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Original article

A phase I dose escalation trial of AXP107-11, a novel multi-component crystalline form of genistein, in combination with gemcitabine in chemotherapy-naive patients with unresectable pancreatic cancer

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ABSTRACT

Background: AXP107-11 is a novel, multi-component crystalline form of the naturally occurring compound genistein. AXP107-11 has improved physiochemical properties and oral bioavailability compared to the natural form of genistein, and it is possible that combining AXP107-11 with chemotherapy may increase the effect and reduce chemoresistance. The purpose of this dose escalation phase Ib study was to assess the safety, maximum tolerated dose (MTD) and pharmacokinetics (PK) of AXP107-11 in combination with gemcitabine in treatment-naïve patients with inoperable pancreatic carcinoma.

Patients and methods: AXP107-11 was given orally in escalating doses (400 mg–1600 mg daily) in combination with standard gemcitabine treatment (1000 mg/m^2/week) for the first seven of eight weeks and thereafter for a maximum of four × four-week treatment cycles. PK, safety, MTD and efficacy of AXP107-11 in combination with gemcitabine were evaluated.

Results: Sixteen patients were enrolled and received AXP107-11. The maximum concentration in serum of unconjugated (free) genistein was 1 μM. Neither dose-limiting toxicities (DLTs) nor signs of hematological or non-hematological toxicities related to AXP107-11 were observed over a period ranging from 0.7 to 13.2 months. The median overall survival time was 4.9 months (range 1.5–19.5 months). Seven patients (44%) survived longer than six months and 19% were alive at the one-year follow-up.

Conclusion: Treatment of pancreatic cancer patients with AXP107-11 in combination with gemcitabine resulted in a favorable PK-profile with high serum levels without signs of either hematological or non-hematological toxicity. Accordingly, we suggest further studies with AXP107-11 in pancreatic cancer patients.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death in the United States and Europe [1] and is predicted to become number two by the year 2030 [2]. In fact, PDAC is one of the few diseases in which the mortality rate almost equals the incidence rate. At diagnosis, approximately 80% of pancreatic cancer patients have locally advanced or metastatic disease, and patient treatment represents a medical emergency [3]. The median survival time is around six months [4], while the five-year survival rate has remained below 5% for the past 25 years and is the lowest for any cancer [5].

PDAC poses one of the greatest unmet medical needs in cancer research as there are no current effective therapies. Gemcitabine, the recommended first-line drug for PDAC patients, is given alone

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or in combination with other agents [6]. However, even with the best available therapy regimens, median survival times do not exceed ten months [7,8]. Numerous efforts have been made to improve the treatment options [9], though these have all proved futile. This failure is attributable to many factors, including resistance to conventional chemotherapeutic approaches, and it is thought that this drug resistance is caused by the many genetic abnormalities present in pancreatic cancer [10]. Thus, understanding and overcoming drug resistance has become the focus in pancreatic cancer therapy [11–13].

One option for overcoming chemoresistance is to co-treat with so-called chemosensitizers – a group of low molecular weight, naturally occurring compounds [14]. One example is genistein (4′,5,7-trihydroxyisoflavone-5,7-dihydroxy-3-[4-hydroxyphenyl]-4H-1-benzopyran-4-one), a natural compound present in plants such as soybeans. Genistein is a potent phytoestrogen that binds to both alpha and beta estrogen receptors to regulate the divergent intracellular signaling cascades of estrogen. It also has the potential to competitively inhibit various ATP utilizing enzymes. Moreover, its very low cytotoxicity and its abundance in readily available foods compared to other isoflavones makes it a promising therapeutic option [15].

Genistein's potential role in the treatment of a number of diseases has been shown in animal models of pancreatic cancer and other solid tumors [16]. The cellular signaling pathways regulated by genistein have been identified, and those related to cancer include targets important for cell growth, apoptosis and metastasis [11,17,18]. The compound acts as a multi-targeted chemosensitizer, enhancing the effect of a number of chemotherapies, including 5-fluorouracil (5-FU) [19] and gemcitabine [20] in xenograft models of pancreatic cancer. Genistein has already been used with some success in pancreatic cancer patients [21], however, its low bioavailability and short half-life makes it difficult to handle in clinical practice. Nevertheless, it was demonstrated to have a profound effect on stroma-inducing growth factors and pathways [19,22–24].

We chose to study the sodium salt dihydrate form of genistein (genistein-SSDH: AXP107-11), having previously demonstrated its efficacy in preclinical pancreatic cancer models [25]. AXP107-11 has demonstrated a 4.2-fold increase in C_{max} and a 3.5-fold increase in bioavailability after intraduodenal administration into rats compared to the naturally occurring crystalline form of genistein [26]. Here we report on the results from a phase Ib study of sixteen chemotherapy-naïve pancreatic cancer patients treated with gemcitabine and AXP107-11.

Patients and methods

Patients

Eligible patients had histologically/cytologically confirmed metastatic or locally advanced pancreatic cancer and had not received prior treatment with chemotherapy or radiotherapy. Patients were aged 18 years or older with a Karnofsky Performance Status $\geq$70 and adequate hematology, blood chemistry, and renal, liver, cardiac and pulmonary function. Patients with chronic inflammatory or autoimmune disease were excluded and no immunotherapy within six weeks was allowed. All patients signed informed consent forms. The local ethics committee approved the study (EPN Diarie-Nummer 2010/1132-31), which was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Study design and treatment

The phase Ib, single site, open-label, clinical study was performed in patients with metastatic pancreatic cancer (Study No. AXP-CT-001, EudraCT No. 2010-019214-25). The primary objective was to evaluate safety profiles, pharmacokinetics (PK) and the maximum tolerated dose (MTD) of AXP107-11, when given together with standard gemcitabine treatment. Dose limiting toxicities (DLTs) were defined as: i) any non-hematologic grade $\geq$ 3; ii) any grade 4 clinical chemistry abnormalities; iii) any grade 4 hematologic (e.g. febrile neutropenia: absolute neutrophil count [ANC] $< 0.5 \times 10^9$/L with fever $\geq$ 38.5 °C); iv) or thrombocytopenia ($<25 \times 10^9$/L) with bleeding; v) any other severe reaction considered by the investigator to indicate that further dose escalation was inappropriate.

The MTD was defined as the dose level at which $\geq$3/6 patients experienced a DLT. The secondary objective was to determine the PK profile of escalating doses of AXP107-11. AXP107-11 was given as 100 mg capsules in the following dose steps: 200 mg (3 pts), 400 mg (3 pts), 600 mg (3 pts) and 800 mg (7 pts). Doses were administered twice daily.

The study consisted of two treatment periods: the first period was a two-week single agent AXP107-11 lead-in treatment in order to elucidate the pharmacokinetic pattern. In the second period, AXP107-11 was given in combination with gemcitabine. The original schedule was employed i.e. gemcitabine 1000 mg/m^2/week during the first seven of eight weeks and thereafter for a maximum of four $\times$ four-week treatment cycles, during which 1000 mg/m^2 was given on days 1, 8, and 15 [27]. The combined treatment period was scheduled for a maximum of six months. Patients who finished the gemcitabine treatment could continue to receive single agent AXP107-11 until disease progression.

Assessments

The Karnofsky Performance Status, a complete physical examination, the record of signs and symptoms, and the patient's hematology/biochemistry results were all assessed at baseline and thereafter weekly throughout the trial. The tumor marker carbohydrate antigen (CA) 19-9 was measured at baseline and thereafter every third week. Patients were scored for quality of life (EORTC QLQ-C30 and PAN-26 modules) at baseline and thereafter every third week. Tumor status was evaluated by multidetector computed tomography and/or magnetic resonance imaging (MRI) at baseline, on days 1, 29 and 50 during the Burris treatment period, and thereafter every sixth week. Tumor status was evaluated according to RECIST criteria (version 1.1) [28]. Toxicity was evaluated according to NCI-CTC criteria (version 2.0).

Pharmacokinetic evaluations

Blood samples for AXP107-11 PK analyses were obtained as follows on the first treatment day: pre-dose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 h post-dose. Blood samples were also drawn before the first three gemcitabine doses (days 1, 8 and 15). The parent drug plasma concentration-time data were analyzed by non-compartmental analysis using Phoenix™ WinNonlin® Version 6.3.

Statistical analysis

Descriptive statistics were used for summarizing discreet variables. Kaplan–Meier curves were created to estimate time-to-event variables (e.g. time to progression, overall survival). The Pearson χ^2-test or Fisher's exact test were used to compare proportions when appropriate. Time to progression and overall survival were calculated from the date of the first AXP107-11 dose given until the date of documented progressive disease (PD) and death, respectively. Response duration was calculated from the date of the first

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