Gemcitabine-Capecitabine plus Intra-arterial Epirubicin-Cisplatin in Pretreated Pancreatic Cancer Patients: A Phase I Study

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Abstract. Background: Gemcitabine plus capecitabine are active in patients (pts) with advanced pancreatic cancer (APC). Intra-arterial chemotherapy showed activity and low toxicity. Combination of systemic and intra-arterial chemotherapy was investigated. Patients and Methods: Patients with APC, progressed after a first-line chemotherapy, were included. Fixed doses of epirubicin 35 mg/m² and cisplatin 42 mg/m² intra-arterially every 28 days, and capecitabine 650 mg/m² twice a day on days 2-15; gemcitabine systemically in increasing doses on day 2. The purpose was to find maximum-tolerated dose (MTD) and dose-limiting toxicity (DLT). Results: Fifteen patients were enrolled. DLT occurred at 1300 mg/m² of gemcitabine and consisted of myelotoxicity (grade 4 febrile neutropenia and grade 4 thrombocytopenia). Conclusion: Limiting toxicity was hematological. For further studies intra-arterial epirubicin 35 mg/m² and cisplatin 42 mg/m²; systemic gemcitabine at 1,000 mg/m² on day 2, and capecitabine at 650 mg/m² twice a day PO on days 2-15 are suggested.

Pancreatic cancer is an important cause of cancer-related morbidity and mortality in Europe and United States, with an overall 5-year survival rate of less than 4% (1). Surgical resection remains the only potentially curative treatment modality (2). Chemotherapy for patients with advanced disease improves clinical symptoms and overall survival, but life expectancy for the majority of these patients is short, with a median survival between 4 and 10 months. Single-agent gemcitabine is considered the standard treatment in patients with advanced disease (3). In order to improve therapeutic efficacy, gemcitabine was combined with antimetabolites, platinum analogs or topoisomerase inhibitors. The most promising results were obtained when gemcitabine was combined with the oral fluoropyrimidine capecitabine, or with platinum compound (4-8). A recent meta-analysis of randomized trials indicated that patients with a good performance status appear to benefit from gemcitabine-based cytotoxic combination, whereas patients with a poor performance status seem to have no survival benefit from combination chemotherapy (9).

Some studies of intra-arterial chemotherapy have demonstrated that pancreatic adenocarcinoma is dose dependently sensitive to drugs administered by intra-arterial route (10, 11). A four-drug regimen (FLEC: 5-FU, leucovorin, epirubicin and carboplatin) has demonstrated a very good tolerance and interesting results in term of response rate and survival (12). In the adjuvant setting the same regimen with or without systemic gemcitabine has shown a favorable impact on disease free interval and overall survival (13). The aim of this study was to find the appropriate dose of gemcitabine to administer with capecitabine and intra-arterial epirubicin and cisplatin.

Patients and Methods

Patients were eligible if their disease was in progression after at least one line of chemotherapy or chemo/radiotherapy. They had to have histologically or cytologically proven, surgically unresectable, locally advanced or metastatic pancreatic adenocarcinoma. Other inclusion criteria were age 18 to 80 years, ECOG performance status ≤1 and adequate organ function (leukocyte count >3,500/μL, haemoglobin >10.0 g/dL, serum creatinine <1.25 times upper limit of normal (ULN), transaminases and alkaline phosphatase <2.5 times ULN, bilirubin <1.5 times ULN). Written informed consent was obtained from each patient. The protocol and the informed consent were approved by the local institutional review boards.

Treatment plan. On day 1, epirubicin 35 mg/m² and cisplatin 42 mg/m² were administered into celiac axis by bolus injection through
a catheter inserted in the femoral artery with the Seldinger method. Capecitabine was given orally at the fixed dose of 650 mg/m² twice a day, on days 2-15. Gemcitabine was administered on day 2 of each cycle at a starting dose of 1,000 mg/m² (intravenously, over 30 minutes) and a 30% dose increase for each consecutive cohort (no intrapatient dose escalation) was planned.

Adverse events were recorded according to the National Cancer Institute of Canada common toxicity criteria (NCIC-CTC). The maximum-tolerated dose (MTD) was defined as one dose level below the dose level at which two or more of six patients experienced dose-limiting toxicity (DLT), which was defined as neutropenia and/or thrombocytopenia grade 4 or any non-hematologic grade 3 or 4 toxic effect occurring during the first two treatment courses. The MTD represents the dose recommended for further studies.

The epirubicine and/or cisplatin and/or capecitabine dosage was adjusted, delayed or omitted for toxic effects ≥ grade 2, based on protocol guidelines.

Statistics. The study design was a classic phase I design: three patients were planned for each cohort. If one of these three patients experienced dose-limiting toxicity (DLT), which was defined as neutropenia and/or thrombocytopenia grade 4 or any non-hematologic grade 3 or 4 toxic effect occurring during the first two treatment courses. The MTD represents the dose recommended for further studies.

The epirubicine and/or cisplatin and/or capecitabine dosage was adjusted, delayed or omitted for toxic effects ≥ grade 2, based on protocol guidelines.

Results

Fifteen patients with advanced or metastatic pancreatic cancer entered this study between August 2006 and February 2008 (Table I). Three patients were planned to receive the dose level 1 (gemcitabine 1000 mg/m², on day 2). These patients tolerated the treatment very well. Next, three patients were treated with the dose level 2 (gemcitabine 1300 mg/m²); a grade 3 thrombocytopenia was observed. So, another 6 patients were treated with the same dosage (level 2). In this group, 2 patients registered with grade 4 thrombocytopenia and 1 patient with grade 4 neutropenia. The toxicity of patients treated with the dose level 2 was considered unacceptable. The last three patients, treated with the dose level 1, did not show any grade 3-4 toxicity. Regarding non-hematologic toxicity, in both levels 4 patients presented with grade 2 mucositis and 4 patients with grade 3 alopecia (Table II). The DLT was defined at the level 2 and the MTD at the level 1.

Discussion

Unresectable pancreatic cancer patients with good performance status benefit from gemcitabine-based chemotherapeutic combination, whereas gemcitabine alone remains the standard treatment for patients with a poor performance status. Two four-drugs regimens have been compared with gemcitabine in advanced pancreatic adenocarcinoma: systemic PEF-G (cisplatin, epirubicin, 5-FU and gemcitabine) and intra-arterial FLEC (12, 14). Both regimens have resulted to be superior to gemcitabine in terms of survival. The objective of this study was to find the appropriate dose of gemcitabine to administer with capecitabine and intra-arterial epirubicin and cisplatin. Dose-limiting toxicity (DLT) was myelotoxicity (grade 4 febrile neutropenia and grade 4 thrombocytopenia) and occurred at the dose of 1300 mg/m² of gemcitabine, without any other significant toxicity. In this group of pretreated patients, it was an expected toxicity, mainly related to gemcitabine. For further studies the following doses are suggested: on day 1 every 28 days intra-arterial epirubicin 35 mg/m² and cisplatin 42 mg/m², on day 2 systemic gemcitabine at 1,000 mg/m² and on days 2-15 capecitabine at 650 mg/m² twice a day.

References


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