epidermal growth factor receptor, *ERK* extracellular signal regulated kinase, *IGF-1R* insulin-like growth factor receptor, *JAK* Janus kinase, *MEK* mitogen-activated protein kinase, *mTOR* mammalian target of rapamycin, *PI3K* phosphatidylinositol 3′ kinase, *VEGFR* vascular endothelial growth factor receptor

studied anti-EGFR mAb. Cetuximab is highly specific, as it interacts only with the EGFR, not with other ErbB receptors [28]. Currently, cetuximab is approved by the FDA as well as the European Medicines Agency (EMA) for the treatment of locally advanced disease in combination with radiotherapy, in combination with platinum-based chemotherapy and 5-fluorouracil (5-FU) for the first-line treatment of metastatic/recurrent disease, and as a single agent for metastatic/recurrent SCCHN after failure of platinum-based chemotherapy. Of note, it has also been approved in the USA and Europe in the treatment of K-Ras-negative, EGFR-positive, metastatic colorectal cancer. Results from several clinical trials have established the role of cetuximab in the treatment of SCCHN.

2.2.1.1 Locally Advanced SCCHN In 2006, the FDA approved the use of cetuximab in combination with radiotherapy for the treatment of locoregionally advanced SCCHN. In a landmark phase III clinical trial involving 424 patients with locoregionally advanced disease, Bonner et al. compared cetuximab in combination with high-dose radiotherapy versus high-dose radiotherapy alone [29]. The addition of cetuximab to high-dose radiation resulted in significant improvement in the median duration of locoregional control (24.4 vs. 14.9 months) and median OS (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, acneiform rash and hypomagnesaemia, the regimen was well tolerated. The incidence of grade 3 or 4 toxicity was similar between the two groups. The addition of cetuximab significantly increased 5-year OS (45.6 vs. 36.4 %) [30].

Cetuximab has also been evaluated in phase II studies in combination with chemotherapy and radiotherapy. One study by Pfister and colleagues evaluated the combination of radiotherapy, cisplatin and cetuximab in 22 patients with locoregionally advanced SCCHN [31]. Grade 3 or 4 cetuximab-related toxicities included acne-like rash (10 %) and hypersensitivity (5 %). However, the study was closed early due to five significant adverse events (AEs) (two deaths, one myocardial infarction, one bacteraemia and one atrial fibrillation) of unclear attribution. Thorough review of the cetuximab clinical trial database was conducted and did not show that these AEs were clearly attributable to investigational therapy. Despite the AEs, the preliminary survival data were encouraging. With a median follow-up of 52 months, the 3-year OS rate was 76 % (95 % CI 58–94) and progression-free survival (PFS) rate was 56 % (95 % CI 35–78).

Preliminary results of the Radiation Therapy Oncology Group (RTOG) 0522 phase III trial evaluated the addition of cetuximab to a chemoradiotherapy regimen in the

treatment of locoregionally advanced SCCHN [32]. In this trial of 942 patients, there were no significant differences in PFS (63 vs. 64 %; hazard rate [HR] 1.05; 95 % CI 0.84–1.29; $p = 0.66$) or in OS (83 vs. 80 %; HR 0.87; 95 % CI 0.66–1.15; $p = 0.17$). The cetuximab arm had higher rates of grade 3–4 mucositis (45 vs. 35 %; $p = 0.003$) and skin reactions (40 vs. 17 %; $p \leq 0.0001$), but no significant difference in grade 3–4 dysphagia rates (62 vs. 66 %; $p = 0.27$) and no significant AEs leading to early study closure were seen. In this trial, 321 samples were evaluable for p16 status (73 % were p16+). Among those, there was a trend towards improved PFS in patients treated with cisplatin alone, although this did not reach significance. Future studies will need to address HPV status separately. For HPV-positive tumours, the goal is toxicity reduction, and the on-going RTOG 1016 trial will compare radiotherapy plus cisplatin with radiotherapy plus cetuximab in HPV-positive tumours.

Preliminary results of the randomized phase II TREMPLIN study evaluated the role of cetuximab in sequential chemoradiotherapy for laryngeal preservation [33]. Patients with previously untreated stage III/IV larynx/hypopharynx cancer ($n = 153$) were enrolled and 74 % underwent the planned induction chemotherapy (docetaxel, cisplatin, 5-FU). In case of response >50 %, patients were then randomized to cisplatin with radiotherapy (group A) versus cetuximab with radiotherapy (group B). In the intent-to-treat evaluation, clinical efficacy was similar in both arms: larynx function preservation at 18 months was 86 versus 82 % and OS was 85 versus 86 %. Late toxicity occurred more often in group A ($p = 0.111$).

2.2.1.2 Recurrent and/or Metastatic SCCHN Several clinical trials have evaluated the use of cetuximab in the recurrent/metastatic SCCHN setting. In the phase III trial ECOG5397 (Eastern Cooperative Oncology Group), 117 patients with recurrent/metastatic SCCHN were randomly assigned to receive cisplatin with or without cetuximab [34]. The primary endpoint of PFS did not meet statistical difference for the cisplatin-cetuximab group (4.2 vs. 2.7 months; $p = 0.09$), neither did OS (9.2 vs. 8 months; $p = 0.21$). While this study did not significantly improve OS or PFS, the addition of cetuximab to cisplatin did improve the overall response rate (26 vs. 10 %; $p = 0.03$). The three most common AEs were fatigue, nausea and vomiting.

The landmark EXTREME (Erbitux in First Line Treatment of Recurrent or Metastatic Head and Neck Cancer) trial investigated the benefit of adding cetuximab to chemotherapy and was the first phase III trial in recurrent/metastatic SCCHN to show a significant improvement in OS [35]. This study enrolled 442 patients with recurrent/metastatic SCCHN and randomized them to receive cisplatin or carboplatin plus 5-FU and cetuximab or chemotherapy alone. The addition of cetuximab to platinum-based chemotherapy significantly prolonged the median OS (10.1 vs. 7.4 months; HR 0.80; 95 % CI 0.64–0.99; $p = 0.04$) as well as the median PFS (5.6 vs. 3.3 months; HR 0.54; $p < 0.001$). The three most common grade 3–4 AEs were neutropenia (22 % for chemotherapy/cetuximab vs. 23 % for chemotherapy alone), anaemia (13 vs. 19 %) and thrombocytopenia (11 % in both groups). Sepsis occurred in nine patients in the cetuximab group and only one patient in the chemotherapy alone group ($p = 0.02$). Of the 219 patients receiving cetuximab, 9 % had grade 3 skin reactions and 3 % had grade 3–4 infusion reactions.

Cetuximab in combination with platinum and 5-FU (PFE) has become a standard in first-line treatment of patients with recurrent/metastatic SCCHN. The phase II ADVANTAGE trial evaluated the efficacy of adding cilengitide to a PFE regimen by randomizing patients to one of three groups (once weekly, twice weekly or control). No benefit was demonstrated in median PFS between arms (6.4 vs. 5.6 vs. 5.7 months) [36]. The phase II GORTEC 2008-03 trial evaluated the efficacy and safety of cetuximab, docetaxel and cisplatin combination (TPEx) as first-line treatment in patients with recurrent/metastatic SCCHN [37]. Results were encouraging, with best overall response rate (ORR) of 54 % (1 complete response [CR], 27 partial responses [PRs]), median PFS 7.1 months, and median OS 15.3 months. Treatment-related toxicities included grade 4 neutropenia, which was managed with granulocyte colony-stimulating factor (G-CSF).

Cetuximab has also been evaluated in three phase II trials in patients with recurrent/metastatic SCCHN who failed to respond to first-line chemotherapy alone [38–40]. Vermorken et al. administered single-agent cetuximab to 103 patients who had previously experienced disease progression on platinum-based chemotherapy. Responses in these three phase II trials were 10–13 % irrespective of reintroducing the originally used platinum agent. The survival of around 5–6 months represented an increase in survival of 2.5 months compared with platinum-refractory historical controls. Based on these results, cetuximab monotherapy seems to be an option for patients with recurrent/metastatic SCCHN refractory to platinum-based therapy.

2.2.2 Panitumumab

Panitumumab is a fully humanized IgG-2 anti-EGFR mAb that binds EGFR with a high affinity, preventing the binding of endogenous ligands such as EGF and TGFα to EGFR [41]. Panitumumab leads to cell cycle arrest and inhibits tumour colony formation in vitro [42]. Panitumumab has been approved in both the USA and Europe for chemotherapy-refractory metastatic colorectal cancer.

Currently the drug is undergoing several clinical trials in SCCHN patients.

The phase II CONCERT-1 trial evaluated the efficacy of chemoradiotherapy with or without panitumumab (chemoradiotherapy vs. chemoradiotherapy plus panitumumab [PCRT]) in patients with unresected, locally advanced SCCHN [43]. This trial randomized 150 patients to receive PRCT versus chemoradiotherapy. Overall, the addition of panitumumab to chemoradiotherapy did not show an increase in efficacy. The 2-year local regional control rate was 61 % in the PRCT group versus 68 % in the chemoradiotherapy group (HR 1.33; 95 % CI 0.77–2.30; $p = 0.3$). PFS was 40 % in the PRCT group versus 35 % in the chemoradiotherapy group (HR 1.15; 95 % CI 0.68–1.96; $p = 0.61$). No difference in fatal AEs were seen between arms; however, the panitumumab arm had an increase in grade 3+ AEs, including mucosal inflammation (55 vs. 24 %), radiation skin injury (28 vs. 13 %), dysphagia (40 vs. 27 %) and rash (11 vs. 0 %). Additionally, analysis of PFS and OS by tumour HPV status showed no differences in outcome.

The phase III SPECTRUM trial (Study of Panitumumab in Patients with Recurrent and/or Metastatic Head and Neck Cancer) evaluated the efficacy of panitumumab in patients with recurrent/metastatic SCCHN [44]. In this trial, 657 patients were randomized to cisplatin-5-FU with or without panitumumab. There was no statistically significant improvement in OS, the primary endpoint, with the addition of panitumumab (11.1 vs. 9.0 months; HR 0.87; 95 % CI 0.73–1.05; $p = 0.14$). However, there was a statistically significant difference in response rate (36 vs. 25 %; $p = 0.007$) and PFS (5.8 vs. 4.6 months; HR 0.78; 95 % CI 0.66–0.92; $p = 0.004$). The most frequently reported AEs included nausea, rash, neutropenia and vomiting.

In a subset analysis of the SPECTRUM trial, Stoehlmacher-Williams et al. evaluated the safety and efficacy of panitumumab in HPV-positive and -negative recurrent/metastatic SCCHN [45]. Of the 657 patients enrolled, 443 had samples evaluable for HPV testing. Patients with HPV-negative recurrent/metastatic SCCHN administered panitumumab plus chemotherapy versus chemotherapy alone had improved median OS (11.7 vs. 8.6 months; HR 0.76; 95 % CI 0.59–0.97; $p = 0.02$) and median PFS (6.0 vs. 5.1 months; HR 0.67; 95 % CI 0.53–0.84; $p = 0.001$). On the contrary, no improvement was observed in HPV-positive tumours administered chemotherapy with or without panitumumab in median OS (11.0 vs. 12.6 months; HR 1.00; 95 % CI 0.61–1.64; $p = 0.98$) or median PFS (5.6 vs. 5.5 months; HR 1.21; 95 % CI 0.76–1.92; $p = 0.43$).

2.2.3 Zalutumumab

Zalutumumab is a human IgG1 mAb that blocks EGFR signalling. A recent phase III trial randomized 286 patients with platinum-refractory recurrent/metastatic SCCHN to receive zalutumumab plus best supportive care or best supportive care plus optional methotrexate [46]. The primary endpoint of median OS showed no statistically significant improvement (6.7 vs. 5.2 months; HR 0.77; 95 % CI 0.57–1.05; $p = 0.0648$), but PFS was longer in the zalutumumab group than in the control group (9.9 vs. 8.4 weeks; HR 0.63; 95 % CI 0.47–0.84; $p = 0.0012$). The grade 3–4 AEs that were more common in the zalutumumab group included rash, hypomagnesaemia, pneumonia and headache.

2.2.4 Nimotuzumab

Nimotuzumab is a humanized anti-EGFR mAb in on-going clinical trials to evaluate its use in SCCHN. It has been granted use in countries outside the USA and Europe for treatment of SCCHN, glioma and nasopharyngeal carcinoma and has been shown to have anti-tumour activity in the absence of the severe skin, renal and GI toxicities seen with cetuximab and panitumumab [47].

In a phase IIb study conducted in India, 92 patients with unresectable SCCHN were randomized to receive chemoradiotherapy with or without nimotuzumab (group 1) or radiotherapy with or without nimotuzumab (group 2) [47]. In group 1, the nimotuzumab arm showed significant increase in ORR at 24 weeks (100 vs. 70 %; $p = 0.02$), PFS at 30 months (56.52 vs. 21.74 %; $p = 0.0157$) and OS rate at 30 months (69.57 vs. 21.74 %; $p = 0.0011$). In group 2, the nimotuzumab arm showed improved ORR at 24 weeks (76 vs. 40 %; $p = 0.023$), PFS rate at 30 months (34.78 vs. 13.04 %; $p = 0.0839$) and OS rate at 30 months (39.13 vs. 21.74 %; $p = 0.199$). There were only four cases of skin reactions in patients receiving nimotuzumab. In the 4-year survival results from this study, the nimotuzumab arm of both groups showed significantly increased OS rates: group 1 = 47 versus 21 %; $p = 0.01$; group 2 = 34 versus 13 %; p-value not significant [48].

In another phase II trial, Rodriguez et al. enrolled 106 patients with unresectable SCCHN and randomized them to radiotherapy with or without nimotuzumab [49]. The primary endpoint of this trial was CR rate, which was 59.5 % of patients receiving nimotuzumab plus radiotherapy versus 34.2 % of patients receiving radiotherapy alone ($p = 0.028$). Additionally, separate survival analyses were done with EGFR-positive patients and showed a significant improvement in median OS (16.5 vs. 7.2 months; $p = 0.0038$) when treated with the addition of nimotuzumab. No significant advantage was seen in EGFR-negative patients treated with nimotuzumab compared with placebo.

2.3 EGFR Tyrosine Kinase Inhibitors

The EGFR is a transmembrane glycoprotein, the intracellular domain of which has tyrosine kinase activity. The small TKIs block the activation and phosphorylation of EGFR. In contrast to the mAbs, the TKIs are small molecules that can be absorbed effectively across the GI tract and are given orally. TKIs are given daily due to their shorter half-lives. TKIs that are discussed include gefitinib and erlotinib, which are reversible specific EGFR TKIs, and lapatinib, a reversible dual EGFR/Her2 TKI. In an effort to address the issue of increasing resistance, additional agents are under investigation that block multiple ErbB family receptors and/or bind their targets irreversibly. These agents include afatinib, an irreversible dual EGFR/Her 2 TKI, and dacomitinib, an irreversible pan-HER TKI.

2.3.1 Gefitinib

Gefitinib is an oral agent that reversibly inhibits the EGFR tyrosine kinase activity. It is currently FDA and EMA approved for use in the treatment of locally advanced and metastatic non-small cell lung cancer (NSCLC) and has been studied for use in SCCHN. The initial phase II trial of gefitinib monotherapy (500 mg/day) for recurrent or metastatic SCCHN was undertaken to assess the activity and tolerability of gefitinib in recurrent/metastatic SCCHN. In this trial of 52 patients, one CR and four PRs were observed for an ORR of 10.6 % (95 % CI 3.5–23.1), and 42.6 % of patients had stable disease (SD) as their best response (95 % CI 28.3–57.8). Therefore, as defined above, 53 % of patients experienced some degree of disease control [50]. However, in the recent IMEX phase III trial that randomized 486 patients with recurrent/metastatic SCCHN to gefitinib 250 mg/day, gefitinib 500 mg/day or methotrexate, neither dose of gefitinib improved OS compared with methotrexate (HR 1.22; 95 % CI 0.95–1.57; $p = 0.12$; HR 1.12; 95 % CI 0.87–1.43; $p = 0.39$) [51]. Median OS was 5.6, 6.0 and 6.7 months, respectively. In a phase III trial conducted by ECOG, the addition of gefitinib to weekly docetaxel in previously treated patient populations with recurrent/metastatic SCCHN was evaluated [52]. This trial was stopped early because there was a <5 % chance to meet the primary endpoint of OS. This study failed to improve OS, PFS or response rate but showed a modest improvement in time to progression (median 3.5 vs. 2.1 months; HR 0.69; 95 % CI 0.49–0.99; $p = 0.047$).

2.3.2 Erlotinib

Erlotinib is another orally available reversible TKI of EGFR approved in the USA and Europe for use in NSCLC and pancreatic cancer. Soulieres et al. conducted a multicentre phase II study using erlotinib as a single agent in patients with locally recurrent and/or metastatic SCCHN [53]. Among 115 patients enrolled, the overall objective response rate was 4.3 %, median OS was 6.0 months and PFS was 9.6 weeks. A phase I/II study was conducted to test erlotinib and cisplatin as a first-line therapy in patients with recurrent or metastatic SCCHN. Siu et al. reported an objective response rate of 21 % in 44 patients, with a median OS of 7.9 months [54]. In a phase II trial, Kim et al. evaluated the efficacy of a combination of erlotinib, cisplatin and docetaxel in advanced SCCHN [55]. A total of 50 patients were enrolled; median OS was 11 months and PFS was 6.01 months.

2.3.3 Lapatinib

Lapatinib is an orally available dual TKI that selectively blocks the activation of both epidermal growth factor receptor (EGFR/ErbB1) and HER2/ErbB2 [56]. 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 and EMA approved for the treatment of metastatic breast cancer in combination with capecitabine.

Lapatinib was studied in a phase II trial that randomized 67 patients with locally advanced SCCHN to receive chemoradiotherapy with or without lapatinib, followed by maintenance with lapatinib or placebo [57]. The CR rate at 6 months post-chemoradiotherapy was 53 % with lapatinib as compared with 36 % with placebo in the intent-to-treat population. The early data showed HRs for PFS and OS by independent review of 0.71 (95 % CI 0.34–1.52) and 0.70 (95 % CI 0.31–1.63). Del Campo et al. evaluated the effects of lapatinib monotherapy in therapy-naive patients with locally advanced SCCHN [58]. Patients ($n = 107$) were randomized to receive lapatinib vs. placebo for 2–6 weeks prior to starting chemoradiotherapy. No difference was seen between groups in detected apoptosis; however, there was a decrease in proliferation observed in the lapatinib group. Despite ambiguous biological results, this study showed an ORR of 17 % after the monotherapy phase, including one CR. Interestingly, all four responders had EGFR overexpression. In a separate phase II trial, Abidoye et al. conducted a phase II trial in 42 patients with recurrent or metastatic SCCHN (27 patients with and 15 without prior EGFR-inhibitor therapy). Although no objective responses were observed, SD was reported in 37 % of patients without prior EGFR inhibitor and in 20 % of patients with prior exposure [59].

2.3.4 Afatinib

Afatinib is an oral, irreversible, ErbB family inhibitor that binds EGFR, ErbB2 and ErbB4. In the preliminary results of a phase II study of patients with recurrent/metastatic SCCHN who had failed on platinum-based chemotherapy, 124 patients were randomized to receive afatinib versus cetuximab. Preliminary efficacy analysis suggests that afatinib is active in recurrent/metastatic SCCHN that has failed platinum-based chemotherapy and compares favourably to cetuximab (PR 18 vs. 8 %, SD 53 vs. 50 % and progressive disease 30 vs. 43 %) [60]. Primary afatinib-related AEs were diarrhoea and skin-related AEs, while skin-related AEs were the primary cetuximab-related AEs.

2.3.5 Dacomitinib

Dacomitinib is an oral, irreversible pan-HER inhibitor that targets EGFR, ErbB2 and ErbB4. The preliminary results of a phase II trial of dacomitinib as a first-line agent in recurrent/metastatic SCCHN showed a median PFS of 2.8 months and OS of 8.3 months [61]. The most common grade 3 AEs were diarrhoea (16 %), fatigue (9 %), acneiform dermatitis (7 %) and hand-foot reaction (4 %).

3 Vascular Endothelial Growth Factor Receptor (VEGFR)-Directed Therapies

3.1 VEGFR Structure and Signalling

Human tumours rely on angiogenesis for growth, progression and metastatic dissemination. VEGF is one of the most essential angiogenic cytokines implicated in tumour vasculogenesis [62]. It has four isoforms: 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 [63]. VEGFR-1 is mainly involved in the early inflammation process, while VEGFR-2 plays a pivotal role in tumour angiogenesis development and haematopoiesis [64]. VEGF-B and VEGF-C are ligands for VEGFR-3, an important receptor for proliferation and survival of lymphovascular cells. Hence, much effort has been devoted to discover inhibitors of VEGFR-2/3 tyrosine kinases as anti-tumour agents [63]. Like most other cancer types, SCCHN requires blood supply for tumour growth. The presence of VEGF has been associated with a worse prognosis in patients with SCCHN. In a meta-analysis conducted by Kyzas et al., VEGF protein overexpression was associated with a worse OS in SCCHN patients [65, 66]. Therefore, the VEGF pathway may represent a target for HNC therapy.

3.2 Monoclonal Antibodies Against the VEGFR

3.2.1 Bevacizumab

Bevacizumab is an anti-angiogenic mAb directed against VEGF. In the USA and Europe, it is approved for use in the treatment of metastatic colorectal cancer, NSCLC, glioblastoma and renal cell carcinoma. In Europe, it is also approved for use in metastatic breast cancer.

Bevacizumab has been evaluated for use in SCCHN in combination with chemotherapy. In a phase II trial of pemetrexed and bevacizumab in patients with recurrent or metastatic SCCHN, 40 patients were enrolled with no prior systemic therapy [67]. This study demonstrated a median time to progression of 5 months (90 % CI 4–7), median OS of 11.3 months (90 % CI 8.7–16.8) and a response rate (RR) of 30 %. Six patients had bleeding of grade 3 or higher.

EGFR activation up-regulates VEGF, which has been correlated with resistance to anti-EGFR agents. Several studies are exploring the combination of anti-VEGF and anti-EGFR therapies for use in SCCHN. In a phase I/II trial conducted by Cohen et al., bevacizumab was combined with erlotinib in patients with recurrent/metastatic SCCHN [68]. Forty-eight patients were enrolled, and demonstrated an RR of 15 %, median OS of 7.1 months (95 % CI 5.7–9.0) and median PFS of 4.1 months (95 % CI 2.8–4.4). The most common AEs were rash, diarrhoea, fatigue, stomatitis and anorexia. Three patients had serious bleeding events of grade 3 or higher.

The final results of a phase II trial of bevacizumab in combination with cetuximab in recurrent/metastatic SCCHN were recently presented by Argiris et al. [69]. Forty-six patients were enrolled and demonstrated a median OS of 7.6 months and PFS of 2.8 months.

3.3 VEGFR Tyrosine Kinase Inhibitors

3.3.1 Sorafenib

Sorafenib is a multiple kinase inhibitor targeting VEGFR-2, VEGFR-3, RAF and platelet-derived growth factor (PDGFR). It is FDA and EMA approved for use in renal cell carcinoma and hepatocellular carcinoma. It has been studied as a single agent in several trials of SCCHN, with disappointing results. A phase II trial by Williamson et al. studied the role of sorafenib in 44 patients with chemotherapy-naive recurrent/metastatic SCCHN [70]. There was one confirmed PR and two unconfirmed PRs; the estimated confirmed response probability was 2 % (95 % CI 0–13). The median OS was 9 months (95 % CI 7–14). Sorafenib was well tolerated in the study; the most common side effects include fatigue, anorexia, stomatitis, hand-foot

syndrome and hypertension. In another phase II trial by Elser et al., 28 patients with recurrent/metastatic SCCHN or nasopharyngeal carcinoma who had received prior chemotherapy were enrolled [71]. One patient had PR (4 %) and ten patients (37 %) had SD. Median time to progression was 1.8 months, and median OS was 4.2 months.

In a recent presentation by Blumenschein et al., sorafenib was evaluated in combination with chemotherapy in recurrent/metastatic SCCHN with encouraging results [72]. Forty-four patients with recurrent/metastatic SCCHN received treatment with paclitaxel, carboplatin and sorafenib (PCS). Response rate was 55 %, median PFS was 8.51 months (95 % CI 5.98–13) and median OS was 22.6 months (95 % CI 13.1–not attained. Grade 3 toxicities included hand-foot syndrome, neutropenia, pain, elevated lipase, anaemia, fatigue, hypertension and neuropathy. Final outcomes and toxicity data are not yet reported.

3.3.2 Sunitinib

Sunitinib is a multiple TKI with activity against VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, RET and c-KIT. Sunitinib is approved in the USA and Europe for the treatment of imatinib-resistant GI stromal tumour, pancreatic neuroendocrine tumours and metastatic renal cell carcinoma. In a phase II study by Machiels et al., the role of sunitinib was evaluated as palliative monotherapy for recurrent/metastatic SCCHN [81]. Thirty-eight patients were enrolled, and demonstrated a low median PFS and OS of 2 and 3.4 months, respectively. Nineteen patients (50 %) achieved SD at 6–8 weeks. There was a high incidence (16 %) of grade 3–5 bleeds. In another phase II study by Choong et al., 28 patients with recurrent/metastatic SCCHN were enrolled for treatment with sunitinib [82]. This study was closed after interim analysis revealed only one of 19 patients had PR.

3.3.3 Vandetanib

Vandetanib is a TKI with activity against EGFR, VEGFR and RET. Vandetanib is currently approved in the USA and Europe for use in medullary thyroid cancer. Vandetanib has been shown to exhibit anti-tumoral effects in both in vitro and in vivo studies of SCCHN cells also treated with cisplatin and radiation [43]. Updated results from a phase I study of vandetanib with radiotherapy with or without cisplatin in locally advanced SCCHN were recently presented and showed vandetanib can be safely combined with radiotherapy with or without cisplatin [45].

4 Potential Agents with Other Mechanisms of Action

4.1 PI3K/AKT/mTOR Pathway Inhibitors

The PI3K/AKT/mTOR pathway can be activated by the upstream activation of tyrosine kinase receptors, including EGFR and IGF-1R. This pathway plays a major role in cell processes, including protein synthesis and cell survival. mTOR is a serine/threonine protein kinase that is involved in regulation of cell growth, cell proliferation, cell motility and protein synthesis and has been shown to be activated in 57–81 % of patients with SCCHN [70]. mTOR inhibitors such as everolimus and temsirolimus are currently under investigation for use in SCCHN.

4.2 MET Receptor Inhibitors

MET is a tyrosine kinase receptor with an only known ligand of HGF. Activation of the MET receptor promotes tyrosine phosphorylation, leading to downstream signalling including the Ras and PI3K/AKT/mTOR pathways. c-MET is the proto-oncogene that normally regulates cell proliferation and survival, cell dissociation, motility, cell polarity, wound healing and tissue regeneration. Overexpression of c-MET is oncogenic and causes enhanced motility, invasion/metastasis and angiogenesis and has been found to be overexpressed in approximately 80 % of SCCHN [33, 72].

Different mechanisms are currently being developed to inhibit the MET/HGF pathway and include mAbs and TKIs. Foretinib, or XL880, is an oral TKI that primarily targets the HGF/MET pathway and VEGF2 by binding in the ATP pocket of both receptors. In pre-clinical studies, foretinib induced tumour haemorrhage and necrosis in human xenografts [73]. A phase II study of foretinib in patients with recurrent/metastatic SCCHN was recently conducted [74]. While the RR in this two-stage phase II trial did not meet criteria to allow progression to stage 2, as there were no responders based on response evaluation criteria in solid tumours (RECIST), signs of moderate activity were evident: 50 % of patients (7/14) showed SD and 43 % of patients (6/14) experienced tumour shrinkage. Further investigation is warranted about the use of MET/HGF pathway inhibitors as single agents as well as in combination with anti-EGFR therapies in patients with SCCHN.

4.3 Type I Insulin-Like Growth Factor-Targeted Therapy

The receptor for the IGF-1R belongs to the insulin receptor subfamily of RTKs [75]. IGF-1R is a tetrameric

transmembrane receptor tyrosine kinase that is widely expressed in human tissues [76]. Binding of endogenous ligands such as IGF-I or IGF-II initiates conformational changes and autophosphorylation, subsequently leading to the activation of downstream signalling cascades including MAPK and PI3K/AKT/mTOR pathways. IGF-1R has been demonstrated to mediate a variety of cellular events, including cell proliferation, differentiation, motility and resistance to apoptosis [77].

Targeting IGF signalling pathways is a new promising therapy in cancer. In both preclinical and clinical studies, IGF type 1 receptor 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 [78–80]. Barnes et al. [77] reported that IGF-1R was over-expressed in SCCHN cell lines, and IGF-1R signalling was associated with the proliferation, motility and tumorigenicity of human SCCHN cell lines. However, in a phase II study of figitumumab, an mAb IgG2 that binds to the IGF-1 receptor, it was found that figitumumab monotherapy showed no clinically significant improvement in median OS or PFS in palliative SCCHN [73].

5 Conclusions

Treatment of SCCHN remains challenging, especially in patients with recurrent or metastatic disease. While conventional chemotherapies continue to play a vital role in treating R/M SCCHN, it is evident that many patients become chemo-resistant and/or develop intolerable AEs necessitating new treatment approaches. Understanding the molecular biology of cancer has fundamentally changed the search for new therapies. Recognition of the diverging prognoses and distinct biology of HPV-positive and HPV-negative SCCHN necessitates future trials that treat them as distinct diseases. The molecular-targeted therapies represent the most promising new treatments for SCCHN. EGFR-targeting agents have shown significant efficacy and are already approved for the treatment of SCCHN. Numerous studies involving additional molecular-targeted therapies are being conducted and include inhibitors of VEGFR, IGF-1R, PI3K/AKT/mTOR and MET. It is unlikely that targeting one receptor will provide meaningful benefits to our patients and, as such, new agents that target multiple receptors, or combination therapy, will likely provide the most therapeutic benefit for patients with SCCHN. Clinical trials looking at tumour HPV status and new combinations of existing treatment modalities with molecularly targeted agents will continue to shift the management of SCCHN towards more personalized and tailored therapeutic approaches.

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