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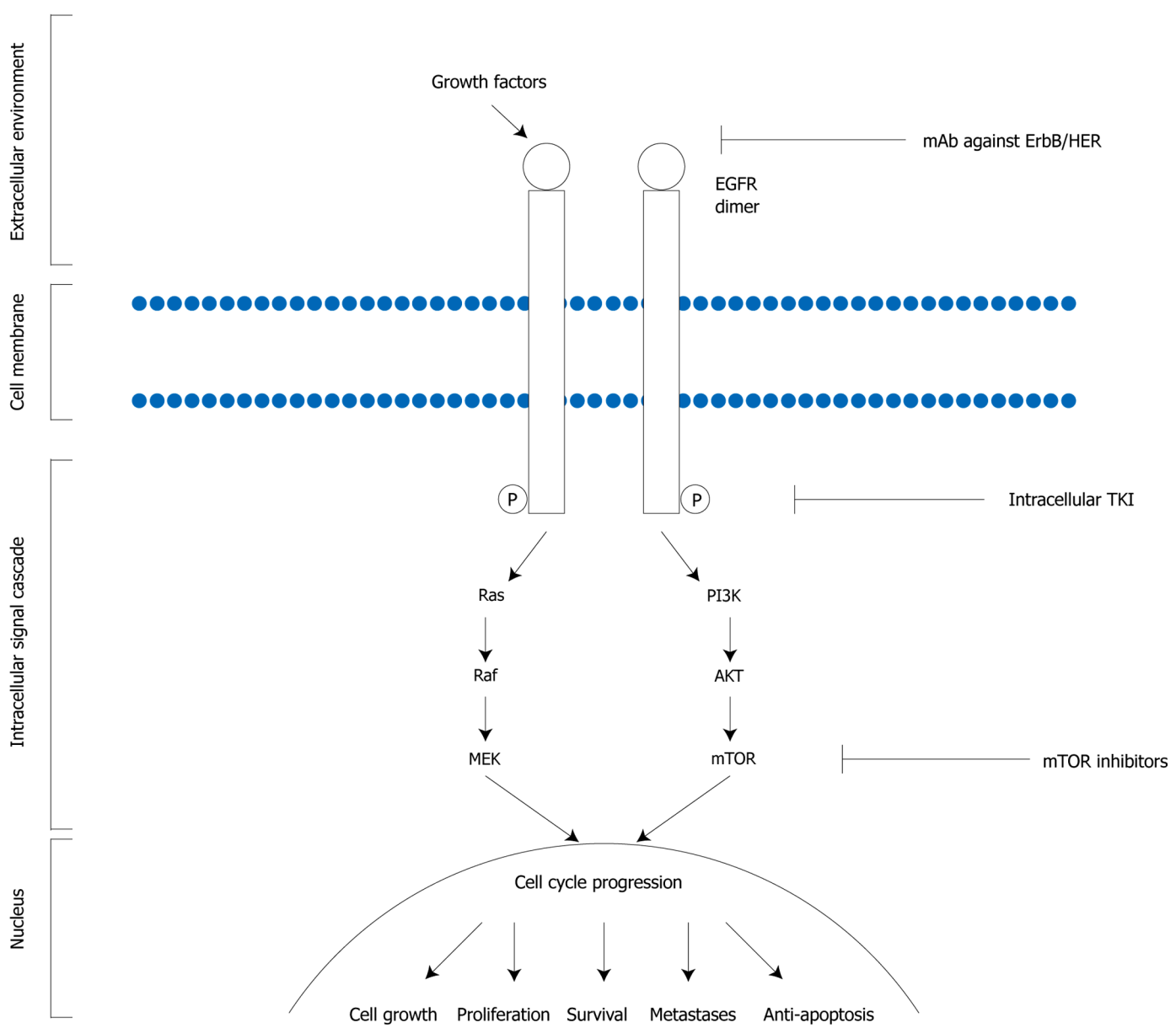

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EDITORIAL

Targeting metastatic upper gastrointestinal adenocarcinomas

Jennifer L Spratlin, Quincy Chu, Sheryl Koski, Karen King, Karen Mulder

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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 tumor 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 tumor 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

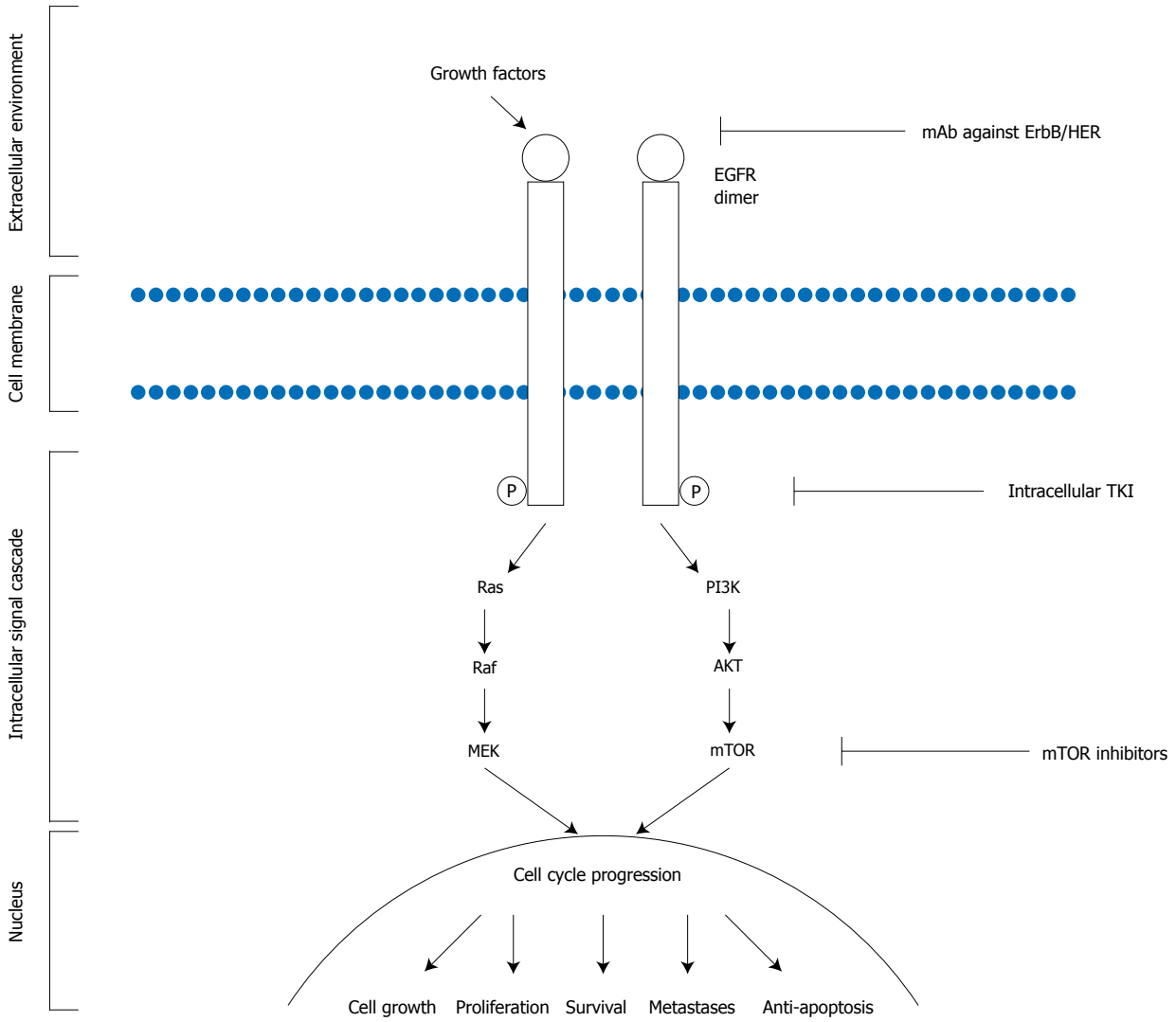

Figure 1 Schematic representation of the epidermal growth factor receptor pathway. EGFR: Epidermal growth factor receptor; mAB: Monoclonal antibody; TKI: Tyrosine kinase inhibitor; mTOR: Mammalian target of rapamycin; PI3K: Phosphoinositide 3-kinases; MEK: MAP kinase or ERK kinase.

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

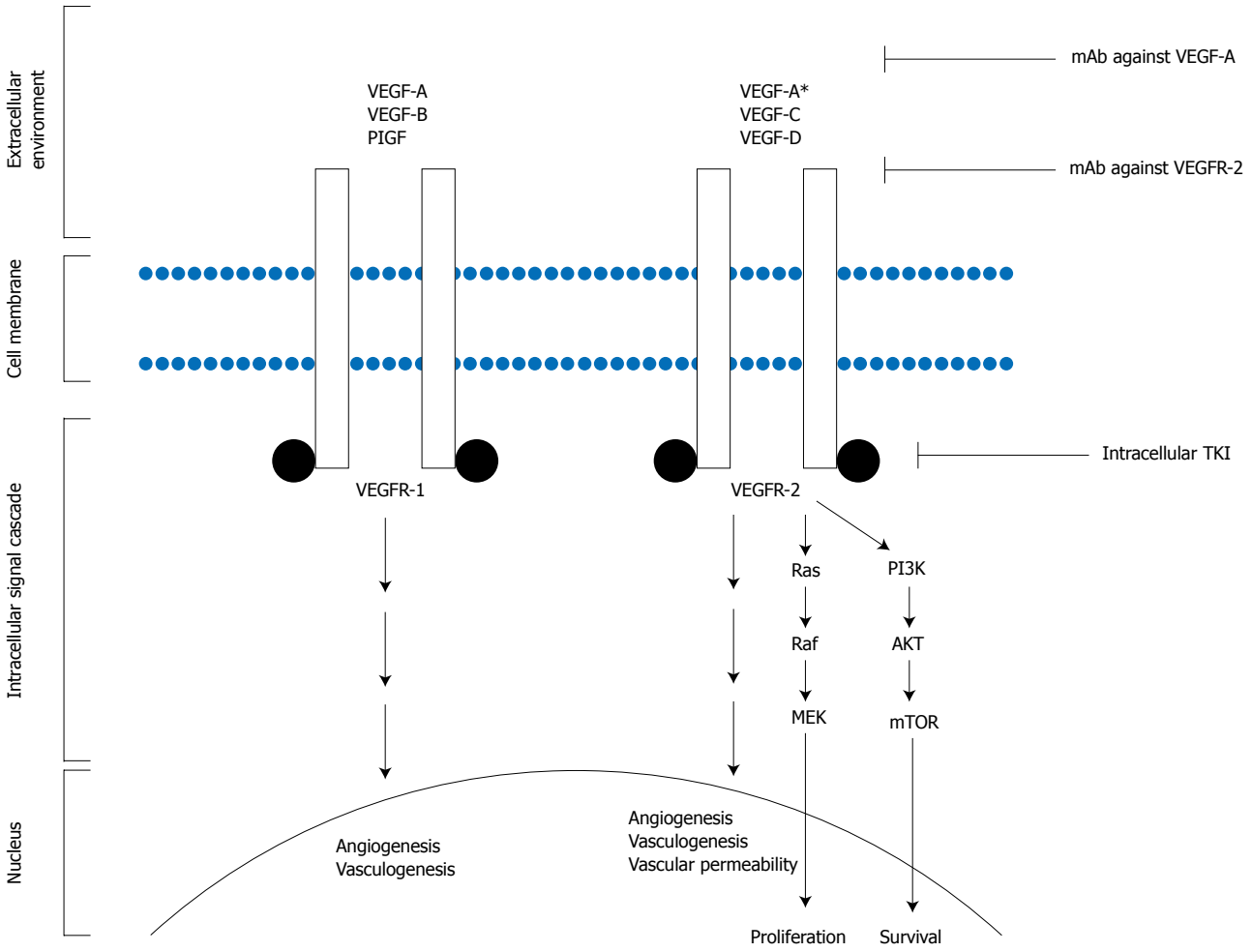

Figure 2 Schematic representation of the vascular endothelial growth factor pathway. VEGF: Vascular endothelial growth factor; PIGF: Placental growth factor; mAb: Monocolonal antibody; VEGFR: Vascular endothelial growth factor receptor; mTOR: Mammalian target of rapamycin; PI3K: Phosphoinositide 3-kinases;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

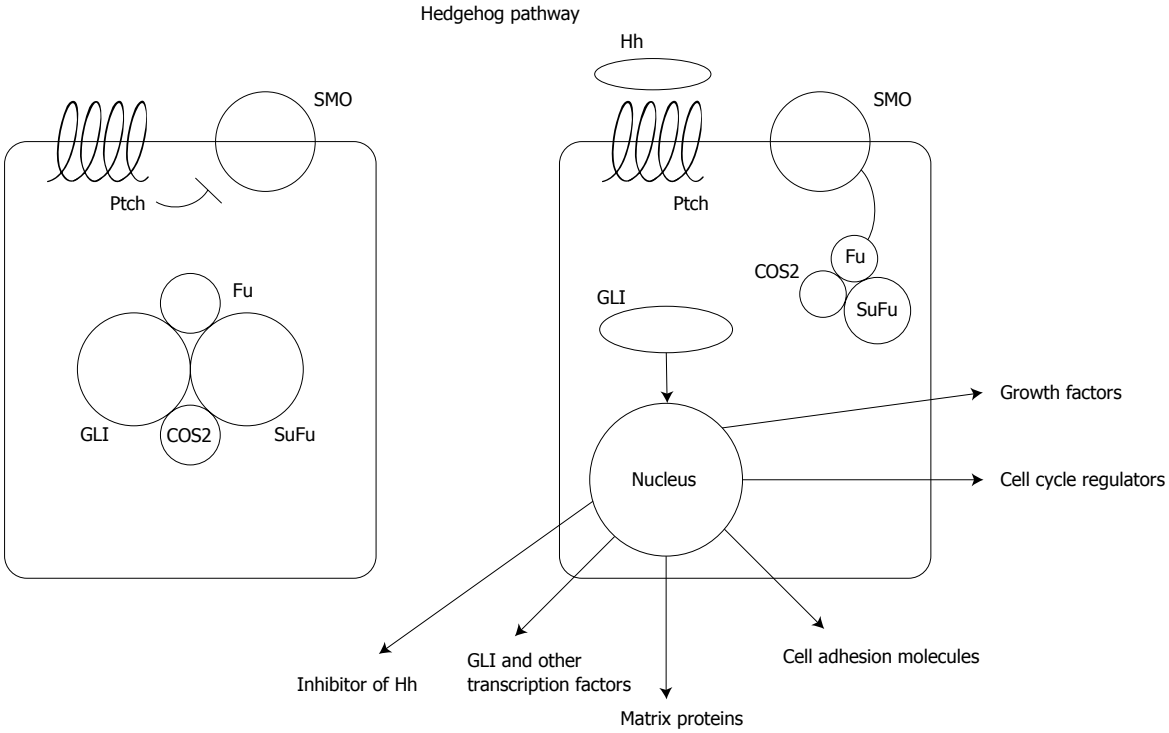

Figure 3 Schematic representation of the hedgehog pathway. Hh: Hedgehog; Ptch: Patched; Smo: Smoothened; Sufu: Fused and suppressor of fused.

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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EDITORIAL

Anaplastic thyroid carcinoma: A comprehensive review of current and future therapeutic options

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Abstract

Anaplastic thyroid carcinoma (ATC) is the rarest, but deadliest histologic type among thyroid malignancies, with a dismal median survival of 3-9 mo. Even though ATC accounts for less than 2% of all thyroid tumors, it is responsible for 14%-39% of thyroid carcinoma-related deaths. ATC clinically presents as a rapidly growing mass in the neck, associated with dyspnoea, dysphagia and vocal cord paralysis. It is usually locally advanced and often metastatic at initial presentation. For operable diseases, the combination of radical surgery with adjuvant radiotherapy or chemotherapy, using agents such as doxorubicin and cisplatin, is the best treatment strategy. Cytotoxic drugs for advanced/metastatic ATC are poorly effective. On the other hand, targeted agents might represent a viable therapeutic option. Axitinib, combretastatin A4, sorafenib and imatinib have been tested in small clinical trials of ATC, with a promising disease control rate ranging from 33% to 75%. Other clinical trials of targeted therapy for thyroid carcinoma are currently ongoing. Biological agents that are under investigation include pazopanib, gefitinib and everolimus. With the very limited therapeutic armamentarium available at the present time, targeted therapy constitutes an exciting new horizon for ATC. In future, biological agents will probably represent the standard of care for this aggressive malignancy, in the same fashion as it has recently occurred for other chemo-refractory tumors, such as kidney and hepatic cancer.

Key words: Anaplastic thyroid cancer; Targeted agents

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INTRODUCTION

Although anaplastic thyroid carcinoma (ATC) accounts for less than 2% of all thyroid malignancies, it is responsible for 14%-39% of deaths related to malignant thyroid tumors[1]. The female/male ratio is 5 to 1 and the peak of incidence is in the sixth and seventh decades of life[2]. In sharp contrast to the behaviour of well differentiated thyroid carcinomas, a diagnosis of ATC is almost inevitably fatal within 3-9 mo of diagnosis, with only 10%-15% of patients alive at two years[3]. The three different morphologic patterns identifiable at histologic analysis (*squamoid*, *spindle cell* and *giant cell)* present similar biological and clinical features[4,5]. The coexistence of both well differentiated and anaplastic thyroid carcinoma has also been reported, with the prognosis being determined by the ATC compo-

nent[6]. Clinically, ATC manifests itself with a rapidly enlarging anterior neck mass, with accompanying dyspnoea, dysphagia and vocal cord paralysis. Death is often caused by tracheal and oesophageal invasion and obstruction, as well as by consequences of metastatic disease. ATC is usually advanced at diagnosis and frequently surgically unresectable[2,4]. Around 20%-50% of patients present with distant metastases, most often pulmonary[7], and another 25% develop new metastasis during the rapid course of the disease. Because of its aggressive nature, ATC is classified as stage Ⅳ according to the American Joint Committee on Cancer, regardless of the tumor size or the presence of lymph node or distant metastasis[8].

The most important prognostic factors are age, gender, presence of distant metastasis and local extent. Younger female patients (< 65 years old), with a small (less than 5 cm or intra-thyroidal) ATC and no distant metastasis at diagnosis, have a better prognosis[2,9].

Treatment of patients diagnosed with ATC is not standardized and the feasible options include surgery, radiotherapy and chemotherapy. These treatment modalities must be combined in order to maximize the clinical outcome, in terms of both local and systemic disease control[10].

TREATMENT MODALITIES

Surgery

The aim of surgery is to obtain a complete macroscopic resection, with microscopically clear resection margins. Achieving a radical resection has been shown to confer a substantial benefit[11-13]. Complete resection has been identified as a prognostic factor in several clinical trials[14-17]. In a retrospective analysis conducted in 33 patients with ATC treated with several types of surgery (either with a radical or palliative intent), Haigh *et al*[13] observed a huge increase in overall survival (OS) in patients who received potentially curative resection followed by adjuvant radiotherapy, compared with those treated with palliative resection followed by radiotherapy (OS: 43 mo *vs* 3 mo, P = 0.002). In a retrospective study of 67 patients, Pierie *et al*[7] reported a 92% 1 year OS in patients who received radical surgery plus adjuvant radiotherapy compared with 35% in those who received debulking surgery and radiotherapy (P = 0.0001). Similar results were obtained in a retrospective analysis of 50 patients by Yau *et al*[11], who demonstrated that younger patients with localized ATC benefited from an aggressive multidisciplinary approach consisting of radical surgery followed by chemoradiotherapy. When feasible, surgery must aim at a radical intent. The categories of patients that may be most suitable for this approach are young patients (< 65 years old) with small lesions (< 6 cm) and no distant metastasis. However, surgery also plays an important role for palliation. Partial resection of the tumor followed by radiotherapy and chemotherapy may delay or avoid airway obstruction, although it can improve survival only by a few months[18]. It is theoretically possible that, in selected patients, even in the setting of metastatic disease, surgery may result in an improved quality of life and prevent death from suffocation[11].

COMBINATION OF SURGERY WITH OTHER TREATMENT MODALITIES

Since surgery alone is not able to control the disease even in patients with small intra-thyroidal masses, adjuvant therapy is always required, and can be administered either with radiotherapy (RT) or chemoradiotherapy. In a retrospective study[19] conducted by Busnardo *et al*, better survival was achieved in patients with ATC undergoing a triple modality treatment (radical surgery followed by chemotherapy and RT, group 1), compared with patients who received chemotherapy alone (group 2) or RT alone (group 3). Median survival was 11 mo for group 1, 5.7 mo for group 2 and 4 mo for group 3. A French study[20] was conducted in 30 patients affected by ATC. Twenty of these patients were treated with a multimodality strategy, consisting of prior surgery followed by sequential chemo-radiation based on two cycles of three-weekly doxorubicin (60 mg/m^2) plus cisplatin (120 mg/m^2) before RT and four cycles of the same schedule after RT. RT consisted of two daily fractions of 1.25 Gy, 5 d a week for a total dose of 40 Gy (a hyperfractionated accelerated regimen). Overall survival rate at 3 years was 27% and median survival was 10 mo. Similar results were observed in a Japanese study[14] enrolling 37 patients with ATC without distant metastasis. Patients underwent surgery followed by RT. Those who had complete resection and RT survived significantly longer than other patients (median overall survival 8.1 mo *vs* 2 mo, P = 0.001).

Whether surgery should be given up-front or after neoadjuvant treatment is a matter of debate. In fact, primary chemotherapy might make inoperable lesions operable, with the additional potential advantage of preventing distant metastasis. Encouraging results in this setting were reported by Tennvall *et al*[21] who analyzed the outcome of 55 patients with ATC treated with three similar protocols of neoadjuvant chemo-radiotherapy between 1984 and 1999. RT was given according to a hyperfractionated schedule and chemotherapy consisted of weekly doxorubicin. The response to primary treatment was 72% and surgery was performed in 40 patients. No patient failed to complete the protocol due to toxicity. In only 13 cases (24%), death was attributed to local failure. Five patients (9%) had a survival exceeding 2 years. No signs of local recurrence were reported in 33 patients (60%). In a recent phase Ⅱ study[22], weekly neoadjuvant paclitaxel was employed in patients with non-metastatic disease. Patients who responded partially (23%) or totally (7%) to induction chemotherapy were subsequently treated with surgery followed by RT or exclusively RT, with an acceptable survival rate. Weekly induction paclitaxel may be considered a promising therapeutic strategy for this category of patients. Hyperfractionated RT seems to be more effective for local control than conventional treatment[23,24] and

doses above 45-50 Gy should be administered in order to achieve a radical intent[7]. RT combined with chemotherapy is more effective than RT alone[23].

SYSTEMIC TREATMENT

Cytotoxic agents

ATC cannot be regarded as a very chemo-sensitive tumor. Doxorubicin is not able to achieve more than a 20% response rate[25]. In a randomized study of the Eastern Cooperative Oncology Group, Shimaoka *et al*[26] observed that combination chemotherapy based on doxorubicin (60 mg/m^2) and cisplatin (40 mg/m^2) was more effective than doxorubicin alone and provided a higher complete response rate. In patients with thyroid carcinomas with varying histologies, De Besi *et al*[27] reported the encouraging activity of a regimen containing doxorubicin (60 mg/m^2), cisplatin (60 mg/m^2) and bleomycin (30 mg/d for three days). More recently, single drug docetaxel was tested as first-line chemotherapy in patients with advanced ATC. Out of seven patients, one obtained a complete response which lasted about 6 mo and two patients obtained stable disease[28]. In a prospective phase Ⅱ clinical trial of paclitaxel, twenty patients with metastatic ATC were enrolled and nineteen were evaluable for response. A remarkable response rate of 53% was obtained[29]. In a preclinical experiment, Voigt *et al*[29] tested the activity of topotecan, oxaliplatin, vinorelbine, gemcitabine and paclitaxel alone or in combination in ATC cell lines, but only paclitaxel, gemcitabine and vinorelbine appeared to be active in ATC[30] and the combinations of vinorelbine/gemcitabine and paclitaxel/gemcitabine seemed to act synergistically. These results should receive confirmation in clinical trials.

Biological agents

Anti-angiogenetic agents: A common feature of thyroid cancers is their markedly increased vascularisation, with an elevated expression of the vascular endothelial growth factor (VEGF) by immunohistochemistry, compared with normal thyroid tissue[31,32]. VEGF levels are correlated with stage, tumor size, nodal involvement, extra-thyroidal invasion and distant metastases[33]. On the basis of these findings, several drugs targeting angiogenesis have been evaluated against ATC.

Combretastatin A4 phosphate (CA4P) is a tubulin-binding vascular disrupting agent that inhibits tumor blood flow. In contrast to other anti-angiogenetic drugs that block the formation of new vessels in tumors, vascular disrupting agents (such as CA4P) stop blood flow through already existing vessels, with the result of depriving tumor cells of oxygen and nutrients[34,35]. CA4P has activity against ATC cell lines and xenograft[36]. In a phase I trial[37], one patient with ATC showed a progression-free survival of 30 mo, however, the drug was found to be associated with significant cardiovascular side effects at the escalating doses employed. In a phase Ⅱ trial by Cooney *et al*[38], CA4P alone was tested in 18 patients with metastatic ATC who had progressed with other standard therapies. Therapy was well tolerated at the dose selected, with no clinically meaningful myelosuppression or cardiac toxicity. No objective responses were reported. Six patients had stable disease and 25% of patients survived longer than 3 mo. On the basis of a possible synergism between CA4P and cytotoxic drugs, Yeung *et al*[39] tested the combination of CA4P with carboplatin-paclitaxel against ATC in a nude mouse xenograft model. This triple-drug combination showed remarkable activity, paving the way for the clinical evaluation of CA4P-paclitaxel-carboplatin. A phase Ⅱ study assessing the safety and activity of this triple combination therapy was carried out in 26 patients with advanced ATC. There were no objective responses and a median survival of 4.7 mo was observed. Interestingly, more than a third of patients experienced a survival longer than 6 mo. Therapy was well tolerated, with only 4% of patients experiencing any kind of G4 toxicity[40].

Axitinib (AG-013736) is an oral, potent and selective inhibitor of VEGFRs 1, 2 and 3. Preclinical studies demonstrated that axitinib rapidly and selectively inhibits VEGF-dependent fenestrations and VEGFR-2 and 3 expression in endothelial cells, with the result of blocking angiogenesis and tumor blood flow[41-44]. The principal mechanism of action of axitinib is inhibition of VEGF signalling[40]. A phase I trial[45] of 36 patients with advanced solid tumors identified axitinib 5 mg twice daily as the recommended dose for further clinical testing. A phase Ⅱ clinical trial was conducted in various types of thyroid cancers. An objective response was reported in 30% of patients, and 38% of patients had stable disease[46]. The drug showed activity in all histologic subtypes and the main side effect, hypertension, was easily managed.

Other anti-angiogenetic compounds have been evaluated in the preclinical setting. In particular, bevacizumab (a monoclonal antibody anti VEGF) was tested alone and in combination with cetuximab in an *in vivo* model compared with doxorubicin. This study demonstrated that both drugs, either alone or in combination, inhibited tumor growth and angiogenesis better than doxorubicin[47,48]. AZD2171, a tyrosine-kinase inhibitor of the VEGFR-1 and VEGFR-2, blocked tumor growth and prolonged survival of ATC-bearing mice[49].

Histone deacetylase inhibitors

Histone deacetylase inhibitors are a promising class of antineoplastic agents that are able to induce cell differentiation, cell-cycle arrest and apoptosis through hyperacetylation of histones, with the potential to enhance the cytotoxicity of drugs such as doxorubicin. Preclinical studies have shown that valproic acid, a potent anti-convulsant agent, is able to enhance the activity of doxorubicin in cell lines derived from ATC alone or in combination with other drugs[50,51].

Noguchi *et al*[52] reported on a patient with a diagnosis of non-metastatic ATC treated with a combination of neoadjuvant chemoradiation plus valproic acid (VA) followed by debulking surgery. The patient received 1200 mg

of oral VA daily, the upper therapeutic dose for epilepsy, concomitant with 100 mg/m^2 of cisplatin and 50 mg/m^2 of doxorubicin, with both drugs given at three-four week intervals with the concomitant administration of a total radiation dose of 40 Gy. The patient achieved a partial response and was then treated with surgery, achieving a disease-free-survival of more than 6 mo[52].

Tyrosine kinase inhibitors

Imatinib (STI571) is an oral inhibitor of the ABL kinase (the product of the fusion of Bcr and Abl gene). In addition, it can specifically inhibit c-Kit and PDGF receptors, which are hyper-functioning in some malignancies. On the basis of the assumption that ATC which overexpresses PDGFR and/or Abl might respond to imatinib, Ha *et al*[53] treated 11 patients with recurrent and pre-treated ATC with single agent imatinib. Of the 8 assessable patients, 2 obtained a partial response and 4 stable disease (disease control rate of 6/8), with a 6-mo progression-free survival rate of 27% and a 6-mo overall survival rate of 46%. Further clinical trials are warranted.

Sorafenib (Bay43-9006, Nexavar) is an oral, small tyrosine kinase inhibitor of the raf.1 protein kinase receptor, VEGFR2 and PDGF-β and displays strong anti-angiogenetic activity. In a phase Ⅱ study, Nagaiah *et al*[54] assessed the safety and activity of sorafenib in 16 pre-treated patients with advanced ATC. The drug was given orally at doses of 400 mg *bid* until disease progression. Disease control rate was 40% and toxicity was manageable. Lymphopenia and cutaneous rash were the main side effects reported. Sorafenib demonstrates an acceptable response rate in pre-treated ATC patients and further clinical studies are warranted.

Anti-EGFR agents

The epidermal growth factor receptor (EGFR) has been implicated in the pathogenesis of several types of cancer. There is supporting evidence that EGFR is expressed at high levels in ATC and papillary thyroid cancers[55,56]. In an *in vitro* study by Bergström *et al*[57], EGFR was expressed in all of the ATC cell lines examined and non-ligand dependent phosphorylation of EGFR was identified in half of the cell lines. High expression of EGFR appears to be a negative prognostic factor in many types of tumors, but few studies have examined its prognostic role in thyroid cancers[58]. Strong EGFR staining in papillary thyroid cancer was associated with poor prognosis[59]. These findings suggest that inhibition of EGFR may have anti-cancer efficacy in ATC.

Gefitinib (ZD1839) is an orally active EGFR inhibitor that blocks EGFR-mediated downstream signal transduction. No clinical trials have been performed to determine the effectiveness of gefitinib in ATC, however, preclinical trials have tested the activity of this drug against *in vitro* or *in vivo* models of ATC. Schiff *et al*[60] were the first to report the *in vivo* effects of EGFR inhibition on ATC xenograft in nude mice. In this study, the administration of gefitinib resulted in significant inhibition of tumor growth.

Cetuximab (C225) is a human-murine chimeric monoclonal antibody against EGFR. It has been approved by the Food and Drug Administration (FDA) for use in metastatic colorectal cancer and head and neck squamous cell carcinoma either metastatic or unresectable. There are no studies in the literature that have examined the effects of cetuximab in ATC. In preclinical trials, Kim *et al*[61] observed that combination therapy with cetuximab/irinotecan inhibits the growth and progression of orthotopic ATC xenografts in nude mice. Clinical trials are warranted to define the impact of EGFR inhibitors on ATC.

Agents targeting the NF-κB pathway

The *26s proteasome* is a large ATP-dependent multimeric complex that degrades intracellular proteins that have been marked for proteolysis by the process of ubiquitination[62]. The ubiquitin-proteasome pathway plays a significant role in neoplastic growth and metastatic spread. The proteasome is also required for activating nuclear factor κB (NF-κB) by degradation of its inhibitory protein factor κB inhibitor (I-κB). NF-κB is a transcription factor that upregulates a number of proteins involved in cancer progression including several anti-angiogenetic and anti-apoptotic factors[63].

Bortezomib (PS-341) is a proteasome inhibitor that has been approved by the FDA for the treatment of multiple myeloma and its mechanisms of action include the inhibition of I-κB, which leads to inactivation of the transcriptional factor NF-κB[64,65]. NF-κB is often constitutively activated in medullary thyroid carcinoma and ATC, and is therefore implicated in their pathophysiology[66]. A preclinical study showed that ATC cell lines are sensitive to bortezomib, alone or in combination with doxorubicin[67]. Bortezomib has also been shown to increase the expression of TRAIL (TNF-related-apoptosis-induced-ligand) receptors (TRAIL-R1 and 2) and to sensitize tumors to TRAIL-mediated killing[68]. The high cytotoxic activity and good *in vivo* tolerability of bortezomib holds promise for its future use in the treatment of ATC patients.

Agents targeting farnesyl-transferase

A new group of therapeutic agents called farnesyl-transferase inhibitors (FTIs) has been used in the treatment of solid tumors. Activating *ras* mutations are common in thyroid cancers[69]. Ras, the protein product of the *ras* proto-oncogene, requires post-translational modification by conjugation of a farnesyl moiety to its C-terminal amino acid. After farnesylation, Ras is localized to the inner surface of the cell membrane and is able to transduce the mitogenic signals mediated by tyrosine kinase receptors. Farnesylation-blocking agents therefore operate by inhibiting Ras activity.

Manumycin A is a natural product of Streptomyces parvulus that inhibits farnesyl transferase and has antitumor activity against a variety of cancers *in vitro* and in xenograft models[70,71]. In a preclinical study, Xu *et al*[72] observed good antitumor activity with the combination of manumycin A and paclitaxel against nude mice bear-

Table 1 Selected clinical trials on targeted agents for advanced/metastatic thyroid carcinomas

Trial	Phase	Setting	Patients	Targeted agent	DCR
Cooney *et al*[38]	II	Advanced pretreated disease	18 with ATC	CA4P alone	33%
Cohen *et al*[46]	II	Advanced pretreated disease	60 (2 with ATC)	Axitinib alone	71%
Ha *et al*[53]	II	Advanced pretreated disease	11 with ATC	Imatinib alone	75%
Nagaiah *et al*[54]	II	Advanced pretreated disease	16 with ATC	Sorafenib alone	40%

ATC: Anaplastic thyroid carcinoma; CA4P: Combretastatin A4; DCR: Disease control rate (complete responses + partial responses + stable disease).

ing ATC xenografts. Concordant results were obtained by Yeung *et al* in a similar study[73]. Apart from inhibition of angiogenesis, manumycin A causes apoptosis by inducing the pro-apoptotic protein Bax[74]. No clinical trials have been performed to determine the activity and/or efficacy of manumycin A against ATC.

Agents targeting matrix metalloproteinases

Matrix metalloproteinases (MMPs) are an important group of enzymes mediating the endothelial cell invasion and migration required for the formation of new capillaries, a crucial step in the angiogenesis process.

Minocycline is a semi-synthetic analogue of tetracycline active against *MMPs* through chelation of the zinc ion at the active site of the enzyme. In a preclinical study, She *et al*[75] investigated the effect of adding minocycline to manumycin A and paclitaxel against human ATC cells xenografted in nude mice, and demonstrated that the triple-drug combination resulted in the lowest average tumor growth rate, yielding significantly better survival than manumycin A alone, paclitaxel alone, or manumycin A plus paclitaxel. This novel combination deserves further investigation for the treatment of ATC.

Agents targeting PPARγ

Peroxisome proliferator-activated receptor gamma (PPARγ) agonists have demonstrated antitumor activity against a variety of human cancers in pre-clinical models and clinical trials[76]. The mechanism of action of the different classes of these compounds, which comprise non-steroidal anti-inflammatory drugs, amino-acid derivatives, polyunsaturated fatty acids, eicosanoids and thiazolidinediones, is attributed to the capacity of binding and activating PPARγ. PPARγ acts as a tumor suppressor gene, upregulating important enzymes which control the cell cycle[77].

Thiazolidonediones represent the most widely investigated pharmaceutical class among PPARγ agonists[78]. In a preclinical study, two agents belonging to this class, ciglitazone and rosiglitazone, showed promising biological effects in ATC cells, such as an increased rate of apoptosis and inhibition of anchorage-dependent and-independent growth and migration. Furthermore, rosiglitazone increased the expression of thyroid-specific differentiation markers, thus inducing a partial reversion of the epithelial-mesenchymal transition in ATC cells, which correlates with ATC growth and dissemination[79].

RS5444 is another thiazolidinedione agent and a PPARγ agonist. RS5444 demonstrated antitumor activity in preclinical studies, with a mechanism which includes the transactivation of genes regulating cell proliferation, apoptosis, and differentiation. In particular, PPARγ activation is able to upregulate p21 protein, which is known to complex and inhibit an eterodimeric complex called *cyclin dependent kinase 2* (CDK2)-cyclin E/A, responsible for cell cycle progression. Cells expressing nuclear *p21* are subsequently arrested in the G0-G1 phase of the cell cycle[80]. Copland *et al* published the first preclinical experience with *RS5444* against ATC. In this study, RS5444 alone did not induce cellular apoptosis, but when added to paclitaxel it managed to double the apoptotic index, in comparison to that of paclitaxel alone. The efficacy of RS5444 is closely linked to the proper functioning of PPARγ[81].

Selected clinical trials carried out on targeted agents are reported in Table 1.

CONCLUSION

On the basis of the data presented in this review article, it appears clear that at the present time, current therapeutic options for ATC are unsatisfactory. Surgery followed by chemoradiotherapy can significantly prolong the survival of patients carrying small, intra-thyroidal tumors, but this kind of presentation is very unusual for this cancer. ATC is often advanced and metastatic at diagnosis. For these patients, the prognosis is very poor, with an overall survival of about 3-6 mo. Patients with localized disease not amenable to surgical resection can be treated with neoadjuvant chemo-radiotherapy, but the role of this treatment modality is still debated.

There are few active compounds against ATC; the combination of doxorubicin and cisplatin has been the standard for many years. At the present time, paclitaxel plus a platinum compound (often carboplatin) also appears to have efficacy. With regard to biological drugs, axitinib, combretastatin A4, sorafenib and imatinib have been tested in clinical trials, with encouraging activity. The results from several ongoing clinical trials on ATC (Table 2), will hopefully expand the limited therapeutic armamentarium for this deadly disease.

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Table 2 Ongoing clinical trials of targeted therapies for thyroid cancer

Clinicaltrials.gov identifier	Investigational drug	Phase study	Eligible population	Planned enrolment	Primary end point	Status
NCT00389441	Axitinib	Phase Ⅱ, single arm	Radioiodine-refractory thyroid cancer, regardless of histology	52	Overall response rate	Active, not recruiting
NCT00510640	Sunitinib	Phase Ⅱ, single arm	Thyroid cancer, regardless of histology	66	Overall response rate	Recruiting
NCT00095836	Gefitinib	Phase Ⅱ, single arm	Thyroid cancer, regardless of histology	38	Overall response rate	Active, not recruiting
NCT01164176	Everolimus	Phase Ⅱ, single arm	Thyroid cancer, regardless of histology	32	Overall response rate	Recruiting
NCT01118065	Everolimus	Phase Ⅱ, single arm	Thyroid cancer, regardless of histology	42	Overall response rate	Recruiting
NCT00654238	Sorafenib	Phase Ⅱ, single arm	Thyroid cancer, regardless of histology	55	Overall response rate	Recruiting
NCT00625846	Pazopanib	Phase Ⅱ, single arm	Thyroid cancer, regardless of histology	188	Overall response rate	Recruiting
NCT01236547	Pazopanib	Phase Ⅱ, two arms Paclitaxel neoadjuvant, concomitant and adjuvant to radiotherapy with or without pazopanib	Anaplastic thyroid cancer	99	Overall response rate	Recruiting
NCT00126568	Sorafenib		Anaplastic thyroid cancer	36	Overall response rate	Recruiting
NCT00603941	CS7017	Phase Ⅰ/Ⅱ	Anaplastic thyroid cancer	54	Maximum tolerated dose/Overall response rate	Active, not recruiting
NCT00115739	Imatinib	Phase Ⅱ	Anaplastic thyroid cancer	29	Overall response rate	Active, not recruiting

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TOPIC HIGHLIGHT

Michiko Yamagata, MD, PhD, *Series Editor*

Recent progress and limitations of chemotherapy for pancreatic and biliary tract cancers

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Abstract

Gemcitabine chemotherapy has been the standard for advanced pancreatic cancer for more than a decade. New oral fluoropyrimidines such as S-1 and capecitabine are other key drugs. Gemcitabine plus erlotinib was the only combination therapy that significantly prolonged survival, although the effect was minimal. Little or no improvement in survival with recent molecular-targeted drugs might be attributed to the very high incidence of K-ras gene mutation in pancreatic cancer. Recently, the non-gemcitabine-based-regimen of FOLFIRINOX showed significantly greater overall survival compared with gemcitabine for the first time. For biliary tract cancer, gemcitabine plus cisplatin combination chemotherapy has been proved to significantly prolong survival and will become the standard therapy. Further improvement in survival is expected by the addition of cetuximab.

Key words: Cisplatin; Epidermal growth factor receptor; Gemcitabine; K-ras; S-1

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INTRODUCTION

Pancreatic cancer and biliary tract cancer are malignancies with an extremely poor prognosis and treatment of these intractable advanced cancers is challenging. Progress in chemotherapy was made after the introduction of gemcitabine as a key drug and the recently developed oral fluoropyrimidines as a second drug. In the present review, we will provide information on the recent prog-

ress, limitations and future perspectives of chemotherapy for these cancers, including our own experience.

CHEMOTHERAPY FOR PANCREATIC CANCER

Gemcitabine

Pancreatic cancer is a devastating disease. The incidence rate is almost identical to the mortality rate highlighting the poor prognosis of this cancer. In addition, the number of patients with pancreatic cancer has been increasing and it is now the fourth or fifth cause of cancer-related death both in Japan and the United States. Little is known about the risks for pancreatic cancer[1]. The majority of patients are identified at unresectable advanced stages such as metastatic or locally advanced disease, and have a median survival of 3 to 6 mo for metastatic disease and 6 to 10 mo for locally advanced disease[2,3].

Systemic chemotherapy with gemcitabine has been the standard therapy for advanced pancreatic cancer after it was confirmed to prolong survival and improve clinical response compared with 5-fluorouracil (5-FU)[4]. In fact, after the introduction of gemcitabine in Japan in 2001, most patients with advanced pancreatic cancer received gemcitabine-based systemic chemotherapy. In our analysis conducted at Tokyo University Hospital, the median survival time and 1-year survival rate were 11.6, 9.3, 6.7, 7.8, 2.4 mo and 47%, 39%, 27%, 22%, 7% in patients treated with gemcitabine, chemoradiotherapy using 5-FU, best supportive care (BSC) for locally advanced disease, and gemcitabine or BSC for metastatic disease, respectively, which showed that both gemcitabine and chemoradiotherapy prolonged overall survival time compared with BSC[5]. Due to the convenience of gemcitabine chemotherapy compared with chemoradiotherapy with 5-FU, and increased toxicities with chemoradiotherapy using gemcitabine, gemcitabine is used in patients with locally advanced disease as well as those with metastases.

S-1

5-FU administered intravenously was the standard chemotherapy for pancreatic cancer before the introduction of gemcitabine. Oral fluoropyrimidines, such as S-1 and capecitabine have recently been developed as new drugs. S-1 is an oral fluoropyrimidine, consisting of tegafur, a prodrug of 5-FU, and two bio-modulators, 5-chloro-2,4-dihydroxypyridine and potassium oxonate, which maintains high serum 5-fluorouracil levels and reduces gastrointestinal toxicity. S-1 has demonstrated efficacy in a variety of solid tumors, especially in Asian patients. This agent has been reported to result in an objective response rate equivalent to that of gemcitabine in patients with advanced pancreatic cancer[6,7]. Therefore, it is now considered to be another important key drug for advanced pancreatic cancer in Japan. In fact, both gemcitabine and S-1 are widely used in our hospital following the introduction of S-1 in February 2005[8].

Combination therapy with gemcitabine

More than 10 years have passed since the systemic administration of gemcitabine became the standard chemotherapy for advanced pancreatic cancer[4]. During this period, numerous attempts have been made to improve survival by combining gemcitabine with other chemotherapeutic agents. However, most of these attempts have failed to prolong overall survival compared with gemcitabine monotherapy. Of the available combinations of cytotoxic drugs, a tendency for better survival was reported for cisplatin, capecitabine, or oxaliplatin, However, significant improvements in survival have not been proved[9-12].

Following the reported efficacy of S-1 as monotherapy, the possibility of improving survival using S-1 in combination with gemcitabine was investigated as a next step[13]. We performed a pilot study using a modified combination chemotherapy regimen with S-1 plus gemcitabine. In our treatment schedule, gemcitabine was administered at a dose of 1000 mg/m^2 by a 30-min intravenous injection on days 1 and 15 of each cycle. S-1 was administered orally at a dose of 40 mg/m^2 twice daily for the first 14 consecutive days followed by a 14-d rest period. This cycle was repeated every 28 d. The median time to progression and the median survival time were 10 and 20 mo, respectively, without significant toxicity, which suggested better survival using this combination therapy[14]. A larger-scale multicenter prospective study to confirm these results has been conducted at our hospital. A phase Ⅲ trial was also performed in another multicenter study in Japan.

Molecular-targeted drugs

Erlotinib: A number of new molecular-targeted drugs have recently been developed for the treatment of malignant tumors. Many of these drugs were investigated for the treatment of pancreatic cancer[15,16]. However, most of these agents failed to prolong overall survival compared with gemcitabine alone. To date, erlotinib in combination with gemcitabine has been the only drug to show prolonged survival in advanced pancreatic cancer[17]. However, the survival benefit was only two weeks despite high costs and greater toxicity than gemcitabine monotherapy.

One of the reasons for little or no improvement in survival benefit with molecular-targeted drugs may be attributed to the characteristic molecular abnormalities in pancreatic cancer. Genetic abnormalities in K-ras, p16, p53 and DPC4 have been identified in pancreatic cancer. Among these, a peculiar feature is that most pancreatic adenocarcinomas contain K-ras gene mutations[18]. Ras gene mutations are prevalent in all human cancers, but the incidence varies among these cancers. Pancreatic cancer has the highest frequency of ras gene mutations of all human cancers. Erlotinib is a low molecular weight drug that inhibits signal transmission by binding to the epidermal growth factor receptor (EGFR), an important cell-surface receptor. As over-expression of the EGFR is associated with tumor progression, inhibition of EGFR leads to an anti-cancer effect. Consequently, it is one of the important molecular targets for anticancer therapies.

Recently, it was shown that cetuximab, a monoclonal antibody against the EGFR, was effective in patients with

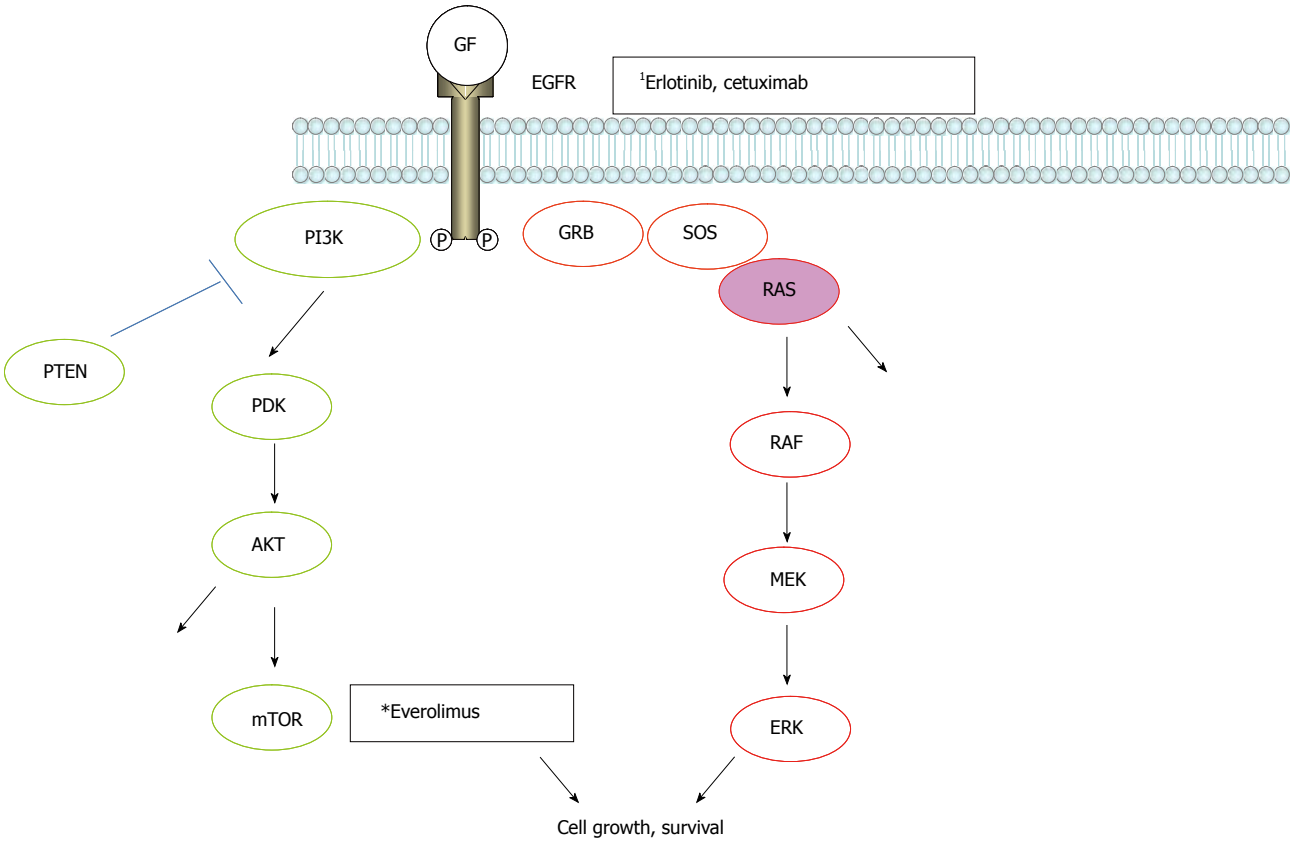

Figure 1 Signal transmission in the epidermal growth factor receptor pathways. RAS/RAF/MAPK and PI3K/AKT/mTOR cascades are major pathways downstream of the epidermal growth factor receptor (EGFR). [1]Inhibition sites by molecular-targeted drugs.

metastatic colorectal cancer. However, it was not effective in cases of colon cancer harboring K-ras gene mutations[19]. There are two major signaling pathways downstream of the EGFR, the RAS/RAF/MAP kinase (MAPK) and PI3K/AKT/mTOR pathways, respectively (Figure 1). K-ras is a small G-protein downstream of the EGFR and an essential component of the EGFR signaling cascade of the RAS/RAF/MAPK pathway. Mutation of the K-ras gene leads to the activation of these intracellular pathways downstream of the EGFR. The fact that K-ras mutation is associated with the inefficacy of cetuximab in colon cancer probably reflects the very strong influence of the K-ras mutational effect on signal transduction of the EGFR related signaling cascade, regardless of inhibition of the EGFR. This characteristic strong influence of K-ras mutation on the EGFR signaling system may explain why erlotinib, another inhibitor of the EGFR, showed minimal survival benefit in pancreatic cancer. To date, no potent inhibitor of ras activation has been developed. If a molecular-targeted drug could be developed that suppresses the RAS/RAF/MAPK signaling cascade, a dramatic survival benefit in patients with pancreatic cancer may be achieved in the future.

Everolimus: Everolimus is a molecular-targeted drug that inhibits the PI3K/AKT/mTOR pathway, which is another major signaling cascade downstream of the EGFR (Figure 1). Following the benefit of everolimus in patients with pancreatic neuroendocrine tumors shown in a phase Ⅱ trial which also had lower toxicity and the convenience of oral dosing[20], the latest results show that everolimus increased progression-free survival to 11 mo, compared with 4.6 mo for placebo and BSC in a phase Ⅲ clinical trial. Pancreatic endocrine tumors are rare compared with adenocarcinoma of the pancreas. Different from pancreatic adenocarcinoma, these tumors rarely contain K-ras mutations. In this sense, it is not surprising that inhibition of one of the major signaling cascades downstream of the EGFR could be effective in this tumor type.

New promising regimens

Angiotensin converting enzyme inhibitors: Angiotensin I converting enzyme inhibitors (ACEIs) and angiotensin Ⅱ type-1 receptor blockers (ARBs) are widely used as anti-hypertensive drugs, and have organ protective effects. Long-term use of these drugs has been reported to reduce the incidence of various types of cancer. Therefore, these drugs could be effective as anti-cancer therapies, although they are neither cytotoxic nor molecular-targeted drugs. Our retrospective analysis suggested that ACEIs or ARBs in combination with gemcitabine might improve clinical outcomes in patients with advanced pancreatic cancer[21]. Following these results, we have initiated a phase I trial of candesartan, an ARB, in combination with gemcitabine.

FOLFIRINOX: FOLFIRINOX (5-FU, leucovorin, irinotecan and oxaliplatin) was the first non-gemcitabine-based

regimen to show a significantly longer overall survival compared with gemcitabine alone in recent a phase Ⅲ randomized study of metastatic pancreatic cancer[22]. This therapy not only improved progression-free survival and response rate but also improved overall survival from 6.8 to 11.1 mo. Good performance status patients are thought to be good candidates for FOLFIRINOX due to its high toxicity, which is characteristic of multiple combinations of cytotoxic drugs.

CHEMOTHERAPY FOR BILIARY TRACT CANCER

Gemcitabine, S-1

Biliary tract cancer is the sixth leading cause of cancer death in Japan, although it is relatively rare worldwide compared with pancreatic cancer. The majority of patients are identified at unresectable advanced stages with a poor prognosis that is comparable to, but slightly better than that of pancreatic cancer. Because of the small number of patients with biliary tract cancer, the efficacy of chemotherapy for biliary cancer is often analyzed by including multiple subtypes, such as extrahepatic bile duct cancer, gallbladder cancer, intrahepatic cholangiocarcinoma, and periampullary carcinoma, although these tumors have different biologic behaviors and are associated with different factors and conditions. In addition, analysis can sometimes include both unresectable advanced cases and recurrent cases following surgery. Management of biliary drainage is critical in patients with biliary tract cancer. Chemotherapy is often interrupted by recurrent biliary obstruction accompanying cholangitis, even in cases with appropriate biliary drainage by stenting, especially when tumor obstruction includes hilar bile ducts of the liver.

Gemcitabine is widely used for the treatment of advanced biliary tract cancer, as several clinical studies including phase Ⅱ trials showed that gemcitabine was moderately effective, although survival did not improve satisfactorily[23,24]. More recently, S-1 was introduced after the results of a few phase Ⅱ studies showed a median overall survival of 8-9 mo, equivalent to that of gemcitabine[25-27].

Recently, as described previously, combination chemotherapy using gemcitabine plus S-1 has shown good antitumor effects and tolerability in patients with advanced pancreatic cancer. We also conducted a multicenter, phase Ⅱ study to evaluate the efficacy and safety of gemcitabine plus S-1 combination chemotherapy in patients with advanced bile duct cancer[28]. The median overall survival time was 11.6 mo and the median time to progression was 5.9 mo, which were equivalent to those of gemcitabine plus cisplatin combination chemotherapy[29]. These results suggested that this regimen has a promising tumor response without an increased risk of severe drug-related adverse events. A phase Ⅲ study of gemcitabine plus S-1 combination chemotherapy *vs* gemcitabine plus cisplatin may be required to identify the most effective regimen.

Gemcitabine plus cisplatin

A large phase Ⅲ study of biliary tract cancer was recently reported which showed for the first time the superiority of gemcitabine plus cisplatin combination chemotherapy compared to gemcitabine monotherapy[29]. The median overall survival and progression-free survival were 11.7 and 8.0 mo in the gemcitabine plus cispatin group and were 8.1 and 5.0 mo in the gemcitabine alone group, respectively. Although this 3-mo extension in survival was modest, the results indicated that the combination of gemcitabine plus cisplatin should be considered a new standard treatment for patients with advanced biliary tract cancer. Because equivalent results were also obtained in Japanese patients included in a randomized phase Ⅱ study[30,31], this regimen will be approved for clinical practice in Japan in the near future.

New promising regimen

Cetuximab plus GEMOX (gemcitabine and oxaliplatin): The finding that the addition of cetuximab to gemcitabine plus oxaliplatin combination therapy was associated with increased antitumor activity in patients with advanced biliary tract cancer was published very recently[32]. In this phase Ⅱ study, the response rate was very high at 63% (19 of 30 patients). In addition, 9 patients (30%) were able to undergo secondary curative resection due to down-staging following this regimen. Different from pancreatic cancer, K-ras mutation is uncommon in biliary tract cancers[33] with the exception of intrahepatic cholangiocarcinoma[34]. Therefore, cetuximab, a monoclonal antibody against the EGFR, could be effective in the majority of biliary tract cancers.

CONCLUSION

Prolonged survival in pancreatic cancer and biliary tract cancer was achieved following the introduction of gemcitabine and oral fluoropyrimidines as key drugs. Although little progress has been obtained with molecular-targeted drugs, further improvement in the survival of pancreatic cancer patients may be expected if molecular drugs which regulate the ras-related signaling cascade are developed in the future.

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REVIEW

Survivin and pancreatic cancer

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Abstract

Pancreatic cancer is estimated to be the fourth most common cancer in men and fifth in women in the world and has poor prognosis. In recent years, more and more effort has been put on the relationship between pancreatic cancer and apoptosis. As a newly discovered inhibitor of apoptosis, survivin has drawn more attention. Strong evidence has shown that survivin is expressed in pancreatic cancer cells on frozen sections. Survivin increases in the development of pancreatic ductal adenocarcinoma and its expression can be a marker in evaluating the prognosis of pancreatic cancer patients. Survivin itself may be a new target in the treatment of pancreatic cancer and a survivin DNA vaccine could generate specific antitumor effects in pancreatic carcinoma models.

Key words: Survivin; Pancreatic cancer; Tumor suppression

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INTRODUCTION

Pancreatic cancer is estimated to be the fourth most common cancer in men and fifth in women in the world. Despite the development of surgical resection, radiotherapy and chemotherapy, the prognosis is poor since 5-year survival after surgery in patients with resectable disease is approximately 15% to 20%[1]. The effort for new targets in the treatment of pancreatic cancer has drawn more and more attention recently.

Inhibition of apoptosis is very important in the development of cancer. Inhibitor of apoptosis can not only accelerate the development of tumor but also promote the resistance to therapy. Survivin is a new member of inhibitor of apoptosis (IAP) family. It is a 16.5 kDa protein and highly conserved. It contains only one baculovirus IAP repeat and lacks a carboxyl-terminal RING finger, which makes survivin different from other IAP proteins. Survivin protein functions to inhibit caspase activation, thereby leading to negative regulation of programmed cell death (apoptosis). It can also partially inhibit the cell death induced by Fas and Bax[2,3] and now is considered as a mitotic regulator[4,5]. As a newly-discovered IAP, survivin is found to be expressed in many carcinomas, including human cancers of lung, colon, pancreas, prostate and breast[2,3]. Strong expression of survivin can also be found in some apoptosis-regulated fetal tissues, including the stem cell layer of stratified epithelia, endocrine pancreas, and thymic medulla. It is also expressed in human fetal lung, liver, heart, kidney, and gastrointestinal tract, which may contribute to tissue homeostasis and differentiation[6]. However, no survivin is detected in normal terminally differentiated adult tissues[2]. The levels of survivin are low in resting endothelial cells and could be up-regulated on activation to proliferate. Vascular endothelial-cadherin (VE-cadherin) expression is believed to be one of the factors to maintain low levels of

survivin in endothelial cells[7]. More studies have focused on the relationship between pancreatic cancer and survivin.

EXPRESSION OF SURVIVIN IN PANCREATIC CANCER

Satoh *et al*[8] found survivin expressed in 76.9% cases of pancreatic duct cell adenocarcinoma (PDC) and 56.3% intraductal papillary-mucinous tumor (IPMT) lesions. Malignant tumors expressed survivin more frequently than benign tumors. In PDC, the increased expression of survivin was accompanied with the reduction of apoptotic index in tumor cells. Sarela *et al*[9] also reported that survivin was expressed in majority of pancreatic adenocarcinomas tested and correlated with both cellular proliferation and apoptosis. Yang *et al*[10] investigated three pancreatic cancer cell lines and found high expression of survivin in these tumor cells.

Jinfeng *et al*[11] investigated twenty-two lesions from patients with IPMT, including 12 benign ones (IPMT adenoma) and 10 malignant ones (4 IPMT Carcinoma in Situ [CIS] and 6 invasive IPMT lesions), and found the expression of survivin and p53 increased in the development from IPMT adenoma to IPMT CIS with the reduction of apoptosis in tumor cells. The results suggest that survivin and p53 may promote the progress from benign lesions to malignant ones.

Studies indicate that survivin may become a future marker for pancreatic cancer cells in frozen sections. Yang *et al*[12], synthesized molecular beacons (MBs, short hairpin oligonucleotide probes which can bind to specific oligonucleotide sequences and show fluorescent signals) targeting transcripts of mutant K-ras and survivin, and examined the specificity for detecting the two genes in pancreatic cancer cells using a fluorescence imaging-based technique. Survivin MBs were found binding to survivin gene and a bright fluorescent signal was produced specifically in pancreatic cancer cells. In frozen sections of pancreatic cancer tissues, survivin MBs were also found to have a high specificity in identifying cancer cells. The results provide pathologists a new choice for detecting pancreatic cancer cells in frozen sections, and may be used in clinical practice in the future. However, Jhala *et al*[13] investigated the biomarkers in diagnosing pancreatic carcinoma using fine needle aspirates and found that survivin expression was not a good marker for separating reactive ductal cells from pancreatic adenocarcinoma.

Increased expression of survivin is also reported in the development of pancreatic ductal adenocarcinoma (PDA). Bhanot *et al*[14] used laser capture microdissection, real-time polymerase chain reaction and immunohistochemistry to measure transcriptional levels of survivin and its protein expression in normal pancreatic ducts, pancreatic intraepithelial neoplasia (PanIN) and PDA. A steady increase in mRNA and protein expression of survivin was found from low-grade lesions (PanINs-1) to high-grade lesions (PanINs-2 and 3) and further to PDA. The results indicate that survivin may promote the changing process and could be a signal for malignant lesions.

SURVIVIN EXPRESSION AS A MARKER FOR EVALUATING PROGNOSIS

Specimens from pancreatic cancer patients who accepted surgery with or without postoperative radiation therapy (PORT) were assessed and the relationship between the expression of survivin and the prognosis was evaluated. Patients with positive survivin expression had shorter survival time than those who had no survivin expression, whereas PORT had no impact on survival time in both survivin positive patients and survivin negative patients. The research indicates that survivin may become a prognostic marker for pancreatic cancer[15].

The study of Grabowski *et al*[16] also showed that nuclear survivin expression was a potent prognostic marker for shorter survival time in gastroenteropancreatic neuroendocrine tumor disease. Determination of nuclear survivin expression may be used to individualize therapeutic strategies. Survivin has been shown to reside in mitochondria, nucleus and cytosol of tumors[17,18]. Tonini *et al*[19] made the first study on the prognostic relevance of survivin expression in pancreatic cancer in relation with its intracellular distribution. They investigated nuclear and cytoplasmic expression of survivin in 67 patients with pancreatic cancer and reported that patients with high nuclear survivin expression had a longer survival time, while patients with high cytoplasmic survivin expression had a shorter survival time. The median survival time for patients with positive nuclear expression was 27 mo while for patients with negative nuclear expression it was only 10 mo. However, the median survival for patients with positive cytoplasmic expression was 10 months compared with 25 months for patients with negative cytoplasmic expression. In other malignant tumors, such as colorectal cancer, cytoplasmic survivin overexpression is also associated with a poor prognosis, while nuclear survivin overexpression is associated with a better one. The mechanisms for the intracellular distribution of survivin in human cancer cells are still unclear; however, determination of the different expression of survivin may make a new marker for evaluating the prognosis of patients with pancreatic cancer[20].

Theodoropoulos *et al*[21], investigated survivin gene polymorphisms and the characteristics of pancreatic cancer. The genotypes of the survivin promoter are GG, CC and CG. The frequency of the 31G/C polymorphism was investigated in 80 patients with pancreatic cancer and 160 controls. A significant relationship was found between survivin C carrier and the advanced T stage accompanied with the presence of lymph node metastasis, indicating that the status of survivin C carriage was related to more aggressive features of the tumor.

SIGNIFICANCE OF SURVIVIN EXPRESSION IN THE TREATMENT OF PANCREATIC CANCER

The expression of survivin may be associated with the route of metastasis and the sensitivity to chemotherapy for

patients with pancreatic cancer. Lee *et al*[22] investigated 49 cases of pancreatic cancer and found that 93.9% of them were positive for survivin expression. In patients with positive expression of survivin, perineural invasion was more common; while in patients with negative expression of survivin, venous invasion seemed more common. These findings suggest that survivin may be associated with perineural or venous invasion, which indicate the metastatic route. However, the reason for the relationship between survivin expression and invasion mode is not clear. Among these patients, 14 received epirubicin, cisplatin and 5-FU combination chemotherapy. Patients with lower expression of survivin were more sensitive to the chemotherapeutic protocol. The results suggest that survivin may be used as a potential predictive marker in chemotherapy.

Expression of survivin is also a radioresistance factor in patients with pancreatic cancer. Asanuma *et al*[23] found an inverse relationship between survivin mRNA expression and radiosensitivity in 5 pancreatic cancer cell lines using a quantitative RT-PCR, indicating that survivin may act as a radioresistance factor in pancreatic cancer cells. They also found that the survivin mRNA increased significantly after X-ray irradiation, implying that survivin was an inducible radioresistance factor in pancreatic cancer cells. Further results of this study suggest that survivin expression directly down-regulates radiosensitivity[24].

Studies also reveal that down-regulation of survivin diminishes radioresistance of pancreatic cancer cells. Kami *et al*[25] evaluated the effect of short interfering RNA (siRNA) directly against survivin expression in radioresistant cells (AsPC-1). The activity of the survivin promoter and the expression of survivin mRNA were examined in 3 pancreatic cancer cell lines. Various levels of survivin mRNA and the transcriptional activity of the survivin promoter were found in pancreatic cancer cells, and both of them correlated with the radiosensitivity of tumor cells. On the other hand, radiation could increase the activity of the survivin promoter and mRNA expression in these cells. However, siRNA treatment markedly decreased the expression of survivin mRNA in AsPC-1 cells, and diminished the radioresistance of pancreatic cancer cells. These results indicate that combined therapy of a survivin inhibitor and radiation may be effective in the treatment of pancreatic cancer.

Guan *et al*[26] also proved that down regulation of survivin expression by small interfering RNA induced apoptosis in pancreatic cancer cells (cell line PC-2) and enhanced its radioactivity. The sequence-specific siRNA markedly decreased survivin mRNA and protein, which resulted in apoptosis in 7.03% of cells treated with siRNA. However, apoptosis was found in 14.58% of cells treated with siRNA combined with radiation, and only 1.66% of cells were found to be apoptotic in the radiation group. These studies give us new hope in the treatment of pancreatic cancer.

In spite of more and more new aggressive therapies, resistance of many tumors to current therapeutic protocols is still a formidable problem. Thus more and more attempts to improve the effects of treatment for cancer patients now depend on methods targeting the resistance of tumor cells[27]. Survivin may be a new target in the treatment of pancreatic cancer. Fulda *et al*[28] used survivin antisense oligonucleotides down-regulating the expression of survivin, and revealed tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induced apoptosis was sensitized in many tumor cells. The cells they used included neuroblastoma, medulloblastoma, glioblastoma, melanoma, pancreatic carcinoma, prostate carcinoma, and breast carcinoma cells. They also found that G1 arrest was associated with less expression of survivin and sensitization for TRAIL-induced apoptosis.

Liang *et al*[29] tried survivin as a new target for pancreatic cancer gene therapy. A 10'-23' anti-survivin mRNA DNAzyme was designed, synthesized and delivered into human pancreatic carcinoma cell PANC-1 through liposomes, and the influence on the growth of PANC-1 cells was evaluated. The results showed that with the destruction of the mRNA substrate of survivin by DNAzyme, apoptosis of PANC-1 was increased and cell growth was inhibited. The designed DNAzyme against survivin mRNA is a promising candidate for gene therapy of human pancreatic carcinoma. Liu *et al*[30] also proved that human pancreatic cancer cell transfected with a siRNA plasmid expression vector against survivin showed decreased cell growth, spontaneous apoptosis, and a specific G0/G1 arrest accompanied with the reduction of survivin mRNA and protein. In addition, the chemosensitivity of pancreatic cancer cells to gemcitabine was increased markedly after suppressing the expression of survivin. Guan *et al*[31] proved that knockdown of survivin expression by siRNA could suppress proliferation of human pancreatic cancer cell PC-2. The research of Tsuji *et al*[32] also suggested that survivin-specific siRNA deserved further investigation as a new approach for the treatment of cancer.

Shen *et al*[33] performed experiments inhibiting the growth of cancer cells by silencing survivin not only *in vitro* but also *in vivo*. In their study, they designed and constructed a short hairpin RNAs (shRNAs) specific to survivin, cloned it into a plasmid vector, and transfected the recombinant plasmids into a human pancreatic cancer cell line Patu8988. The proliferation rates of the cancer cells were reduced markedly when transfected with the survivin-shRNA plasmids. When Patu8988 cells with survivin-shRNA were inoculated into BALB/c nude mice, the growth of the tumor was lower and the size of the tumor was smaller compared with the control group. The results showed that vector-based survivin-shRNAs could inhibit the expression of survivin in human pancreatic cancer Patu8988 cells and ultimately inhibit cell proliferation both *in vitro* and *in vivo*. Thus, knockdown expression of survivin may be a future way to treat pancreatic cancer.

Encouraging results have also been obtained in humans. Wobser *et al*[34] used survivin-based peptide vaccinations consisting of a modified HLA-A2 restricted survivin epitope on a 72-year old patient who suffered from pancreatic cancer with liver metastasis. The patient got partial remission of liver metastasis under vaccination with survivin peptides and later a complete remission with a dura-

tion of 8 mo. Although the disease relapsed 6 mo after vaccination stopped, it was the first case of a successful use of survivin-based vaccination, which threw light on the gloomy prognosis of advanced pancreatic cancer.

It has been reported that survivin DNA vaccine generates specific antitumor effects in pancreatic carcinoma in mouse models. Human or mouse survivin DNA was given to a murine pancreatic cancer model and the effect of the vaccination was evaluated. Slower tumor growth and longer lifetime were found in mice vaccinated with survivin DNA, no matter whether it was from human or mouse source. Greater infiltration of lymphocytes was found in tumors of the immunized mice. The research showed that survivin DNA vaccination could generate specific antitumor effects with increased lymphocyte infiltration at the tumor sites, and both xenogeneic survivin and congeneric ones had the same immune response[35].

Now more and more attention is being paid to the relationship between apoptosis and pancreatic cancer, including its development and therapy. As a novel IAP member, survivin inhibits caspase activity thereby negatively regulating apoptosis, which draws more attention in the study of cancer. Further studies of survivin should provide a new choice for the marker in diagnosis and the target treatment of the disease.

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Meetings

Events Calendar 2011

January 13-14, 2011
3rd Breast-Gynecology International Cancer Conference BGICC, Cairo, Egypt

January 15-16, 2011
Melanoma 2011: 21st Annual Cutaneous Malignancy Update, San Diego, CA, United States

January 15, 2011
Current Trends in Breast Cancer: Updates From the 2010 San Antonio Breast Cancer Symposium, Dallas, TX, United States

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011, San Francisco, CA, United States

January 21-23, 2011
8th Meeting of the EAU Section of Oncological Urology, London, England, United Kingdom

January 27-28, 2011
2nd National Conference: Recent Advances in Renal and Bladder Cancer, London, United Kingdom

January 27-28, 2011
8th Annual Cancer Drugs Research & Development, San Diego, CA, United States

February 10-12, 2011
17th Annual NOCR Meeting, Las Vegas, NV, United States

February 19-22, 2011
Scripps Cancer Center's 31st Annual Conference: Clinical Hematology and Oncology, San Diego, CA, United States

February 24-26, 2011
European Multidisciplinary Conference in Thoracic Oncology (Lung 2011-EMCTO), Lugano, Switzerland

February 25-27, 2011
7th European Congress on Hematologic Malignancies: From Clinical Science to Clinical Practice, Budapest, Hungary

March 02-05, 2011
64th Society of Surgical Oncology Annual Cancer Symposium 2011, San Antonio, TX, United States

March 04-06, 2011
8th Annual Oncology Nursing Advanced Practice: Innovation through Practice, San Diego, CA, United States

March 07-09, 2011
9th International Symposium on Targeted Anticancer Therapies, Paris, France

March 09-13, 2011
16th National Comprehensive Cancer Network Annual Conference (NCCN 2011), Hollywood, FL, United States

March 11-12, 2011
12th European Congress: Perspectives in Lung Cancer, Torino, Italy

March 14-18, 2011
Oncology Imaging Update in Costa Rica, Guanacaste, Costa Rica

March 17-19, 2011
International Cancer Prevention Update Symposium, New York, United States

March 18-22, 2011
Vienna, Austria
26th Annual EAU Congress

April 02-06, 2011
AACR 102nd Annual Meeting, Orlando, FL, United States

April 08-10, 2011
Asian Oncology Summit 2011, Hong Kong, China

April 20-23, 2011
9th International Gastric Cancer Congress, Seoul, South Korea

April 29-30, 2011
Cancer Survivorship Conference, Minneapolis, MN, United States

May 23-24, 2011
4th International Conference on Ovarian Cancer Screening, London, United Kingdom

June 03-07, 2011
47th American Society of Clinical Oncology Annual Meeting, Chicago, IL, United States

June 20-23, 2011
7th EADO Congress European Association of Dermato-Oncology, Nantes, France

June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer, Barcelona, Spain

June 23-25, 2011
"MASCC/ISOO 2011 International Symposium, Athens, Greece

July 03-07, 2011
14th World Conference on Lung Cancer, Amsterdam, Netherlands

July 14-17, 2011
3rd World Congress of the International Academy of Oral Oncology 2011, Singapore, Singapore

August 15-17, 2011
International Conference and Exhibition on Cancer Science & Therapy, Las Vegas, Nevada, United States

September 1-3, 2011
Tri-Society Head and Neck Oncology, Singapore, Singapore

September 7-10, 2011
Hallmarks and Horizons of Cancer, Lausanne, Switzerland

September 23-27, 2011
Joint 16th ECCO and 36th ESMO Multidisciplinary Cancer Congress, Stockholm, Sweden

October 06-07, 2011
Current Status and Future of Anti-Cancer Targeted Therapies, Buenos Aires, Argentina

November 30-December 03, 2011
AORTIC 2011-Entering the 21st Century for Cancer Control in Africa, Cairo, Egypt

November 6-9, 2011
NCRI Cancer Conference, Liverpool, United Kingdom

November 10-12, 2011
21st Asia Pacific Cancer Conference 2011, Kuala Lumpur, Wilayah Persekutuan, Malaysia

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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