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PHASE II STUDIES

A phase II study of the halichondrin B analog eribulin mesylate in gemcitabine refractory advanced pancreatic cancer

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Summary *Background* Eribulin mesylate is a halichondrin B analog that inhibits microtubule dynamics. Pre-clinical studies have suggested anti-tumor activity in pancreatic cancer. This phase II study of eribulin in patients with advanced pancreatic cancer previously treated with gemcitabine was conducted by the Princess Margaret Hospital Phase II consortium. *Patients and Methods* Eligibility criteria included locally advanced or metastatic pancreatic adenocarcinoma and previous treatment with gemcitabine. The study was a single arm phase II trial using a Simon 2-stage design. The primary endpoint was response rate, secondary endpoints included time to progression and overall survival. *Results* Fifteen patients were enrolled, 14 received treatment, and 12 were evaluable for response. The median age was 61, and the majority of patients were ECOG performance status 1. Grade 3 or greater adverse events included neutropenia (29%), fatigue (14%), peripheral neuropathy (7%) and thrombosis (7%). There were no complete or partial responses and therefore the study was closed after the first stage. The best response was stable disease in 5/12 (42%) of patients. Of these five patients, three had stable disease for 9 months or greater. Median time to progression was 1.4 months, and median overall survival was 6.1 months. *Conclusion* Eribulin was well tolerated but did not result in any objective responses in gemcitabine refractory pancreatic cancer. However, several patients had prolonged stable disease, suggesting that further studies of eribulin in pancreatic cancer may be warranted.

Keywords Pancreatic cancer · Halichodrin B · Eribulin mesylate · Phase II

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Introduction

Pancreatic cancer is the fourth leading cause of cancer related death in North America [1]. Response rates to cytotoxic chemotherapy are low, and median survival in advanced disease remains in the range of only 6–7 months [2–4]. Gemcitabine continues to be regarded as the standard first line treatment for advanced pancreatic cancer based upon a trial that demonstrated an improvement in median and one-year survival with the use of gemcitabine versus fluorouracil [5].

Once patients have progressed after gemcitabine-based chemotherapy, there is limited evidence of benefit from further systemic therapy. One comparative trial demonstrated a modest survival benefit from treatment with fluorouracil and

oxaliplatin [6]. Most phase II studies in this setting have shown low response rates and median times to progression of 2 to 4 months months or less [7–16]. In most centers second line therapies are limited to either fluorouracil +/− oxaliplatin, clinical trials, or best supportive care [17], thus new therapies are desperately needed for this patient population.

Eribulin mesylate (E7389) is an analog of the marine sponge product halichondrin B. It acts as a tubulin-binding agent that interferes with microtubule dynamics and causes inhibition of microtubule polymerization [18]. Preclinical data has demonstrated that eribulin inhibits cancer cell proliferation via cell cycle arrest at G2-M phase, disruption of mitotic spindle formation, and the induction of apoptosis [18–21].

Preclinical and early phase data suggest that taxanes, another class of antitubulin agents, have activity in pancreatic cancer [22–24]. Eribulin has a unique interaction with tubulin [25], and this may help to overcome resistance mechanisms that limited the effectiveness of other agents [26]. Eribulin has potent anticancer effects that surpassed other antitubulin agents (vinblastine and paclitaxel) when tested against a broad range of tumors in preclinical models, and eribulin has displayed promising activity in a pancreatic cancer xenograft model [27]. In addition, eribulin may have a role in inactivating Bcl-2 family proteins [19] which are a mediator of chemoresistance in pancreatic cancer [28]. Anti-tumour activity has also been demonstrated in several phase II studies, and more recently a phase III trial in breast cancer [29–31]. Importantly for the generally unwell pancreatic cancer population, phase I and II studies have demonstrated that eribulin is generally well tolerated, with neutropenia and fatigue being the most common toxicities [29–34].

Given the need for treatment options in gemcitabine refractory pancreatic cancer and the encouraging early clinical data supporting the use of eribulin, the Princess Margaret Hospital Phase II consortium undertook a phase II study of eribulin in patients with advanced gemcitabine refractory pancreatic cancer.

Patients and methods

Patient selection

The study population consisted of patients with locally advanced or metastatic pancreatic cancer who had received prior treatment with gemcitabine. To be eligible, patients required Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2, an absolute granulocyte count $\geq 1.5\times10^9$/L, platelet count $\geq 100\times10^9$/L, and had normal serum creatinine and bilirubin ≤1.5× the upper limit of normal (ULN) . Aspartate aminotransferase (AST) and alanine transaminase (ALT) were required to be ≤2.0× the ULN, unless liver metastases were present (≤5 × ULN). Patients were required to have measurable disease using Response Evaluation Criteria in Solid Tumors [RECIST 1.0]. Exclusion criteria included concurrent other malignancies and any serious medical conditions that would impair the ability of the patient to receive protocol treatment. The institutional review boards of the participating institutions approved the study, and all patients provided written informed consent.

Study design

This phase II study of eribulin (NCT Registration ID: NCT00383769) was conducted using a two-stage Simon design, with the primary endpoint being response rate. The study was funded by the National Cancer Institute (NCI) (protocol #7448). Eribulin was administered at a dose of 1.4 mg/m2 as an intravenous bolus on Days 1 and 8 of a 3 week cycle, which was the recommended phase II dosing schedule. Baseline radiological investigations were performed within 28 days prior to study treatment. Radiological assessments for tumor measurements were conducted after every second cycle (every 6 weeks). Study treatment continued until unacceptable toxicity, patient request, or progression.

Dose modifications

Hematologic toxicity

On day 1 of a cycle, treatment was held for 1 week if the absolute granulocyte level (ANC) was $<1.5\times10^9$/L or platelet level was $<100\times10^9$/L. If the levels recovered after 1 week then the dose was reduced by 0.3 mg/m^2. If the levels required greater then 1 week to recover then the dose was reduced by 0.6 mg/m^2. If there was an episode of febrile neutropenia in the previous cycle the dose was reduced by 0.3 mg/m^2. On day 8, the dose was the same as day 1 if the ANC was $\geq 1.0\times10^9$/L and platelet level was $\geq 100\times10^9$/L. If the ANC was $0.5–0.99\times10^9$/L or the platelet count was $50–99\times10^9$/L the dose was reduced by 0.3 mg/m^2, and if the levels were below this the dose was held.

Non-hematological toxicity

For grade 2 toxicity not immediately resolving with symptomatic treatment, eribulin was held until the toxicity improved to ≤ grade 1 and then resumed without dose reduction. On second occurrence, the dose was reduced by 0.3 mg/m2. For grade 3 toxicity, eribulin was withheld until ≤ grade 1 and then resumed at a 0.3 mg/m2 dose reduction. For grade 4 toxicity protocol, therapy was

Table 1 Patient demographics

Characteristic	Enrolled patients (n=15)
Age, years	
Median	62
Range	34–79
Gender	
Male	8
Female	7
ECOG performance status	
0	1
1	12
2	2
Stage	
Locally advanced	0
Metastatic	15
Prior therapy number of treatment regimens	
1	13
2[a]	2

[a] Also received single agent erlotinib

discontinued. The dose modification schedule was similar to that used in other studies with the same dosing schedule [30].

Statistical methods

The primary endpoint was the response rate (complete and partial response), Secondary endpoints included overall survival, duration of response or stable disease, progression-free survival, and toxicity. The optimal Simon two-stage phase II design was used with results indicating lack of efficacy resulting in study termination after stage 1 [35]. The treatment combination was assumed to be inactive if the response rate was at most 5% and active if it was at least 20%. The first stage involved the accrual of 12 response evaluable patients and if at least 1 of these patients had a response, the study would proceed to stage II. The second stage would involve accrual of an additional 25 patients. If 4 or more of the 37 total patients respond, the drug will be deemed active. The true alpha is 0.093, and power is 0.90 for this design.

Standard descriptive statistics, such as the mean, median, range and proportions were used to summarize the patient sample and toxicity. Kaplan-Meier method was used to estimate time to progression and overall survival.

Results

Fifteen patients were enrolled over 18 months (between July 2006 and January 2008), and 14 received treatment

Table 2 Possibly related grade 3 or 4 adverse events

Adverse event (Grade 3–4)	Eribulin (n=14[a]) n (%)
Non-hematological	
Fatigue	2 (14)
Diarrhea	1 (7)
Peripheral sensory neuropathy	1 (7)
Thrombosis	1 (7)
Hematological	
Neutropenia	4 (29)
Leukopenia	3 (21)
Lymphopenia	1 (7)
Elevation in GGT	1 (7)

[a] 1 patient withdrew consent prior to receiving eribulin

(Table 1). All patients had metastatic disease at the time of study enrolment. The median number of cycles administered was 2 (range of 1–16). Eleven patients came off study due to objective progression, 1 due to clinical progression, and 3 due to patient request. Of the latter, one patient had grade 2 vomiting prior to starting treatment and chose not to proceed with the study. A second patient had a grade 4 elevation in creatinine (unrelated to study drug as was secondary to ureteric obstruction which had occurred previously and recurred 1 week after starting on study). This resolved with a placement of a percutaneous nephrostomy tube, but the patient chose not to continue on study after this. The third patient did not experience any adverse

Table 3 Selected second line studies in advanced pancreatic cancer

Investigational agent	Number of patients	Response rate	Median overall survival
Halicondrin (Renouf et al. 2011)	14	0%	6.1 months
Capecitabine and Docetaxel (Katopodis et al. 2011) [15]	31	9.7%	6.3 months
Sunitinib (O'Reilly et al. 2010) [16]	77	1.4%	3.78 months
Everolimus (Wolpin et al. 2009) [14]	33	0%	4.5 months
Capecitabine and Oxaliplatin (Xiong et al. 2008) [12]	41	2.6%	23 weeks
Fluorouracil, Leucovorin and Oxaliplatin (Pelzer et al. 2008) [6]	76[a]	NR[b]	26 weeks
Capecitabine and Erlotinib (Kulke et al. 2007) [7]	30	10%	6.5 months
Gemcitabine and Oxaliplatin (Demols et al. 2006) [11]	31	22.6%	6 months

[a] 76 patients on this treatment arm

[b] Not reported

events, but chose to come off study drug prior to objective evaluation.

Twelve patients were evaluable for response to complete the first stage of enrollment. There were no complete or partial responses noted, therefore the study was closed at the end of stage 1. The best response was stable disease in 5/12 (42%) of patients. Of these 5 patients, 3 had stabilization of metastatic disease for 12 cycles or greater (range 12–16 cycles). Two of these patients had metastatic disease with objective progression on gemcitabine prior to study enrollment. Neither of these patients had sustained benefit from gemcitabine in the first line setting. The third patient had metastatic disease and had intolerable toxicity related to gemcitabine and radiation prior to study enrollment.

All patients who received treatment were included in the survival analysis. Median time to progression was 1.4 months (95% CI: 1.2–8.5), with a 6 months progression free rate of 25% (95% CI: 6–59%). Median overall survival was 6.1 months (95% CI: 1.4–20.8) with 6 months overall survival rate of 58% (95% CI: 25–81%).

Adverse events are listed in Table 2. Grade 3 or greater adverse events at least possibly related to eribulin included neutropenia (29%), fatigue (14%), diarrhea (7%), peripheral neuropathy (7%), and thrombosis (7%). There was one grade 4 toxicity noted, which was an episode of grade 4 neutropenia. Dose reductions were required in 14% of patients and 29% of patients had a dose delay due to toxicity or patient request.

Discussion

The development of new agents for treatment of advanced pancreatic cancer continues to pose a significant challenge. While eribulin is a novel microtubule inhibitor, and has preclinical activity against pancreatic cancer, we did not see substantial efficacy as measured by objective response rate in this phase II study. However, the drug was reasonably well tolerated, and sustained stable disease was evident in some patients, with 3/12 (25%) of evaluable patients having stable disease for 9 months or longer.

Pancreatic cancer is usually a rapidly progressive disease and median progression free survival ranges from 2 to 4 months or less in the gemcitabine refractory setting [7–16]. Numerous studies have assessed second line regimes with generally low response rates, yet moderate improvements in stable disease and survival have been seen, therefore response rate may not be an optimal endpoint for assessing the efficacy of novel agents in second line pancreatic cancer trials. Table 3 summarizes some of the recent phase II trials in the gemcitabine refractory setting and reflects the low response rates that have been noted. A potentially alternative endpoint would be the use of a multinomial endpoint based on disease control (response plus stable disease) which may represent a more efficient stopping rule compared with tumor response alone [36, 37].

In retrospect, a study design with a multinomial endpoint such as disease control rate as the primary endpoint may have been a more appropriate measure to assess the efficacy of eribulin given the efficacy results noted with the use of this agent in other cancers. Phase II trials of eribulin in breast cancer found relatively low response rates of 9.3–11.5%, but more impressive clinical benefit rates (partial response and/or stable disease ≥6 months) of 17.2–17.3% [29, 30], and encouraging survival times. A phase III study of eribulin in breast cancer demonstrated a significant improvement in overall survival with eribulin compared to physician's choice in heavily pre-treated metastatic breast cancer patients [31]. Given the benefit of this agent in breast cancer, and that the rate of sustained stable disease for patient that received at least one dose of eribulin noted in our study (3/14, 21%) is comparable to the clinical benefit rate noted in the breast cancer literature, further trials investigating eribulin in pancreatic cancer designed with a disease control endpoint may be considered.

In summary, in this phase II study eribulin was well tolerated but did not result in any responses for patients with advanced pancreatic cancer resistant to gemcitabine.

Conflicts of interest None of the authors have any conflicts of interest to declare.

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