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TOPIC HIGHLIGHT

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c-Met targeted therapy of cholangiocarcinoma

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Abstract

Cholangiocarcinoma continues to be a challenging disease to treat. Systemic therapy is used in unresectable disease, disease progression after surgery, and in the palliative setting. Unfortunately, results of multiple phase Ⅱ trials have rarely yielded positive results. As data on the molecular carcinogenesis of cholangiocarcinoma is developing, we are more able to understand the disease process and can use this understanding to create unique targeted therapies. We reviewed the role of c-Met/hepatocyte growth factor (HGF) in the development of cholangiocarcinoma. Furthermore, we explored the use of the c-Met guided cascade as a target to treat cholangiocarcinoma. We reviewed the current use and options for future development of c-Met agents to treat this disease.

Key words: Cholangiocarcinoma; c-Met; Chemotherapy; Target therapy

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CHOLANGIOCARCINOMA

Cholangiocarcinoma continues to be a challenging disease to treat. The only curative option remains surgical resection. Recent trends have allowed previously inoperable patients to undergo potentially curative surgery. Most recently, liver transplantation has been used in locally unresectable tumors with variable results[1-3]. Becker *et al*[4] reported outcome analysis for 280 patients treated at multiple centers over an 18-year period. Their data shows 5 and 10 years survivals of 74% and 38% respectively. Unfortunately, relatively few patients are diagnosed with limited stage disease that is amenable to surgical intervention (either resection or transplantation). Systemic therapy has been used in unresectable disease, disease progression after surgery, and in the palliative setting. Results of multiple phase Ⅱ trials have rarely yielded positive results[5]. Average median survival remains less than one year and response rates are generally under 30%. Although the benefit is minimal, the most efficacious and clinically utilized chemotherapy regimens have been either gemcitabine or 5-fluorouracil (5FU)-based. Alberts *et al*[6] conducted a Phase Ⅱ trial of gemcitabine, 5FU, and Leucovorin in advanced biliary disease. This study delivered 4 wk cycles of gemcitabine/5FU/Leucovorin on d 1, 8 and 15. The study enrolled carcinoma of the gallbladder and cholangiocarcinoma. For our scope, we will focus on their cholangiocarcinoma data. The study enrolled 28 patients with biliary cancer at multiple centers. Using the Response Evaluation Criteria in Solid Tumors (RECIST)[7] criteria two patients with biliary tract cancer achieved a partial response. The median time to disease progression was 4.6 mo and median survival was 9.9 mo. The primary endpoint of the study was successfully achieved, namely, to determine 6 mo survival. The overall data is fairly consistent with the previously reported data for single agent 5FU or gemcitabine. Although it is clear that 5FU and gemcitabine are active in cholangiocarcinoma, this study showed that the combination of the two most potent agents failed to produce a greater response rate or duration of response than either agent alone. This study and others like it increases suspicion that traditional chemotherapy is unlikely to make tangible progress in this devastating disease.

MOLECULAR BIOLOGY OF CHOLANGIOCARCINOMA

Like many other malignancies, cholangiocarcinoma cells over-express epidermal growth factor receptors (EGFR)[8-10]. This observation led several investigators to postulate that Erlotinib (an oral inhibitor of EGFR/

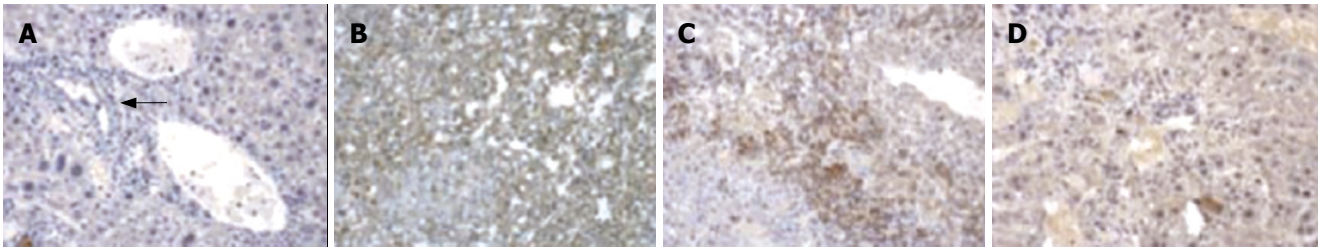

Figure 1 c-Met immunohistochemistry performed on: **A**: Normal liver; **B**: Cholangiocarcinoma; **C**: Early stage cholangiocarcinoma; **D**: Bile duct hyperplasia reproduced from Fazari (19) with permission.

HER1 tyrosine kinase) would show activity against cholangiocarcinoma. This interest intensified when activity was demonstrated against other malignancies such as lung[11] and pancreatic cancer[12]. Philip *et al*[13] reported a Phase Ⅱ trial in 42 patients with advanced biliary cancer. Using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria three patients achieved a partial response (7%). Median time to disease progression was only 2.6 mo, and median overall survival was 7.5 mo. Interestingly, there was a certain subgroup (17%) that seemed to achieve prolonged (greater than 24 wk) disease stability. There did not appear to be a correlation between *EGFR/HER1* gene over-expression and response. This was not unexpected since *EGFR* mutations, *K-Ras* mutations, *p-AKT* levels, and proteomic signatures are also important predictors of erlotinib response and signal pathway dependence is difficult to predict from gene expression alone[11,14,15]. Although these results are promising, clinicians are left searching for better treatment options. Further advancement in the treatment of cholangiocarcinoma begins with a better understanding of the molecular mechanisms of carcinogenesis.

Data on the molecular carcinogenesis of cholangiocarcinoma is developing rapidly[16,17]. As in most cancers, multiple genes have been implicated in the molecular transformation of normally functioning tissue to malignant cells. These genetic changes cause a cascade of effects that include activation of oncogenes, inactivation of tumor suppressor genes, alterations in cell signaling, resistance to apoptosis, and direct induction of DNA damage. These genetic alterations affect all phases of the cell cycle and work in concert to transform bile secreting cells into an aggressive carcinoma. A detailed description of all of these mutations and their specific role in cholangiocarcinogenesis is beyond the scope of this publication. Here, we focus on the role of c-Met/hepatocyte growth factor (HGF) and its possible therapeutic implications. It has been reported that c-Met is over-expressed in more than half of biliary carcinomas[18]. As shown in Figure 1, Farazi *et al*[19] demonstrated c-met over-expression in 80% of humanoid murine intrahepatic cholangiocarcinoma. Radaeva *et al*[20] confirmed that cholangiocarcinoma expressed strong cell-surface immunoreactivity for c-Met. *c-Met* is a proto-oncogene located on chromosome 7q that codes for a tyrosine kinase growth factor receptor called HGF receptor[21]. HGF (also known as scatter factor) binds to c-Met and initiates autophosphorylation of an intracellular tyrosine kinase on the beta-subunit of the receptor. This activation allows the binding and ultimate activation of

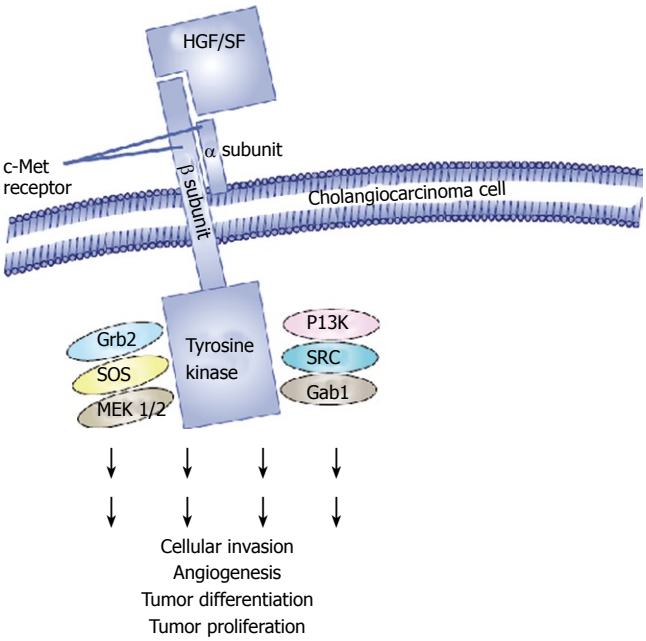

Figure 2 Schema of *c-Met* signaling pathways.

multiple signaling molecules such as Src, P13K, Gab1, SOS, Grb2, and MEK1/2 (Figure 2). The interaction of this multi-faceted activation system ultimately results in cellular alterations that contribute to carcinogenesis. It has been suggested in multiple studies that over-expression of c-Met is linked to cell invasion, angiogenesis, and tumor differentiation/proliferation[22-24] (www.vai.org/met). Although the data is not conclusive, several researchers have suggested that c-Met behaves differently in intrahepatic and extrahepatic cholangiocarcinoma[25,26]. Leelawat *et al*[27] demonstrated that stimulated over-expression of the *c-Met* gene in cholangiocarcinoma cells resulted in increased cell migration and invasion. Conversely, inhibition of *c-Met* expression decreased cellular phosphorylation and ultimately reduced cellular invasiveness. The presence of the *c-Met* oncogene and its unique cell signaling pathway provides one of many avenues by which specific cell targeting can be used to achieve better tumor control in cholangiocarcinoma[28].

C-MET THERAPIES

There are multiple focal points for interrupting c-Met activity with clinical compounds[29]. The earliest target in the cascade focuses on inhibition of the interaction

between HGF and the c-met receptor. Blocking the binding of the HGF to the transmembranous c-Met receptor works to halt c-Met signaling at the earliest point. Ultimately, c-Met fails to dimerize and tyrosine kinase activation does not occur. The alteration of this HGF/c-Met interaction can occur via multiple modalities including small interference RNAs (siRNA) which block c-Met expression, monoclonal antibodies against c-Met or HGF, and soluble c-Met fragment which can block HGF binding. Another target in the c-Met system is the direct tyrosine kinase inhibition. Similar to the tyrosine kinase inhibitors in chronicmyeloidleukemia (CML) and other tumors, designer compounds that are specific to the *c-Met* gene tyrosine kinase are administered. Although the interaction between HGF and the c-Met receptor is preserved, the cascade is halted by the selective binding of the inhibitor to the tyrosine kinase. Theoretically, all of these mechanisms would function to reduce cellular invasion, migration, angiogenesis, and ultimately, halt the process of carcinogenesis.

C-MET THERAPIES FOR CHOLANGIOCARCINOMA

To date, only one study has reported c-Met targeted therapy in an animal model of cholangiocarcinoma[27]. This study showed that inhibition in c-Met expression or its downstream target MEK1/2 through specific targeted therapy is effective in halting disease progression *in vivo*. Inhibition was achieved through two molecular strategies. First, c-Met expression was altered through a *c-Met* specific small interfering RNA (siRNA) binding to the c-Met coded receptor. Second, siRNA specific binding to the *c-Met* downhill cascade product, MEK1/2, resulted in blunting of the cellular invasiveness of cholangiocarcinoma cells.

A number of c-Met and HGF antibody directed therapies receptor interaction have been shown biological activity in non-biliary cancer animal models[30,31] and human studies[32]. AMG102 is a fully human IgG2 monoclonal antibody against HGF. This compound has completed both preclinical trials and phase I dosing trials[33]. Although, the dose-escalating trials were performed on a variety of solid tumors, there is not current data on cholangiocarcinoma. A one-armed c-Met antibody has shown activity in preclinical studies[34]. Again, patients with cholangiocarcinoma have not been treated. Decoy met[35] is a soluble met receptor that interferes with HGF binding. It has been shown *in vivo* to have multiple anti-malignant properties including inhibiting angiogenesis, suppressing metastasis, and halting cellular proliferation. Decoy met functions to block the c-Met receptor as well as altering met dimerization. Decoy met has several properties that may make it more desirable than standard antibody directed therapies. For example, decoy met has a logarithmically greater affinity for the c-met receptor.

A series of c-Met tyrosine kinase inhibitors have been examined. XL880 is an oral c-Met tyrosine kinase inhibitor that is completing Phase I trials and beginning Phase Ⅱ trials in humans. XL880 is a multi-kinase inhibitor that affects both the HGF/c-Met receptor family and the VEGF receptor family. The most common side effect of XL880 is hypertension. Although XL880-induced hypertension is very common, in phase I testing, it was manageable with anti-hypertensive medications[36]. XL880 is currently undergoing phase Ⅱ clinical trials in a number of cancers. Early Phase Ⅱ data on renal cell cancer has been positive[37]. It has shown activity in lung cancer (both small cell and non-small cell) xenografts in immunocompromised mice[38]. Additional tyrosine kinase inhibitors that are specific to the c-Met receptor have been developed[39-41]. ARQ 197 is a c-Met specific receptor tyrosine kinase inhibitor. This compound has completed Phase I dose escalation and has reached the recommended phase Ⅱ dose. Partial responses and durable long term disease control have been achieved in several malignancies[42]. PHA665752 is a selective small molecule tyrosine kinase inhibitor of c-Met[38,43]. It has been shown to inhibit angiogenesis and induce apoptosis and cell cycle arrest. Interestingly, PHA665752 has been shown to have a cooperative effect when administered with rapamycin[43]. No current data on PHA665752 in humans is available.

Table 1 Target sites of c-Met therapies

Target	Example	Current phase
HGF/c-met monoclonal antibody	AMG102[33]	Phase Ⅱ
Soluble c-met receptor	Decoy met[35]	Phase Ⅰ
Tyrosine kinase inhibition	ARQ 197[42]	Phase Ⅱ
	XL880[36,37]	Phase Ⅱ
	PHA665752[38]	Animal testing

CLINICAL TRIALS WITH C-MET THERAPIES

There is scant data for any of the compounds in patients with cholangiocarcinomas (Table 1). The previously mentioned XL880 Phase I trial included 1 patient with cholangiocarcinoma. The slides presented at the 2007 ASCO meeting indicated that there was as 5 mo duration of response in Phase I testing. Unfortunately, the XL880 trial did not select for tumors over-expressing c-Met. Progress is rapidly being made through inhibition of the c-Met cascade. Hopefully, this will result in treatment advances in cholangiocarcinoma. Furthermore, other molecular mechanisms exist for using c-Met to target cellular death in cholangiocarcinoma. The possibility of using HGF or a monoclonal antibody to c-Met for immunotoxin construction should also be explored[45]. This would result in preferential introduction of deadly toxins into the cholangiocarcinoma cellular environment sparing normal cells (non c-Met expressing). As treatments directed against aggressive incurable cancers develop, their success will likely depend on their ability to deliver tumor selective, highly toxic treatments to carcinoma cells while sparing normal tissue. The c-Met cascade and others like it provide such an opportunity. Through these rapid developments, researchers, clinicians, and patients have hope of better treatments in the future.

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