New advances in targeted therapies for squamous cell carcinoma of the head and neck

Jean-Pascal Machiels and Sandra Schmitz

Several molecular pathways are deregulated and activated in squamous cell carcinoma of the head and neck making this disease attractive for targeted molecular therapies. Cetuximab, a monoclonal antibody that binds to the epidermal growth factor receptor, improves the overall survival when combined with radiation therapy or chemotherapy. Novels agents targeting different molecular pathways in squamous cell carcinoma of the head and neck are currently under development. Among them, dual (epidermal growth factor receptor/human epidermal growth factor receptor-2) or pan-human epidermal growth factor receptor inhibitors and drugs that target the insulin growth factor-1 receptor, the MET receptor, or the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway have shown either interesting preclinical activity or promising preliminary clinical efficacy. Angiogenesis inhibitors should be used with caution in squamous cell carcinoma of the head and neck due to the risk of tumor bleeding. However, only a minority of patients seems to benefit from these new approaches. Understanding the primary and acquired resistance mechanisms to predict the treatment efficacy is of crucial importance to allow a better patient selection. *Anti-Cancer Drugs* **22:626–633**

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Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth cause of cancer with more than 500 000 people diagnosed with head and neck cancer worldwide each year. The multimodal curative treatment of locally advanced SCCHN includes radiation therapy and/or surgery, and/or chemotherapy [1]. Despite this aggressive approach more than 50% of these patients will relapse. However, further therapeutic improvement is difficult with these standard treatment modalities because we are at the maximal toxicity that our patients can tolerate. One way to improve the therapeutic index is either to replace chemotherapy by a targeted agent to improve the toxicity profile with the aim of obtaining the same treatment efficacy or to add a new agent that does not have cross-toxicities such as molecular targeted agent to increase the treatment efficacy. In addition, the prognosis of patients with distant metastases or locoregional relapse not amenable to radical surgery or radiation therapy is poor with a median overall survival (OS) of approximately 7–10 months underlying the importance of investigating new drugs [2].

Several molecular pathways are deregulated and activated in SCCHN making this disease attractive for molecular targeted therapies (Fig. 1). This review will describe the most recent advances in this field and discuss their clinical implications.

Epidermal growth factor receptor inhibitors

The epidermal growth factor receptor (ErbB1, EGFR, HER-1) is a member of the human epidermal growth factor receptor (HER) tyrosine kinase receptor family and is overexpressed in up to 90% of all SCCHN [3–6]. HER receptor family consists of four different receptors (EGFR/ErbB1, ErbB2/HER-2-neu, ErbB3/HER-3, and ErbB4/HER-4). These receptors are transmembrane proteins with tyrosine kinase activity. The EGFR extracellular domain provides a ligand-binding site. The epidermal growth factor (EGF) transforming growth factor-α (TGF-α), and amphiregulin are probably the most important ligands and are specific to the EGFR. Upon ligand fixation, EGFR homodimerization or heterodimization with another HER receptor occurs leading to the activation of downstream signaling molecular pathways such as the Ras/Raf/Mek/extracellular signal-regulated protein kinase and the phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) pathways involved in tumor proliferation, apoptosis, angiogenesis, and cell migration or invasion [3]. High expression levels of EGFR, and its ligand TGF-α, are associated with decreased disease-free survival and OS [5]. Moreover, several studies have described that high EGFR gene copy number is also linked to poor prognosis [7–10].

EGFR pathway inhibition can be achieved with low molecular weight tyrosine kinase inhibitors (TKIs) or

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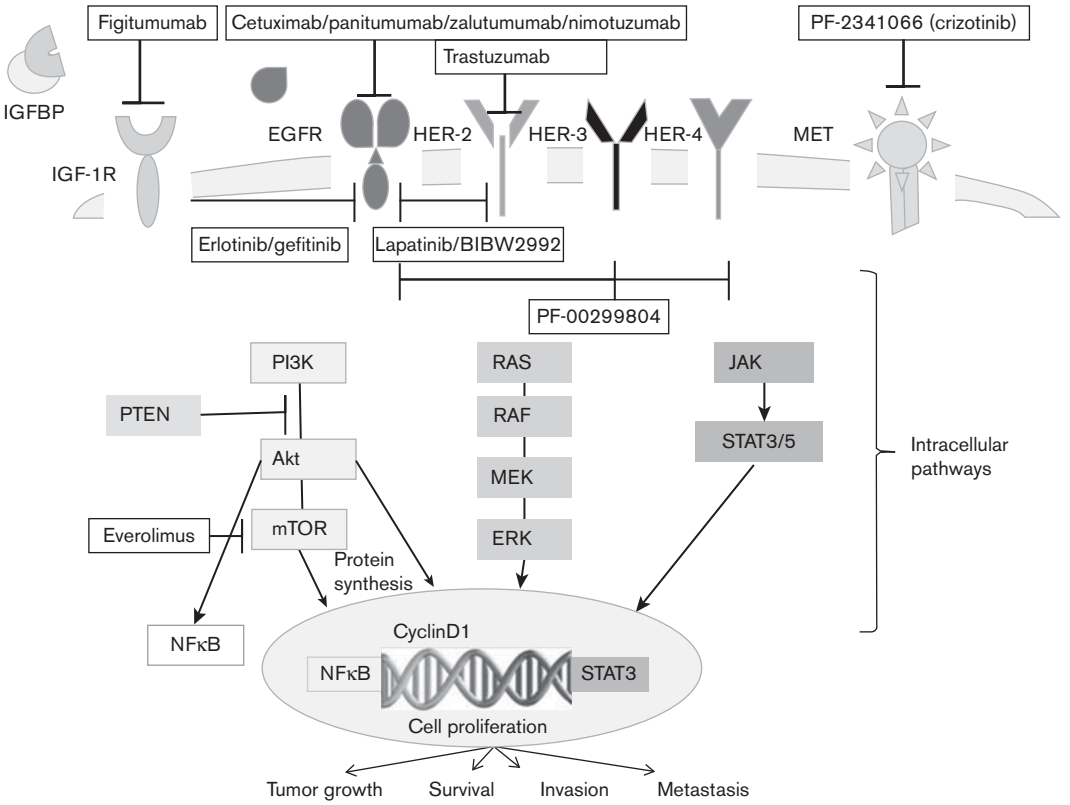
Fig. 1



Potential molecular targets for new agents. EGFR, epidermal growth factor receptor; ERK; extracellular signal-regulated protein kinase; HER; human epidermal growth factor receptor; IGFBP, insulin-like growth factor binding protein; IGF-1R; insulin-like growth factor-1 receptor; mTOR; mammalian target of rapamycin; PI3K; phosphatidylinositol-3-kinase.

with monoclonal antibodies (MoAbs) (Table 1). TKIs bind intracellularly to EGFR tyrosine kinase and inhibit phosphorylation and downstream signaling pathways. The two main compounds are erlotinib and gefitinib. The most studied MoAbs is cetuximab. Cetuximab is a chimeric IgG1 MoAb that specifically binds to the EGFR with high affinity, blocking ligand-induced EGFR phosphorylation. Panitumumab and zalutumumab are two completely humanized anti-EGFR MoAbs under development. Nimotuzumab is a humanized MoAbs with intermediate affinity for EGFR, which has some activity in some solid tumors with decreased EGFR phosphorylation but does induce skin rash as classically described with the other anti-EGFR agents [16].

Epidermal growth factor receptor inhibition in combination with radiation therapy

In irradiated cells, the EGFR is upregulated and can promote DNA repair and the arrest of cells in S phase leading to radio resistance [17–20]. Some EGFR inhibitors show synergism with radiotherapy in preclinical models [21]. On the basis of this background, cetuximab has been combined with radiation therapy in clinical trials. A phase I study [22] showed that cetuximab could be safely administrated in combination with radiotherapy in patients with SCCHN. The recommended dose is a loading dose of 400 mg/m^2 starting 1 week before radiotherapy and then a weekly maintenance dose of 250 mg/m^2 during radiation therapy. Bonner *et al.* conducted a phase III study that compared cetuximab plus radiotherapy versus radiotherapy alone. A significant improvement in locoregional control (median: 24.4 vs. 14.9 months) and OS (median 49 vs. 29.3 months) was found in favor of the cetuximab and radiotherapy association [11,12]. Remarkably, the frequency of grade 3 to 4 adverse events classically related to radiotherapy such as mucositis was not increased by the addition of cetuximab, except infusion reaction and acneiform rash linked to cetuximab administration. Since then, grade $^3/_4$ radiation dermatitis in patients treated with concurrent cetuximab has been described. A survey by the European Organisation for Research and Treatment of Cancer (EORTC) found that 49% of SCCHN patients treated with concomitant radiotherapy and cetuximab developed grade $^3/_4$ radiation dermatitis, which is more frequent than the rate observed with radiation therapy alone. Close monitoring of this complication is therefore recommended with interruption of cetuximab in case of early occurrence of grade $^3/_4$ radiation dermatitis [23].

Table 1 Selected randomized trials with anti-EGFR therapy in SCCHN

Regimens	*N*	ORR (%)	Median survival (months)	References
Radiotherapy + cetuximab versus	424	NA	49	Bonner *et al.* [11,12]
Radiotherapy[a]			29.3	
Cisplatin/5-FU/cetuximab versus	442	36	10.1	Vermorken *et al.* [2]
Cisplatin/5-FU[b]		20 $P<0.001$	7.4 $P=0.04$	
Methotrexate versus	486	3.9	6.7	Stewart *et al.* [13]
Gefitinib 250 versus		2.7	5.6	
Gefitinib 500[b]		7.6	6	
Best supportive care or methotrexate versus	286	1.1	5.2	Machiels *et al.* [14]
Zalutumumab[b]		6.3	6.7	
Docetaxel/placebo versus	270	6	6	Argiris *et al.* [15]
Docetaxel/gefitinib[b]		14	6.8	
Cisplatin/5-FU/ panitumumab versus	658	36	11.1	Amgen Press Release, August 11th, 2010
Cisplatin/5-FU[b]		25	9	

EGFR, epidermal growth factor receptor; 5-FU, 5-Fluorouracil; NA, Non applicable; ORR, overall response rate; SCCHN, squamous cell carcinoma of the head and neck.
[a]Locoregionally advanced SCCHN: primary treatment.
[b]Recurrent or metastatic SCCHN.

On the basis of the hypothesis that anti-EGFR MoAbs and chemotherapy could act additively to radio-sensitize tumors, trials combining radiotherapy, chemotherapy, and anti-EGFR MoAbs have been initiated. Pfister *et al.* tested the association of concomitant boost radiotherapy (1.8 Gy/days, weeks 1–6; boost: 1.6 Gy 4–6 h later weeks 5–6; total dose: 70 Gy) with cisplatin (100 mg/m^2 intravenously, weeks 1 and 4) and cetuximab (400 mg/m^2 intravenously, week 1, followed by 250 mg/m^2, weeks 2–10). They found an encouraging long-term survival (76% at 3 years) with this triple combination although significant toxicities were observed with two deaths, two grade 4 cardiac toxicities and one bacteremia [24]. The Eastern Cooperative oncology group investigated conventional radiotherapy (70 Gy) with concomitant cisplatin (75 mg/m^2, three times) and cetuximab (Eastern Cooperative oncology group 3303). The regimen was found feasible in fit patients, even if 97% of the patients experienced grade of at least 3 toxicity with 54% mucositis and 26% neutropenia [25]. Recently, a phase I study established the safety of weekly cisplatin (40 mg/m^2 per week) with cetuximab and hyperfractionated–accelerated radiotherapy [26]. Panitumumab, carboplatin, and paclitaxel in combination with intensity-modulated radiotherapy for stage III-IVB SCCHN was also investigated in a phase I trial with an interesting preliminary activity [27].

The results of these phase I/II trials may suggest a benefit of adding anti-EGFR to chemoradiation. To validate this hypothesis, phase III studies comparing chemoradiation versus chemoradiation with the addition of an anti-EGFR MoAbs (cetuximab, panitumumab or zalutumumab) in the primary curative treatment for locally advanced SCCHN or in the postoperative setting for high-risk patients who were resected are currently planned or ongoing. The Radiotherapy Therapy Oncology Group phase III study (0522-NCT00265941) that added cetuximab to chemoradiation according to the Pfister regimen has recently completed accrual and the results of this trial will give important information regarding the potential benefit of this approach.

TKIs, mainly gefitinib, have been also combined with radiotherapy or chemoradiation in phaseI/II trials [28,29]. In a randomized phase II trial, gefitinib has also been combined with cisplatin and radiation therapy in stage III–IV, untreated, unresected, and nonmetastatic patients with SCCHN. In this study, gefinitib did not significantly improve the local control rate compared with placebo when given concomitantly with chemoradiotherapy or when given as maintenance therapy alone (Gregoire and Raben, oral communication International Conference on Innovative Approaches in Head and Neck Oncology Barcelona 2009).

Epidermal growth factor receptor inhibition in combination with neoadjuvant chemotherapy

Induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (5-FU; TPF) improves OS compared with induction with cisplatin and 5-FU. A phase I study investigated the feasibility of combining TPF [cisplatin (100 mg/m^2), docetaxel (75 mg/m^2), and 5-FU (three dose levels: 700, 850, and 1000 mg/m^2 per day)] for 4 days with cetuximab (400 mg/m^2 as initial dose followed by 250 mg/m^2 per week; C-TPF) [30]. Dose-limiting toxicities, mainly gastro-intestinal (mucositis, enteritis, and diarrhea), were observed with 5-FU (1000/mg/m^2) and the recommended dose for further investigation was C-TPF with 5-FU (850 mg/m^2). Mesia *et al.* [31] also combined TPF [cisplatin (75 mg/m^2), docetaxel (75 mg/m^2), and 5-FU (750 mg/m^2 per day) for 5 days] with cetuximab (250 mg/m^2/weekly). Objective response rate (ORR) was 70% after four cycles. Serious grade $^3/_4$ adverse events were: neutropenia 24%, neutropenic fever 20%, and diarrhea 12%. There were two adverse event-related deaths (febrile neutropenia and hepatic insufficiency) suggesting that this regimen could potentially induce substantial toxicities and need to be reserved to fit patients under specialized care.

Induction chemotherapy with carboplatin, paclitaxel, and cetuximab was investigated in two studies [32,33]. Kies *et al.* included unresectable and resectable SCCHN (stage IVA or IVB SCCHN and nodal staging of N2b/c or N3), whereas Wanebo *et al.* included only resectable disease (Stage III/IV). This regimen was found feasible with clinical complete response after induction chemotherapy observed in 19 and 59%, respectively.

Epidermal growth factor receptor inhibition as maintenance therapy

Maintenance (adjuvant) therapy consists of starting or continuing a targeted agent after the radical treatment. Preclinical study in mouse models suggested that cetuximab enhanced the efficacy of fractionated radiation and that the effect was greater if administration was extended beyond the end of radiotherapy [34]. Different clinical studies with anti-EGFR inhibitors have shown the safety of this approach [25,35,36]. Two-year, progression-free-survival (PFS) was 70% in 39 stage III/IVA-B patients receiving cisplatin/docetaxel/cetuximab as induction therapy followed by cisplatin/cetuximab/radiotherapy and continuing cetuximab for a maximum of 6 months [36]. A prospective, randomized multicenter phase II trial investigated the efficacy and safety of cetuximab maintenance therapy given during 12 weeks after radiation therapy with concomitant cetuximab in patients with stage III/IV oropharyngeal cancer [37]. At 1 year, locoregional control (60.5 vs. 58.6%) and OS (87 vs. 75.6%) were in favor of the maintenance group. Phase III trials are planned or ongoing with different compounds.

Epidermal growth factor receptor inhibition in combination with palliative chemotherapy

Cetuximab and panitumumab have been investigated as a first-line treatment in patients with incurable recurrent or metastatic disease in combination with chemotherapy (Table 1). Vermorken *et al.* [2] (EXTREME trial) showed that the addition of cetuximab to 5-FU and platinum-based therapy prolonged the OS and PFS in this setting. The median OS was prolonged by 36.5% (10.1 vs. 7.4 months) and the median PFS by 70% (5.6 vs. 3.3 months). Panitumumab in combination with cisplatin and 5-FU was investigated in a large phase III trial in the same indication using a similar study design. OS was not significantly improved by the addition of panitumumab to chemotherapy (9 vs. 11.1 months; Amgen, press release, August 11 2010).

Cetuximab has been evaluated as monotherapy or in combination with chemotherapy in cisplatin refractory patients [38–40]. ORR was approximately 10%, but it is not clear whether this was because of the reversal of platinum resistance or the action of cetuximab alone because the ORR remained similar regardless of whether cetuximab was used alone or in combination with cisplatin. In patients who failed platinum-based therapies earlier, efficacy data pooled from three prospective phase II studies ($n = 278$ patients), that administered cetuximab as a single agent ($n = 103$ patients) or combined with a platinum compound, were compared with the results from a retrospective study of patients who received various second-line treatments. Median OS of the patients treated with cetuximab ranged between 5.2 and 6.1 months and compared favorably with those from the retrospective studies: 3.4 months ($n = 151$, best supportive care only) and 3.6 months ($n = 43$, patients treated with chemotherapy) [40]. These data suggested that cetuximab has the potential to increase OS after platinum failure and led to the approval of cetuximab monotherapy in this indication by the Food and Drug Administration, despite no prospective randomized trial in this indication. In this context, Machiels *et al.* tested zalutumumab, another anti-EGFR MoAbs, in patients with noncurable SCCHN in disease progression after platinum-based therapy. The patients were randomized between zalutumumab monotherapy and best supportive care or methotrexate. The primary endpoint of the trial was the OS. Although a median OS of 6.7 months was observed in the zalutumumab group compared with 5.2 months in the best supportive care group, the difference was not statistically significant ($P = 0.065$) despite a significant improvement in PFS ($P = 0.001$) [14].

Phase II trials have shown an ORR of between 0 and 15% in palliative patients with TKIs such as gefitinib, lapatinib, and erlotinib [41]. Gefitinib has also been investigated in two phase III trials in palliative patients but did not show any relevant clinical activity [13,15]. The first study randomized 486 patients between gefitinib (250 or 500 mg/day) and methotrexate [13]. Gefitinib did not improve the OS compared with methotrexate: median OS 5.6 months for gefitinib (250 mg/day), 6.0 months for gefitinib (500 mg/day), and 6.7 months for the methotrexate group. Disappointing results were also observed in the second trial that compared docetaxel plus gefitinib versus docetaxel plus placebo: median OS 6.8 and 6 months, respectively [15].

Dual (HER-1/HER-2) or pan-HER inhibitors

ErbB-2/HER-2-neu, ErbB-3/HER-3, and ErbB-4/HER-4 are other members of the HER tyrosine kinase receptor family. Possible mechanisms of primary or acquired resistance to anti-EGFR MoAbs or TKIs may be because of the transactivation of the EGFR intracellular tyrosine kinase by other HER receptors such as HER-2 or HER-3 or because of the presence of the EGFR variant III [42]. On the basis of this background, dual or pan-HER TKIs that block more than one HER receptor have been developed. Lapatinib is an oral small molecule that acts as a reversible inhibitor of both the EGFR and HER-2 tyrosine kinases. In a phase II trial, lapatinib showed limited activity in recurrent palliative patients with no objective response and 37% of stable disease [43]. A randomized phase II trial compared lapatinib (1500 mg/day) or placebo with concurrent chemoradiation followed by maintenance therapy with lapatinib or placebo [44]. Complete response rate at 6 months post chemoradiation was 53% with lapatinib versus 36% with placebo suggesting a benefit of this approach. Larger phase III trials with lapatinib are ongoing. TPF has also been investigated in association with lapatinib in a phase 1 trial [45]. However, dose-limiting toxicities (nephrotoxicity,

dehydration, diarrhea) were observed at the first dose level suggesting that lapatinib should not be combined with TPF.

BIBW 2992 (afatinib) is an orally bioavailable irreversible inhibitor of both EGFR and HER-2 kinases. Irreversible tyrosine kinase blockade may result in longer suppression of EGFR/HER-2 signaling than the one obtained with reversible inhibitors. This could increase the treatment activity [46]. The preliminary results of a randomized phase II study of BIBW 2992 versus cetuximab in patients with metastatic or recurrent SCCHN after failure of platinum-containing therapy were recently reported [47]. Patients were randomized to receive 50 mg of BIBW 2992 daily or cetuximab 400 mg/m^2 (loading) and 250 mg/m^2 thereafter until disease progression or unacceptable toxicities. Crossover to the opposite treatment was allowed after disease progression. Preliminary efficacy analysis on the first 34 evaluated patients suggested that BIBW 2992 (partial response 18% and stable disease 53%) was active in the patients with metastatic or recurrent SCCHN and compared favorably with the patients receiving cetuximab. Both drugs showed a comparable safety profile. Phase III trials with BIBW 2992 in SCCHN were planned.

Pan-HER tyrosine kinase inhibitors, which may inhibit the different HER receptors, have shown preclinical activity in SCCHN [48]. PF-00299804 is an irreversible and potent small molecule pan-HER tyrosine kinase inhibitor that showed interesting preliminary activity in SCCHN. In a phase II trial, 35 patients with no earlier treatment for recurrent SCCHN were treated with PF-00299804 [49]. Two (7%) patients had a partial response and 18 patients (64%) had stable disease with a median PFS of 3.1 month and 6-month progression-free rate of 24%.

The MET receptor

The MET activation stimulates downstream molecular pathways implicated in the tumor growth, metastasis, and angiogenesis. Knowles *et al.* [50] reported that approximately 80% of primary SCCHN tumors express hepatocyte growth factor (HGF), MET, or both. MET mutations and increased MET gene copy number have been also detected in 13.5 and 13% SSCHN tumors, respectively [51].

Different approaches are currently being developed to inhibit the HGF/MET pathway and include MoAbs, which target either MET, or HGF and small molecule tyrosine kinase inhibitors. Recently, Knowles *et al.* [50] showed that PF-2341066 (crizotinib), a MET TKI, could delay the SCCHN tumor growth in a preclinical animal model. The EGFR shares common molecular pathways with MET [52] and it is postulated that the HGF/MET pathway may cross activate downstream the EGFR signaling pathways, bypassing the EGFR inhibition by MoAbs or TKIs. All these data support the investigation of MET inhibitors in SCCHN in monotherapy or in combination with anti-EGFR.

Insulin-like growth factor-1 receptor

The insulin-like growth factor-1 receptor (IGF-1R) is a transmembrane heterotetramer receptor that consists of two α and two β subunits. After ligand binding to IGF-1R (IGF-1 and IGF-2), the PI3K/AKT/mTOR and the Ras/Raf/mitogen-activated protein kinase pathways can be activated. The IGF-1R plays an important role in cellular growth and protects against cancer cell apoptosis but also leads to cell proliferation, cell differentiation, and tumor invasion [53]. Jun *et al.* [54] concluded that IGF-1R expression explored by immunochemistry is frequent in SCCHN and is correlated with poor survival in advanced-stage patients. These studies suggest that the IGF-1R is an interesting therapeutic target for the cancer treatment.

Schmitz *et al.* [55] tested figitumumab, a fully human MoAb IgG2 subtype that specifically binds to the IGF-1R, in palliative SCCHN patients. They found that figitumumab monotherapy has no clinically relevant activity. The most frequently observed toxicity was grade 3–4 hyperglycemia (41%). The MoAb, IMC-A12 is currently undergoing clinical testing in SCCHN. In a phase II trial, IMC-A12 is being evaluated as a single agent and also in combination with cetuximab in patients with recurrent or metastatic SCCHN (NTC00617734).

Phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin pathway inhibitors

The PI3K/AKT/mammalian target of rapamycin (mTOR) pathway can be activated indirectly through the activation of upstream tyrosine kinase receptors (EGFR, IGF-1-R, etc) or directly through several genetic alterations such as PTEN loss or activating mutation or gene amplification of PIK3CA or AKT1 [56]. In SCCHN, PI3K/AKT/mTOR pathway activation is found in approximately 50% of cases [57–59]. Amplification of the chromosome 3q26, which amplifies among others PIK3CA, is frequently observed and is associated with tumor progression and poor prognosis [57]. PI3KCA activating mutations have also been described in approximately 10% of cases [58]. Although alterations of PTEN seem to be rare in SCCHN, downregulation of the PTEN protein has been described suggesting a potential oncogenic role that required further investigation [59].

The patients with downregulation of PTEN detected by immunochemistry had tumor regression when challenged with drugs targeting the PI3K/AKT/mTOR pathway, as found in phase I protocols that included, among others, SCCHN patients [60]. Similarly, patients with PI3KCA mutations (exon 9 or exon 20) seemed also to benefit from these inhibitors [61]. Further investigations in SCCHN are warranted.

mTOR is a serine/threonine protein kinase, which regulates the cell growth, cell proliferation, cell motility, protein synthesis, and transcription [62]. Everolimus is worthy of

investigation in SCCHN because of the frequent activation of this molecular pathway and clinical trials are testing this agent in the palliative setting as monotherapy (NCT010 51791), in association with cetuximab and cisplatin (NCT0 1009346) or in association with erlotinib (NCT00942734). Trials with curative intent are also ongoing in which everolimus is being tested in combination with cisplatin and radiotherapy (NCT00858663, NCT01058408) or in combination with cisplatin and docetaxel as induction therapy (NCT00935961).

Angiogenesis inhibitors

Angiogenesis is required for the tumor growth and the metastatic spread. The majority of SCCHN overexpresses the vascular endothelial growth factor (VEGF) or the VEGF-2 and VEGF-3 receptors, making angiogenesis inhibition an attractive treatment target [63,64]. A meta analysis involving 1002 patients showed that VEGF tumor overexpression evaluated by immunohistochemistry was associated with a decreased survival [65].

Many ongoing studies are investigating angiogenesis inhibitors in SCCHN in combination modalities or alone. The most clinical advanced tyrosine kinase inhibitors are sorafenib and sunitinib, which inhibits multiple tyrosine kinase receptors including the VEGFR-2 and VEGFR-3 receptors and the platelet-derived growth factor receptor-β. Sorafenib has been evaluated in two trials with modest clinical results. The first trial included patients with nasopharyngeal cancers and SCCHN. Stable disease was recorded in 10 out of 26 (37%) patients [66]. In the second study, only one patient (3%) had a confirmed partial response but the median PFS (4 months) and the median OS (9 months) were encouraging [67].

Machiels *et al.* [68] investigated sunitinib in a phase II trial in patients with recurrent or metastatic SCCHN progressing after platin-based therapy. A limited activity was found with 19 (50%) patients who achieved a stable disease at 6–8 weeks with some degree of tumor shrinkage recorded in 12 of these 19 patients. The median PFS and OS were low: 2 and 3.4 months, respectively. In addition, important complications were observed with high incidence (16%) of grade 3–5 bleeds. Local complications defined as apparition or worsening of tumor skin ulceration or tumor fistula were also recorded in 41% of the patients.

Bevacizumab, an anti-VEGF MoAb, has not been evaluated in monotherapy. Erlotinib and bevacizumab were combined in a phase I/II study in SCCHN patients. This association was well tolerated with promising results: ORR 15%, median OS 7.1 months, and median PFS 4.1 months [69].

Conclusion

Cetuximab improves OS when combined with radiation therapy or chemotherapy. Other anti-EGFR MoAbs have shown promising activities. Novels agents targeting different molecular pathways in SCCHN are currently under development (EGFR/HER-2, pan-HER, IGF1-R, MET, angiogenesis inhibitors) and have the potential to improve the outcome. However, only a minority of patients seems to benefit from these new approaches. Understanding the primary and acquired resistance mechanisms is of crucial importance to allow a better patient selection.

Regarding anti-EGFR MoAbs, in contrast to colon cancer in which K-ras mutations predict the treatment resistance, little is known about predictive parameters of treatment resistance or efficacy in SCCHN [70]. EGFR variant III, which lacks the ligand-binding domain, occurs in up to 40% of SCCHN and confers resistance to EGFR-targeted MoAbs in preclinical models [42]. However, the clinical implications of the presence of EGFR variant III have not been studied in prospective clinical trials. Another potential reason for EGFR inhibitor resistance may be the activation of downstream signaling EGFR molecular pathways (Ras/Raf/mitogen-activated protein kinase and PI3-K/AKT/mTOR) induced, for example, by RAS-activating mutations or PTEN alteration or PI3-K-activating mutations, or by other tyrosine kinase receptors such as MET or IGF-1 receptors bypassing, therefore, the EGFR inhibition [71]. Translational research linked to well-designed clinical trials is needed to better approach these mechanisms and to improve our understanding of response or nonresponse to the anti-EGFR therapy or other targeted therapies.

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