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A Phase II study of Ganetespib as second- or third-line therapy for metastatic pancreatic cancer

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Abstract

Objectives—Heat shock protein 90 (HSP90) regulates multiple signaling proteins involved in key pathways of pancreatic cancer pathogenesis. Ganetespib binds to HSP90 and interferes with its binding to client proteins thus leading to inactivation and degradation of the signaling proteins that promote cancer progression. This phase II study was designed to evaluate the efficacy of ganetespib in patients with refractory metastatic pancreatic cancer (rMPC).

Methods—Patients with rMPC received 175 mg/m² ganetespib intravenously once weekly for three weeks in four week cycles. Primary endpoint was disease control rate (DCR) at eight weeks, with a goal of 70%. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety. Simon's two-stage design was used to assess futility and efficacy. Ganetespib was considered inactive if eight patients among the first 15 treated had disease control after eight weeks of treatment.

Results—Fourteen patients were treated on study. Grade 3 treatment-related toxicities were diarrhea, abdominal pain, fatigue, nausea, vomiting, and hyponatremia. DCR at eight weeks was 28.6%, and median PFS and OS were 1.58 months and 4.57 months, respectively. Early stopping rules for lack of clinical efficacy led to study closure.

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Conclusions—Single agent ganetespib was tolerable with only modest disease control in rMPC. This disease is resistant to chemotherapy, and given the emerging data in lung and rectal cancers, as well as in pancreatic cancer cell lines, suggesting improved activity of ganetespib in combination with cytotoxic agents, studies combining this agent with chemotherapy in rMPC are more likely to yield success.

Keywords

heat shock protein 90; pancreatic cancer; ganetespib; phase II clinical trial

Introduction

Pancreas adenocarcinoma (hereafter referred to as pancreatic cancer) is one of the most lethal of all human malignancies, and is currently the 4th leading cause of cancer death in the United States [1]. Pancreatic cancer is a highly resistant and aggressive neoplasm with a dismal five-year survival rate of less than 5% [2]. Several treatment strategies have been explored with limited success. For decades, gemcitabine has been the only chemotherapy drug available for treatment of advanced pancreatic cancer patients. Recently, therapeutic combinations of gemcitabine with erlotinib or nab-paclitaxel, as well as the non-gemcitabine combination of 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan, including the nanoliposomal irinotecan, have shown some promising clinical activity [3–7]; however, the median overall survival of patients with advanced pancreatic cancer remains approximately one year [8,9], and the 5-year survival rate is less than 10% [10]. Thus, the need for effective systemic therapy is great in this patient population.

Novel agents that specifically target cellular processes or pathways have gained interest as potential treatments to effectively halt at least some of the aberrant signaling pathways that are crucial in pathogenesis of pancreatic cancer [11]. Heat shock proteins (HSPs) are a class of molecular chaperone proteins that help modulate cellular responses to environmental stress. Chaperones are important for normal cellular functions, but in tissues subject to external stressors, e.g., hypoxia or acidosis, these HSPs are expressed at higher levels thus aiding cell survival. In particular, HSP90 regulates the folding, stability, and function of signaling proteins such as B-RAF, c-KIT, c-MET, EGFR, HER2, and PDGFRA [12]. Given the diversity of currently identified HSP90 client proteins, many of which are known to be critical regulators of cancer cell proliferation and survival [12], HSP90 inhibitors would be expected to show activity against a wide variety of human tumor types. Preclinical studies have revealed potent HSP90 inhibition and activity against a range of models including lung, prostate, colon, breast, melanoma, and leukemia [13–18]. Furthermore, early clinical trials with HSP90 inhibitors have demonstrated responses in several types of cancer supporting the importance of HSP90 as a potential therapeutic target [19–21].

Ganetespib (STA-9090) is a second-generation small molecule inhibitor of HSP90, and is currently in clinical trials for a number of human cancers [22]. Ganetespib has a novel chemical structure, unlike geldanamycin [23], with a resorcinol-containing triazole compound that binds to the adenosine triphosphate (ATP) pocket in the N-terminus of HSP90. It prevents HSP90 from binding to client proteins thus leading to inactivation and

disruption of cell signaling networks that promote cancer progression. *In vitro* and *in vivo* data show promising results from both a biochemical standpoint in altering the expression of key proteins important for the machinery of the cell, as well as from a purely cytotoxic standpoint [24,25]. Treatment of bone marrow-derived cultured mast cells, malignant mast cell lines, and fresh malignant cells with ganetespib induced growth inhibition, caspase 3/7-dependent apoptosis, and downregulation of the total and phosphorylated Kit and AKT [25]. In non-small cell lung cancer cells and xenograft models, ganetespib effectively destabilized a number of oncogenic drivers, thereby inactivating downstream MAPK and AKT signaling to induce apoptosis [26]. In the first-in-human phase I trial of patients with solid tumors, single-agent ganetespib administered once-weekly had an acceptable toxicity profile and showed some clinical activity with one partial response and a substantial number (45.3%) of patients with durable stable disease [19].

Given that pharmacologic inhibition of HSP90 resulted in a marked decrease of the proliferative activity in pancreatic cell lines and suppression of pancreatic xenograft growth [27,28] in combination with the observed clinical activity of the HSP90 inhibitor ganetespib, we designed a phase II study to evaluate the efficacy of ganetespib in patients with advanced pancreatic cancer who have failed one or two lines of previous therapy. An unmet clinical need exists as few therapeutic options are available for this group of patients.

Patients and Methods

Study design

We conducted a two-center clinical trial sponsored by the Vanderbilt-Ingram Cancer Center support grant (P30CA68485) and Synta Pharmaceuticals (clinicaltrials.gov identifier NCT 01227018). The protocol was approved at the Institutional Review Boards of the participating institutions, and written informed consent was obtained for all patients prior to performing study-related procedures in accordance with federal and institutional guidelines. Patients were enrolled at the Vanderbilt-Ingram Cancer Center and at the Jones Clinic.

This is a nonrandomized, open-label, single arm study conducted at two centers in patients with metastatic refractory pancreatic cancer. The primary objective was to measure the eight-week disease control rate (DCR) of ganetespib in patients with metastatic pancreatic cancer who have failed (either progressed or did not tolerate) one or two lines of prior therapy. DCR is defined as the ratio of the number of patients who achieve a complete response (CR), partial response (PR), or stable disease (SD) to the total number of patients enrolled on study. Our study goal was to achieve a DCR of 70% or better after eight weeks of therapy based on historical control data and preliminary data from the CONKO-003 trial presented at the 2008 ASCO annual meeting [29]. Secondary objectives were to determine response rate (RR), overall survival (OS), and toxicity profile.

Eligibility criteria

Eligible patients had pathologically confirmed metastatic pancreatic cancer, had received one or two prior chemotherapy regimens for metastatic disease, and were ≥ 18 years of age with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

Adequate organ (hematologic, renal, and hepatic) function and ventricular ejection fraction ($\geq 55\%$) were required. The patients who received adjuvant or neoadjuvant therapy were also eligible if they had progressed within six months of completing therapy and had not received a metastatic regimen, or if they progressed > 6 months after completing therapy and have received one or two lines of therapy for metastatic disease. Clinically and radiologically stable brain metastases were allowed.

Patients were excluded for any of the following: a major surgery or use of any investigational agent within four weeks prior to entering the study; pregnant or lactating women; treatment with chronic immune suppressants (e.g., cyclosporine following transplantation or systemic steroids for treatment of autoimmune disease); uncontrolled central nervous system metastases; New York Heart Association class III/IV congestive heart failure requiring active treatment; active coronary artery disease, myocardial infarction, angina pectoris, angioplasty, or coronary bypass surgery within six months of study registration; ventricular arrhythmia requiring antiarrhythmic agents; grade 2 or greater left bundle branch block; baseline QTc interval of > 470 ms; patients with uncontrolled illness/active infection including HIV-positive subjects receiving combination antiretroviral therapy; severe acute/chronic psychiatric condition; or laboratory abnormality that might interfere with study drug administration or with the interpretation of study results in the judgment of the investigator.

Study treatment

All patients were treated with 175 mg/m^2 of ganetespib once weekly by a 60-minute intravenous infusion for three consecutive weeks followed by a one-week dose-free interval in four-week cycles. Dose delays and reductions were permitted for grade 2 or 3 ganetespib-related toxicities. Treatment with ganetespib continued until disease progression, unacceptable toxicity, or patient withdrawal.

Study assessments

Patient demographics and medical history were recorded at baseline. Safety assessments were conducted at baseline and weekly during treatment. An electrocardiogram (ECG) was conducted at baseline, as well as at pre dose and post dose (within one hour) on day 1 of each cycle to evaluate for QTc prolongation. Adverse events (AE) were assessed at baseline and weekly during treatment, and toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. Clinical activity was assessed by computed tomography (CT) scans at baseline and every eight weeks thereafter while on the study. Tumor responses were categorized per Response Evaluation Criteria in solid Tumors (RECIST) v1.1. Participants who had measurable disease at baseline and received at least one dose of therapy were considered evaluable for response. Patients who were unable to have their disease reevaluated or did not return for follow-up were considered non-responders.

Statistical analysis

The sample size calculation was based on a standard Simon's optimal two-stage design. Given historical control data as well as the preliminary results of the CONKO-003 trial [29],

we would consider ganetespib insufficiently active if it elicits a true 8-week DCR of 50%. In the first stage, 15 patients were entered in the study. If eight or fewer patients among the first 15 treated achieved a DCR (CR + PR + SD) at eight weeks after treatment, the study would be closed. Otherwise, additional patients would be accrued to a maximum size of 43 patients. Ganetespib was considered sufficiently active to warrant further study in more definitive clinical trials if 27 or more patients demonstrated disease control at eight weeks. If a low eight-week disease control rate (e.g., 50%) was noted, the expected sample size was 24 patients with a 70% probability of early termination. The study design had a 5% type I error rate of incorrectly declaring promising activity if the true DCR at eight weeks was < 50%, and 80% probability (power) of declaring sufficient activity if the true DCR at eight weeks was > 70%.

Results

Patients and treatment

The characteristics of eligible patients are summarized in Table 1. Between January 2011 and November 2012, 15 patients were enrolled into the study; however, 1 patient did not receive study drug due to active disease progression prior to treatment initiation. The median age was 65 (range: 33–77), and a majority of the patients were male (73.3%) and had a PS of 1 (79%). Eight patients had received one line of therapy while the other six patients received two prior lines of therapy for their disease.

Clinical activity

Among the 15 patients enrolled, nine patients came off study due to radiographic disease progression, two patients were removed from the study based on unacceptable toxicity, and four patients decided to withdraw from the study based on reasons other than protocol-defined toxicity or progression. Clinical response was not evaluable in one patient who experience disease progression before initiating treatment. Two patients did not return to have their disease reevaluated after starting therapy, and therefore these patients were considered non-responders. No documented complete or partial responses were observed, however three patients (21.4%) achieved a best response of stable disease. The overall disease control rate at 8 weeks was 28.6% (95% Confidence Interval [CI]: 11.7 to 54.6%). Due to lack of efficacy in the interim analysis, the trial was stopped. The median progression-free and overall survival was 1.58 months (95% CI: 1.15 to 4.7 months) and 4.57 months (95% CI: 3.25 to 11.8), respectively (Figure 1). The median number of treatment cycles for all patients was 1.4 (range: 0.5 to 3.7).

Toxicity

Among the 14 patients evaluated for safety, 13 (86.7%) reported toxicities related to study treatment; one patient did not experience a toxicity related to the study drug. The most common (frequency > 20%) adverse events were diarrhea, fatigue, nausea, abdominal pain, anorexia, constipation, vomiting, elevated ALT, AST, ALK, and blood bilirubin, lymphopenia, and thrombocytopenia (Table 2). The majority of these observed events were grade 1 or 2; however, 7 patients experienced grade 3 toxicities, including diarrhea (n = 4), abdominal pain (n = 1), nausea (n = 1), vomiting (n = 1), fatigue (n = 2), and hyponatremia

(n = 1). No instances of ganetespib-related visual disturbances were reported. Additionally, no grade 4 or 5 treatment-related events were reported. A total of four patients (28.6%) required dose modifications due to adverse events; three patients had at least one dose omission while one patient had both a dose omission and reduction during treatment.

Discussion

Several studies have observed high levels of HSP90 mRNA among pancreatic carcinoma tumor samples [30–32], and pharmacologic inhibition of HSP90 resulted in antitumor activity *in vivo* [27,28]. Additionally, several HSP90 client proteins have been shown to be important in pancreatic cancer initiation, progression, and maintenance [12]. Therefore, therapies directed towards inhibition of HSP90 could simultaneously disrupt multiple key oncogenic proteins, and thus have emerged as potential treatment strategies for pancreatic cancer [33]. Ganetespib is one HSP90 inhibitor that has gained recent interest in the treatment of solid tumors. In phase I and II trials, ganetespib demonstrated a favorable safety profile in patients with refractory metastatic or locally advanced solid tumors with some hint of efficacy [19,34]. Based on these results, we designed the current phase II study with the hypothesis that inhibition of HSP90 with ganetespib monotherapy would be safe and efficacious in patients with pancreatic cancer.

To the best of our knowledge, this was the first study to investigate single agent ganetespib in the treatment of patients with metastatic pancreatic cancer who have progressed following one or two lines of previous therapy. Ganetespib monotherapy was well tolerated with minimal adverse events. Most of the treatment-related toxicities were grade 1 or 2 and no treatment-related deaths were observed. The primary study endpoint was disease control rate after 8 weeks of therapy, which was 28.6%. Based on the planned interim analysis, this study was terminated early due to lack of pre-specified clinical efficacy. It is important to mention, however, that the patients included in this trial were heavily pretreated who received ganetespib as a second or third-line therapy.

Ganetespib as a monotherapy has also been investigated in additional cancers, including hepatocellular carcinoma [35], metastatic breast cancer [20], and non-small cell lung cancer [21]; however, similar to the current study, limited clinical benefit in these patient populations was observed. Due to the limited efficacy as a single agent therapy, numerous ongoing clinical trials are investigating ganetespib in combination with a variety of chemotherapeutic and targeted agents. Two recent studies investigating ganetespib combination therapies observed acceptable toxicity profiles and encouraging efficacy data in the treatment of rectal [36] and lung [37] cancers. In the phase II GALAXY-1 trial, ganetespib was investigated in combination with docetaxel as a second-line therapy in advanced non-small cell lung cancer; however, the combination therapy failed to improve progression-free survival [38]. Nonetheless, a trend in clinical benefit was observed in a subgroup of patients with adenocarcinoma that were diagnosed with advanced disease greater than six months before study entry; these results led to the design of the phase III GALAXY-2 trial for patients of that subgroup. Despite the trend in the phase II trial, the phase III trial closed early for futility. Although ganetespib plus docetaxel failed in lung cancer, combination therapies are still under investigation in ovarian (NCT02012192) and

breast (NCT01042379) cancer, as well as acute myeloid leukemia and high-risk myelodysplastic syndrome (NCT01236144).

While clinical trials investigating ganetespib treatment combinations have been performed in a variety of other cancers, combination regimens in pancreatic cancer have not been tested. Nagaraju et al. recently investigated ganetespib in combination with 5FU and oxaliplatin in pancreatic tumor xenografts and observed a significant increase in tumor growth inhibition with the triplet combination compared to ganetespib or oxaliplatin/5-fluorouracil thereby providing evidence to suggest that ganetespib enhances the activity of chemotherapy in pancreatic cancer [39]. These results, therefore, provide motivation for investigating ganetespib-containing combination regimens in the treatment of advanced malignancies such as pancreatic cancer. In conclusion, ganetespib had an acceptable toxicity profile with modest clinical activity in patients with previously treated advanced pancreatic cancer. However, given the absence of tumor response and the limited activity when given as a monotherapy, ganetespib in combination with other cytotoxic chemotherapies should be investigated.

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Figure 1. Kaplan-Meier estimates of progression-free survival (A) and overall survival (B). The median progression-free survival and overall survival was 1.58 months (95% CI: 1.15 to 4.7) and 4.57 months (95% CI: 3.25 to 11.8), respectively.

Table 1

Patient demographics and clinical characteristics

Data	Results
Consented	17
Enrolled and received study drug	14
Enrollment site	
Vanderbilt-Ingram Cancer Center	12
The Jones Clinic	2
Enrolled and received study drug	14
Median age in years (range)	65 (33 – 77)
Gender	
Male	10
Female	4
PS (ECOG)	
0	3
1	11
Line of therapy for unresectable disease	
1st	8
2nd	6
Median CA 19-9 levels at baseline (range)	5672 (1 – 49402)

PS: performance status; ECOG: Eastern Cooperative Oncology Group

Table 2

Most common (frequency > 20%) treatment-related adverse events categorized by highest grade experienced per patient (n = 14)

	All Grades	Grade 1	Grade 2	Grade 3
Non-hematological				
Diarrhea	8 (58%)	1	3	4
Fatigue	8 (58%)	1	5	2
Nausea	5 (36%)	0	4	1
Abdominal pain	4 (29%)	1	2	1
Constipation	3 (22%)	1	2	0
Vomiting	3 (22%)	1	1	1
Anorexia	3 (22%)	0	3	0
Elevated ALT	4 (29%)	3	1	0
Elevated AST	4 (29%)	3	1	0
Elevated Alkaline phosphatase	3 (22%)	1	2	0
Elevated bilirubin	3 (22%)	2	1	0
Hematological				
Lymphopenia	4 (29%)	1	3	0
Thrombocytopenia	3 (22%)	3	0	0