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HIGHLIGHT ARTICLE

Update on Phase I Studies in Advanced Pancreatic Adenocarcinoma. Hunting in Darkness?

Highlights from the "2013 ASCO Annual Meeting". Chicago, IL, USA; May 30 - June 4, 2013

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Summary

Over the last twenty years, there is a limited number of effective cytotoxic or biological agents that managed to get approval in advanced pancreatic ductal adenocarcinoma. Despite numerous trials, investments in translational research and generally in health care, the survival of pancreatic cancer patients has improved by a few only months. This disappointing reality necessitates a better understanding of the pathogenesis of this disease and the identification of targetable alterations which might lead to development of more effective drugs or better combinations. At the 2013 Annual Meeting of the American Society of Clinical Oncology, few novel agents and new therapeutic concepts, tested in phase I studies in advanced pancreatic ductal adenocarcinoma, were presented. The first notable phase I study referred to the combination of chemotherapy with local delivery of silencing RNA against the K-*ras* mutation G12D, in advanced pancreatic ductal adenocarcinoma, which was well tolerated and promising (Abstract #4037). The second one referred to a combination of gemcitabine with pegylated recombinant human hyaluronidase (PEGPH20), an inhibitor of hyaluronan which as a matrix glycosaminoglycan is believed to play role in the reduced drug delivery to cancer (Abstract #4010). The other notable abstract was related to an early phase study which tested the safety and toxicity of arctigenin, a traditional herbal agent found in *Arctium lappa* Linné, administered as an oral formulation (GMS-01) in pancreatic ductal adenocarcinoma patient resistant to standard chemotherapy (Abstract #2559). The aforementioned early phase studies open new therapeutic approaches which deserve further testing in advanced pancreatic cancer.

Introduction

Though pancreatic cancer is a rare malignancy; it is the 4th commonest cause of death from cancer in Western countries, with a low 5-year survival rate even in the early stage disease when resection is feasible [1]. Fit patients are offered systemic chemotherapy either post resection as adjuvant treatment or upfront in advanced pancreatic ductal adenocarcinoma. Unfortunately, many of the patients seen in clinics are less fit than those enrolled in clinical trials therefore systemic therapy is rather based on gemcitabine than on the new most intensive regimens.

Key words Antibodies; Clinical Trials, Phase I as Topic; Herbals; Pancreatic Neoplasms; RNA, Small Interfering

Abbreviations DLT: dose limited toxicity; LODER: Local Drug EluteR; MTD: maximum tolerated dose; siRNA: silencing RNA

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What Did We Know Before the 2013 ASCO Annual Meeting?

It is well accepted that small improvements have been achieved in pancreatic cancer with the enrichment of the standard cytotoxics (gemcitabine, fluoropyrimidines and platinum agents) with newer drugs such as irinotecan and recently nab-paclitaxel, used as single agents or in various combinations [2, 3, 4]. The use of cytotoxic therapies and the lack of a truly targeted agent in this disease simply admits that we remain in an complete shadow regarding the principal and driving pathogenetic molecular alterations that make pancreatic ductal adenocarcinoma such an aggressive and resistant disease. The paradoxical fact that the only targeted agent approved so far in pancreatic ductal adenocarcinoma, the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) erlotinib, inhibits the deranged pathway at a higher level from where the most common mutation (K-*ras*) is located highlights how little we know about this disease. Before this year's ASCO Annual Meeting, we knew that this disease is

characterized by a prominent peritumoral stroma which seems to play role in the limited effect of and resistance to our treatments, and that multiple genetic changes occur in the cancer cells with K-*ras* mutations listed first. In this sense, there is role of targeting alteration occurring at the stroma environment such as those affecting sonic hedgehog (SHH) or hyaluronan, or dominant mutations in the cells such as the K-*ras* mutations.

What Did We Learnt from the 2013 ASCO Annual Meeting?

The current paper highlights interesting phase I studies which are believed to be further tested in clinical trials in pancreatic cancer patients and which might give a new perspective of how we approach this disease.

A phase I trial of a Local Delivery of siRNA Against K-ras in Combination with Chemotherapy for Locally Advanced Pancreatic Adenocarcinoma (Abstract #4037 [5])

The G12D mutation in K-*ras* gene is by far the commonest observed in pancreatic cancer [6]. There are not effective biological agents against this molecular alteration so far, and even drugs targeting downstream its pathway, have failed to show benefit suggesting significant cross talk and signal bypass. It is also well known that many reasons hamper systematic delivery of many drugs in pancreatic ductal adenocarcinoma such as the matrix properties and reduced vasculature. In the present study, Golan *et al* from Israel tested the local delivery of silencing RNA (siRNA) in locally advanced pancreatic tumors in combination with systemic chemotherapy, aiming to determine its safety, the dose limited toxicities (DLTs) and the maximum tolerated doses (MTDs). The researchers inserted the drug (anti-K-*ras* G12D siRNA) via endoscopic ultrasound (EUS) biopsy at the region of the tumor in the form of a gradually biodegradable polymeric matrix. The drug also named siG12D LODER (Local Drug EluteR) was inserted in 15 patients and purposed to be continuously released for a period of 4 months. In the dose escalation phase, siRNA doses of 0.025 mg, 0.75 mg and 3.0 mg were tested in combination with weekly intravenous gemcitabine 1,000 mg/m^2 (Table 1). The recommended dose for the phase II study was 3.0 mg of siRNA and was combined with modified FOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 150 mg/m^2 and 5-fluorouracil 2,400 mg/m^2 as a 46 hours infusion) chemotherapy every 2 weeks. Thirteen of the fifteen patients were finally eligible for analysis, as two patients were found to have metastatic disease on the imaging performed the day following EUS biopsy. The procedure was safe as only one patient developed serious related complications. Most patients showed minimal (grade 1-2) toxicities, while three patients developed serious adverse events (SAE). The authors reported that no dose limited toxicities were seen and the MDT was not reached. All patients showed disease stability on imaging with tumor marker CA 19-9 response in 64% of them. Out of the 13 evaluable patients 8 were still alive and the median survival of the whole cohort reached 16 months. The study was expanded to include also operable patients and to perform pharmacodynamic examinations. The phase II study of this agent has been already designed and planned (NCT01676259 – www.clinicaltrials.gov).

A Phase Ib Study of Gemcitabine Plus PEGPH20 (Pegylated Recombinant Human Hyaluronidase) in Patients with Stage IV Previously Untreated Pancreatic Cancer (Abstract #4010 [7])

As said above, extracellular matrix properties, with increased desmoplasia and poor vascular permeability, affects adversely the delivery of an effective drug within the pancreatic tumours and the cancer cells. Hyaluronan is a macromolecule that is found in the stroma of various tissues and plays role in their integrity, permeability and softness [8]. Increased levels of this glycosaminoglycan have been observed in pancreatic cancer stroma [9]. This results to significantly increased interstitial fluid pressures that ultimately attributes to the observed hypovasculature and reduced vascular permeability seen in pancreatic ductal adenocarcinoma [8]. In this abstract, Hingorani *et al* from Seattle, Washington, reported results of a phase Ib study of the combination on PEGPH20 (a human recombinant inhibitor of hyaluronan) with gemcitabine, conducted in untreated advanced pancreatic ductal adenocarcinoma. Based on a previous phase I study where the maximum tolerated dose was set at 3.0 μg/kg, the authors herein tried to find the recommended phase II dose (RP2D), escalating from 1 μg/kg up to 3.0 μg/kg (Table 1). Enrolled patients received PEGPH20 at 1 μg/kg, 1.6 μg/kg or 3 mg/kg intravenously (i.v.) twice a week for 4 weeks and then weekly for weeks 5-7 followed by 1 week rest. Concomitantly, gemcitabine was given at 1,000 mg/m^2 i.v. once a week for 7 weeks followed by 1 week rest. Thereafter, both drugs were administered weekly in a 3-week on, 1-week off fashion per month. Results of this study are summarized in Table 1. A total of 28 patients were enrolled and the recommended dose for phase II studies was set at 3 μg/kg (cohort of 20 patients). Apart from musculoskeletal symptoms (43%, grade 1 and 2) and some fatigue (23%, grade 1 and 2), similar to the phase I previous study, no other worrying toxicity was observed and the treatment was well tolerated. Only 2 patients required a dose reduction of the

Table 1. List of phase I studies in pancreatic adenocarcinoma presented in 2013 ASCO Annual Meeting.

Abstract, author, country	Investigational agent and mode of action	Setting and design	Primary end-point Secondary end-point	Results and conclusions
#4037 [5] Golan, Israel	siRNA G12D LODER Silencing RNA against the K-*ras* mutation G12D Inserted locally by EUS biopsy Combined with gemcitabine or modified FOLFIRINOX (oxaliplatin, irinotecan and 5-fluorouracil)	First line, locally advanced PDA, phase I study Dose escalation cohorts: • 0.025 mg • 0.75 mg • 3.0 mg No. of patients: 13 Median age: 70 years	Dose limiting toxicities (DLTs) Maximum tolerated dose (MTD) Recommended phase II dose (RP2D) Efficacy	No DLTs: 4 patients with serious adverse events MTD not reached RP2D: 3.0 mg/day 100% disease stability 64% of patients had CA 19-9 response Median overall survival: 16 months
#4010 [7] Hingorani, USA	PEGPH20 (pegylated recombinant human hyaluronidase) Degradation of hyaluronan -> reduction of interstitial fluid pressures and stromal desmoplasia Combined with gemcitabine	First line, stage IV PDA, phase Ib study Dose escalation cohorts: • 1.0 µg/kg i.v. (4 patients) • 1.6 µg/kg i.v. (4 patients) • 3.0 µg/kg i.v. (20 patients) No. of patients: 28 Median age: 58 years	Recommended phase II dose (RP2D) Toxicities Efficacy Biomarker analysis	RP2D: 3.0 µg/kg i.v. No major toxicities. 10 patients required dose reduction of gemcitabine and 2 patients of PEGPH20 Common adverse effects (grade 1-2): musculoskeletal (43%), fatigue (32%) 21 patients evaluable for efficacy: 7 partial response (33% response rate) and 9 stable disease 12 patients evaluable for hyaluronan staining 9 high expression (5 showed partial response) 3 low expression
#2559 [10] Ikeda, Japan	GBS-01 Oral agent rich in arctigenin (traditional herbal phyto-estrogen in the seeds of the plant *Arctium lappa* Linné) Antitumor activity by rendering cancer cells sensitive to glucose deprivation	Refractory advanced PDA, phase I study Dose escalation cohorts: • 3 g (3 patients) • 7.5 g (3patients) • 12 g (9 patients) No. of patients: 15	Dose limiting toxicities (DLTs) Maximum tolerated dose (MTD) Recommended phase II dose (RP2D) Response Survival	No DLTs observed Commonest adverse effects: Increase in gamma-GT, total bilirubin and serum glucose RP2D: 12 g per day Best response: 1 partial response; 4 stable disease Progression free survival: 1.05 months Overall survival: 5.68 months

i.v.: intravenously; LODER: Local Drug EluteR; PDA: pancreatic ductal adenocarcinoma

investigational drug from 3 to 1.6 µg/kg. Hyaluronan staining was also performed in tumor biopsies from 12 patients with adequate material, and found increased in 9 of them. Of the 9 patients with high hyaluronan staining 5 showed a partial response to treatment (response rate 56%). In the whole cohort of evaluable for efficacy patients (21 patients), partial response was noticed in 7 (33%) while 9 had had disease stabilization lasting for at least 2 months. The phase II study is already planned and might give more information on the efficacy potential of this exciting combination.

A Phase I Trial of GBS-01 for Advanced Pancreatic Cancer Refractory to Gemcitabine (Abstract #2559 [10])

Arctigenin is a phytochemical compound found in the seeds of the plant *Arctium lappa* Linne' (Figure 1). This plant is linked with many properties and it is used in culinary, cosmetic and alternative medicine due to antioxidant properties [11]. There are preclinical data suggesting arctigenin might bears anticancerous properties [12].

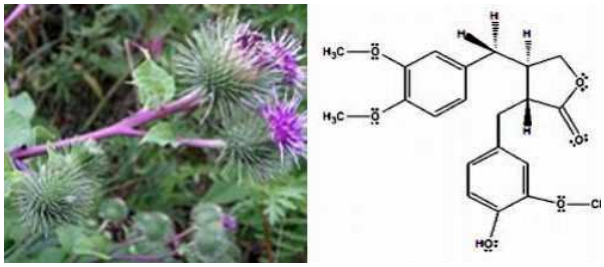

Figure 1. The biennial plant *Arctium lappa* Linné (left) and the chemical structure of arctigenin (right).

Investigators from Japan, tested the safety, tolerance and toxicity profile of GBS-01, an oral drug containing high levels of arctigenin. Patients with advanced pancreatic cancer resistant to gemcitabine were administered arctigenin in cohorts of 3 g to 12 g per day. Primary end-points were dose limited toxicities, hematological grade 4 and non-hematological grade 3-4 toxicities, in the first 4 weeks. The study details are summarized in Table 1. It is notable that no dose limited toxicities were observed in the fifteen patients enrolled in all cohorts. The main adverse effects of GBS-01 were slight increase of gamma-GT, total bilirubin and glucose serum levels. Therefore, the recommended phase II dose was set at 12 g a day. Response, a secondary endpoint, was observed in 1/15 patients while another 4 showed stable disease. The median overall survival was over 5 months in this pretreated group of patients.

Discussion

Clinicians and researchers around the world are desperate to understand the inner mechanisms of treatment failure in the vast majority of pancreatic cancer patients, while in other solid tumors with similar natural history great progress has been observed (e.g., malignant melanoma). A widely accepted fact suggests that the microenvironment of pancreatic cancer characterized by poor vasculature and dense stroma desmoplasia prevents cytotoxic treatments from reaching at adequate levels their target and novel agents with broad antivascular properties from having any impact. Therefore, strategies to overcome the above hurdles are promising and more than welcome. First, the local release of siRNA against G12D K-*ras* mutation might prove a success story as it manages to transfer the wanted doses of a drug against the most common molecular alteration seen in pancreatic ductal adenocarcinoma. Reasons to make it difficult happen in real practice include the demanding technology and know-how and facilities only available in tertiary centers. Other possible reasons for failure might include the complex mechanisms in pathogenesis of this disease, with many simultaneous genetic changes and cross talk and other unknown factors to date.

Similarly, use of PEGPH20 aiming to reduce the levels of hyaluronan, might reduce the effect of the peritumoral stroma barrier, restore vasculature, reduce interstitial fluid pressures and allow the existing drugs entering in proper doses into the cancer cells. If this concept is confirmed in the phase II study we might have a real ally and start re-using many of the drugs that did not show benefit in the previous years including anti-angiogenic therapies. The preliminary efficacy results show that there is future in this approach. Furthermore, the identification of a biomarker (hyaluronan) which is also a target raises hope for an individualized approach. But, we have learnt now to be somehow skeptical before the completion and confirmation of the early findings in large clinical trials, after growing experience of disappointing results of what initially thought to be promising.

Last, many of us believe that there is something important hiding in many phytochemical and traditional compounds. This is not unusual if we consider the way many of the mainstream drugs have been developed (e.g., camptothecin, taxanes, etc). The question often arising is why then do they fail in clinical trials. A simple answer might be the difficulty of formulating these compounds in proper oral well tolerated doses in order to produce meaningful pharmacological effect. A more complex explanation, but closer to reality, is the diverse properties of most natural products, often pro- and anti-apoptotic, and the multiple targets at various cellular levels, tissues and systems which prevents from a based on reason use.

Nevertheless, as science makes progress, we might in future better comprehend the culprits of the disease and the precise benefits of each of the tested agents. Then, we will be more able to combine many toxic and not toxic compounds together for a better outcome. In any case this disease, with the complex pathogenesis, teaches us that we are more likely to succeed only by acting at various levels all together.

Conflict of interest The authors have no potential conflicts of interest

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