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EDITORIAL

Targeting metastatic upper gastrointestinal adenocarcinomas

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Abstract

Upper gastrointestinal (GI) tumors, including adenocarcinoma of the esophagus, stomach, pancreas, and biliary tree, have traditionally been difficult to treat with cytotoxic chemotherapeutic agents. There has been little drug development success in treating these cancers over the last 20 years, perhaps a reflection of a combination of the aggressive biology of these tumors, the void in effective and specific drug development for these varied tumors, and the lack of properly designed, biologically-based clinical trials. Recently, so called "targeted agents" have risen to the forefront in the care of cancer patients and have made strong impacts in many areas of oncology, particularly gastrointestinal stromal tumors (GIST), colon, breast, and lung cancers. Unfortunately, slow progress has been made using such agents in upper GI tumors. However, more recently, trials in some tumor types have demonstrated gains in progression free survival and overall survival. In this review, we discuss the drugs and pathways that have been most successful in the treatment of upper GI tumors and present the relevant data supporting their use for each tumor site. Additionally, we will explore a few novel pathways that may prove effective in the treatment of upper GI malignancies in the near future.

Key words: Targeted therapy; Epidermal growth factor inhibition; Angiogenesis; Antiangiogenic agents; Mammalian target of rapamycin; Her2/neu; Tyrosine kinase inhibition; Pancreatic cancer; Gastric cancer; Biliary cancer; Hepatocellular cancer

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INTRODUCTION

Metastatic or locally advanced tumors of the stomach, liver, biliary tree, and pancreas have some of the worst prognoses of any cancer. Usually found at a stage when curative surgical resection is not possible, these tumors have incidence rates that approach mortality rates. Until recently there were no systemic therapy options for hepatocellular or biliary cancers. Cytotoxic therapies for gastric and pancreatic adenocarcinoma have limited benefit and there has been little advancement in the drug or drug combinations available to treat these diseases. In recent years, efforts to improve the outcomes for patients with metastatic gastrointestinal (GI) malignancies have focused

on agents targeting one or more pathways involved in cell growth, proliferation, and/or metastases. Below, we explore these pathways and targets as well as evaluate several of the key areas that have been investigated using novel agents in advanced upper GI malignancies.

Human epidermal growth factor receptor (ErbB/HER) family cellular growth is a complex process regulated by a network of growth factors, growth factor receptors, and signal transduction pathways allowing essential communication between the outer and inner cellular environments[1]. The ErbB/HER family is comprised of four related tyrosine receptors: epidermal growth factor receptor (EGFR, ERBB1, Her-1), human EGFR-2 (HER-2, ERBB2), HER-3 (ERBB3), and HER-4 (ERBB4), each with a ligand binding extracellular, transmembrane, and intracellular tyrosine kinase (TK) domain[2,3]. Activation of the extracellular domain by a growth factor, leads to homo- or hetero-dimerization with another ErbB/HER family member, causing phosphorylation of intracellular TK residues and thereby downstream signaling[4,5]. ErbB/HER signal transduction is responsible for many normal cellular growth activities but constitutive or aberrant activation has been implicated in tumor progression *via* promotion of cell survival, proliferation, angiogenesis, anti-apoptosis, and metastases[4-7] (Figure 1). Inhibition of EGFR-1, HER-2, or both has been successful in the treatment of several upper GI malignancies. To date, monoclonal antibodies directed at EGFR or HER-2 and tyrosine kinase inhibitors (TKI) blocking downstream signal transduction pathways have had some success. Drugs targeting this pathway which have shown activity in upper GI adenocarcinomas are listed in Table 1.

Table 1 Human epidermal growth factor receptor family inhibitors in upper gastrointestinal malignancies

Drug	Mechanism of action	Applicable tumour site(s)
Cetuximab	Intravenous IgG1 monoclonal antibody inhibiting the extracellular domain of EGFR thereby preventing receptor activation	Gastric Biliary tract Pancreas
Erlotinib	Oral intracellular small molecule selective EGFR TKI	Biliary tract Pancreas
Trastuzumab	Intravenous recombinant humanized anti-HER2 monoclonal antibody directed against the HER-2 extracellular domain	Gastric
Lapatinib	Oral TKI targeting EGFR and HER-2	Gastric

EGFR: Endothelial growth factor receptor; TKI: Tyrosine kinase inhibitor; HER: Human epidermal growth factor receptor.

Table 2 Antiangiogenic agents in upper gastrointestinal malignancies

Drug	Mechanism of action	Applicable tumour sites
Bevacizumab	Intravenous recombinant humanized monoclonal antibody against VEGF	Gastric Hepatocellular Biliary tract Pancreas
Sunitinib	Oral multitargeted TKI inhibiting VEGFR-1, VEGFR-2, PDGFR-β, c-KIT, FLT3, and RET	Gastric Hepatocellular
Sorafenib	Oral multitargeted TKI inhibiting VEGFR-1, VEGFR-2, PDGFR-β, Raf-1, B-Raf, and intracellular serine-threonine kinases	Gastric Hepatocellular Pancreas

VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; TKI: Tyrosine kinase inhibitor; PDGFR: Platelet-derived growth factor receptors.

Angiogenesis

Angiogenesis is the process of new blood vessel formation from pre-existing vascular structures and is modulated by various inhibitors and inducers. Persistent up-regulation of this process is an important factor in development and maintenance of malignancy and is required for tumor growth and progression[8,9]. The vascular endothelial growth factor (VEGF) family of ligands and receptors are the most essential components in tumor angiogenesis. VEGF ligands include VEGF-A (VEGF), VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor. Of these, VEGF is considered the critical regulator of endothelial proliferation, permeability, and survival. VEGF binds to VEGF receptor-1 and -2 (VEGFR-1, -2), expression of which is up-regulated in endothelial cells of the tumor vasculature. VEGF/VEGFR binding triggers a large spectrum of cellular changes including proliferation, vascular cell differentiation, changes in vascular permeability, and cellular migration[10-17]. Similarly to activation of EGFR, extracellular activation of VEGFRs induces receptor dimerization. Autophosphorylation of the receptor then results in activation of downstream proteins and effector molecules (Figure 2).

Inhibition of angiogenesis is considered a promising area of anti-cancer research and therapy. The first approved indication for the use of an antiangiogenic agent in cancer therapy was the use of bevacizumab in metastatic colorectal cancer which demonstrated an almost 5 mo benefit in survival in the bevacizumab arm[18]. Since then, multiple avenues have been used in attempts to inhibit angiogenesis in other GI tumors, including inhibition of the ligand VEGF with bevacizumab, inhibition of the VEGFRs, and inhibition of intracellular tyrosine kinase pathways. Antiangiogenic drugs which have shown activity in upper GI adenocarcinomas, including bevacizumab, sunitinib and sorafenib, are discussed below. Mechanisms of action of these drugs are described in Table 2.

Mammalian target of rapamycin

Rapamycin, an immunosuppressant and anti-fungal, was the first drug to implicate mammalian target of rapamycin (mTOR) as a possible target for anti-cancer therapy[19]. As a member of the phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt) pathways, mTOR plays an

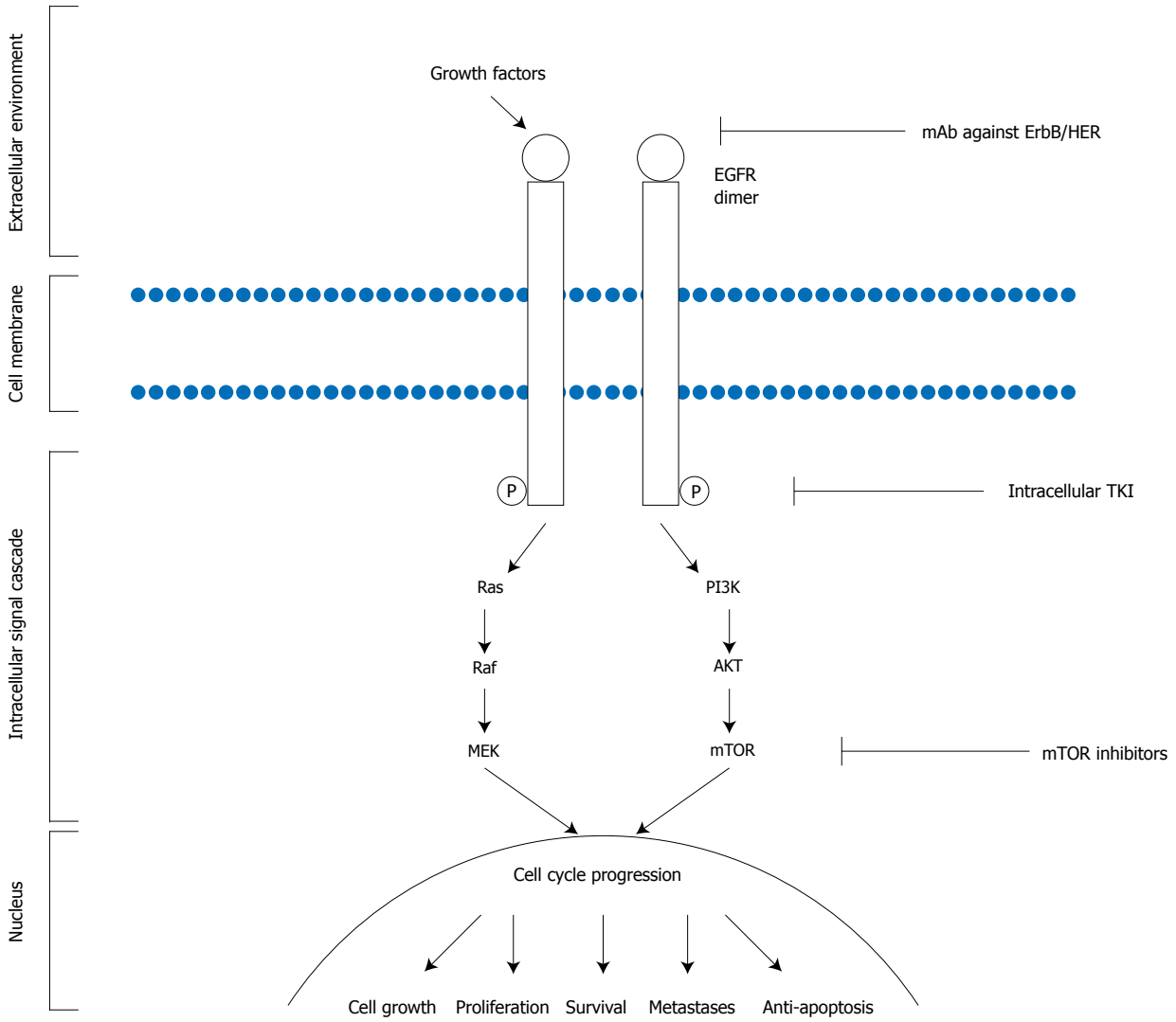

Figure 1 Schematic representation of the epidermal growth factor receptor pathway. EGFR: Epidermal growth factor receptor; mAB: Monoclonal antibody; TKI: Tyrosine kinase inhibitor; mTOR: Mammalian target of rapamycin; PI3K: Phosphoinositide 3-kinases; MEK: MAP kinase or ERK kinase.

important role in ribosomal synthesis and protein translation required for cell cycle progression, cell growth, proliferation, and survival. Additionally, the mTOR pathway is affected by other growth factors and nutrition[20-22] (Figure 1). The activity of mTOR is orchestrated through two complexes, mTOR complexes 1 and 2 (TORC1 and TORC2), whose interaction and signaling systems are still incompletely understood[23-25].

Mammalian target of rapamycin inhibitors have demonstrated *in vitro* and *in vivo* growth inhibition against a number of different cancers, the most successful of which has been renal cell carcinoma (RCC) with phase Ⅲ study data establishing mTOR inhibition has survival advantage for poor prognosis RCC patients[26]. Limited mature data exists for the use of mTOR inhibitors in upper GI malignancies. The exception is a phase Ⅲ study evaluating everolimus in gemcitabine refractory pancreatic cancer which showed limited clinical benefit[27].

Matrix metalloproteinases

The tumor microenvironment is increasingly being investigated to determine its role in cancer growth and spread. Included within this microenvironment is a complex interplay between the cancer cell and surrounding stroma including non-malignant cells, vasculature, and enzymes. Matrix metalloproteinases (MMPs), found within the cellular microenvironment, are a family of endopeptidases with proteolytic activity having critical roles in inflammation, tissue remodeling, and tumorigenesis[28-31]. There are 23 known MMPs, the activity of which is tightly regulated by their requirement for activation by proteolytic enzymes and the presence or absence of MMP inhibitors[31,32]. Physiologic MMP inhibitors exist and are found at sites of cancer[33]. Synthetic inhibitors have been tested alone and in combination with chemotherapeutics in clinical trials with manageable toxicities. Unfortunately, the effectiveness of MMPs in cancer patients on clinical trials has been disappointing despite their proven roles in the development of malignant proliferation and metastases.

Esophagogastric cancer

Gastric and esophageal cancers are the second and sixth

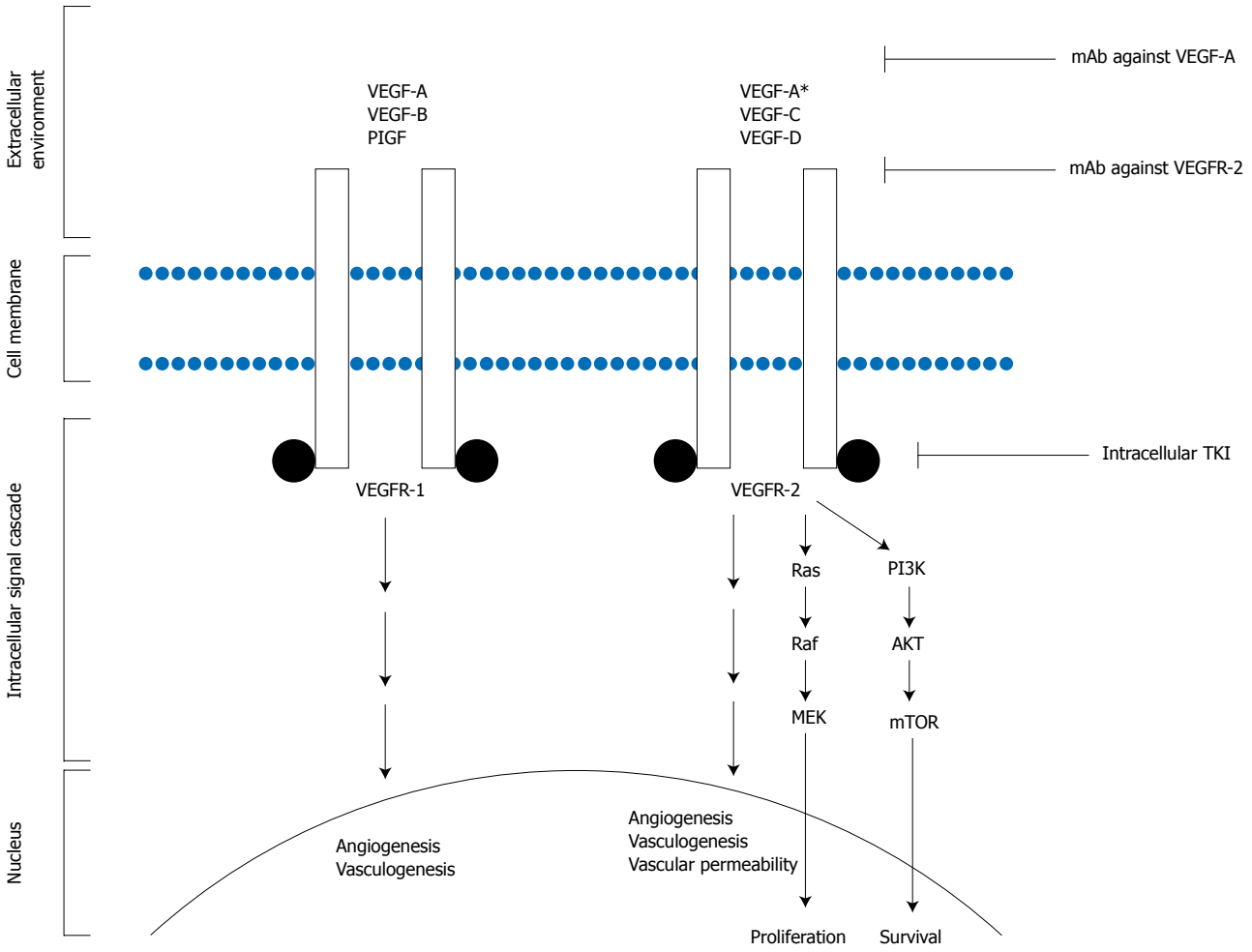

Figure 2 Schematic representation of the vascular endothelial growth factor pathway. VEGF: Vascular endothelial growth factor; PIGF: Placental growth factor; mAb: Monocolonal antibody; VEGFR: Vascular endothelial growth factor receptor; mTOR: Mammalian target of rapamycin; PI3K: Phosphoinositide 3-kinases; MEK: MAP kinase or ERK kinase; TKI: Tyrosine kinase inhibitor.

leading causes, respectively, of cancer-related death worldwide[34]. Advanced esophageal adenocarcinomas are usually treated akin to advanced gastric cancer adenocarcinoma as it is often difficult to determine if the cancer originates in the gastroesophageal junction (GEJ) or distal esophagus. Most patient with esophagogastric cancer (EGC) present with advanced, inoperable, or metastatic disease; 5 year survival rates are approximately 10%-15%. Palliative cytotoxic chemotherapy improves survival compared to best supportive care[35-37]. There is no internationally accepted standard of care despite a large number of chemotherapy regimens being tested in randomized trials. The best survival rates are achieved with three drug regimens compared to doublet therapy[38]. Capecitabine and oxaliplatin are as effective as 5-fluorouracil (FU) and cisplatin, respectively, when combined with epirubicin[39]. The addition of docetaxel to cisplatin and FU (DCF) showed a small survival benefit over FU/cisplatin but increased toxicity limits its widespread use[40]. DCF has not been compared to a FU/anthracycline/platinum regimen. As the benefits of palliative chemotherapy remain modest, novel target agents are being tested in EGC.

Angiogenesis inhibitors

Phase Ⅱ studies of bevacizumab combined with chemotherapy (irinotecan + cisplatin; oxaliplatin + docetaxel or FU; DCF) showed promising results in previously treated and untreated patients (response rate (RR) 63%-71%)[41-44]. AVAGAST, a Phase Ⅲ study of bevacizumab versus placebo combined with capecitabine and cisplatin showed a significant improvement in overall RR (ORR 38% *vs* 29.5%) and progression free survival (PFS 6.7 mo *vs* 5.3 mo)[45]. However, the addition of bevacizumab failed to improve overall survival (OS), the primary endpoint of this study.

Several small molecule multitargeted TKIs to VEGFRs have been tested in phase Ⅱ studies. Sorafenib in combination with docetaxel and cisplatin in treatment naive patients with metastatic EGC demonstrated 41% partial response (PR), median PFS of 5.8 mo and median OS of 13.6 mo[46]. Sunitinib as a second-line single agent treatment for advanced EGC demonstrated a disease control rate (DCR) of 35%[47]. Further randomized trials are required to assess the benefit of these agents.

Ramucirumab, a monoclonal antibody directed against VEGFR-2, is currently being tested in the second-line setting

of EGC in a randomized phase Ⅲ study (NCT00917384) after a heavily pre-treated gastric cancer patient had prolonged response to the drug in the phase I dose finding study[48].

EGFR inhibitors

In pretreated EGC patients, single agent cetuximab has poor RR (5%)[49]. However, in previously untreated patients in combination with FU and oxaliplatin or irinotecan, an RR of 45%-65% was observed[50,51]. As a second line treatment, cetuximab combined with docetaxel resulted in 43% stable disease (SD)[52]. A randomized phase Ⅲ trial (EXPAND) comparing capecitabine and cisplatin with or without cetuximab in advanced EGC is ongoing (NCT00678535). Most phase Ⅱ clinical trials using EGFR TKIs as single agents in EGC have shown minimal efficacy. Erlotinib has a 10% RR in previously untreated patients[53]; gefitinib an 18% SD rate in previously treated patients[54] and lapatinib showed a 5% RR and 20% of patients had SD in untreated patients[55]. In the phase I trial of matuzumab in combination with epirubicin, cisplatin and capecitabine the DCR was 43%-57% which looked very promising[56]. The subsequent phase Ⅱ trial failed to show a significant benefit[57].

Her-2 /neu inhibitors

Reported rates of over-expression and amplification of ERBB2/HER-2 in EGC varies widely due to sample sizes and methodological differences. The largest data set of advanced EGC samples had an HER-2 positivity rate of 22.9%[58]. Differences were found based on tumor location with higher HER-2 positivity in GEJ tumors compared to gastric tumors (33.2% *vs* 20.9%) as well as increased rates in intestinal versus diffuse/mixed cancers (32.2% *vs* 6.1%).

A small phase Ⅱ study in advanced EGC with HER -2 overexpression/amplification (n = 21) receiving trastuzumab in combination with cisplatin observed a RR of 35%and SD of 17%[59]. The first randomized controlled phase Ⅲ study, ToGA, comparing combination chemotherapy with a fluoropyrimidine (5-FU or capecitabine) plus cisplatin with or without trastuzumab in HER2 positive ECG patients showed a statistically significant improvement in median OS with the addition of trastuzumab (13.5 mo *vs* 11.1 mo, P = 0.0048) and a 26% reduction in the risk of death[60]. Furthermore, the addition of trastuzumab improved PFS (6.7 mo *vs* 5.5 mo, P = 0.0002) and DCR (47.3% *vs* 34.5%, P = 0.0017). Safety profiles were similar in both groups, including cardiotoxicity. In a preplanned analysis, patients with high immunohistochemistry (IHC) positivity for HER-2 had a trend for better survival; furthermore, those patients with HER-2 IHC2+/FISH + or IHC3+ had a longer survival (16 mo) with trastuzumab compared to chemotherapy alone (11.8 mo).

Lapatinib, an oral TKI, which targets EGFR1 and 2 (HER-2), is currently being tested in a phase Ⅲ study, LOGiC (NCT00680901). Patients with HER2 amplified EGC will receive capecitabine and oxaliplatin with lapatinib or placebo with the primary endpoint being PFS.

Summary

Despite advances in the treatment of locally advanced or metastatic EGC, prognosis remains poor; novel treatment options and predictors of treatment response are needed. Trastuzumab in combination with cisplatin and a fluoropyrimidine, is the only targeted therapy to date to have modest but clinically significant improvement in OS compared to chemotherapy alone in patients with HER2 positive gastric cancer. Unfortunately, only about 20% of patients would be potential candidates for this treatment. Furthermore, it is not clear if this benefit would be observed if compared to proven triplet regimens.

HEPATOCELLULAR CANCER

Hepatocellular carcinoma (HCC) is the third leading cause of death worldwide after lung and gastric cancers[61]. Although 5-year survival rates can exceed 70% with surgical management, < 30% of patients are eligible for surgery due to an advanced stage of disease at presentation. The treatment of advanced disease with cytotoxic chemotherapy has been disappointing with multiple studies failing to show an improvement in OS[62]. Several molecular pathways have been identified in the tumorigenesis of HCC including angiogenesis, the epidermal growth factor receptor pathway and the RAS/RAF/MAP kinase pathway[63].

Angiogenesis inhibitors

HCCs are highly vascular tumors. With high microvessel density and levels of circulating VEGF being associated with poorer outcomes, the angiogenesis pathway is an attractive therapeutic target[63-68]. Sorafenib and sunitinib, both of which target VEGFR-1, -2 and -3, have shown clinical activity in Phase Ⅱ and Ⅲ clinical trials.

Sorafenib is the first targeted agent that has demonstrated an improvement in OS for patients with advanced HCC and is the first systemic therapy approved for this indication. An initial phase Ⅱ study of 137 patients showed promising activity for sorafenib in patients with advanced HCC with a median OS of 9.2 mo and a median time to progression (TTP) of 5.5 mo[69]. Patients with Childs-Pugh Class B liver function had a similar incidence of drug-related adverse events but had more frequent worsening of liver disease than patients with Childs-Pugh A liver function. OS was also significantly shorter in Childs-Pugh B patients (14 wk *vs* 41 wk)[70]. Subsequently, two phase Ⅲ, multicentre, randomized, placebo-controlled studies confirmed the activity of this agent[71,72]. Enrollment was limited to patients with Childs-Pugh A liver function. The SHARP study enrolled patients from Europe, North and South America and Australasia and had hepatitis C and alcohol as the predominant risk factors for HCC. The Asia-Pacific trial enrolled patients from China, South Korea and Taiwan

and had hepatitis B as the predominant risk factor for HCC. Both studies demonstrated a significant improvement in OS (SHARP: 10.7 mo *vs* 7.9 mo, HR 0.69, $P < 0.001$; Asia-Pacific: 6.5 mo *vs* 4.2 mo, HR 0.68, $P = 0.014$) and DCR (SHARP: 43% *vs* 32%, $P = 0.0002$; Asia-Pacific: 35.5% *vs* 15.8%, $P = 0.0019$) for sorafenib compared to best supportive care.

Sunitinib has also demonstrated activity in the treatment of advanced HCC[73,74]. However, a phase Ⅲ clinical trial comparing sunitinib to sorafenib was terminated in April 2010 due to increased toxicity in the sunitinib arm and because sunitinib did not meet the pre-defined criteria for superiority or non-inferiority (NCT00699374).

Two phase Ⅱ studies examining the activity of bevacizumab in the treatment of advanced HCC both demonstrate promising antitumor activity (RR 12.5%-13%; PFS 6.9 mo) but toxicity, in particular GI bleeding, is concerning[75,76]. There have been three single arm phase Ⅱ studies of bevacizumab in combination with a variety of chemotherapy regimens which show evidence of clinical activity but randomized comparisons are required[77-79].

EGFR inhibitors

EGFR is known to be expressed in HCCs and this pathway has been implicated in hepatocarcinogenesis[63]. However, the role of EGFR inhibitors in HCC is unclear. Minimal activity has been seen with the use of single agent lapatinib, gefitinib or cetuximab[80-85]. Modest activity is seen with the use of erlotinib but increased grade 3/4 toxicity was seen in a large proportion of patients in one of these studies, particularly those with Childs-Pugh Class B liver function[86,87]. A randomized phase Ⅲ study of sorafenib plus erlotinib versus sorafenib is currently underway (NCT00901901). To date, there has been no correlation demonstrated between expression of EGFR and response to EGFR-directed therapies in HCC.

Combination therapy

Interest has been raised by results seen with the combination of erlotinib and bevacizumab. In the initial report of a 40 patient phase Ⅱ study there was a confirmed PR of 25% and 16 wk PFS of 62.5%[88]. Updated data with 58 patients reports a confirmed PR of 28%, SD 62% and 16 wk PFS of 72%. The median PFS is 7.9 mo and median OS 12.8 mo[89]. Due to a significant incidence of GI bleeding early in the study, a protocol amendment required all patients with portal hypertension undergo screening for varices prior to enrollment, and treatment thereof if detected. A preliminary report of this combination in Asian patients demonstrates 2 confirmed and 1 unconfirmed PR in 51 patients enrolled[90]. A randomized phase Ⅱ trial of bevacizumab plus erlotinib *vs* sorafenib is currently underway (NCT00881751).

Summary

The use of targeted therapy in advanced/unresectable HCC has generated considerable interest. The greatest activity has been shown with dual blockage of both angiogenesis and EGFR mediated growth.

BILIARY CANCERS

Biliary tract cancer (BTC), consisting of intra- and extrahepatic cholangiocarcinoma as well as gallbladder malignancies, are rare tumors and only account for 3%-4% of gastrointestinal cancers. Surgery is the only curative option, but the majority of patients present with unresectable disease[91]. There are numerous phase Ⅱ clinical trials of cytotoxic chemotherapy, with most activity seen with gemcitabine in combination with either a fluoropyrimidine or a platinum analogue. Only recently has treatment with gemcitabine and cisplatin demonstrated a clear improvement in OS[92]. With limited options for these patients, there is great interest in exploring new treatments with targeted agents.

Angiogenesis inhibitors

In contrast to HCC, metastases from BTC tend to be hypovascular. However, VEGF expression has been detected in these tumors and correlates with advanced disease stage and poor prognosis[93,94]. A phase Ⅱ clinical trial using gemcitabine + oxaliplatin (GEMOX) in combination with bevacizumab demonstrated modest activity with an ORR 40% and SD 29%, median PFS was 7.0 mo, and median OS was 12.7 mo. The 6-mo PFS of 63% did not meet the pre-specified endpoint of an improvement from 50% to 70% as compared to GEMOX alone[95]. Randomized comparisons are needed to evaluate the true added benefit of bevacizumab. TKI inhibition has been less fruitful with two phase Ⅱ clinical trials of sorafenib failing to show significant clinical activity[96,97].

EGFR inhibitors

EGFR is overexpressed in the majority of cancers of the gallbladder and biliary tract, leading to a potential therapeutic target. Promising activity has been seen with the use of erlotinib. A phase Ⅱ study of erlotinib as a first- or second-line treatment in 42 patients with advanced BTC demonstrated a DCR of 51% and 24 wk PFS of 17%, median TTP 2.6 mo and median OS 7.5 mo[98]. In contrast, dual targeting of EGFR-1 and -2 with lapatinib failed to demonstrate any significant clinical activity[81].

Two single arm studies of cetuximab in combination with chemotherapy have shown activity. In a first-line study of 22 patients, GEMOX + cetuximab demonstrated an ORR 58% [including 1 complete response (CR)], SD 32% and median PFS 9.0 mo. Six initially unresectable patients subsequently underwent curative resection following a major response[99]. A second smaller study of 9 patients with intrahepatic BTC, who had previously progressed on GEMOX, received cetuximab in addition to GEMOX demonstrating an ORR 33% (including 1 CR) with median PFS 4 mo and median OS 7 mo[100]. Randomized comparisons are needed to evaluate the added benefit of cetuximab over chemotherapy alone.

Combination therapy

A preliminary report of a multicentre, phase Ⅱ clinical trial of the combination of bevacizumab and erlotinib suggests favourable results. In the first 20 evaluable patients, there is a confirmed PR 20% and an additional 7 patients have SD > 4 mo. Further results are anticipated shortly[101].

Summary

The role of targeted therapy in the treatment of advanced BTC is still under development, with many clinical trials ongoing. Promising preliminary results have been reported for the combination of erlotinib and bevacizumab[101]. Impressive activity was seen with the combination of GEMOX plus cetuximab, both in the first-line and second-line setting, but randomized comparisons are needed[99,100].

PANCREATIC CANCER

Worldwide, pancreatic adenocarcinoma is the eighth leading cause of cancer death[102]. The prognosis for pancreatic cancer is poor, with one and five year survival rates for all stages of 23% and 5%, respectively[103]. Only 15%-20% of patients will present with surgically resectable disease, and of these, only 20% will survive 5 years[104]. The OS for patients with metastatic or locally advanced disease ranges from 4-9 mo. Single agent gemcitabine is considered the standard treatment with only modest improvements in median OS[105]. A clear benefit in OS when adding a second chemotherapeutic, such as FU, oxaliplatin, or capecitabine to gemcitabine has not been observed[106-108]. An increase in the understanding of the unique molecular and genetic alterations in the development of pancreatic carcinoma has allowed for rational design of treatment strategies with targeted agents. Since gemcitabine is considered the standard treatment, most clinical trials of targeted agents have been directed at combining the novel agent with gemcitabine.

Angiogenesis inhibitors

Multiple anti-angiogenic agents have been tested in the pancreatic cancer population, including but not limited to bevacizumab, sorafenib, sunitinib, and axitinib and have failed to show a survival advantage[109-116].

EGFR inhibitors

A pivotal phase Ⅲ trial randomized 569 unresectable, locally advanced, or metastatic patients to receive standard gemcitabine or gemcitabine + erlotinib (100 or 150 mg orally daily)[117]. Statistically significant improvement in OS (6.24 mo *vs* 5.91 mo, $P = 0.038$) was observed along with prolonged one year survival (23% *vs* 17%, $P = 0.023$) in the combination arm. Subgroup analysis suggested benefit from erlotinib regardless of EGFR status. Despite these positive results, there has been hesitancy in the general medical oncology community to recommend gemcitabine + erlotinib as the standard of care for these patients as results demonstrate limited OS benefit and questionable clinical benefit.

A phase Ⅱ study of 41 patients with EGFR expressing pancreatic cancer receiving gemcitabine and cetuximab showed a promising median OS of 7.1 mo with a 12% PR and 63.4% SD[118]. The subsequent phase Ⅲ clinical trial which randomized 735 patients between gemcitabine alone or gemcitabine + cetuximab failed to show a statistical advantage in OS or PFS in the patients exposed to cetuximab[119].

Combination therapy

Early studies looking at the efficacy of combining HER1/EGFR and VEGF inhibition alone or in combination with chemotherapy in pancreatic carcinoma are underway or have been completed. In a phase Ⅲ trial, 607 patients with metastatic pancreatic cancer were randomized to gemcitabine + erlotinib plus/minus bevacizumab[115]. The addition of bevacizumab did not prolong OS although there was an improvement in disease free survival (DFS). A phase Ⅱ trial enrolled 139 patients who received gemcitabine, bevacizumab + erlotinib or gemcitabine, bevacizumab + cetuximab but did not show improvement in OS or PFS[110].

Other novel targets

The PI3K/Akt/mTOR pathway is activated in the majority of pancreatic cancers and preclinical studies have shown that inhibition of this pathway has an antitumor effect. However, the oral mTOR inhibitor everolimus, had minimal clinical activity in gemcitabine refractory disease[27]. Furthermore, the MMPs marimastat and talomastat failed to show significant clinical activity[120,121].

Summary

Pancreatic cancer is a devastating disease. For more than 20 years, the standard of care for patients with advanced disease has been single agent gemcitabine. Erlotinib was the first targeted agent in pancreatic cancer to improve OS in a randomized phase Ⅲ setting but despite a statistical benefit the medical community has been hesitant to adopt its use. Clearly, novel therapies, biomarkers and better clinical trial planning and development are needed for patients afflicted with this disease.

INVESTIGATIONAL NEW DRUGS TO BE CONSIDERED IN UPPER GI MALIGNANCIES

As described, novel anti-cancer agents targeting angiogenesis, the epidermal growth factor family of receptors and others, either alone or in combination with cytotoxic chemotherapy, have achieved modest success in upper GI malignancies. There is an urgent need to identify novel therapeutic options for these patients. We have elected to discuss two promising novel targets: the hedgehog (Hh) pathway and poly (ADP-ribose) polymerases (PARP) inhibition.

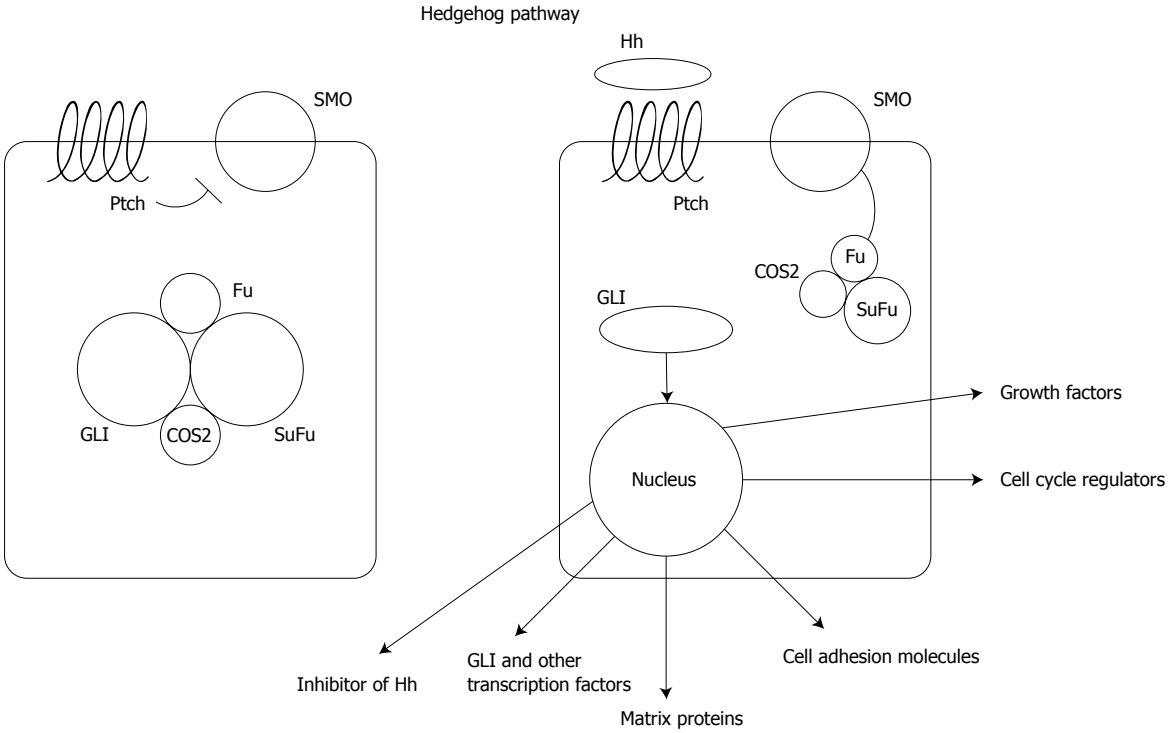

Figure 3 Schematic representation of the hedgehog pathway. Hh: Hedgehog; Ptch: Patched; Smo: Smoothened; Sufu: Fused and suppressor of fused.

Hedgehog pathway

The Hh pathway was originally identified as a normal developmental pathway in *Drosophila*[122,123]. Three mammalian homologues, Sonic, Indian and Desert Hh, have been identified as being required for embryonic development among which Sonic Hh is essential for lung, skin, foregut, brain and limb development[124,125]. All three are extracellular proteins that bind to a 12-transmembrane hedgehog receptor, Patched (Ptch). In the absence of Hh, Ptch inhibits Smoothened (Smo) and the downstream pathway. Smo is de-repressed upon binding by Hh, leading to dissociation of Gli transcription factors from the inhibitory complex of serine/threonine protein kinase Fused and Suppressor of Fused (Sufu)[126]. Gli is then transported into the nucleus leading to regulation of the expression of multiple pathways including growth factors, cell cycle regulators, cell adhesion molecules, matrix proteins, other transcription factors, and inhibitors of the Hh pathway itself[127-133] (Figure 3).

Alterations of the Hh pathway have been identified in various malignancies, including: (1) somatic mutation of Ptch; (2) mutation of Smo; (3) autocrine or paracrine overexpression of Sonic Hh; (4) amplification or overexpression of Gli-1; and (5) dysregulation of HIP in a Sonic Hh independent fashion, most likely through methylation of *HIP* gene[134-145]. In GI malignancies, the Hh pathway is activated through overexpression of Sonic Hh[139,146-148]. In gastric cancer xenografts, blockade of the pathway led to tumor apoptosis and regression[139]. In pancreatic cancer, the Hh pathway is important in both the development and maintenance of the malignant phenotype[139,147]. In HBCs, decreased proliferation and cell cycle arrest has been demonstrated with Hh inhibition[149].

The first member of the Hh pathway being explored in the clinic is inhibition of Smo, with the first tested Smo inhibitor being GDC-0449[150]. Nineteen patients were treated over 3 dose levels with the recommended phase Ⅱ dose being 150 mg daily. The drug was well tolerated with no dose-limiting toxicities observed. Common grade 1-2 toxicities included fatigue, dysguesia, and hyponatremia. Various single agent or combination phase Ⅰ or Ⅱ studies are ongoing with GDC-0449 in colorectal, ovarian, and advanced basal cell carcinoma. In 2010, preliminary results from two other agents inhibiting Hh were presented and further information should be forthcoming[151,152].

A number of other strategies against various parts of the Hh pathway are in preclinical or early clinical development, including Hh antagonist and Gli inhibitor.

Poly (ADP-ribose) polymerases

Poly (ADP-ribose) polymerases (PARP) is a superfamily of 17 proteins which senses the presence of DNA damage and has conserved catalytic domains among which, the function and biology of the nuclear protein PARP1 is the best characterized[153-155]. PARP1 consists of three functional domains: a DNA binding fragment, an auto-modification domain, and a NAD+-binding C-terminal catalytic domain[156]. The presence of single strand DNA damage leads PARP1 to undergo an NAD+-dependent polymerization of ADP-ribose to base excision repair proteins (XRCC1, DNA polymerase beta and ligase Ⅲ), histones H1 and H2B, and PARP1 itself[157,158]. These will in turn affect DNA replication, transcription, differentiation, gene regulation, protein degradation, and spindle maintenance.

In knockout mouse models, PARP1 is only responsible for 90% of the DNA repair, the rest completed by PARP2, which is critical in the absence of PARP1[156,159]. PARP1 is also involved in the detection of double-strand DNA damage *via* the homologous recombination repair by *BRCA1* and *BRCA2* and nonhomologous recombination repair by XRCC1 and DNA ligase Ⅲ[159-163].

Cell lines and xenografts that have homozygous deletion of *BRCA1* or *BRCA2* gene are very sensitive to PARP1 inhibition[161,162]. It is postulated that PARP1 inhibition in BRCA deficient cells cannot undergo the most effective DNA repair by homologous recombination repair after single strand breaks, leading to double strand breaks and thus apoptosis. Germline loss of *BRCA1/2* is commonly associated with breast and ovarian cancer; pancreatic cancer represents the third most common malignancy associated with this syndrome and thus PARP inhibition may be efficacious[164].

PTEN exerts transcriptional control of *RAD51* gene expression, a gene involved in repair of double stranded DNA breaks. PTEN deficient astrocytes are sensitive to PARP1 inhibition[165]. Additionally, truncated PTEN mutation but not point mutations is the biomarker for sensitivity to PARP1 inhibition[166]. Homozygous loss of PTEN has been observed in a number of cancers including colorectal cancer and HCC. Furthermore, methylation of PTEN genes have been observed in gastric cancer and 50% of pancreatic cancers harbour *K-ras* mutations which lead to increase in transforming growth factor-beta expression which in turn decreases PTEN expression[167,168]. Finally, treatment of HCC cell lines with a PARP inhibitor leads to a decrease in tumor size, mitosis, angiogenesis and an increase in apoptosis through decrease in VEGFR-1, EGFR, HIF-2 and HGF expression[169].

With the above noted pre-clinical findings, multiple early phase clinical trials are underway with the use of various PARP inhibitors. As of yet, limited data is available as to their use and efficacy and tolerability in upper GI malignancies though a number of proof of concept phase I and Ⅱ studies in GI malignancies are currently ongoing in microsatellite unstable colorectal cancer, locally advanced or metastatic colon cancer and gastric cancer (NCT00912743, NCT01063517, NCT00535353). Further investigations will look into the benefit of PARP inhibition in pancreatic cancer.

CONCLUSIONS AND FUTURE DIRECTIONS

Upper GI malignancies are aggressive tumors and often present with poor prognoses at an incurable stage. To date, cytotoxic chemotherapies have been the mainstay of treatment, unfortunately with less than desirable benefits in PFS, OS, or clinical benefit.

Though there has been some advancement in the treatment of these diseases with targeted therapies, most notably with sorafenib in HCC and trastuzumab in gastric cancers expressing HER-2, many studies have failed. Those drugs or drug combinations that have shown promise in phase Ⅱ clinical trial require validation in randomized phase Ⅲ studies in order to prove efficacy. Over the next decade it is hoped that further advances will be made in the treatment of upper GI malignancies.

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