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A phase II/III study comparing intravenous ZD9331 with gemcitabine in patients with pancreatic cancer

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Abstract

ZD9331 is a novel antifolate inhibitor of thymidylate synthase (TS). This multicentre, randomised, phase II/III study compared the efficacy and safety of ZD9331 with gemcitabine in 55 patients with chemonaïve, locally advanced or metastatic pancreatic cancer. Patients received intravenous (i.v.) ZD9331 ($n=30$), on days 1 and 8 of a 3-week cycle or i.v. gemcitabine ($n=25$), once a week for 7 weeks followed by a 1-week rest, then on days 1, 8 and 15 of a 4-week cycle. Objective tumour response and clinical benefit response (CBR) were similar for both groups. More ZD9331 patients were alive at the data cut-off point compared with gemcitabine patients (13 and 8%, respectively). Median survival (152 versus 109 days, respectively) and time to progression (70 versus 58 days, respectively) were longer in the ZD9331 group. Nausea and vomiting (grade 1/2) were the most common toxicities in both groups. These results suggest that, in pancreatic cancer, ZD9331 is equivalent to gemcitabine and may offer a promising alternative to current therapies.

Keywords: Pancreatic cancer; ZD9331; Gemcitabine; Efficacy; Safety

1. Introduction

Pancreatic cancer is the sixth most common cause of adult cancer-related deaths in the more developed countries of the world, although it accounts for only 2–3% of all new cancer cases in these countries [1]. More than half of the patients presenting with pancreatic cancer have metastatic disease, and only around 10% can be resected. The prognosis is dismal, with an overall 5-year survival rate of 4%. For those with unresectable disease, the median survival is <4 months [2]. Convincing improvements in survival have yet to be demonstrated with palliative chemotherapy. Patients cannot tolerate aggressive treatment and pancreatic tumours are commonly chemo-resistant, although symptomatic palliation rates may exceed the rates of objective tumour response [3].

Chemotherapy options for treating pancreatic cancer commonly include 5-fluorouracil (5-FU) or gemcitabine. 5-FU is the most widely used drug in patients with advanced pancreatic cancer. However, the true objective tumour response rates to both single-agent and modulated 5-FU have rarely exceeded 10% [3–5]. Furthermore, using 5-FU in combination with other agents, such as mitomycin C, has little impact on either the response rate or survival [6–8]. In the phase III trial reported by Kelsen and colleagues [8], the median survival of patients randomised to streptozotocin, mitomycin C and 5-FU was 10 months, although only a total of 82 patients were included. However, gemcitabine appears to offer better control of tumour-related symptoms than 5-FU [9] and may be considered the treatment of choice for advanced pancreatic cancer. Burris and colleagues [9] reported a significant difference in the median survival of patients randomised to gemcitabine or 5-FU (5.65 and 4.41 months, respectively). Nevertheless, new treatments are urgently needed to improve the outcome in this disease.

ZD9331 is a novel, direct-acting antifolate and a specific inhibitor of thymidylate synthase (TS). TS catalyses the production of thymidylate from deoxyuridine monophosphate in the DNA synthesis pathway.

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ZD9331 does not require polyglutamation, and so may be active against tumours with low folylpolyglutamate synthetase (FPGS) levels [10,11]. A low level of FPGS is a common resistance mechanism against TS inhibitors. In phase I studies, ZD9331 had a manageable toxicity profile [12–15]. Dose-limiting toxicity (DLT) was commonly myelosuppression. Preliminary evidence of activity was reported against a range of tumours, including colon, ovary and melanoma.

In preclinical studies, ZD9331 demonstrated rapid clearance, therefore initial phase I clinical trials of ZD9331 used either daily dosing for 5 days, or continuous infusion for 5 days of a 3-weekly cycle. However, pharmacokinetic data from these trials suggested that ZD9331 had an elimination half-life in humans ranging from 1.5 to 7.5 days [13,15]. Furthermore, ZD9331 had non-linear pharmacokinetics and the renal route was found to contribute significantly to the clearance of ZD9331, accounting for approximately 40% of the mean total clearance (at a dose of 6 mg/m^2/day, 5-days continuous infusion) [16]. Intermittent dosing schedules were therefore investigated, and a dosing schedule with 130 mg/m^2 ZD9331 given on days 1 and 8 of a 3-week cycle was chosen for future studies. This choice was based on considerations of safety and also evidence of pharmacological action, as expressed by elevated plasma deoxyuridine levels, at this dose and below.

We report here an open, randomised, multicentre phase II/III trial comparing the efficacy and tolerability of ZD9331 and gemcitabine, in patients with chemonaïve, locally advanced or metastatic pancreatic cancer. In addition, an evaluation of the relative health economics of ZD9331 is provided.

2. Patients and methods

2.1. Patients

To be eligible for this study, patients were required to have histologically- or cytologically-confirmed cancer of the exocrine pancreas with chemonaïve, measurable, locally advanced or metastatic disease. Patients were aged $\geqslant$18 years, with a Karnofsky performance status (KPS) $\geqslant$50 and a life expectancy $>$8 weeks. Patients were excluded if any of the following criteria were met: prior treatment with radiosensitisers; not fully recovered from previous surgery or radiotherapy; neutrophils $<1.5\times10^9$/l or platelets $<100\times10^9$/l; serum bilirubin $\geqslant1.5\times$upper normal limit (UNL), or alanine or aspartate aminotransferases $>5\times$UNL; creatinine clearance $<$1 ml/s (Cockcroft–Gault formula); current intestinal obstruction; diagnosis of islet-cell tumour or lymphoma of the pancreas; evidence of severe or uncontrolled systemic disease; metastasis to the central nervous system; or concomitant use of folic acid. All patients gave written informed consent before entering the study. Ethics Committee approval was obtained at all centres.

2.2. Treatment

Patients were randomised to receive either ZD9331 or gemcitabine. ZD9331 was given as a 30-min intravenous (i.v.) infusion at a dose of 130 mg/m^2, on days 1 and 8 of a 3-week cycle. The day 8 dose was withheld in the event of a neutrophil count $\leqslant$50% of the day 1 count for that cycle; neutrophils $<1.5\times10^9$/l; platelets $<75\times10^9$/l; or bilirubin $\geqslant1.25\times$UNL. Subsequent cycles were delayed by up to 14 days if any of the following occurred during a given cycle: neutrophils $<1.5\times10^9$/l; platelets $<75\times10^9$/l; calculated creatinine clearance $<$1 ml/s; bilirubin $\geqslant1.25\times$UNL; albumin $<$lower normal limit. If the neutrophil or platelet counts had not recovered within 14 days, the patient was withdrawn from the study. Toxicities were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0. Depending on the type and grade of toxicity, the dose for the next cycle could be modified in steps of 25%, to a minimum of 50% (65 mg/m^2) and a maximum of 125% (162.5 mg/m^2) of the starting dose. The variables considered for dose modification included: neutrophil and platelet counts, diarrhoea, mucositis, rash and calculated creatinine clearance. The first cycle of gemcitabine comprised once-weekly 30-min i.v. infusions at a dose of 1.0 g/m^2 for 7 weeks, followed by a week of rest. Subsequent cycles lasted 4 weeks, with treatment given on days 1, 8 and 15. The dose of gemcitabine was reduced or withheld at any point during a cycle, depending on the nature and grade of toxicity seen. Subsequent cycles were delayed by up to 3 weeks in the event of granulocytes $<1.5\times10^9$/l or platelets $<100\times10^9$/l. If the granulocyte or platelet counts had not recovered within this period, the patient was withdrawn from the study. The dose of gemcitabine could be increased to 1.25 g/m^2 if a patient completed an entire cycle at 1.0 g/m^2, provided that the neutrophil and platelet nadirs exceeded 1.5×10^9/l and 100×10^9/l, respectively, and that non-haematological toxicities were not $>$grade 1. A second escalation step to 1.5 g/m^2 was permitted, applying the same criteria. Treatment with ZD9331 or gemcitabine was continued until disease progression (PD), or until the patient was withdrawn for another reason.

2.3. Assessments

Overall survival and time to PD were measured from the date of randomisation. Tumour response was assessed according to the revised World Health Organization Response Evaluation Criteria in Solid Tumours (WHO-RECIST) [17], approximately every 8 weeks until PD.

Clinical benefit response (CBR) was assessed in eligible patients using previously published criteria based on composite measurements of pain (pain intensity and analgesic consumption), KPS and weight [9]. Safety of treatment was assessed by monitoring adverse events (AEs), vital signs, and haematological and biochemical parameters.

Health economics were investigated as an exploratory endpoint. Frequency and duration of inpatient care, outpatient visits, medications, patient time and travel, and major medical procedures used to treat toxicities were all recorded.

2.4. Study design

All patients entering the study completed a run-in phase to characterise pain and analgesic consumption. Patients were then randomised to receive either ZD9331 or gemcitabine and were stratified by centre and eligibility for assessment of CBR. The trial was designed to have three stages, with early stopping rules to be applied in the event of poor performance of ZD9331. The stopping guideline for the first stage was based on the rate of CBR seen. A data summary was planned after 17 patients eligible for CBR assessment had been randomised to ZD9331 and had been followed for at least 3 months. For a drug with a true CBR of $\geqslant 25\%$, there was a $<5\%$ chance of observing 0 or 1 CBR in the first 17 patients treated with ZD9331 who were eligible for CBR [18]. At the time of the interim analysis of efficacy, there were apparently no CBR to ZD9331 and consequently the trial was halted. As a result, descriptive statistics were used to analyse the safety and efficacy results presented here.

3. Results

In total, 55 patients were randomised from 22 European centres: ZD9331 (30 patients) and gemcitabine (25 patients). All patients were included in the intent-to-treat population for the efficacy and safety analyses reported here. Twenty-seven of the patients randomised to ZD9331 were withdrawn from treatment: 15 following PD, 10 after AEs, and 2 for other reasons. 20 patients were withdrawn from gemcitabine treatment: 14 following PD, 5 after AEs, and 1 for other reasons.

Baseline characteristics are summarised in Table 1 and were well matched between the two treatment groups. All patients randomised to ZD9331 or gemcitabine had either locally advanced disease (90 and 92%, respectively) or metastatic disease (70 and 84%, respectively), or both. Tumour node metastases staging was not assessable in approximately half of the patients, but of the remainder, most had stage IV disease.

Table 1
Baseline characteristics and previous treatment for pancreatic cancer

Characteristic	Treatment group	
	ZD9331 ($n=30$)	Gemcitabine ($n=25$)
Age (years)		
18–40	2	1
41–65	19	15
>65	9	9
Mean age (range)	59.8 (23–75)	60.8 (40–76)
Gender		
Male	19	15
Female	11	10
KPS		
60	0	2
70	6	5
80	12	6
90	5	9
100	7	2
NR	0	1
TNM staging (%)		
I	2 (7)	0 (0)
II	2 (7)	1 (4)
III	1 (3)	1 (4)
IV	10 (33)	10 (40)
Not assessable	14 (47)	12 (48)
NR	1 (3)	1 (4)
Previous cancer treatment[a]		
None	11	7
Radiotherapy	1	0
Surgery	18	17
Other therapy	2	1

KPS, Karnofsky performance status; NR, not recorded; TNM, tumour node metastases; *n*, number of patients.
[a] Some patients had >1 prior treatment.

3.1. Efficacy

A greater proportion of patients randomised to ZD9331 were alive at data cut-off compared with those treated with gemcitabine (4/30 patients (13%) and 2/25 (8%), respectively). In addition, the median duration of survival was longer in patients treated with ZD9331 than in patients receiving gemcitabine (152 versus 109 days, respectively), as was the time to progression (70 versus 58 days, respectively). Furthermore, the proportion of patients with progressive disease was lower in the group receiving ZD9331 (70%) than in patients randomised to gemcitabine (92%). Survival rates and PD are shown in Table 2 and Fig. 1.

Analysis of objective tumour response and CBR gave similar results for both groups. Partial responses (PRs) were confirmed in 1 patient (3%) treated with ZD9331 and in 2 patients (8%) treated with gemcitabine. In the patient treated with ZD9331, the PR was maintained at the time of data cut-off, over 122 days since it was first observed. The PRs seen in patients

Table 2
Survival and disease progression at the time of data cut-off

	Treatment group	
	ZD9331 ($n=30$)	Gemcitabine ($n=25$)
Survival parameters		
Alive, *n* (%)	4 (13)	2 (8)
Dead, *n* (%)	16 (53)	17 (68)
Status unknown, *n* (%)	10 (30)	6 (24)
Median duration of survival (days) (95% CI)	152 (98–263)	109 (50–250)
Disease progression		
Progression, *n* (%)	21 (70)	23 (92)
No progression, *n* (%)	8 (27)	2 (8)
Status unknown, *n* (%)	1 (3)	0 (0)
Median time to progression (days) (95% CI)	70 (56–152)	58 (50–106)

n, number of patients; CI, confidence interval.

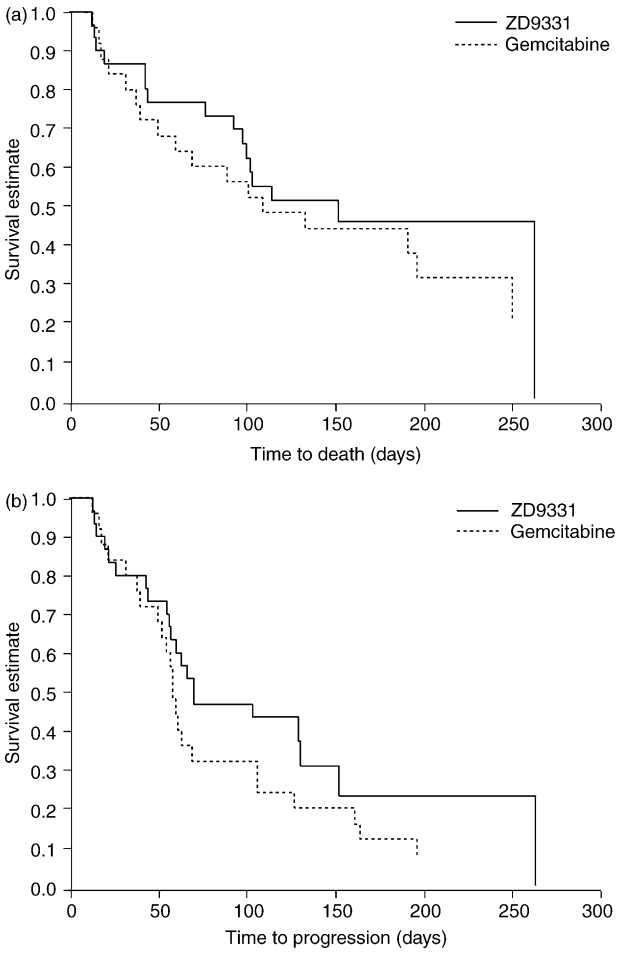

Fig. 1. Kaplan–Meier plots for (a) time to death and (b) time to disease progression.

treated with gemcitabine were of approximately 161 and 196 days duration, respectively. The proportion of patients with stable disease was higher in patients treated with ZD9331 (10 patients, 33%) than in those receiving gemcitabine (6 patients, 24%). 20 (67%) and 14 (56%) patients randomised to ZD9331 and gemcitabine, respectively, were eligible for assessment of CBR, with 3 (15%) and 2 (14%) patients in each group, respectively, sustaining a benefit from treatment.

3.2. Toxicity

ZD9331 was given in 3-week cycles, with dosing scheduled for days 1 and 8. The median number of ZD9331 treatment cycles given was 3 (range 1–13), with a total of 120 cycles given across all patients. Treatment was given on schedule, with no dose reductions, to 14 of the 30 patients in this group. Dosing was delayed, reduced or omitted in 16 patients 12 of whom had a dose delay, reduction or omission due to toxicity. The dose of ZD9331 was increased in 1 patient. Gemcitabine was given once a week for 7 weeks in an 8-week cycle, and then in 28-day cycles, with dosing scheduled on days 1, 8 and 15. A total of 75 cycles of gemcitabine was given, with a median of 1 cycle per patient (range 1–9). In 11 of the 25 gemcitabine patients, dosing was given on schedule and without a dose reduction. 12 patients required dose delays, reductions or omissions 10 of whom due to toxicity, and the dose of gemcitabine was increased in two of the remaining patients.

Drug-related haematological toxicities (as judged by abnormal haematological parameters) were common and overall had a similar incidence in both treatment groups (haemoglobin: 7, 16%; leucocytes: 17, 12%; neutrophils: 30, 20%; platelets: 23, 24%, in the ZD9331 and gemcitabine groups, respectively), although grade 3/4 haematological toxicities were slightly more common in the ZD9331 group (Table 3).

Nausea and vomiting were the most frequently occurring toxicities in both treatment groups, while asthenia and diarrhoea were more common in patients receiving ZD9331 (Table 3). Assessment of non-haematological and haematological abnormalities by CTC grade did not indicate any significant difference between treatments. The incidence of serious AEs was similar between treatments (Table 3), although more patients were withdrawn from the ZD9331 group as a result.

10 patients (33%) were withdrawn from the ZD9331 group as a result of AEs, and 5 patients (20%) from the gemcitabine group. Seven of the ten ZD9331 patients were withdrawn for toxicity considered to be treatment-related. These included 4 cases of grade 4 myelosuppression (1 also with grade 3 mucositis), 2 of which were fatal (1 with sepsis); 1 case of grade 4 mucositis; 1 case of necrosis with purpura and pain, all attributed to treatment; and 1 case in which grade 1 thrombocytopenia was cited as the reason for patient withdrawal. This patient also had vomiting, dehydration, fever and con-

Table 3
Number of patients with drug-related toxicity by worst CTC grade, for toxicities seen in >10% of patients in either treatment group

CTC grade[a]	Treatment group									
	ZD9331 ($n=30$)					Gemcitabine ($n=25$)				
	1	2	3	4	Total (%)	1	2	3	4	Total (%)
Haematological										
Haemoglobin	1	1	0	0	2 (7)	1	2	1	0	4 (16)
Leucocytes	0	2	1	2	5 (17)	0	3	0	0	3 (12)
Neutrophils	0	4	2	3	9 (30)	0	4	1	0	5 (20)
Platelets	3	0	2	2	7 (23)	4	1	1	0	6 (24)
Non-haematological										
Diarrhoea	7	4	2	0	13 (43)	2	2	1	0	5 (20)
Fatigue[b]	7	4	1	2	14 (47)	3	4	0	0	7 (28)
Haemorrhage[c]	2	1	1	0	4 (13)	0	0	0	0	0
Infection	0	0	1	1	2 (7)	0	3	2	0	5 (20)
Nausea	11	4	1	0	16 (53)	6	3	0	0	9 (36)
Rash	2	1	0	0	3 (10)	3	1	0	0	4 (16)
Stomatitis[d]	3	1	1	1	6 (20)	4	3	0	0	7 (28)
Transaminase	0	1	2	0	3 (10)	3	0	3	0	6 (24)
Vomiting	8	5	2	0	15 (50)	6	5	0	0	11 (44)

CTC, common toxicity criteria; *n*, number of patients.
[a] A patient may have had >1 type of toxicity, but will only be included once for a given toxicity.
[b] Includes asthenia.
[c] Includes 2 cases of epistaxis, 1 of melaena and 1 of purpura.
[d] Includes mucositis and oral candidiasis.

stipation at the time of withdrawal, which were all also attributed to treatment. Three patients treated with ZD9331 and two treated with gemcitabine died following AEs during the study. Two of the deaths attributed to treatment with ZD9331 (sepsis and myelosuppression) occurred during the first cycle of treatment.

3.3. Health economics

Data collected during this trial evaluates the direct medical resource use, inpatient stay, outpatient visits, major medical procedures or diagnostics tests required to support patients on ZD9331 compared with gemcitabine. No significant differences were seen between treatment groups. Eleven patients (37%) in the ZD9331 group required an inpatient stay for the management of AEs compared with 9 patients (36%) in the gemcitabine group. Similar proportions of patients in each group required inpatient stay for dosing only (ZD9331, 4 patients (13%) versus gemcitabine, 2 patients (8%)). However, patients treated with ZD9331 were reported to have only one inpatient stay (3%) for AE management and dosing combined, compared with six reports (24%) for the gemcitabine group. In addition, fewer ZD9331 patients (37%) were reported to require major medical interventions or diagnostic tests compared with gemcitabine (56%).

4. Discussion

In this study, we compared the efficacy and safety of the novel TS inhibitor, ZD9331, with gemcitabine, in patients with locally advanced or metastatic pancreatic cancer. The Clinical Advisory Group halted the trial early due to two drug-related deaths and because the efficacy of ZD9331 appeared to be lower than that required for continuation. However, full assessment of the data available until the data cut-off showed that a greater proportion of patients in the ZD9331 group were alive at data cut-off compared with the gemcitabine group. Median duration of survival, time to progression, and duration of disease control were also longer with ZD9331 than gemcitabine. Objective tumour response and CBR gave similar results for both groups. In addition, health economic variables indicate that there may be a trend towards lower direct medical resource use by patients treated with ZD9331 compared with those treated with gemcitabine. Although these results are based on small patient numbers because of the early termination of the trial, the data collectively suggest that ZD9331 may be as effective as gemcitabine in the management of pancreatic cancer.

Concerns in relation to the ZD9331 treatment group in this study centred on the 2 patients who died after receiving only a single dose of the drug. However, prior to this there has only been one death attributed to ZD9331 among 196 phase I patients treated with ZD9331 [12]. DLT was been seen sporadically at several dose levels below the maximum tolerated dose in three of the four initial phase I trials of ZD9331 [12–14]. This interpatient variability in toxicity may be explained by the pharmacokinetics of ZD9331. Goh and colleagues [13] found a significant correlation between clearance and dose, consistent with renal excretion, but noted considerable interpatient variability in the clearance of ZD9331 at each dose level studied. It was suggested that it may be important to avoid if possible, co-administration of any drug which might inhibit renal elimination and lead to increased exposure to ZD9331 (area under the curve [AUC]) and possibly greater toxicity. Rees and colleagues [16] also found that clearance of ZD9331 increased with dose and that the renal route contributed significantly to the clearance in man. Diab and colleagues [12] noted that 2 patients in their study who experienced grade 4 myelosuppression had higher AUC values and lower plasma clearance values compared with other patients treated at the same dose levels who did not experience haematological toxicity. These results were broadly consistent with those of Plummer and colleagues [14], although in a larger patient population they found no correlation between AUC and toxicity. Notwithstanding the clinical importance of two treatment-related deaths following a single dose of

ZD9331, it should be evaluated against the otherwise manageable profile for ZD9331 to date.

The incidence of treatment-related toxicities was similar in patients receiving ZD9331 or gemcitabine and the type of toxicities were consistent with the safety profiles of each drug. However, the incidence of AEs leading to withdrawal was higher with ZD9331 than with gemcitabine, with myelosuppression accounting for four of the seven withdrawals. This initially suggests that the overall safety risk might appear slightly higher for ZD9331 than for gemcitabine; however, the number of patients treated in this trial was too small to make a conclusive comparison. In addition, it should be noted that this trial was open-label and it is possible that patients were ethically withdrawn from ZD9331 treatment due to the occurrence of serious AEs because this was the drug under test, and not because the AEs were more serious; in fact the incidence of serious AEs was similar between treatments. In a phase III trial comparing gemcitabine and 5-FU, 63 patients with pancreatic cancer were treated with the same dosing schedule of gemcitabine as used in this study [9]. The incidence of grade 4 neutropenia in these patients was approximately 7%, grade 3 neutropenia was seen in a further 19% and grade 3 thrombocytopenia in approximately 10% of patients. Grade 4 thrombocytopenia was not seen. These levels of haematological toxicity are similar to those seen with ZD9331 in this study, although here, grade 4 neutropenia occurred in approximately 10% of patients and grade 4 thrombocytopenia occurred in approximately 7%. Grade 4 non-haematological toxicities may also be slightly more common with ZD9331 compared with gemcitabine treatment. Overall, however, these data indicated that the toxicity profiles for the two treatments may not differ markedly.

The consistency of results, considering the small patient population, suggests that ZD9331 treatment may be as effective as gemcitabine treatment and may be worthy of further research in the current context of alternative treatments for pancreatic cancer.

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