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EDITORIAL

Targeted treatments for metastatic esophageal squamous cell cancer

Antonia Digklia, Ioannis A Voutsadakis

Antonia Digklia, Ioannis A Voutsadakis, Centre Pluridisciplinaire d'Oncologie, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland
Author contributions: Digklia A performed literature search and wrote part of the manuscript; Voutsadakis IA conceived the paper, wrote parts and revised the manuscript.
Correspondence to: Ioannis A Voutsadakis, MD, PhD, Centre Pluridisciplinaire d'Oncologie, Centre Hospitalier Universitaire Vaudois, Bugnon 46, 1011 Lausanne, Switzerland. ivoutsadakis@yahoo.com
Telephone: +41-21-3145122 Fax: +41-21-2140188
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Abstract

Squamous cell carcinoma, one of the two major subtypes of esophageal carcinomas, constitutes the great majority of tumors in the upper and middle third of the organ. Declining in incidence in western countries, it continues to be a significant public health problem in the far east. Targeted treatments are novel therapies introduced in the clinical therapeutic armamentarium of oncology in the last 10-15 years. They represent a rational way of treating various cancers based on their molecular lesions. Although no such agent has been approved so far for the treatment of esophageal squamous cell carcinomas (ESCC), several are in clinical trials and several others have displayed pre-clinical activity that would justify the efforts and risks of pursuing their clinical development in this disease. This paper discusses some of these targeted agents in more advanced development in metastatic ESCC, as well as some promising drugs with pre-clinical or initial clinical data in the disease.

Key words: Esophageal carcinoma; Squamous; Targeted therapies; Clinical trials; Epidermal growth factor receptor; Vascular endothelial growth factor receptor; Mammalian target of rapamycin

Core tip: This paper discusses some of these targeted agents in more advanced development in metastatic esophageal squamous cell carcinomas, as well as some promising drugs with pre-clinical or initial clinical data in the disease.

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INTRODUCTION

Two major histologic types of esophageal cancers exist and differ in their epidemiology and risk factors. Esophageal adenocarcinomas arise almost exclusively in the lower third of the esophagus and esophagogastric junction, have an increasing incidence in western populations and are associated with Barrett's metaplasia and chronic gastro-esophageal reflux[1]. In contrast, esophageal squamous cell carcinomas (ESCC) are mostly situated in the upper two thirds of the organ and are associated with smoking and alcohol[2]. Salty foods and nitrosamine compounds in foods have also been implicated[3]. Their incidence decreases in western countries but remains a significant public issue in Asian populations[4].

Unfortunately, despite these differences that imply a distinct pathogenesis, the two types are mostly lumped together in clinical trials, a fact that would dilute a possible benefit in only one of the two histologies if the other histology would not benefit from a given treatment. Although this may be true even for chemotherapy as evidenced in the case of pulmonary adenocarcinomas and

squamous cell carcinomas where differences in response to various regimens have been revealed[5], it is particularly important for targeted therapies that would work only if the intended target is expressed, functional and involved in the pathogenesis of a carcinoma. A recent change in the trend of trials in the field of esophageal cancers necessitated by the development of targeted therapies adjoins esophageal adenocarcinomas and adenocarcinomas of the gastro-esophageal junction with gastric adenocarcinomas with which they share a common histology and are at times difficult to discern at the margins of the two organs. For the development of trastuzumab therapy, adenocarcinomas of the gastro-esophageal junction have been included in the trials and those of lower esophagus are often treated with the drug if they display an increased expression or amplification of human epidermal growth factor receptor 2 (HER-2)/Neu[6]. With these facts in perspective, the current paper will discuss only data concerning targeted therapies in metastatic or locally advanced inoperable ESCC. For studies that have included both esophageal histologies, discussion will be restricted to patients with squamous histology. When there are significant data available specifically for ESCC on expression of a possible tumor target and preclinical anti-tumor activity of a corresponding therapy, they will be mentioned, as they might represent an opportunity for future clinical development.

ANTI-EPIDERMAL GROWTH FACTOR RECEPTOR THERAPIES

Immunohistochemical (IHC) studies showed epidermal growth factor receptor (EGFR) protein over-expression in 50% of patients with ESCC and gene amplification was evident in 28% of over-expressors (or 14% of the total patients in the series)[7]. Over-expression was significantly correlated with the depth of tumor invasion[7]. Mutations in exons 19 and 21 of EGFR were not identified in any of the patients examined. Others have found amplification of EGFR in 15% in a series of 55 patients with ESCC[8] and rare EGFR mutations in ESCC specimens and a ESCC cell line[9,10]. Half of the patients displayed high levels of EGFR protein expression measured by a semi-quantitative IHC-based method. Protein expression correlated with gene amplification in this and in another series of 105 ESCC patients[11]. In this last series EGFR amplification or polysomy by fluorescence *in situ* hybridization (FISH) was seen in 31% of patients[11].

Several studies have examined the efficacy of anti-EGFR therapies in ESCC. Two types of agents targeting the EGFR signaling pathway are available: the anti-EGFR monoclonal antibodies cetuximab and panitumumab and the small molecule tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib.

In metastatic ESCC, a randomized phase Ⅱ study compared cisplatin 100 mg/m^2, day 1 and 5-fluorouracil (5-FU) 1000 mg/m^2/d continuous infusion, days 1-5 every 4 wk with or without cetuximab 250 mg/m^2 weekly (after a loading dose of 400 mg/m^2) in the first line setting[12]. A trend towards longer progression-free survival (PFS) (5.9 mo *vs* 3.6 mo) and overall survival (OS) (9.5 mo *vs* 5.5 mo) was noted in the cetuximab arm. Of interest cetuximab did not exacerbate grade 3 or 4 toxicities, except for rash and diarrhea. A randomized three arm phase Ⅱ study (CALGB 80403/ECOG 1206) took a reverse approach and sought to determine what chemotherapy is best in combination with cetuximab in metastatic esophageal and gastroesophageal junction cancer[13]. Patients were randomized to epirubicin, cisplatin, 5-FU (ECF) or 5-FU, folinic acid, oxaliplatin (FOLFOX) or irinotecan/cisplatin. All three arms received concomitant cetuximab. Only a few (about 10%) of patients had ESCC. Results have been presented so far in an abstract form for the adenocarcinoma patients. The two first arms were more effective and the FOLFOX arm less toxic[13]. Conclusions regarding the clinical utility of adding cetuximab to first line chemotherapy are awaiting information from ongoing randomized phase Ⅲ trials.

Regarding the role of cetuximab in the 2nd line chemotherapy setting there is a lack of published trials. A phase Ⅱ study in the 2nd line setting adding cetuximab to cisplatin and irinotecan in patients with irinotecan and cisplatin-refractory metastatic esophageal cancer (NCT 00397904) has completed accrual. This study has included both squamous and adenocarcinomas and results are awaited.

The other clinically available anti-EGFR monoclonal antibody, panitumumab is investigated in combination with chemotherapy in a phase Ⅲ study (NCT01627379) of non-resectable advanced or metastatic ESCC. Patients included have not been treated with chemotherapy previously (except in the neo-adjuvant setting). All patients receive cisplatin and 5-FU and are randomized to receive or not panitumumab.

A third investigational anti-EGFR antibody, nimotuzumab has been studied in patients with ESCC in the first line metastatic setting in combination with paclitaxel and cisplatin[14]. Results of 25 patients treated in a phase Ⅱ study showed a 63.6% partial response (PR) rate and 31.8% stable disease (SD). The same investigators study nimotuzumab in the second line setting in combination with mFOLFIRI chemotherapy (Trial NCT01486992).

Both orally active TKIs gefitinib and erlotinib that are currently available in clinical practice have been tested in metastatic ESCC. These TKIs block the ATP binding site of the EGFR tyrosine kinase molecule. A phase Ⅱ trial of gefitinib 500 mg daily in the 2nd line treatment of metastatic esophageal cancer showed a higher disease control rate (PR *plus* SD) in patients with SCCs compared with adenocarcinomas (P = 0.013). Patients with high EGFR expression and lower levels of phosphorylated kinase adams kara taylor (Akt) had higher disease control rates (P = 0.002 and 0.009 respectively)[15]. Nine patients with SCC were among the 36 patients enrolled in this study and five (55.5%) showed a PR or SD. Five of six patients tested had a strong expression of EGFR (more than 25%

of tumor cells stained strongly) by IHC. Among the five patients with a PR or SD, all four tested had high EGFR expression. Another phase Ⅱ trial of gefitinib in recurrent or metastatic esophageal or gastroesophageal junction cancer included 58 patients but only 4 among them had squamous histology[16]. Authors state that both histologies derived a clinical benefit but obviously the small number of ESCC patients precludes any definitive conclusion from this study.

A phase Ⅲ study (NCT01243398) randomizing patients with ESCC and adenocarcinoma to gefitinib versus placebo after one or two lines of chemotherapy is currently ongoing.

Recently a phase Ⅱ study of erlotinib monotherapy in previously treated esophageal cancer was published[17]. Similarly to gefitinib, erlotinib shows activity in squamous cancer. Among the 30 patients included in this study, thirteen patients had squamous histology and twelve of them had some degree of EGFR positivity by IHC (defined as more than 10% of tumor cells staining for the receptor tyrosine kinase). Two patients obtained a response which lasted for 5.5 and 7 mo while seven additional patients had stable disease for a median of 5 mo. The median time to disease progression in all squamous histology patients in the study was 3.3 mo. No correlation of EGFR status and degree of expression with erlotinib efficacy could be established possibly due to the small number of patients.

Overall, interesting activity with acceptable toxicity of anti-EGFR agents is seen in these initial studies. More definitive results from larger trials are expected. Well-validated biomarkers will certainly help to define sub-sets of patients that will benefit most.

ANTI-HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 THERAPIES

The benefit of treatment with the humanized anti-HER-2 monoclonal antibody trastuzumab in cases of HER-2 protein over-expressing or gene amplified metastatic breast and gastric adenocarcinomas is well established[6,18]. About 15%-20% of squamous esophageal cancers show over-expression of HER-2 by IHC and about 1%-20% show gene amplification by FISH[19-22]. Few studies correlated HER-2 status with clinical outcomes in ESCC[20,21]. These retrospective studies have shown a worse survival in ESCC when HER-2 is over-expressed. Preclinical data show that trastuzumab, targeting the extracellular domain of the HER-2 protein, has anti-proliferative activity directly but also through antibody dependent cellular cytotoxicity in esophageal carcinoma cells[23-26] , providing a rational for clinical trials in ESCC with HER-2 over-expression/amplification. Nevertheless no such studies investigating trastuzumab treatment or treatment with the newer anti-HER-2 agents pertuzumab and trastuzumab emtansine in ESCC have been conducted so far. A phase Ⅰ study of paclitaxel and trastuzumab with interleukin 12 (trying to take advantage of a natural killer cell mediated cytotoxicity) in HER-2 overexpressing carcinomas has included 4 patients with ESCC[27]. Two of them had a partial response lasting for 25 and 43 wk.

DUAL ANTI-EGFR AND ANTI-HER-2 THERAPIES

Given that a percentage of ESCC overexpress both EGFR and HER-2[25], there is a rational for use of drugs that inhibit both receptors. Lapatinib is a small TKI that inhibits both EGFR and HER-2. A phase Ⅱ study of lapatinib in recurrent or metastatic ESCC has been initiated (NCT00239200) but has been terminated and there are no published data regarding the outcomes. Another oral TKI pan-HER inhibitor, PF-00299804 is studied in a Korean phase Ⅱ trial in patients with recurrent and metastatic ESCC (trial NCT01608022). The dual EGFR and HER-2 inhibitor afatinib has been investigated in a phase Ⅰ study in which one of 7 esophageal cancer patients participating had an unconfirmed partial response[28]. Phase Ⅱ development is pursued only in esophago-gastric adenocarcinomas. Based on the accumulated evidence from other malignancies, it can be expected that the efficacy of anti-EGFR/anti-HER-2 agents would be restricted to tumors with high expression or specific mutations of these receptors. Further development of targeted EGFR/HER-2 drugs should be focused to these sub-sets of ESCC. Although this focusing would limit the pool of available patients and make clinical trials more cumbersome and slow to accrue, it will, on the other hand, increase the probability of obtaining positive results.

ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPIES

Angiogenesis plays a crucial role in carcinogenesis and progression of malignancies. Vascular endothelial growth factor (VEGF) pathway is among the important signal transducers in this process[29]. Several ligands including VEGF-A, -B, -C and -D initiate signals by binding cell surface receptor tyrosine kinases VEGF-R1 (also known as flt1), VEGF-R2 (also known as flk1) and VEGF-R3 (also known as flt4) and triggering down-stream cascades of cell proliferation and survival. VEGF pathway alterations are involved in pathogenesis of esophageal cancer[30]. VEGF-A expression is present in most ESCC and ranges between 24%-93% in different studies[31]. Moreover the over-expression of VEGF isoforms has been significantly correlated with poorer prognosis of ESCC[32,33].

Bevacizumab is a monoclonal antibody targeting VEGF. It is used clinically in colon, breast, ovarian and lung adenocarcinomas. Its development in gastric and gastro-esophageal junction adenocarcinomas has progressed through phase Ⅲ trials[34] but in squamous

cancers there is a reluctance to pursue development given safety issues with hemorrhage in squamous non-small cell lung cancer[35]. Small molecule TKI of VEGF receptor (VEGFR) have been studied in early trials that have included ESCC patients. Pazopanib, a TKI targeting VEGFR, platelet-derived growth factor receptor and c-Kit is already approved for the treatment of clear cell renal carcinoma. A phase I study combining it with carboplatin and paclitaxel in patients with various advanced cancers found the maximal tolerated dose to be 200 mg daily[36]. Among the patients in this trial there were 4 with esophageal carcinoma (histology not specified) and two of them had a complete response. The TKI sunitinib is evaluated in phase II studies as a single agent or in combination with paclitaxel in patients with advanced esophagogastric cancer of both histologies[37,38]. Another anti-VEGF TKI, sorafenib is studied as monotherapy. Responses so far have been reported in adenocarcinomas but only 2 patients with ESCC were included in this preliminary report[39]. A fourth anti-VEGFR TKI, vandetanib is in phase I development in combination with oxaliplatin and docetaxel in advanced esophageal and gastroesophageal junction adenocarcinomas and squamous carcinomas (trial number NCT00732745). It is evident from these data that the field of anti-VEGF therapy development in esophageal cancer is dominated by adenocarcinoma histology and few results for ESCC are available. It remains to be seen if further development, optimally aided by predictive markers, will be pursued in ESCC.

ANTI-MTOR THERAPIES

Mammalian target of rapamycin (mTOR) is an intracellular serine/threonine kinase that plays important roles in RNA translation, cell proliferation and angiogenesis. Inhibition of mTOR by everolimus has shown activity and is used clinically in renal cell carcinoma[40], pancreatic neuroendocrine tumors[41] and in breast cancer where it has been found to reverse tumor resistance to hormonal treatments[42]. In ESCC mTOR is reported to be activated in 25% of cases and co-relates with a lower degree of differentiation[43]. Another group found activation of mTOR in 50% to 70% of ESCC and showed worse overall and cancer specific survival in cases with activated mTOR compared with non-activated cases[44,45]. Proliferation of ESCC cell lines with activated mTOR was inhibited by everolimus *in vitro* and *in vivo* in mouse xenograft models[44].

Very few clinical data on mTOR inhibitors in ESCC are available. In a phase I trial of everolimus a single esophageal cancer patient included (histology not reported) treated with 10 mg/d showed a marked response in a metastatic supraclavicular lymphadenopathy before dying of tumor-related hemorrhage[46]. An additional strategy for mTOR inhibitor development in ESCC would be their combination with other targeted treatments. As mTOR may be activated by the phosphatidylinositol 3-kinase (PI3K)/Akt pathway down-stream of receptor tyrosine kinases, a combined inhibition with inhibitors of these kinases may be advisable. Combination with direct inhibitors of PI3K could be an alternative. PI3K inhibitors are in development[47,48]. The hedgehog pathway is also co-operating with the PI3K/Akt pathway[49] and is activated in a sub-set of ESCC[50,51]. Hedgehog signaling is important in foregut development, a fact that may underline its importance in carcinogenesis in both squamous and adenocarcinomas of the esophagus[51]. Hedgehog pathway inhibitor vismodegib is used for the treatment of basal cell cutaneous carcinomas[52]. Preclinical studies have shown synergy of vismodegib with everolimus in esophageal adenocarcinomas[53]. A phase II study of the addition of vismodegib to FOLFOX chemotherapy in gastroesophageal adenocarcinomas is in progress[54]. Further development of mTOR inhibitors in ESCC enriched for activated mTOR with or without other targeted or chemotherapeutic treatments seems to be warranted.

OTHER TARGETED THERAPIES

Hepatocyte growth factor/scatter factor (HGF) is the ligand for proto-oncogenic cell surface receptor c-Met. c-Met transduces proliferative and pro-angiogenic signals and has been related to prognosis of different malignancies[55,56]. A study in ESCC patients has shown that the serum level of HGF is higher than controls and correlates with levels of interleukin-8 and VEGF, both important mediators of angiogenesis[57]. HGF was also an independent prognostic factor for survival. Patients with higher than the median serum HGF had a median survival of 34 mo and a 2 year survival of 63% while those with serum HGF lower than the median had a median survival of only 15 mo and a 2 year survival of 37%[57]. Antibodies blocking this pathway could be a potential therapeutic strategy in ESCC. The small molecule kinase inhibitor against anaplastic lymphoma kinase crizotinib is concomitantly an inhibitor of c-Met and could be used to target this pathway.

Bryostatin-1 is an agent with antitumor activity *via* the inhibition of protein kinase C and has synergistic activity with chemotherapeutic agents such as paclitaxel[58]. In esophageal cancer a phase II trial of weekly paclitaxel and bryostatin-1 that included 22 patients demonstrated a response rate above 25% and up to 40% in the higher doses reached[59]. Nevertheless this trial has included only 2 patients with ESCC and had to close prematurely because of high rates of toxicities (myalgia) and two possibly treatment-related deaths. Bryostatin-1 analogs have been synthesized and could be alternatively developed if proved to have a better toxicity profile[60].

Bortezomib is a proteasome inhibitor that is used in the treatment of myeloma and lymphoma. In pre-clinical studies in ESCC, bortezomib has shown activity by co-operating with both intrinsic and extrinsic pathways in

apoptosis induction[61,62]. A possible role of the drug in enhancing radiotherapy-induced cell death was suggested[62]. Despite the rational in targeting the proteasome as an anti-neoplastic treatment, in several solid tumors bortezomib has shown minimal activity. Thus an alternative approach with the identification and use of predictive biomarkers could be more effective if bortezomib (or other newer proteasome inhibitors such as carfilzomib[63]) were to be developed in ESCC.

The inducible form of the pathway enzyme cyclooxygenase (COX)-2 plays a role in the promotion of ESCC. Studies in preclinical models have shown that COX-2 inhibition has anti-tumor effects in ESCC cells[64]. These effects have been attributed to induction of apoptosis, inhibition of angiogenesis and suppression of invasion. In human ESCC, increased COX-2 expression correlates with reduced OS[65,66] and more aggressive tumor characteristics[67]. Furthermore, increased expression of EP2, the receptor for the COX-2 product prostaglandin PGE2, is associated with worse survival in patients with localized ESCC[68]. Dawson *et al*[69] report a response rate of 54% in a phase Ⅰ/Ⅱ study of the COX-2 inhibitor celecoxib in combination with 5-FU/cisplatin/radiotherapy in 13 patients, with 3 of them having squamous histological type. This small number precludes any conclusions and no data are available in the metastatic setting. Moreover there are safety concerns with the coxib class of COX-2 inhibitors that limits their potential for further development. A recent study demonstrates that celecoxib antagonizes the cytotoxicity of cisplatin[70], further complicating a putative development of coxibs in ESCC. Other non-steroidal anti-inflammatory drugs with a better safety record such as aspirin may be preferable, although many of them lack the selectivity of coxibs for COX-2 and inhibit concomitantly the constitutive form, COX-1.

Other opportunities for targeted treatments clearly exist based on detected abnormalities in ESCC cells. For example global histone H3 and H4 hypoacetylation was detected in tumors from patients with ESCC[71]. This may be the result of increased histone deacetylase 1 (HDAC1) expression in ESCC cells compared with adjacent normal tissues[72]. Inhibition of the expression of HDAC1 by RNAi resulted in enhanced radiosensitivity of ESCC cells *in vitro*. Histone deacetylase inhibitor vorinostat inhibited invasion of ESCC cells pretreated with tumor necrosis factor α and transforming growth factor β in an *in vitro* assay[73]. The combination of vorinostat with the aforementioned proteasome inhibitor bortezomib further increased these invasion-inhibiting effects. Despite these pre-clinical encouraging data, no clinical data in ESCC are available for the time being regarding HDAC inhibitors.

Natural products contained in berries have been found to prevent ESCC in Fischer-344 rats treated with *N*-nitrosomethyl benzylamine (NMBA)[74]. This is a model of ESCC in which rats develop pre-neoplastic lesions passing from hyperplasia to dysplasia and finally to neoplasia (papillomas). In a clinical trial conducted in China, treatment with 60 mg daily of freeze-dried strawberries reversed mild to moderate dysplasia of esophagus[75]. Several carcinogenesis-involved molecules such as COX-2, nuclear factor κB and targets of the mTOR pathway have been modified after this treatment. Whether the treatment could have beneficial effect in established carcinomas and what compound or compounds in the extracts provide the beneficial effect remains to be investigated.

CONCLUSION

No targeted treatment agent has been introduced in the clinic for the treatment of ESCC until now. This relates to several factors that impede the clinical development of new drugs in ESCC. The rarity of these tumors not only makes the execution of trials with satisfactory numbers to extract conclusions more difficult but also obliges investigators to perform trials with both histologies in the organ or even including gastric cancer patients. As a result, effective treatments for only one of the histologies may be missed. The problem of patient recruitment will not be helped in the future as ESCC incidence (fortunately) decreases in western countries. Thus other solutions are needed including judicious "use" of the patient pool at hand. This implies that new agents to be entered in the clinical development face should have robust pre-clinical data supporting them and a molecular rational.

Another factor that may dilute possible positive results even within the same histology stems from the significant heterogeneity of cancer. This is probably of even greater importance for the development of targeted treatments than for chemotherapy agents. A promising strategy to overcome the heterogeneity barrier is the identification of prognostic markers which can help in the selection of patients. Such identification would lead in trials that will test a new targeted agent only in patients whose tumors over-express the target or express a mutated form of it. In some instances mere over-expression of the target is not enough or is not even present and demonstration of lesions in other proteins of the pathway(s) in which it participates is required for determination of sensitive sub-groups of a given tumor type. An illustrative example is anti-EGFR agents in colorectal cancer which are more effective in the sub-group of tumors with wild type Kras protein[76]. This protein is a down-stream effector of EGFR and when mutated blunts the activity of anti-EGFR agents because it is active even without receiving signals from the EGFR up-stream.

Related to the problem of tumor heterogeneity is the theory of tumor stem or tumor initiating cells. According to this theory only a generally small sub-set of neoplastic cells has the ability to propagate the tumor, while the bulk of the tumor derived from the sub-set of stem cells is less important because it lacks the capacity to proliferate indeterminably except if it acquires a stem cell phenotype[77]. In addition stem cells have been found to be drug

resistant and possess the ability to undergo epithelial to mesenchymal transition, a process endowing them with metastatic potential[78]. Thus a potential strategy for clinical development of targeted agents would be to determine the expression of their targets in stem cells and the dependence of those cells to these targets. By targeting tumor initiating cells one can argue that the anti-tumor effect would be more pronounced and durable.

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