Biweekly Gemcitabine (GEM) in Combination with Erlotinib (ERL): An Active and Convenient Regimen for Advanced Pancreatic Cancer

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Abstract. *Background: Pancreatic cancer remains a disease of high mortality and one of the most frustrating, resistant solid neoplasms to treat. The aim of this study was to evaluate a biweekly gemcitabine plus daily erlotinib regimen in patients with advanced (stage III-IV) pancreatic cancer in terms of overall survival and time to progression of the disease. The secondary aim was to record treatment related toxicities. Patients and Methods: Twenty-seven patients with metastatic non-operable pancreatic adenocarcinoma, stage III-IV, consented to receive chemotherapy with gemcitabine and erlotinib. Patients received first-line treatment with gemcitabine (2 g/m^2 via 90 min i.v. infusion every two weeks) and 100 mg erlotinib per os every day, for at least 12 consecutive courses (6 cycles). Treatment was discontinued at disease progression and/or serious toxicity. Results: The objective response rate was 25.9% (95% confidence interval [CI]: 11.1-46.3%) and the stable disease rate was 59.3% (95% CI: 38.8-77.6%). The one-year overall survival was 20%. The median overall survival and time to progression at the time of assessment was 7.5 months (95% CI: 3.6-42 months) and 5.5 months (95% CI: 1.5-10 months), respectively. Overall survival and time to progression were related to response ($p<0.001$), while time to progression was further related to disease stage ($p=0.011$). No grade 4 haematological or non-haematological toxicities were observed. Conclusion: The biweekly regimen of gemcitabine plus erlotinib has similar toxicity and efficacy to weekly administration, presenting both patients and hospital resource departments with a clearly more convenient therapy alternative.*

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Pancreatic adenocarcinoma remains one of the leading causes of cancer deaths in Europe and the United States, while a recent UK report sets the relative 5-year survival rate at less than 3%, in both sexes (1, 2). No significant improvement in therapy has occurred during the last two decades and despite progress in diagnostic procedures, the percentage of patients diagnosed with operable, low stages of disease remains extremely low (3, 4). Gemcitabine (GEM) is a fluorinated pyrimidine antagonist that is considered effective in the treatment of patients with locally advanced, non-operable, stage III or IV metastatic pancreatic adenocarcinoma, with antitumor activity and palliative properties (4-8). However, although chemotherapy with single-agent GEM produces significant improvement in terms of survival and objective tumor response, these improvements remain considerably modest.

There is an increasing number of studies focusing towards the potential additive or synergistic effects of GEM combined with other cytotoxic drugs or therapeutic agents. However, most of these studies failed show improvements in primary endpoints of overall survival and quality of life compared to single-agent GEM (9-20). Erlotinib (ERL) on the other hand, an inhibitor of the epidermal growth factor receptor (EGFR) pathway, has shown promising results in treatment of other types of cancer such as non-small cell lung cancer (NSCLC) (21), and recently obtained approval for the treatment of non operable pancreatic adenocarcinoma, showing improvement in terms of the 1-year survival rate compared to GEM single-agent therapy (22).

Weekly administration of GEM has been the treatment of choice; however several investigations that employed a biweekly regimen of GEM, either alone or in combination with other agents, have shown comparable results in terms of survival and disease progression, with a mild safety profile (18, 23-25).

Recent pharmacoeconomic analyses in pancreatic cancer place the results of ERL plus GEM treatment well above the cost-effectiveness threshold, questioning the significance and

value of ERL as an additive to GEM monotherapy (26). Hence adopting a more convenient but equally effective chemotherapy regimen for advanced pancreatic adenocarcinoma could be beneficial both in terms of patient responses and hospital resources.

The present study was thus conducted to assess a biweekly regimen of GEM plus ERL *via* standard endpoints of overall survival and time to progression in a group of stage III-IV patients with pancreatic adenocarcinoma. Moreover the major toxicological events during treatment were recorded.

Patients and Methods

Patient and tumour characteristics. A total of 27 patients with histologically confirmed pancreatic adenocarcinoma received chemotherapy with biweekly GEM plus daily *per os* administration of ERL. All patients had locally advanced non-metastatic inoperable adenocarcinoma of the pancreas, stages III or IV.

Patients were also required to have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), (27) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and life expectancy of at least 12 weeks. Renal (serum creatinine concentration <1.2 mg/dl), hepatic (total serum bilirubin concentration <3 mg/dl) and bone marrow function (granulocyte count ≥1,500/dl platelet count ≥120,000/dl) also had to be adequate at initiation of study treatment, provided that serum transaminases and protein levels were normal. Prior surgery was allowed provided that it had been carried out at least 4 weeks prior to enrolment. Patients with active infection or other primary tumours were excluded from the study. All patients consented to participate after being informed of the objectives and procedures of the study.

Histological evaluation was performed on tumour samples and differentiation was categorised according to Klöppel *et al*. (28). These were categorised as: (i) poorly differentiated, where tumour cells lacked well-formed glands and infiltrate as either single cells or sheets of cells displaying increased cytologic atypia; (ii) well-differentiated pancreatic adenocarcinoma, where well-formed infiltrative glands were present along with minimal to mild cytological atypia; and (iii) moderately differentiated, intermediate between the poorly and well-differentiated morphologies.

Administration of chemotherapy with GEM and ERL. Patients were administered 2,000 mg/m^2 GEM (Gemzar®; Eli Lilly, Indianapolis, IN, USA), *q2w via* a 90-minute *i.v.* infusion. ERL (Tarceva®; F. Hoffmann-La Roche, Basel, Switzerland) was also administered at 100 mg/m^2 *per os* daily until disease progression or occurrence of intolerable toxicity (grade 3-4) for at least 12 consecutive courses (6 cycles).

Study definitions. The primary variables evaluated in the present study were the objective response rate (ORR), defined as the percentage of patients who showed complete response (CR) and partial response (PR); the stable disease rate (SDR), defined as the percentage of patients who showed complete response, partial response and stable disease (SD); and time to progression (TTP), defined as the interval between the start of treatment until the documentation of local progression or metastasis by imaging procedures computed tomography (CT) or magnetic resonance imaging (MRI). CR was defined as complete resolution of all evidence of the tumour without development of new lesions during the time of evaluation. PR was diagnosed when tumour showed an at least 50% reduction of the maximum perpendicular tumour measurement without the appearance of new lesions. SD required a modification of lesion measurements ranging from less than 50% reduction to less than 25% increase. Progressive disease (PD) was defined as an increase of tumour lesions by greater than 25% or the occurrence of new lesions. Median overall survival was measured from the time of histological diagnosis until patient death. Chemotherapy was generally started subsequent to diagnosis. Toxicities related to chemotherapy were assessed according to the common toxicity criteria (CTC) for the grading of acute and sub-acute side-effects (29).

Table I. *Patient characteristics and therapy cycles (n=27).*

Characteristic	Value
Age (years), (median, range)	63 (47-74)
Gender, n (%)	
Male	16 (59.3%)
Female	11 (40.7%)
Histological differentiation (n, %)	
1	10 (37.0%)
2	13 (48.1%)
3	4 (14.8%)
Stage (n, %)	
III	17 (63.0%)
IV	10 (37.0)
Therapy cycles (n, %)	
2	4 (14.8%)
3	2 (7.4%)
4	2 (7.4%)
5	3 (11.1%)
6	16 (59.3%)

Ethics. The present study was conducted according to the World Medical Association – Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects as revised in Tokyo 2004. All participants were informed, in plain language, of the objectives and the procedures of the study and they signed and dated an informed consent form prior to any study related procedures.

Statistics. The association of response to current treatment with baseline characteristics (sex, stage, histological differentiation) and therapy cycles was investigated by chi-squared statistic. Differences of survival distribution curves and time to progression curves between groups of interest were tested by the log-rank statistic. Graphical representation of survival distribution curves and TTP curves was according to the Kaplan-Meier method.

Results

A total of 27 patients were included in the study and received at least 2 cycles of chemotherapy (6 cycles maximum, 12 consecutive courses). The demographic and related characteristics of the patients are shown in Table I.

Table II. *Overall response rate (ORR=CR+PR), stable disease rate (SDR=CR+PR+SD) and response type.*

	Response
ORR (%, 95% CI)	25.9% (11.1-46.3%)
SDR (%, 95% CI)	59.3% (38.8-77.6%)
Response type (n, %)	
CR	1 (3.7%)
PR	6 (22.2%)
SD	9 (33.3%)
PD	11 (40.7%)

CR, Confirmed response; PR, partial response; SD, stable disease; PD, progressive disease.

Table III. *Relationship of ORR (CR+PR) and patients' basal characteristics: gender, disease stage, histological differentiation.*

	ORR (CR+PR)	SD+PD	
	N	N	*p*-Value
Gender			
Male	3	13	0.391
Female	4	7	
Stage			
III	7	10	0.026
IV	0	10	
Histological differentiation			
1	3	7	1.000
2	3	10	
3	1	3	

Response. The primary end point of the study was ORR, as measured by RECIST (27).

All patients were evaluable for response. Response to combined chemotherapy is presented in Table II. CR as documented by CT imaging was observed in one (3.7%) female patient with stage pancreatic adenocarcinoma, and good histological differentiation. Six patients (22.2%) had PR to therapy. The ORR was 25.9% (range: 11.1%-46.3%) (Table I). The SDR was 59.3% (range: 32.8%-77.6%) (Table II). The ORR was significantly better for stage III than stage IV patients (p=0.026; Table III).

Survival. The median overall survival (OS) and TTP at the time of assessment was 7.5 months (95% CI: 3.6-42 months) and 5.5+ months (95% CI: 1.5-10 months) respectively (Figure 1). The 1-year survival rate was estimated at approximately 20% (Figure 1). Sixteen patients (59%) completed six chemotherapy cycles and had a median OS of 10 months (95% CI: 7-42 months). The log-rank test comparing the survival distribution of response curves revealed significantly longer TTP for stage III *vs*. stage IV patients (Figure 2). Significant differences were also detected between the response type for ORR and TTP (Figure 3).

Toxicities and complications. The major toxicities occurring during the study are given in Table IV. No WHO grade 4 toxicities or deaths related to toxicities were observed. The most frequent haematological toxicities were grade 1 thrombocytopenia in 12 patients (44.4%), anaemia in 10 patients (37.0%) and leucopenia in 9 patients (33.3%). The most common grade III haematological toxicities were thrombocytopenia and anaemia occurring in 2 patients (7.4%). The most common non-haematological toxicities were cutaneous reactions and diarrhoea occurring mainly with mild intensity, grade I 66.6% and 29.6% respectively, while 2 patients (7.4%) experienced grade 3 cutaneous reactions and diarrhoea.

Table IV. *Treatment-related toxicities experienced during the observation period of the study.*

Toxicity (n, %)	Grade			
	1	2	3	4
Haematological				
Anaemia	10 (37.03%)	4 (14.81%)	2 (7.40%)	0
Leukopenia	9 (33.33%)	3 (11.11%)	1 (3.70%)	0
Neutropenia	8 (29.62%)	3 (11.11%)	1 (3.70%)	0
Thrombocytopenia	12 (44.44%)	4 (14.81%)	2 (7.40%)	0
Non-haematological				
Total bilirubin	7 (25.92%)	2 (7.40%)	1 (3.70%)	0
Alkaline phosphatase	7 (25.92%)	1 (3.70%)	1 (3.70%)	0
Serum transaminases (SGOT, SGPT)	5 (18.51%)	2 (7.40%)	0	0
Other				
Alopecia	5 (18.51%)	2 (7.40%)	0	0
Constipation	9 (33.33%)	3 (11.11%)	0	0
Diarrhoea	8 (29.62%)	4 (14.81%)	2 (7.40%)	0
Fever	11 (40.74%)	3 (11.11%)	0	0
Nausea/vomiting	4 (14.81%)	3 (11.11%)	0	0
Cutaneous	18 (66.66%)	4 (14.81%)	2 (7.40%)	0
Phlebitis	3 (11.11%)	1 (3.70%)	0	0

SGOT, Serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

Discussion

Pancreatic cancer remains a disease of high mortality and one of the most frustrating, resistant solid neoplasms to treat. Combination treatment of GEM with cytotoxic drugs, including 5-fluorouracil (5-FU), cisplatin, oxaliplatin, irinotecan, pemetrexed and capecitabine, present confounding and inconclusive results. The 5-FU/GEM combination does not appear to be a suitable replacement for

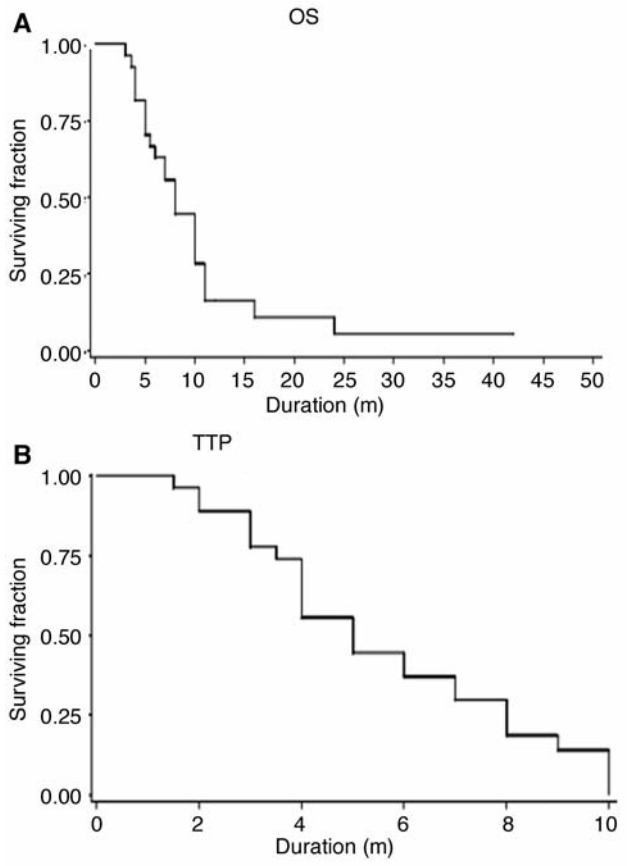

Figure 1. *A, Overall survival (OS) and B, time to progression (TTP) for all evaluable patients (n=27).*

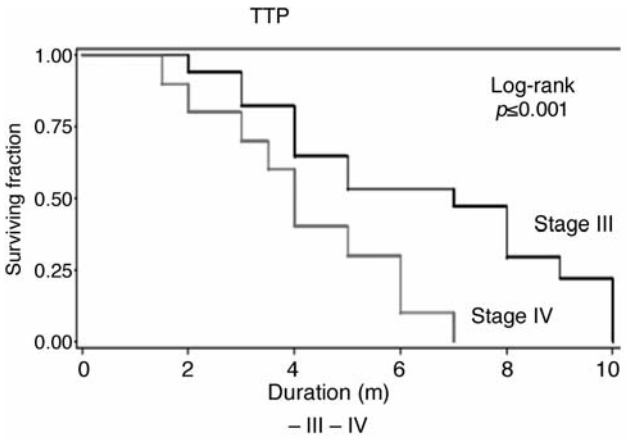

Figure 2. *Time to progression (TTP) by stage of disease (III vs. IV).*

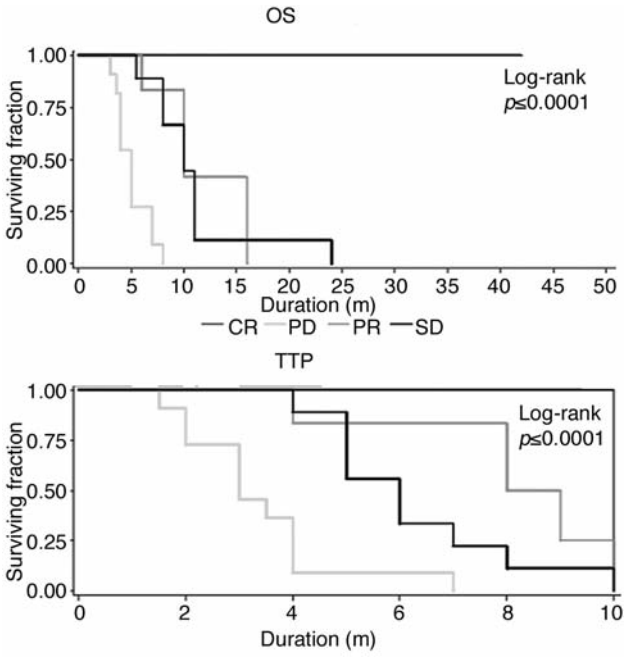

Figure 3. *A, Overall survival (OS) and B, time to progression (TTP) by response (CR complete response; PD progressive disease; PR partial response; SD stable disease).*

GEM monotherapy since no differences in median survival were detected between GEM/5-FU and GEM monotherapy, although progression-free survival was in favor of the combination treatment (10). Cisplatin combined with GEM is a biologically sensible approach due to the synergistic effect of cisplatin on GEM and its affects on GEM metabolism through inhibition of ribonucleotide reductase (9, 30). Addition of cisplatin to GEM treatment resulted in longer median TTP and higher response rate (26.4% *vs.* 9.2%), however, below the level of statistical significance (31). A more recent study of cisplatin plus GEM showed significant improvements in terms of TTP and rate of disease control (PR+SD), however OS did not reach statistical significance (14). Oxaliplatin combination showed significant differences in terms of progression-free survival (PFS) and objective response but OS remained below the level of significance (15). Similarly, combination of irinotecan with GEM reached statistical significance only for the objective response rate (16.1% *vs.* 4.4% for irinotecan/GEM and GEM monotherapy respectively) (17). Finally, the combination of pemetrexed produced significant differences in TTP and ORR; however, no differences were observed between the two arms in terms of OS or 1-year survival. Moreover, the pemetrexed/GEM combination was associated with higher rates of grade III/IV haematological toxicities (32).

The combination of GEM and ERL has received approval for the treatment of advanced pancreatic adenocarcinoma based on the results of Moore *et al.*, which showed significantly

prolonged OS of the GEM/ERL combination compared to GEM monotherapy (22). PFS was also significantly longer for the combination treatment, and increments, although not significant were observed in 1-year survival and the ORR. A recent phase I study on ERL and GEM reported PR and SD of 35% and 53%, respectively, while the estimated median survival was 18.7 months (13). In our study, we report similar ORR and SD (25.9% and 59.3%, respectively).

Studies employing different schedules of GEM administration in combination with other cytotoxic drugs reported little effect on median survival, although they did show higher response rates (6, 8, 10, 15, 33-35) and improved clinical benefit (15). However, most of these studies reported increased incidence of grade 3-4 haematological and non-haematological toxicities. In terms of the biweekly GEM administration, several other studies have reported interesting and promising results suggesting that biweekly administration could be an effective alternative regimen for advanced pancreatic cancer. Ulrich-Pur and co-workers (23) administered a high dose of GEM (2,200 mg/m^2) on day 1 and 15 for a total of 6 months. Median TTP in this study was 5.3 months, with a median survival of 8.8 months and 1-year survival probability rate of 26.3%. Similarly, Chang *et al*. (25) administered low-dose GEM (800 mg/m^2) on day 1 and 15 of a 4-week schedule along with a 2-h infusion of oxaliplatin and 48-h infusion of 5-FU/leucovorin (LV), reporting an objective tumor response for 33.1% of patients.

Another study that utilized a biweekly schedule of 1,000 mg/m^2 GEM followed by 5-FU reported a median TTP of 9.75 months and median OS of 13.1 months (12). Finally, when GEM was administered biweekly at 40 mg/m^2 following chemoradiation, the median survival was 15.0 months, median PFS 8.0 months, while the estimated overall 1-year survival rate was 60% (36).

Biweekly GEM administration also seems to be well tolerated, since toxicity results from studies that employed a biweekly schedule of GEM administration did not report any grade 4 haematological or non-haematological toxicities (12, 18, 23, 36). Neutropenia and leucopenia were reported as the most frequent grade 3 haematological toxicities (18, 23), whereas one study reported grade 3-4 toxicities of neutropenia (30%), thrombocytopenia (14%), anemia (8%) and neutropenic fever (2%) in patients receiving biweekly GEM accompanied by 5-FU/LV and cisplatin (24). In our study, there were no WHO grade 4 haematological or non-haematological toxicities observed, while the most common grade 3 toxic effects were neutropenia, anaemia, diarrhoea and cutaneous reactions. Interestingly, in our study the incidence of diarrhoea was lower than that usually reported for higher doses of ERL. Higher doses of ERL (*i.e*. 125 to 150 mg/m^2) are further associated with additional toxic effects such as neutropenia and thrombocytopenia (22, 37), resulting in dose reduction of therapy.

It is interesting, and in line with several previous observations, that no WHO grade 4 toxicities were observed under biweekly GEM plus ERL treatment. Moreover, the biweekly regimen of GEM administration showed comparable results in terms of 1-year OS, median TTP and OS to studies employing weekly administration of GEM performed for a larger number of patients. In conclusion, biweekly administration of GEM with ERL seems to be an effective and well-tolerated alternative treatment of advanced non-operable pancreatic adenocarcinoma. Hence biweekly GEM administration in combination with ERL may present an effective alternative therapy, beneficial both to patients and hospital resource departments by reducing the inherent costs of treatment administration.

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