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HIGHLIGHT ARTICLE

Novel Agents in the Treatment of Pancreatic Adenocarcinoma

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Summary

The development of new agents and treatment strategies against pancreatic adenocarcinoma is vital, given the poor prognosis of the patients with this particular type of cancer. Three novel compounds were tested at different phases of clinical research and the results were presented in the recent ASCO Gastrointestinal Cancers Symposium. FG-3019 inhibits the connective tissue growth factor which is important in the biology of pancreatic cancer and was shown to be relatively safe in a phase I study (Abstract #213). In addition, ASG-5ME, an antibody specific for SLC44A4 that is universally expressed in pancreatic cancer and also carries a conjugate chemotherapy particle was safe at the appropriate dosing in a phase I trial (Abstract #176). Last but not least, tanespimycin, a molecule that inhibits heat shock protein 90 was not effective in the first line treatment of patients with pancreatic cancer in a phase II study (Abstract #245). Further studying of FG-3019 and ASG-5ME will show the potential activity if any of these compounds in patients with pancreatic cancer.

What Did We Know Before the 2013 ASCO Gastro-intestinal Cancers Symposium?

The prognosis of patients with pancreatic cancer remains dismal raising the need for new treatment strategies [1]. Most of the patients are diagnosed at a point when the tumor is already metastatic. The combination of 5-FU, irinotecan and oxaliplatin (FOLFIRINOX) offers an improved outcome over the standard gemcitabine therapy in patients with a good performance status that can tolerate the toxic regimen [2]. In addition, the recognition of drug delivery as a major determinant of chemotherapy efficacy has resulted in the emergence of *nab*-paclitaxel in addition to gemcitabine as a potential new standard first-line chemotherapy [3]. A new set of agents that utilize this approach are currently under several phases of clinical investigation [4].

The thick stroma that surrounds the pancreatic adenocarcinoma cells limits the access of the active compounds to their targets. Furthermore, the tumor desmoplasia interacts with the tumor cells in a way that promotes tumor growth and metastasis. Connective tissue growth factor (CTGF/CCN2) which is secreted by the pancreatic adenocarcinoma cells, plays a major role in the desmoplastic reaction of the tumor in reaction to hypoxic stimuli and is therefore an attractive target for treatment design [5]. Another way of optimizing the delivery of chemotherapeutics to the pancreatic cancer tissue employs pancreatic adeno-carcinoma cell specific antibodies that are conjugated to chemotherapeutic agents. In this context, SLC44A4 is an ion transporter which is expressed in the majority of pancreatic ductal adenocarcinomas. ASG-5ME is a SLC44A4 specific antibody that is conjugated to an anti-microtubule compound which that way enters the pancreatic adenocarcinoma cells selectively [6]. A third methodology to overcome resistance to chemotherapy is by inhibiting heat shock protein 90. Heat shock protein 90 protects several targets of anticancer treatment from degradation [7]. Thus, inhibition of heat shock protein 90 is a reasonable approach that can augment the anti-neoplastic effect of chemotherapy.

Key words Connective Tissue Growth Factor; HSP90 Heat-Shock Proteins; Pancreatic Neoplasms; tanespimycin; Tumor Micro-environment

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What Have We Learnt from the 2013 ASCO Gastrointestinal Cancers Symposium?

FG-3019, a Human Monoclonal Antibody to CTGF, with Gemcitabine/Erlotinib in Patients with Locally Advanced or Metastatic Pancreatic Ductal Adeno-carcinoma (Abstract #213) [8]

FG-3019 is a monoclonal antibody specific for connective tissue growth factor (CTGF). FG-3019 was added to gemcitabine and erlotinib in a phase I study that recruited treatment naïve patients with locally advanced or metastatic pancreatic cancer as described in Abstract #213 [8]. The dose of FG-3019 was

escalated starting from 3 mg/kg to 10, 15, 25, 35 and 45 mg/kg every 2 weeks. Next, a dose of 35 mg/kg on the first day of treatment was followed by weekly 17.5 mg/kg and the final dosing group of patients received 45 mg/kg once and then weekly 22.5 mg/kg thereafter. Even in the final high dosing group, the drug was considered safe with no serious adverse events reported. In terms of efficacy, the progression free survival was 4.3 months and the overall survival was 9.4 months. Interestingly there was a correlation of FG-3019 levels with efficacy. Specifically, the higher the serum levels of the compound after the first dose, the higher the overall survival and the more the reduction in CA 19-9. Additionally, the patients who achieved a minimum FG-3019 concentration of 150 µg/mL after several cycles on day 43 had significantly higher overall survival compared to the patients who did not meet this goal.

A Phase I Study of ASG-5ME, a Novel Antibody-Drug Conjugate, in Pancreatic Ductal Adenocarcinoma (Abstract #176) [9]

ASG-5ME is an antibody with specificity for SLC44A4 and carries an active conjugate. The safety of ASG-5ME is described in Abstract #176 where different doses of this novel agent are escalated in the context of a phase I trial in mostly pretreated metastatic pancreatic cancer [9]. Maximal tolerated dose was set at 1.2 mg/kg on days 1, 8 and 15 of a 28 day cycle as at a higher dose a patient experienced a grade 4 gastrointestinal bleeding and four patients had neutropenia grade 3 or 4. Fatigue, abdominal pain, vomiting and neutropenia were the most common grade 3 or 4 toxicities that were observed at the maximal tolerated dose. A partial response was noted in one patient and the disease was stable in 12 patients.

Phase II Consortium (P2C) Study of Gemcitabine and Tanespimycin (17AAG) for Metastatic Pancreatic Cancer (Abstract #245) [10]

Tanespimycin increases the concentration of client proteins that mediate chemotherapy activity by inhibiting heat shock protein 90. The efficacy of tanespimycin was evaluated in a phase II study which is described in Abstract #245 [10]. The combination of the study drug with gemcitabine was evaluated for safety and efficacy in 21 patients with metastatic disease and no prior treatment other than adjuvant. Grade 3-4 toxicities were common, with 50% of the patients experiencing a grade 3 adverse event and 15% having a grade 4 event. Nausea and vomiting, constipation, dehydration, anorexia, lymphopenia, leucopenia and neutropenia were the most common side effects. Median overall survival was 5.4 months with no patients achieving an objective response.

Table 1 summarizes the novel agents that were presented in the 2013 ASCO Gastrointestinal Cancer Symposium for the treatment of pancreatic cancer.

Discussion

The dismal prognosis of pancreatic adenocarcinoma raises the need for novel agents to be tested in clinical trials along with parallel basic and translational research of the underlying biology. FG-3019 and ASG-5ME were tested to be safe at the appropriate dosing in the corresponding phase I studies that were presented at the recent ASCO Gastrointestinal Cancer Symposium. Limited conclusions can be drawn about the efficacy of those compounds as dictated by the design of the trials. The pharmacodynamic data for FG-3019 in particular might suggest that the efficacy of the drug might be dose related. FG-3019 and ASG-5ME represent two different ways of optimizing drug delivery in pancreatic cancer. The former might achieve better penetration for chemotherapy as it disrupts the thick stroma that surrounds the pancreatic adenocarcinoma cells and the latter specifically binds to a target which is expressed in the majority of pancreatic adenocarcinoma cells and it is conjugated to a chemotherapy compound at the same time. In addition, connective tissue growth factor blockade by FG-3019 potentially stops the cross talking between the pancreatic adenocarcinoma cells and their micro environment that otherwise would promote tumor growth, survival and metastasis. Finally, the heat shock protein 90 inhibitor tanespimycin, although promising in the initial reports, does not seem to be cost effective in pancreatic cancer and further investigation of this drug in this setting is not recommended.

Table 1. Summary of the novel agent studies presented at the 2013 ASCO Gastrointestinal Cancers Symposium.

Novel agent	**FG-3019** (Abstract #213) [8]	**ASG-5ME** (Abstract #176) [9]	**Tanespimycin** (Abstract #245) [10]
Study design	First-line, phase I	Pretreated, phase I	First-line, phase II
No. of patients	75	35	21
Regimen	FG-3019 plus erlotinib plus gemcitabine	ASG-5ME alone	Tanespimycin plus gemcitabine
Grade 3/4 toxicities	No serious adverse event reported	Fatigue (28%) Abdominal pain (22%) Vomiting (17%) Neutropenia (17%)	Nausea (20%) Vomiting (20%) Constipation (15%) Dehydration (15%) Anorexia (10%) Lymphopenia (15%) Leucopenia (10%) Neutropenia (10%)
Partial response	Not reported	1/35 (2.9%)	None

Conflict of interest The authors have no potential conflicts of interest

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