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Review

Molecular targeted therapy of head and neck cancer: Review and clinical development challenges

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ABSTRACT

Recently, new targets have been identified in head and neck squamous cell carcinomas (HNSCC) as playing key roles in tumour proliferation and metastases. The first target that has led to the approval of a molecularly based therapy in HNSCC has been the epidermal growth factor receptor (EGFR). Indeed, cetuximab, a monoclonal antibody directed against EGFR, has recently been approved in combination with radiation therapy in patients with locally advanced HNSCC, and in patients with platinum-refractory recurrent or metastatic (R/M) HNSCC. This review discusses novel targeted anticancer agents that do not exclusively target EGFR. The initial assessments of novel agents have typically been in patients with heavily pre-treated R/M HNSCC, with response rates and times to progression that are often disappointing. Evaluation of novel agents in the pre-operative 'window' setting, or as first-line therapy for R/M disease, may offer a more optimal understanding of their molecular and clinical effects.

1. Introduction

More than 500,000 new patients with head and neck squamous cell carcinomas (HNSCC) are diagnosed each year worldwide. Patients who relapse after primary therapy for locoregional disease and those who present with distant metastases have limited prognosis. New antitumour agents are highly needed, particularly for overcoming resistance that occurs with failures of primary therapy. In 2006, the United States Food and Drug Administration (FDA) announced the approval of a chimeric monoclonal antibody against the epidermal growth factor receptor (EGFR), cetuximab (Erbitux®), for use in combination with radiation therapy in patients with locally advanced (LA) HNSCC.[1] Furthermore, the addition of cetuximab to cisplatin as first-line therapy in patients with recurrent or metastatic (R/M) HNSCC has significantly improved the overall response rate when compared to cisplatin alone.[2] Phase II data of cetuximab given as monotherapy in R/M HNSCC patients who have progressed on platinum-based therapy have demonstrated an overall response rate of 13% and a median survival of about 6 months.[3] Based on these results, the FDA has also approved cetuximab monotherapy use for this indication in R/M HNSCC.

The use of EGFR inhibitors in HNSCC has recently been reviewed in the literature.[4] New targets besides EGFR have been identified in HNSCC as playing key roles in tumour proliferation and metastases (Fig. 1). This review will discuss novel targeted agents that do not exclusively target EGFR, as well as

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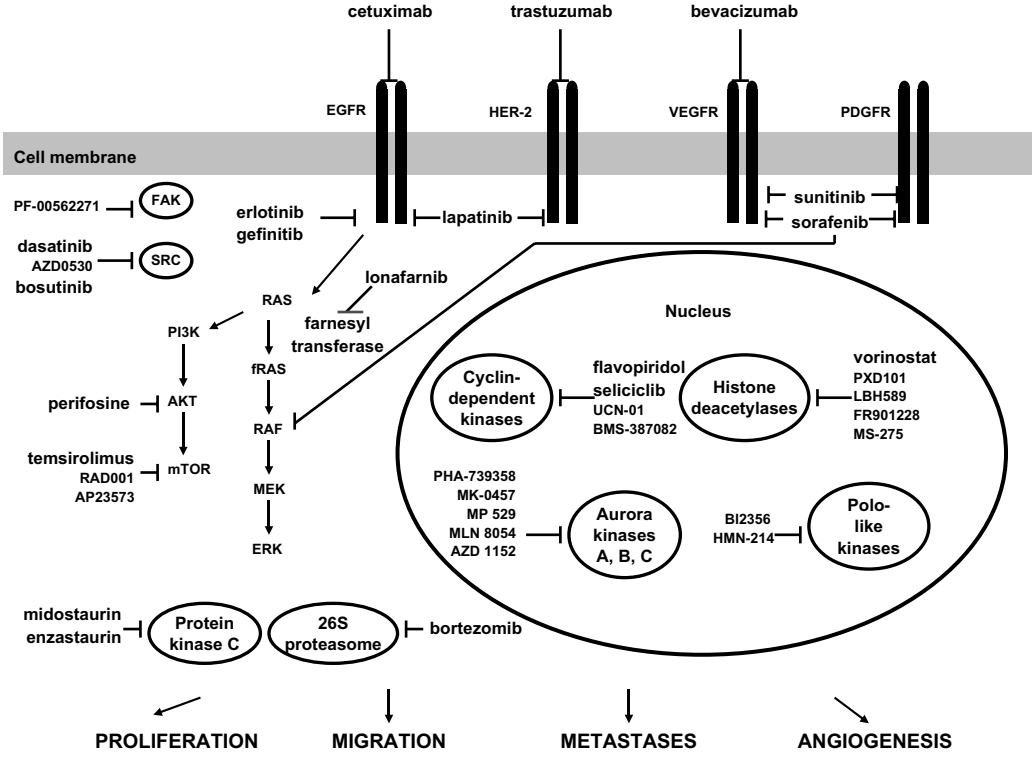

Fig. 1 – Selected signalling pathways and targets involved in head and neck cancer and their corresponding targeted anticancer agents.

some of the challenges of new drug development in this disease site.

2. Monoclonal antibodies

2.1. *Bevacizumab*

Bevacizumab is an antiangiogenic monoclonal antibody directed against the vascular endothelial growth factor (VEGF). VEGF expression has been demonstrated to be highly correlated with prognosis in patients with HNSCC.[5] It has been demonstrated that EGFR activation can upregulate VEGF, and this phenomenon can be correlated with resistance to antiEGFR agents.[6] Therefore, Vokes and colleagues conducted a phase I/II study of bevacizumab in combination with erlotinib, an EGFR small molecule receptor tyrosine kinase inhibitor, in 51 patients with R/M HNSCC.[7] Most common adverse events were rash, fatigue and diarrhoea. There were three severe adverse events related to bleeding, one of which was fatal. At the recommended dose of 15 mg/kg of bevacizumab every 3 weeks and 150 mg of erlotinib daily, two patients (4%) out of 48 had complete response and 5 (10%) had partial response (Table 1). Median progression-free survival and overall survival were 4 months and 7 months, respectively. More favourable outcome was seen among those receiving the study regimen as first-line therapy. Serum VEGF and TGF-α levels did not correlate with clinical outcome. Among patients with prior therapy for R/M HNSCC, the results are similar to those obtained with erlotinib alone. Bevacizumab is currently being studied in a phase II trial in combination with cetuximab in R/M HNSCC.[8] Karamouzis and colleagues performed a phase II trial of pemetrexed and bevacizumab without platinum compounds in the R/M setting.[9] At interim analysis, 14 patients received pemetrexed 500 mg/m^2 and bevacizumab 15 mg/kg every 3 weeks. Five patients had haemorrhagic events, two of which were grade 3 in intensity. Among 11 evaluable patients, two (18%) had complete response and three (27%) had partial response. Median progression-free survival was 6 months. Given these interesting preliminary results in comparison to historical controls, study accrual continues. Nevertheless, attention should be focused on vascular complications to ultimately determine the therapeutic index of this regimen.

Bevacizumab has been demonstrated *in vitro* to potentiate the efficacy of radiation.[10] Savvides and colleagues recently presented preliminary results of a phase II trial in which 12 untreated patients with stage IV LA HNSCC received standard radiation in combination with weekly concurrent docetaxel, along with biweekly bevacizumab during and for up to 1 year following radiation.[11] Interestingly, nine of the ten patients who completed concurrent chemoradiation had a complete response, suggesting a high efficacy of this combination. In addition, the University of Chicago conducted a 2:1 randomised phase II trial of concomitant chemoradiation with 5-fluorouracil and hydroxyurea with or without bevacizumab in intermediate stage HNSCC.[12] At interim analysis, 25 patients with stage II to IVA disease had been enrolled. An increased vascular complication rate of 19% was observed in the bevacizumab arm. High pathological complete response rates documented on biopsy were observed in both arms. Surprisingly, four of the five patients with stage IVA disease in the experimental arm developed recurrence within 2 years. Thus, the study is currently on hold pending analysis.

Table 1 – Antitumour activity of selected targeted agents in head and neck cancer currently in phase II development

Compound	Main identified molecular target(s)	Tumour type and treatment setting	*n*	Antitumour activity
Monoclonal antibodies				
Bevacizumab (*Avastin*®)	VEGF	First- or second-line R/M HNSCC in combination with erlotinib[7]	51	CR = 4%; PR = 10%; SD = 56%; PFS = 4 mo; OS = 7 mo
		First-line R/M HNSCC in combination with pemetrexed[9]	14	CR = 18%; PR = 27%; SD = 54%; PFS = 6 mo
		Locally advanced stage IV HNSCC in combination with RT and docetaxel[11]	12	CR = 90%; PR = 0%
		Locally advanced stage II to IVA HNSCC in combination with RT and 5-fluorouracil and hydroxyurea[12]	25	Without bevacizumab: CR = 100% With bevacizumab: CR = 92%
Trastuzumab (Herceptin®)	HER-2	R/M HNSCC in combination with cisplatin and paclitaxel[14]	61	ORR = 36%; TTP = 4.3 mo
Receptor tyrosine kinase inhibitors				
Lapatinib (*Tykerb*®)	EGFR, HER-2	R/M HNSCC with (A) or without (B) prior EGFR inhibitor[19]	42	A: SD = 37%; TTP = 1.6 mo B: SD = 20%; TTP = 1.7 mo
		Locally advanced HNSCC in combination with RT and cisplatin[20]	19	CR = 74%; PR = 26%
Sorafenib (*Nexavar*®)	VEGFR, PDGFR, KIT, RET, RAF	First-line R/M HNSCC[27]	44	PR = 3%; SD = 45%; TTP = 4 mo; OS = 8 mo
		R/M HNSCC or NPC after first-line treatment failure[28]	28	PR = 4%; SD = 37%; TTP = 2 mo; OS = 4 mo
Intracytoplasmic proteins inhibitors				
Lonafarnib (Serasar®)	Farnesyl transferase	Locally advanced HNSCC after platinum failure[45]	15	ORR = 0%; SD = 53%; TTP = 2 mo
Perifosine	AKT, PKB	First- or second-line R/M HNSCC[36]	19	SD = 5%; TTP = 1.7 mo; OS = 5.5 mo
Nuclear proteins inhibitors				
Vorinostat	Histone deacetylase	Second- and third-line R/M HNSCC[94]	13	ORR = 0%; SD = 40%

HNSCC: Head and neck squamous cell carcinoma; ORR: overall response rate; CR: complete response; PR: partial response; SD: stable disease; TTP: time to progression; OS: overall survival; PFS: progression-free survival; RT: radiation therapy; mo: month(s); R/M: recurrent or metastatic; PKB: Protein Kinase B.

2.2. *Trastuzumab*

Trastuzumab is a monoclonal antibody directed against HER-2 and has been approved in HER-2-overexpressing breast cancer. Overexpression of HER-2 as quantitated by membranous staining on immunohistochemical examination is seen in about 15–20% of patients with HNSCC.[13] Trastuzumab has been studied in combination with paclitaxel and cisplatin in 61 patients with R/M HNSCC.[14] HER-2 expression, as indicated by membrane staining of $\geqslant$10% of cells by immunohistochemistry, was rare (7%), and no amplification by fluorescent *in situ* hybridisation was observed. Trastuzumab did not appear to add adverse events to those typically observed with paclitaxel and cisplatin. Partial responses were reported in 36% of patients (Table 1). Median time to progression was 4.3 months. HER-2 expression did not correlate with clinical response. In this patient population, trastuzumab does not seem to improve response, likely due to the rarity of HER-2 expression and gene amplification. The inhibition of HER-2 alone appears insufficient in HNSCC, or at least in those unselected for HER-2 overexpression or gene amplification.

3. Receptor tyrosine kinase inhibitors

Receptor tyrosine kinase inhibitors that are in clinical development in HNSCC include non-antiangiogenic molecules that target both tumour cell EGFR and HER-2, and molecules that have antiangiogenic properties by targeting VEGFR on endothelial cells and/or platelet-derived growth factor receptor (PDGFR) on pericytes. Little has been published on the prognostic relevance of PDGF, but high amounts of both VEGF and PDGF are found in the supernatant of primary HNSCC cultures.[15]

3.1. *Non-antiangiogenic receptor tyrosine kinase inhibitors*

EGFR expression occurs in up to 90% of HNSCC. EGFR expression is associated with poor prognosis and resistance of HNSCC to therapy.[4,5,16] HER-2 is the preferred dimerisation partner of EGFR. EGFR/HER-2 heterodimers may potentiate receptor signalling and resistance to EGFR inhibitors.[17] Therefore, molecules that target both EGFR and HER-2 have been studied in HNSCC.

3.1.1. *Lapatinib*

Lapatinib is a dual EGFR and HER-2 receptor tyrosine kinase inhibitor that has demonstrated promising preclinical activity in HNSCC models.[18] Abidoye and colleagues performed a phase II trial that enrolled 42 patients with R/M HNSCC into two cohorts: 27 without (arm A) and 15 with (arm B) prior exposure to an EGFR inhibitor, respectively.[19] All subjects were treated with lapatinib 1500 mg daily per os. Diarrhoea was the most frequent adverse event, occurring in 40% of patients. No objective responses were observed in either arm (Table 1). Stable disease was the best response observed in 37% of arm A and 20% of arm B subjects. Lapatinib as a single agent appears to have no significant antitumour activity in either EGFR inhibitor-naïve or -refractory patients with R/M HNSCC.

Despite the lack of single agent activity in R/M HNSCC, the exploration of lapatinib in combination with radiotherapy as primary therapy has yielded interesting results. Bourhis and colleagues performed a phase I trial of lapatinib in combination with standard fractionation radiation therapy and full dose concurrent cisplatin (100 mg/m^2 days 1, 22 and 43) in 19 patients with LA HNSCC.[20] No dose-limiting toxicity was observed using lapatinib at 1500 mg daily. Fourteen patients (74%) achieved complete responses and five (26%) achieved partial responses. Given these encouraging results, a phase II trial of this regimen is ongoing.

3.1.2. *Other non-antiangiogenic receptor tyrosine kinase inhibitors*

There are other dual EGFR/HER-2 inhibitors currently in phase I clinical development. BIBW 2992 and ARRY-543 are two such compounds undergoing phase I evaluations in advanced solid tumours.[21–24] Their phase II development may involve R/M HNSCC, although in light of existent negative data with lapatinib and trastuzumab in this patient population, an alternative strategy or patient selection may be more desirable.

3.2. *Antiangiogenic receptor tyrosine kinase inhibitors*

3.2.1. *Sorafenib*

Sorafenib is a multi-targeted agent that inhibits VEGFR, RAF and other kinases. In xenograft models, sorafenib has demonstrated inhibition of ERK phosphorylation, reduction of microvessel density and induction of apoptosis.[25,26] Williamson and colleagues performed a phase II trial of sorafenib 400 mg bid in 44 patients who were chemotherapy naïve for their R/M HNSCC.[27] Most common adverse events were fatigue, mucositis, nausea, hypertension, rash and hand–foot syndrome. Grade 3 or 4 toxicity was rare. One patient (3%) had partial response and 14 patients (45%) had stable disease (Table 1). Median time to progression and overall survival were 4 months and 8 months, respectively.

Sorafenib has also been studied in first- or second-line treatment at the same dosage in 28 patients with R/M HNSCC or nasopharyngeal carcinoma, which reported similar toxicities.[28] About 70% of patients had received prior chemotherapy, and 52% of patients received sorafenib as their first-line regimen for recurrent or metastatic disease. One patient (4%) had partial response and 10 patients (37%) had stable disease. Median time to progression and overall survival were 2 months and 4 months, respectively. Given the prior chemotherapy exposure of most of the patients, the efficacy results of sofarenib in this study are not surprisingly worse than those obtained by Williamson and colleagues.

Based on these results, sorafenib as a single agent in heavily pretreated patients with R/M HNSCC does not demonstrate sufficient antitumour activity. Its use in first-line therapy for recurrence seems more satisfactory, and the exploration of its combination with chemoradiotherapy may be warranted.

3.2.2. *Other antiangiogenic receptor tyrosine kinase inhibitors*

Other multi-targeted agents that have antiangiogenic and antitumour properties have entered clinical development. The University of Chicago is conducting a phase II study in R/M HNSCC with sunitinib,[29] a multi-kinase antiangiogenic agent. Several other multi-targeted agents have entered early clinical development, such as vatalanib (PTK787), axitinib (AG-013736), vandetanib (ZD6474), pazopanib (GW786034), brivanib (BMS-582664), AZD2171, AEE788, BIBF1120, BAY-579352, AMG706, CHIR-258, XL820 and XL999, and some may eventually be studied in HNSCC. AZD2171 is currently being studied in a phase I trial in combination with gefitinib, an EGFR small molecule receptor tyrosine kinase inhibitor, in HNSCC and non-small cell lung cancer.[30] In addition, vandetanib is currently being studied in combination with docetaxel in patients with LA or metastatic HNSCC,[31] as well as in combination with radiation alone or chemoradiation with weekly cisplatin.[32]

4. Intracytoplasmic proteins inhibitors

4.1. *AKT inhibitors*

Preclinical studies have demonstrated that AKT inhibition induces apoptosis and anoikis in HNSCC.[31] The PI3K/AKT/mTOR pathway is activated in 57–81% of patients with HNSCC, and AKT is usually upregulated.[33] In addition, loss of PTEN expression and AKT activation have been associated with worse clinical outcome in tongue squamous cell cancers.[34,35] Argiris and colleagues performed a phase II trial with perifosine, an oral alkylphospholipid that inhibits AKT phophorylation, in 19 patients with R/M HNSCC.[36] Most common adverse events were fatigue and gastrointestinal symptoms. No objective responses were observed (Table 1). As a single agent, perifosine does not demonstrate any antitumour activity in HNSCC. However, since AKT activation is a possible mechanism of resistance to EGFR blockade,[37] the combination of AKT inhibitors with antiEGFR agents would be of potential interest.

4.2. *Mammalian target of rapamycin inhibitors*

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that regulates cell growth, proliferation and apoptosis through modulation of cell cycle progression, cap-dependent translation and ribosomal function.[38] Rapamycin, an mTOR inhibitor, has been demonstrated to have antiproliferative effects on HNSCC cell lines.[39] In HNSCC xenografts, rapamycin targets DNA synthesis, induces apoptosis and results in tumour regression.[40] Several mTOR inhibitors are in

clinical development, including sirolimus (rapamycin), temsirolimus (CCI-779), everolimus (RAD001), and AP23573. In a phase I trial of temsirolimus, dose-limiting toxicity appeared to be mainly thrombocytopaenia.[41] Other class-related toxicities of mTOR inhibitors included asthenia, skin toxicity, stomatitis, hyperglycaemia, hyperlipidemia and interstitial pneumonitis. Buck and colleagues demonstrated, in multiple xenograft models, synergistic activity with rapamycin and erlotinib.[42] Hence, disease-specific evaluation of mTOR inhibitors in HNSCC would be of interest, especially in combination with EGFR inhibitors.

4.3. *Farnesyl transferase inhibitors*

Farnesyl transferase inhibitors block farnesylation of a wide range of proteins, including Ras, ultimately resulting in cell growth arrest. [43] In preclinical models, farnesyl transferase inhibitors showed great potency against HNSCC cells.[44] Yang and colleagues performed a phase II trial of lonafarnib, a novel tricyclic peptidomimetic compound that specifically inhibits farnesyl protein transferase, in 15 patients with cisplatin-refractory R/M HNSCC.[45] The most common adverse events were diarrhoea, nausea and fatigue. No objective response was observed (Table 1). The activity of lonafarnib as a single agent appears minimal in pretreated patients with R/M HNSCC. However, as preclinical data have suggested that blockade of farnesyl transferase may potentiate EGFR inhibition in HNSCC cells, the combination of lonafarnib with anti-EGFR agents could be considered.[46]

4.4. *Src kinase and focal adhesion kinase (FAK) inhibitors*

Src kinase and FAK are non-receptor cytoplasmic tyrosine kinases that play a key role in modulating cellular invasion, adhesion, motility, migration proliferation and survival. Both Src and FAK regulate signals from cell surface molecules, including growth factor receptors and G-protein coupled receptors. Furthermore, upon integrin receptor clustering, FAK is activated and recruits Src to form the FAK/Src complex, which in turn mediates downstream effector processes.[47] Preclinical evaluations demonstrated a strong rationale for targeting Src and FAK in HNSCC. Src inhibition using dasatinib (BMS-354825) in HNSCC cell lines has led to cell cycle arrest and apoptosis.[48] In a clinicopathological analysis of 211 HNSCC tumour specimens, FAK protein was overexpressed in 62% and was correlated with lymph nodal metastases.[49] Inhibitors of Src kinase such as dasatinib, AZD0530, bosutinib (SKI-606), and FAK such as PF-00562271 are currently undergoing phase I/II evaluations in advanced solid tumours.[50,51]

4.5. *Proteasome inhibitors*

The 26S proteasome is central for the ubiquitin–proteasome degradation pathway. Bortezomib is a selective inhibitor of the 26S proteasome with radiosensitising and antitumour activities in preclinical HNSCC models.[52,53] Conley and colleagues demonstrated that twice weekly bortezomib in combination with reirradiation in patients with HNSCC was poorly tolerated, with dose-limiting grade 3 hypotension and hyponatraemia.[54,55] Other schedules of bortezomib to be combined with radiotherapy, and its role as a systemic therapy for HNSCC, remain subjects of further research. Bortezomib is currently being studied in phase II trials in combination with irinotecan[56] and docetaxel in R/M HNSCC.[57]

4.6. *Protein kinase C inhibitors*

Protein kinase C (PKC) is a family of serine-threonine kinases that regulate a variety of cell functions and have demonstrated antiproliferative effects in HNSCC cells.[58–60] PKC inhibitors, such as midostaurin and enzastaurin have undergone phase I evaluation.[61,62] The most frequent toxicities observed with midostaurin were nausea, vomiting, fatigue and diarrhoea, while QTc changes were dose-limiting for enzastaurin. Results on PKC expression in HNSCC are conflicting, although some studies suggest a high expression of some isoforms.[63] In addition, Cohen and colleagues demonstrated that PKC may mediate EGFR-dependent proliferation in HNSCC cells,[63] suggesting that PKC may be a valid target in this tumour type.

5. Nuclear protein inhibitors

5.1. *Aurora kinase inhibitors*

The Aurora kinases belong to a family of cell cycle-regulating serine-threonine kinases. Aurora A functions in early mitosis in centrosomal separation and mitotic spindle assembly. Aurora B is a chromosomal passenger protein that regulates chromosome segregation and cytokinesis. The cellular function of Aurora C has not been well elucidated.[64] Reiter and colleagues examined tumour tissues from 66 patients with HNSCC and demonstrated that Aurora A mRNA overexpression was strongly correlated with tumour stage, nodal and distant metastases.[65] Elevated Aurora A mRNA level was significantly correlated with progression-free survival and overall survival. Several Aurora kinase inhibitors are undergoing preclinical or early clinical development, including those that target all Aurora kinases (e.g. PHA-739358, MK-0457), those selective against Aurora kinase A (e.g. MP529, MLN8054) and those selective against Aurora kinase B (e.g. AZD1152). In phase I trials of Aurora kinase inhibitors, dose-limiting toxicity appears to be mainly neutropaenia.[66,67] Phase II trials in HNSCC are awaited.

5.2. *Cyclin-dependent kinase inhibitors*

Cyclin-dependent kinases are critical regulators of cell cycle progression.[68] Several agents inhibiting multiple cyclin-dependent kinases have entered clinical development. Flavopiridol has been demonstrated to exert antitumour activity in HNSCC cells and xenografts.[69] In phase I solid tumour studies, the dose-limiting toxicity of flavopiridol was neutropaenia with bolus schedules,[70] and diarrhoea on continuous infusion schedules.[71,72] Seliciclib is an orally bioavailable inhibitor of cyclin-dependent kinases that has demonstrated antiproliferative activity in HNSCC cells.[73] Dose-limiting toxicities encountered in phase I trials were fatigue, skin rash, hyponatraemia and hypokalaemia.[74,75] In phase I trials of another cyclin-dependent kinase inhibitor, BMS-387032, major

reported adverse events were fatigue, gastrointestinal toxicity, elevated aminotransferases, and increased creatinine.[76–78] Finally, UCN-01 is a cyclin-dependent kinase modulator that has also demonstrated antitumour activity in HNSCC cells and xenografts.[79] In phase I trials, dose-limiting toxicities were hyperglycaemia and hypotension.[80,81] The preclinical results observed in HNSCC cells and xenografts with some of these agents support their clinical evaluation in this tumour type.

5.3. *Histone deacetylase inhibitors*

Histone deacetylases (HDACs) regulate chromatin structure and function by removing acetyl modification from lysine residues of histones, resulting in gene silencing and oncogenic transformation.[82] An important target of HDAC is NF-κB that is constitutively active in HNSCC cell lines.[83] HDAC inhibitors induce growth arrest and apoptosis *in vitro*, and inhibit tumour growth in animal models.[84] Moreover, preclinical studies have demonstrated that HDAC inhibitors enhance radiation sensitivity in HNSCC cells.[85] Several HDAC inhibitors have entered clinical development, such as vorinostat, PXD101, LBH589, FR901228 and MS-275. In phase I clinical studies with these agents, dose-limiting toxicities included dysrhythmia, fatigue, thrombocytopaenia, nausea and diarrhoea.[86–93]

A partial response has been obtained in a patient with metastatic laryngeal cancer with oral vorinostat during its phase I development.[86] Thus, a phase II trial of vorinostat in patients with R/M HNSCC was initiated.[94] Thirteen patients who had up to two prior chemotherapies were enrolled with no clinical responses observed (Table 1). Vorinostat given as a single agent in heavily pretreated HNSCC patients was inactive. Interestingly, in a phase I trial of vorinostat given in combination with capecitabine for patients with advanced solid tumours, three partial responses were observed in patients with head and neck malignancies, two with nasopharyngeal cancer and one with HNSCC. Dose-limiting toxicities were grade 3 fatigue, nausea and vomiting.[95] The use of vorinostat in first-line therapy for recurrence, especially in combination with capecitabine, and the exploration of its role as a radiosensitiser in primary therapy for LA HNSCC, may be considered.

5.4. *Polo-like kinase inhibitors*

Polo-like kinases are serine-threonine kinases implicated in the regulation of various steps of the cell cycle, such as activation of the phosphatase CDC25, bipolar spindle assembly and cytokinesis.[96] Knecht and colleagues have examined 89 patients with HNSCC and found elevated polo-like kinase mRNA expression in the vast majority of tumours which correlated with metastases.[97] Polo-like kinase inhibitors, such as Bl 2356 and HMN-214, have undergone phase I evaluation.[98–100] Dose-limiting toxicities appeared to be neutropaenia for Bl 2536 and hyperglycaemia and myalgia/bone pain for HMN-214.

6. Discussion

There are many challenges that exist in the development of novel therapeutics in HNSCC. Given the complexities of molecular wiring in human malignancies, it is unlikely that focusing on one single target would result in significant therapeutic success. The development of tyrosine kinase inhibitors which have the capacity to hit multiple targets, and the combination of different agents with their own unique potencies against specific pathways, are both appealing strategies.

Another challenge exists in the conduct of screening phase II trials of molecularly targeted compounds to determine their single agent antitumour activity, generally in patients with R/M HNSCC. Conventionally, a two-stage design is used and objective tumour response is often the primary endpoint of interest in single-arm phase II trials. From the published literature, it is clear that objective response rates of 15–20% typically stated in the alternative hypothesis of two-stage trials are unlikely to be attainable even with the most active compounds. Possible solutions to this challenge might include the incorporation of prolonged stable disease (e.g. >4–6 months) or progression-based endpoints as an evaluation of clinical benefit or disease control, which may provide more realistic assessments of antitumour activity. In addition, innovative pharmacodynamic endpoints such as intratumoural blood flow perfusion parameters on dynamic contrast enhanced CT/MRI may be more relevant than conventional response criteria for antiangiogenic agents.

Furthermore, most of the targeted anticancer agents that are currently in clinical development for HNSCC are studied in the R/M setting. This strategy has two main disadvantages. First, most patients in this population had prior chemotherapy and/or radiation therapy. Due to the development of resistance, the greater the exposure to prior treatments, the less likely a tumour may respond to new anticancer agents. For example, this is the case for bevacizumab which has nearly no antitumour activity as third-line treatment in patients with metastatic colorectal cancer.[101] Another example is illustrated by the use of cetuximab in patients with advanced HNSCC. While the response rate is limited to about 13% when cetuximab is given to patients who were primarily refractory to platinum,[3] it reaches almost 20% when administered to those who were stable on platinum therapy.[102] An even more striking evidence is the overall survival gain (10.1 versus 7.4 months, $p = 0.036$) observed with the addition of cetuximab to platinum-5-fluorouracil regimen in the first-line treatment of R/M HNSCC.[103] Hence, in the R/M setting, given the lack of survival benefits with aggressive cytotoxic chemotherapeutic regimens, one would advocate the testing of new agents as first-line therapy.[104] Secondly, studies of molecularly targeted therapies in the R/M setting reduce the feasibility of performing translational research, as it is technically and ethically difficult to mandate research-related tumour biopsies. The presence of cumulative resistance pathways in this patient population also raises concerns of the generalisability of results for target validation. For these reasons, an attractive alternative strategy would be to evaluate new compounds in the preoperative 'window' setting (Fig. 2). This approach enables the procurement of biopsies before treatment at the time of diagnosis, and after treatment, either before locoregional therapy or at the time of surgery. Translational research can be conducted to assess predictive molecular markers that may help identifying subgroups of patients most likely to respond to therapy, or in contrast, develop primary resistance. In addition, the ability to obtain paired tu-

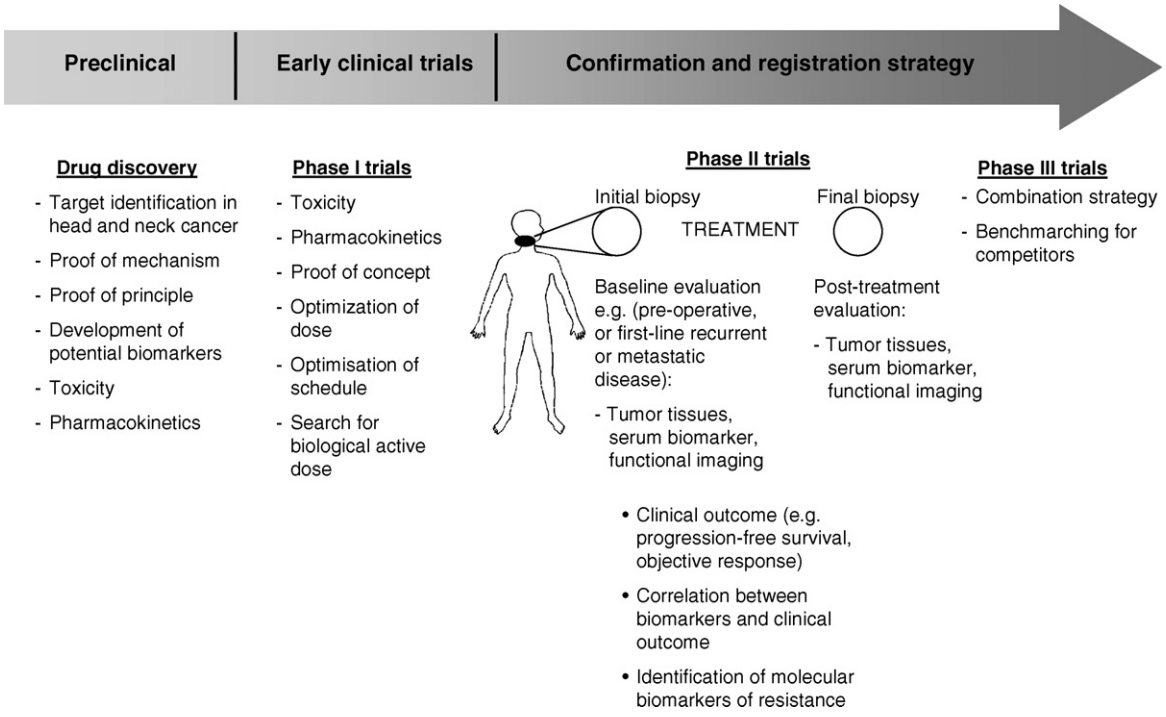

Fig. 2 – Suggested approach for targeted therapy clinical development strategy in head and neck cancer.

mour specimens may provide insights into the pharmacodynamic effects of novel agents, and yield proof-of-mechanism evidence.

In conclusion, targeted therapy already belongs to the treatment strategy for patients with HNSCC. Novel molecular targets and corresponding therapies continue to emerge. Appropriate selection of patients and innovative trial designs are imperative to efficiently bring promising compounds to the clinical arena.

Conflict of interest statement

Christophe Le Tourneau and Sandrine Faivre: None declared.

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