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Gemcitabine–radiotherapy in patients with locally advanced pancreatic cancer

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Abstract

A feasibility study was performed to assess the toxicity and efficacy of a combination of gemcitabine–radiotherapy in patients with locally advanced pancreatic cancer (LAPC). 24 patients (15 females and 9 males) with measurable LAPC were included; the median age of the patients was 63 years (range 39–74 years). The performance status ranged from 0 to 2. Gemcitabine was administered at a dose of 300 mg/m^2, concurrent with radiotherapy, three fractions of 8 Gy, on days 1, 8 and 15. When compliance allowed, gemcitabine alone was continued thereafter, at 1000 mg/m^2, weekly times 3, every 4 weeks, depending on the response and toxicity. All patients were evaluable for toxicity and response. The objective response rate was 29.2% (1 complete remission + 6 partial remissions); 12 patients had stable disease. However, 2 of the radiological partial remissions were shown to be complete remissions by pathology assessment. Median duration of response was 3 months (range 1–35 + months). Median time to progression was 7 months (range 2–37 + months). Median survival was 10 months (range 3–37 + months). Dose reduction or omission of gemcitabine was necessary in 10 patients. Non-haematological toxicity consisted of 87.5% nausea and vomiting grade I-II, diarrhoea 54%, ulceration in stomach and duodenum 37.5% (20.8% ulceration with bleeding); 1 patient developed a fistula between the duodenum and aorta, 5 months after treatment. Anaemia grade III-IV was observed in 8.3% of the patients. Neutropenia grade III-IV was observed in 8.3%, thrombocytopenia grades III-IV in 16.7%. In 1 patient who underwent resection postchemoradiation, no viable tumour cells were found. In addition, in the patient who suddenly died of a fistula between the duodenum and aorta, no viable tumour cells were detectable at autopsy. Although the toxicity of this treatment was occasionally severe, the response and survival are encouraging and warrant further studies of this combination. © 2002 Published by Elsevier Science Ltd.

Keywords: Gemcitabine; Locally advanced pancreatic cancer; Radiotherapy

1. Introduction

In the Western world, approximately 5% of the cancer mortality is due to pancreatic cancer [1]. At presentation, only 10–20% of patients with pancreatic cancer have localised disease that can be considered for resection, but even when resection is performed pancreatic cancer has a poor prognosis. Most patients have locally advanced or metastatic disease. Life expectancy in these patients is very short, with a median survival of approximately 3 months, and a one year survival of 2% [2].

The course of pancreatic cancer is often very aggressive and patients complain of significant weight loss (95%), pain (75%), anorexia (64%), nausea (50%), lethargy, depression, weakness, and consequently have an impaired performance status [3].

Moreover, pancreatic cancer is very resistant to chemotherapy [4]. 5-Fluorouracil (5-FU), until recently the most applied agent in pancreatic cancer, has a response rate below 10%. Of the newer agents, paclitaxel, docetaxel, topotecan, raltitrexed and temozolomide

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showed only limited activity with response rates of 5–17% in phase II studies [2]. Gemcitabine (2′-2′-difluorodeoxycytidine), a new deoxycytidine analogue, has been shown to have an impact on disease-related symptoms and survival of advanced pancreatic carcinoma, although the magnitude of this improvement was limited [5]. It was noted that some patients experienced clinical benefit, defined as $\geqslant 50\%$ reduction in pain intensity, and/ or $\geqslant 50\%$ reduction in daily analgesics consumption, or $\geqslant 20\%$ improvement on the Karnofsky Performance Scale that was sustained for $\geqslant 4$ weeks, or a weight gain of $\geqslant 7\%$ [2].

In a randomised phase III clinical study in 126 patients, gemcitabine was compared with 5-FU. In the gemcitabine arm, 24% of the patients experienced clinical benefit, while only 5% of the patients randomised to 5-FU did. However, objective response rates were very low in both study arms, only 5% in the gemcitabine treated patients and 0% in the 5-FU treated patients. Patients had a median survival of 5.6 months when treated with gemcitabine, while patients treated with 5-FU had a median survival of 4.1 months ($P = 0.0025$) [5]. Chemoradiation studies, where the combination of 5-FU and radiotherapy was used, did not show significant improvement of local control or survival in patients with pancreatic cancer [6].

Radiotherapy alone may be a treatment modality with transient effect on pain which is often present in patients with pancreatic cancer. However, the effect is usually limited in time, and the overall survival is similar to non-treated patients [7].

Gemcitabine is a potent radiosensitiser [8,9]. Radiosensitisation by gemcitabine can be caused by different mechanisms. First, at the genomic level, gemcitabine inhibits the repair of chromosome damage induced by irradiation, but has no demonstrable effect on the repair of DNA double-strand breaks. Second, in both *in vitro* and *in vivo* models, gemcitabine was reported to induce cell cycle redistribution [10]. Therefore, it is likely that an accumulation of a cohort of cells into a more radiosensitive phase of the cell cycle may contribute to the radiosensitisation of gemcitabine. Third, the preferential depletion of S-phase cells by apoptosis after gemcitabine treatment might both decrease tumour cell proliferation and enhance tumour reoxygenation due to increased cell loss [10]. Fourth, radiosensitisation by gemcitabine has been associated with a depletion of the deoxyadenosine triphosphate (dATP) pool, suggesting that inhibition of ribonucleotide reductase is of primary importance [11]; however, recent evidence suggests that dATP depletion may contribute to, but is not the main determinant of radiosensitisation [12]. Lastly, it has recently been observed in mouse tumour cells that radiosensitisation by gemcitabine might critically depend on the level of dCK expression [13].

We have performed a clinical study to explore the radiotherapy–gemcitabine interaction in patients with non-metastatic, irresectable pancreatic cancer. In this study, we assessed whether this combination was feasible and has sufficient activity for further testing.

2. Patients and methods

This was a single-centre feasibility study to assess the toxicity and efficacy of combined gemcitabine–radiotherapy in locally advanced pancreatic cancer (LAPC).

2.1. Patients

Eligible patients had histologically- or cytologically-confirmed adenocarcinoma of the pancreas and the disease had to be measurable on a Computed Tomography (CT)-scan. The patients had to be aged $\geqslant 18$ years, with a World Health Organization (WHO) performance status $\leqslant 2$, and a life expectancy $\geqslant 3$ months. Adequate haematological, renal and liver function tests were required, and were defined as white blood cell (WBC) count $\geqslant 4\times10^9$/l, absolute neutrophil cell (ANC) count $\geqslant 2\times10^9$/l, platelets $\geqslant 100\times10^9$/l, bilirubin $\leqslant 25$ μmol/l, aspartate aminotransferase/alanine aminotransferase (ASAT/ALAT) within 2× the upper normal limit, creatinine $\leqslant 120$ μmol/l, or creatinine clearance $\geqslant 1$ ml/s. No patients with poor medical risks because of non-malignant disease or uncontrolled infection could participate in the study. This study was approved by the institutional ethics committee, and all patients gave informed consent.

2.2. Assessments and treatment

Pretreatment evaluation included a history and physical examination. Height, weight, performance status, and tumour assessment were recorded. A chest film, an abdominal CT scan and an electrocardiogram (ECG) were also performed, as well as a pretreatment assessment and laboratory studies. Gemcitabine was administered at a dose of 300 mg/m^2 by intravenous (i.v.) infusion over 30 min, 2–4 h before radiotherapy on days 1, 8 and 15. The radiotherapy dose was 24 Gy (3 weekly fractions of 8 Gy) given concurrently with gemcitabine.

Gemcitabine alone was continued thereafter (after a treatment-free interval of 1 week), weekly times 3, every 4 weeks, depending on the response and toxicity. This was defined as 1 cycle. Gemcitabine alone was administered at a dose of 1000 mg/m^2 for as long as indicated.

The radiation therapy consisted of a schedule of 24 Gy in three fractions of 8 Gy (1 fraction/week) and was delivered to the tumour, peripancreatic nodal regions, and a 1.0–2.0 cm margin (around the gross tumour volume to account for microscopic tumour extension,

set-up variation, patient motion and uncertainty). CT scan-based treatment planning was performed and, in general, a three- or four-field technique was used. To decrease the irradiation of the kidneys, renography was performed prior to therapy; in case of normal renographic findings, one kidney was left out of the irradiation field completely, while the other kidney was exposed as little as possible. Toxicities were graded using the National Cancer Institute of Canada (NCIC) common toxicity criteria [14]. The dose of gemcitabine was reduced (25–50%) in cases of grade III and IV haematological and non-haematological toxicities. Evaluation during treatment included weekly history, physical examination, haematology and toxicity assessment. Biochemical tests, including CA 19.9, were determined every 4 weeks. CT scans were repeated every 2 months. Patients were followed until death.

Responses were defined according to the WHO criteria [15].

2.3. Statistical analysis

Duration of survival and time to progression were calculated by the Kaplan-Meier method.

3. Results

Table 1 shows the characteristics of the 24 patients entered in the study. The inclusion period for this feasibility study was January 1996 until December 1999. The median Eastern Cooperative Oncology Group (ECOG) performance status was 1. Two patients had received prior chemotherapy, one for non-Hodgkin's lymphoma, three cycles of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) and radiotherapy, 3 years before the diagnosis of pancreatic cancer. The other patient received carboplatin-ethyol in a phase I study. With this therapy, stable disease was achieved. A few months later, progression occurred and gemcitabine–radiotherapy was started. Seven patients had prior surgery, consisting of explorative laparotomy and biliodigestive anastomosis.

Table 1
Patient characteristics

Total no. of patients	24
Age (years)	
Median (range)	63 (39–74)
Sex	
Female	15
Male	9
ECOG performance status	
0	11
1	12
2	1
Prior therapy	
Surgery	7
Chemotherapy	2
Radiotherapy	1

ECOG, Eastern Cooperative Oncology Group.

Twnety-three patients received all of the planned three cycles of gemcitabine concurrent with radiotherapy. One patient received only two cycles; the third cycle was not given because of severe diarrhoea. After chemoradiation, 218 weekly cycles of single agent gemcitabine were administered with a median of 13 cycles per patient (range 0–18). Gemcitabine was discontinued in 15 patients because of progressive disease, in 4 patients because of toxicity, in 1 patient because of abdominal pain and poor condition, in 1 patient because a pancreaticoduodenectomy was performed, and in 1 patient after an explorative laparotomy, which revealed irresectable disease. One patient stopped chemotherapy 12 months after the establishment of a complete remission. One patient is still on study.

3.1. Toxicity

All patients were evaluable for non-haematological and haematological toxicity. Side-effects have been summarised in Table 2 and separated for toxicity

Table 2
Toxicities

	Grade (NCI Common Toxicity Criteria)				
	0	1	2	3	4
Gemcitabine plus radiotherapy					
Anaemia	6	18			
Leucopenia	10	9	4	1	
Thrombocytopenia	9	12	2	1	
Nausea	1	19	4		
Vomiting	8	11	5		
Diarrhoea	11	10	2	1	
Constipation	23	1			
Abdominal pain	11	13			
Fatigue	12	10	2		
Gemcitabine					
Anaemia	3	13	6	1	1
Leucopenia	9	7	7	1	
Thrombocytopenia	10	7	4	3	
Nausea	10	9	5		
Vomiting	18	3	3		
Fever in absence of infection	20	2	1	1	
Diarrhoea	18	5	1		
Constipation	21	3			
Abdominal pain	9	7	5	3	
Fatigue	12	8	4		
Late side-effects					
Gastric/duodenal ulcera	15		4	5	
Aortaduodenal fistula	23				1

resulting from chemo-radiation, subsequent gemcitabine alone, and late side-effects.

Dose reduction of 25–50% or omission of gemcitabine was necessary in 6 patients for grade III haematological and in 4 patients for grade III non-haematological toxicity. The reduction during the concurrent treatment was 25% in 1 patient because of myelosuppression and, in another patient, one dose of gemcitabine and radiotherapy was omitted because of severe diarrhoea. The other 8 patients had a 25–50% reduction of the gemcitabine dose, when gemcitabine was given as a single agent.

Haematological toxicity was mild, anaemia grade III-IV was observed in 8.3%, neutropenia grade III was observed in 8.3%, and thrombocytopenia grade III in 16.6% of the patients.

Non-haematological toxicity consisted of nausea and vomiting grade I-II in 87.5% of the patients, diarrhoea in 54%, and ulceration in the stomach and duodenum in 37.5% (20.8% ulceration with bleeding). One patient died of a haemorrhage due to ulceration of the stomach. One patient suddenly died of a fistula between the duodenum and aorta, 5 months after treatment.

3.2. Objective response

All patients were evaluable for response. One patient had a complete remission and 6 patients had a partial remission for an overall objective response rate of 29.2% (Table 3). 12 patients had stable disease, and 5 patients had progressive disease. The median duration of response was 3 months (range 1–35+months). The median time to progression was 7 months (range 2–37+ months). Treatment failure occurred in 19 patients and consisted of local failure in 5 patients, local failure and distant metastases in 7 patients and distant metastases only also in 7 patients. Median survival was 10 months (range 3–37+months) (Fig. 1). 19 patients died, 17 because of malignant disease and two due to toxicity. One of these 2 patients died of a fistula between the duodenum and aorta, and the second of bleeding due to ulceration of the stomach.

CA 19.9 determinations were performed in all patients before treatment (Table 3). In 19 patients, CA 19.9 was elevated (>22 U/ml). Serial CA 19.9 determinations were performed in 17 patients. Of the 7 responding patients, 3 had abnormal baseline determinations and all 3 patients had decreases of >50% in CA 19.9 for at least 8 weeks. All 12 patients with stable disease had an abnormal CA 19.9 at baseline and 11 of these patients had a decrease in CA 19.9 of >50%. Of the 5 patients with progressive disease, 4 had an abnormal CA 19.9 at baseline, and none of these patients had a decrease in CA 19.9 of >50%. These data suggest that there is an association between a decrease in CA 19.9 of >50% and the achievement of a tumour response or stabilisation during treatment with gemcitabine–radiotherapy followed by gemcitabine as a single agent.

Remarkably, in 1 patient who underwent resection of the tumour postchemoradiation, no vital tumour cells were found in the surgical specimen. Nevertheless, this patient developed recurrent disease 5 months after surgery and died 3 months later. In addition, the patient who suddenly died of a fistula between the duodenum and aorta did not have vital tumour detectable at autopsy.

Table 3
Response and CA 19.9 determinations

Response	Total no of patients	Initial Ca 19.9 Elevated	Ca 19.9 Decrease of > 50%
CR/PR	7	3	3
SD	12	12	11
PD	5	4	0

CR/PR, Complete Response/Partial Response; SD, Stable Disease; PD, Progressive Disease.

4. Discussion

Gemcitabine–radiotherapy, followed by gemcitabine alone, when delivered according to the present dosage and schedule, resulted in objective responses, one complete remission and six partial remissions in 24 patients with non-metastatic irresectable pancreatic cancer. However, the toxicity of this treatment was occasionally severe. This included ulceration in stomach and duodenum in 37.5% of the patients, while in 20.8% of the patients this was accompanied by bleeding. However, gastroscopy was only performed when indicated, and the incidence of ulceration may have been underestimated. Also of concern was the acute death in the patient with a fistula between the duodenum and aorta,

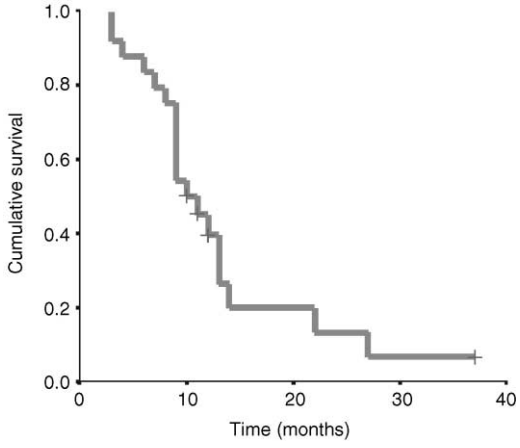

Fig. 1. Kaplan–Meier plot of survival of patients with locally advanced pancreatic cancer.

and the second sudden death in the patient with a bleeding ulceration. It cannot be excluded that our radiotherapy schedule with three high dose fractions of 800 cGy has been responsible for these late events. An aorto-duodenal fistula after abdominal irradiation has been described before by Zarembok and colleagues in Hodgkin's disease. The mechanism of this complication seemed to be related to radiation-induced necrosis of a mass invading the aorta and duodenum [16]. After 18 patients were included in the study, prophylactic omeprazol was prescribed which seemed to result in less severe upper gastrointestinal side-effects. This drug might reduce this type of toxicity probably because it may protect against the effect of gemcitabine–radiotherapy on normal tissue. Of note, patients with pancreatic cancer are more at risk for gastrointestinal bleeding.

The usual dose of gemcitabine as a single agent is 800–1250 mg/m^2 [17]. When gemcitabine is combined with radiotherapy, this dose is too toxic. In non-small cell lung cancer, gemcitabine has been combined with radiotherapy. At a dose of 600 mg/m^2, severe pulmonary toxicity consisting of acute pneumonitis and pulmonary fibrosis was observed. Doses of 300 and 450 mg/m^2 appeared to be safe in combination with radiotherapy in this disease [18]. Another study of combined treatment modality in non-small cell lung cancer was performed by Vokes and colleagues. In this study, gemcitabine was combined with cisplatin as induction therapy followed by additional cycles of the same drugs with concomitant radiotherapy (66 Gy). The dose of cisplatin was 80 mg/m^2, the dose of gemcitabine was 1250 or 600 mg/m^2 depending on the day of the cycle. Toxicities were granulocytopenia, thrombocytopenia and esophagitis. This combined treatment can be safely used at this dose and schedule [19].

In our study, we used a gemcitabine dose of 300 mg/m^2.

The radiotherapy dose normally used in pancreatic cancer varies between 45 and 60 Gy in five daily fractions, during 4–6 weeks. In rectal cancer, a study has been conducted with a lower total dose of radiotherapy of 25 Gy, but in high daily fractions of 5 Gy. This radiotherapy scheme has demonstrated an impressive reduction in cancer mortality and morbidity rates with acceptable complication rates [20]. To our knowledge, there is no experience with the radiotherapy schedule applied in our study, however, extensive experience also exists with hypofractionated radiotherapy for the palliative treatment of tumours at different sites. Additionally, this fractionation scheme was also chosen because in the near future we will use extracranial stereotactic radiotherapy using a few high dose radiation fractions, in patients with pancreatic cancer. In addition, radiobiological studies have shown that pancreatic tumour cells *in vitro* are radiosensitive [21]. A non-randomised phase II study by Ceha and colleagues with high-dose conformal radiotherapy (70–72 Gy) in 44 patients showed more toxicity compared with a lower dose in high daily fractions. Acute toxicity was mainly grades I and II (in 70 and 57% of patients, respectively), whereas grade III toxicity was seen in 9% of patients. Late grades III and IV gastrointestinal toxicity was seen in 3 and 2 patients, respectively. Late toxic death, due to gastrointestinal bleeding was observed in 3 patients [22].

Gemcitabine–radiotherapy in pancreatic cancer has also been studied by other investigators. In a phase I study, Blackstock and colleagues applied gemcitabine twice weekly for 5 weeks at doses of 20–60 mg/m^2 until dose-limiting toxicity, concurrent with 50.4 Gy of radiation therapy (in five daily fractions of 2 Gy for 5 weeks) in 19 patients [23]. Side-effects consisted of nausea and vomiting, thrombocytopenia and neutropenia. The maximum tolerable dose (MTD) of gemcitabine in this study was 40 mg/m^2. Another phase I study by McGinn and colleagues in 37 patients, applied gemcitabine at 1000 mg/m^2 on days 1, 8, and 15 of a 28 day cycle. Radiation therapy was initiated on day 1. 15 fractions of 1.6–2.8 Gy until dose-limiting toxicity. A second cycle of gemcitabine alone was given after a week's rest. Side-effects were neutropenia, thrombocytopenia, vomiting, and abdominal pain secondary to gastric and duodenal ulceration. The MTD of radiotherapy in this study was 2.4 Gy. The objective response rate in this study was 30%. The median survival was 11.6 months [24]. Another phase I study by McGinn colleagues applied gemcitabine once weekly at a starting dose of 300 mg/m^2, concurrently with 50.4 Gy radiotherapy in 13 patients [25]. One patient experienced dose-limiting toxicity at 300 mg/m^2, consisting of grade 3 neutropenia. 10 patients have subsequently been treated without dose-limiting toxicity. The predominant toxicity was nausea and vomiting. In 1 patient, late toxicity was reported consisting of gastric/duodenal ulceration occurring 3 months following completion of the treatment. At the time of the report, the MTD had not been reached and the study was planned to continue with a gemcitabine dose of 500 mg/m^2.

Crane and colleagues described a similar study of chemoradiation in 51 patients with locally advanced pancreatic cancer. Gemcitabine was given at a dose of 250–500 mg/m^2 weekly for 7 weeks and radiotherapy 30–33 Gy in 10–11 fractions over 2 weeks. The median survival was 11 months, the median time to local progression was 6 months, and the median time to distant progression was 9 months [26].

In our study, we decided not to further escalate the dose of gemcitabine, because of severe local side-effects.

Studies have also been conducted with neoadjuvant chemoradiation applying different chemotherapy and radiotherapy regimens. In a study of White and colleagues applying 5-FU, mitomycin-C or cisplatin, or both, with concurrent radiotherapy in 25 patients showed that a potentially curative resection could be performed

in 5 patients (20%) [27]. Of these patients, 1 had a complete and 4 had a partial remission. Similarly, in a study of Wanebo and colleagues that combined 5-FU and cisplatin with concurrent radiotherapy in 14 patients, 9 patients had a resection, while in 2 patients a pathological complete remission was achieved [28].

In terms of survival and response, the results of our study are encouraging. Based on the results of this study, we plan to assess this combined treatment in a neo-adjuvant setting in patients with potentially resectable pancreatic cancer.

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