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Report

Effects of impaired renal function on the pharmacokinetics and toxicity of i.v. ZD9331, a novel non-polyglutamated thymidylate synthase inhibitor, in adult patients with solid tumors

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ZD9331 is a potent thymidylate synthase inhibitor. Renal and hepatic clearances were found to be important routes of elimination. The objectives of this pharmacologic trial were to investigate the effect of renal impairment on the pharmacokinetics of ZD9331, to study the toxicity profile and to document any antitumor effects of ZD9331 when administered i.v. to patients with different degrees of renal impairment. Patients were treated with ZD9331 130 mg/m^2 given as an i.v. infusion on day 1 of a 4-week cycle to allow full pharmacokinetic assessment. Subsequent cycles involved the administration of ZD9331 on days 1 and 8, every 3 weeks. Patients were stratified according to their renal function assessed by the creatinine clearance: normal renal function (creatinine clearance $\geqslant$60 ml/min), mildly impaired renal function (creatinine clearance $\geqslant$40 to $<$60 ml/min) and moderately impaired renal function (creatinine clearance $>$25 to $<$40 ml/min). For pharmacokinetic analysis plasma sampling was performed during the first course and assayed using a validated liquid chromatographic tandem mass spectrometry assay. Twenty-three patients were entered on the study, of whom 21 received 130 mg/m^2 ZD9331 in the first treatment cycle. No relationship was seen between renal impairment and plasma clearance nor with the area under the concentration–time curve of free ZD9331. Increasing renal impairment was associated with a greater incidence of myelosuppression. No predictive relationship between the clearance of free ZD9331 and the degree of renal impairment as determined by creatinine clearance could be assessed. However, data from this trial indicate that increased renal impairment may be associated with greater ZD9331-induced toxicity, particularly myelosuppression, although this cannot be attributed to any alteration in the plasma pharmacokinetics of ZD9331. Therefore, it may be necessary to administer a reduced dose of ZD9331 to patients with impaired renal function. [© 2002 Lippincott Williams & Wilkins.]

Key words: Pharmacology, renal dysfunction, thymidylate synthase inhibition.

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Introduction

Thymidylate synthase (TS) is the rate-limiting enzyme in the biosynthesis of DNA catalyzing the methylation of deoxyuridine monophosphate (dUMP) to thymidine monophosphate (TMP), an essential precursor for DNA synthesis.[1] ZD9331 [(*S*)-2-(2-fluor-4[*N*-(4-hydroxy-2,7-dimethylquinazolin-6-ylmethyl)-*N*-(prop-2-ynyl)amino]benzamido)-4-(1H-1,2,3,4-tetrazol-5-yl)-butyric acid] is a novel water-soluble folate analog that potently and specifically inhibits TS (Figure 1). Since thymidine nucleotides are used exclusively for DNA synthesis, the development of TS inhibitors has been an area of much interest in drug development. Indeed, several folate-based TS inhibitors have been developed and have demonstrated clinical activity.[2–4] Prolonged drug exposure of tumor cells to antimetabolites in order to inhibit proliferation is generally believed to be important. TS inhibitors, such as

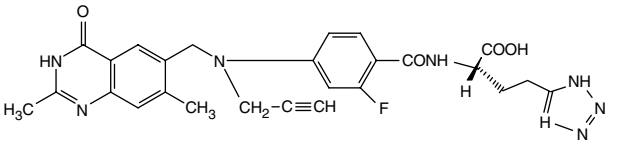

Figure 1. Chemical structure of ZD9331.

raltitrexed, that are capable of forming intracellular polyglutamates can achieve this because of prolonged drug retention in the cell. However, resistance to selective TS inhibitors might originate in impaired activation by folylpolyglutamate synthetase (FPGS)[5–7] and/or high folylpolyglutamyl hydrolase (FPGH) activity.[5,8,9] To avoid the resistance due to alterations in FPGS expression or high FPGH activity, a common form of acquired and probably intrinsic resistance to polyglutamated antifolates, a non-polyglutamatable TS inhibitor, ZD9331, was developed.

ZD9331 is actively transported into cells by reduced folate carrier proteins, which are thought to be expressed to a greater extent by tumor cells than by normal cells, thus potentially giving the drug a degree of tumor selectivity.[10,11] *In vitro* studies have shown that ZD9331 is a potent TS inhibitor,[12] and antitumor activity has been documented *in vivo* against human ovarian, colon, non-small cell lung and gastric carcinoma xenograft models.[13] In addition, antitumor activity has been observed following i.v. administration of ZD9331 in patients with a variety of solid tumors.[14–17]

Phase I trials in humans employed daily dosing for 5 days, continuous infusion for 5 days, and the administration of ZD9331 on days 1 and 8 of a 3-weekly cycle.[15–17] The regimen with administration of ZD9331 on days 1 and 8 of a 3-weekly cycle was chosen as the most appropriate regimen for phase II trials based on the optimal drug exposure achieved. This schedule also offers additional flexibility of dosing since in case of toxicity the administration on day 8 can be withheld. The dose recommended for further study in this schedule was identified as 130 mg/m^2/administration. Toxicity observed constituted of myelosuppression, gastrointestinal toxicity and a skin rash. Pharmacokinetic data derived from these phase I trials showed that the plasma clearance of ZD9331 was non-linear, increasing with the dose of the drug and approached 8 ml/min with a terminal elimination half-life of about 3 days.[15,17] Renal clearance was found to be an important route of elimination, accounting for 70% of the total clearance. In a multiple linear regression analysis using clearance of ZD9331 as the dependent variable, calculated creatinine clearance was a significant covariate.[15] ZD9331 is also highly bound to plasma proteins in man (>98%), the majority to plasma albumin.

Recent phase II studies of ZD9331 in patients with advanced colorectal or ovarian cancer have reported evidence of antitumor activity.[18,19] As many of these patients may have abnormal renal function tests, it was deemed vital to gain information on the effect of renal impairment on ZD9331 pharmacokinetics to allow the definition of appropriate dose modification schedules in this patient subset.

The objectives of this pharmacologic trial were to investigate the effect of renal impairment, as assessed by creatinine clearance, on the pharmacokinetics of ZD9331, to study the toxicity profile of ZD9331 in patients with normal, mild or moderately impaired renal function and to document any antitumor effects of ZD9331 when administered i.v. to patients with advanced solid tumors.

Methods

Study design

This was an open, non-randomized, multicenter trial of ZD9331 administered i.v. in adult patients with refractory solid tumors. Patients had normal, mildly or moderately impaired renal function. In the first treatment cycle ZD9331 was administered i.v. over 30 min on day 1 of a 4-week cycle to allow full pharmacokinetic assessment of ZD9331. Subsequent cycles involved the administration of ZD9331 on days 1 and 8, every 3 weeks.

The trial was designed to comply with the ethical principals of Good Clinical Practice and in accordance with the Declaration of Helsinki. The study was approved by the institutions medical ethics committees and all patients had to give written informed consent before study entry.

Patient selection

Patients with a histologically or cytologically confirmed diagnosis of a malignant solid tumor refractory to standard forms of therapy were eligible. Other eligibility criteria included the following: age ⩾18 years; WHO performance status ⩽2; estimated life expectancy >12 weeks; no ascites or pleural effusion: no previous anticancer therapy for at least 4 weeks (6 weeks for nitrosoureas or mitomycin C)

and adequate hematopoietic [absolute peripheral granulocyte count (ANC) $\geqslant 1.5 \times 10^9$/l and platelet count $\geqslant 100 \times 10^9$/l] and hepatic function [bilirubin $\leqslant 1.25$ times upper limit of normal (ULN) and serum aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase $\leqslant 2.5 \times$ ULN or $\leqslant 5 \times$ ULN in case of liver metastases]. Concomitant administration of folic acid as a vitamin supplement was not allowed, neither was the administration of medication known to possibly affect the renal function. Patients were to abstain from alcohol for 24 h before and after dosing of ZD9331. Based on the creatinine clearance patients were assigned to three cohorts as follows: normal renal function, creatinine clearance $\geqslant 60$ ml/min; mild renal impairment, creatinine clearance $\geqslant 40$ and < 60 ml/min; and moderate renal impairment, creatinine clearance $\geqslant 25$ and < 40 ml/min as determined by the 24-h creatinine clearance and the Cockroft–Gould formula.

Treatment and dose modification

ZD9331 was supplied as a sterile isotonic 0.2% weight per volume solution packed in glass vials. Each vial contained 20 mg of ZD9331 at a concentration of 2 mg/ml in a volume of 10 ml. The contents of each vial were diluted in 5% dextrose to a final concentration ranging from 0.0004 to 2.0 mg/ml. The vials were stored at 2–8°C and protected from light. Patients were treated on an outpatient basis. Only during the first treatment course could they be hospitalized for logistical reasons in order to perform pharmacokinetic sampling.

The starting dose of ZD9331 for all patients, 130 mg/m^2 by 30-min infusion, was based on the recommended dose defined in the phase I study.[16] During the first course, patients received only one administration of ZD9331 on day 1, in order to determine the toxicity profile in patients with impaired renal function and to allow full pharmacokinetic evaluation. Treatment was resumed on day 29, when the ANC had recovered to $\geqslant 1.5 \times 10^9$/l, platelet count to $\geqslant 75 \times 10^9$/l, serum creatinine < 1.25 times the baseline value and all other entry criteria were re-met. Dosing could be delayed for up to 2 weeks. Subsequent courses were to be repeated every 21 days with administration of ZD9331 on days 1 and 8. Dose modifications were based on the toxicity observed during the previous cycle. In case of a decline in ANC on day 8 of $\geqslant 50\%$ compared to the baseline value at start of the cycle, the administration of ZD9331 on day 8 was withheld and the dose of ZD9331 was reduced by 25% in the next cycle. The dosing of ZD9331 on day 8 was also omitted if the ANC was $< 1.5 \times 10^9$/l or the platelet count was $< 75 \times 10^9$/l. In the absence of toxicity in the previous cycle, a dose escalation to 125% of the starting dose was permitted from cycle 3 onwards.

Treatment assessment

Before therapy a complete medical history was taken and a physical examination was performed. A complete blood cell count (CBC) including white blood cell differential and serum biochemistry, which involved sodium, potassium, calcium, bicarbonate, phosphorus, urea, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, ASAT, ALAT and lactate dehydrogenase acid, was performed, as were urinalysis, 24-h urine collection to determine creatinine clearance, serum folate, red blood cell folate and ECG. Weekly evaluations included history, physical examination, toxicity assessment according to the CTC criteria (December 1994 version), and serum chemistry and CBC. Evaluation of the tumor response was not the primary endpoint of the study. Tumor response was evaluated according to the UICC/WHO criteria after four treatment cycles or earlier at the investigator's discretion. Patients were taken off protocol at the onset of disease progression.

Sample collection and drug analysis

For pharmacokinetic analysis, 17 blood samples (about 3 ml) were obtained from an indwelling i.v. canula and collected in vials containing lithium heparin as anticoagulant. The samples were taken pre-dose, at the end of the infusion (0.5 h), and at 1, 2, 4, 6, 8, 12 and 24 h after the start of the infusion on day 1. Additional samples were taken on days 3, 4, 5, 6, 8, 15, 22 and 29 of the first course. All samples were centrifuged immediately after sampling for 20 min at 1000 *g*, and the plasma supernatant was snap-frozen at −20°C and remained frozen until analysis. For determination of the free fraction of ZD9331, additional blood samples (about 5 ml) were taken at 0.5 and 1 h, and centrifuged at 37°C. The plasma supernatant was transferred to an Amicon ultrafiltration device and centrifuged at 37°C for 30 min at 2000 *g* to obtain ultrafiltrate.

Concentrations of ZD9331 were determined according to a validated LC-MS-MS assay by Quintiles (UK). The lower limit of quantification for ZD9331 was 1 ng/ml and for free ZD9331 was 3 ng/ml.

Pharmacokinetic data analysis

The terminal disposition half-life [$t_{1/2}(z)$] of both total and free ZD9331 was calculated as ln2/k, where k is the terminal elimination rate constant (expressed in h^{-1}) following the last dose. The peak plasma concentrations (C_{max}) and the time to peak plasma concentration (T_{max}) were determined graphically from the (observed) experimental values. The area under the plasma concentration–time curve (AUC) of both total and unbound ZD9331 was estimated using the experimental values (trapezoidal rule) with extrapolation to infinity using the terminal elimination rate constant, defined as the slope of at least the final three data points of the log-linear concentration–time plot. The plasma clearance (CL) and the volume of distribution (V_{ss}) were also calculated. The ratio of the free to total plasma concentrations of ZD9331 was determined in the 0.5 and 1 h post-dose samples.

Statistical analysis

The relationship between the pharmacokinetic parameters of the patients and creatinine clearance was assessed. The relationship was also investigated using (non-)linear models for the pharmacokinetic parameters of ZD9331 and fitted to the data.

In order to detect a 50% decrease in clearance of free ZD9331, which was considered of clinical relevance, with 80% power at the 5% significance level, six patients with moderate renal impairment, 12 patients with mild renal impairment and 12 patients with normal renal function were to be entered on the study.

All pharmacokinetic data are reported as mean $\pm$ SD or as reported otherwise.

Results

Between June 1999 and June 2000, 23 patients were enrolled onto the study in seven centers. The study was interrupted before the intended 30 patients were entered, because of the observed toxicity in the patients with impaired renal function to allow an interim analysis of the side effects and pharmacokinetic data. The interim analysis of the pharmacokinetic data at that time indicated that further recruitment would not alter the present conclusion. In view of this information, it was decided to stop further accrual to the study. Two patients, who already had given their informed consent at the moment the decision to stop the study was taken, were allowed to enter the trial at a lower dose level of 65 mg/m^2. Thus, 21 patients received ZD9331 130 mg/m^2 during the first treatment cycle and two

Table 1. Patient characteristics

Demographic characteristic	Normal renal function	Mildly impaired renal function[a]	Moderately impaired renal function
No. patients	10	10	3
Age (years)			
median	52	59	57
range	31–74	49–70	53–65
Sex (no. patients)			
male	4	7	1
female	6	3	2
WHO PS (no. patients)			
0	4	3	0
1	3	4	2
2	3	3	1
Tumor type (no. of patients)			
gastrointestinal	6	2	0
genitourinary	1	3	2
non-small cell lung	2	1	0
miscellaneous	1	4	1
Creatinine clearance (ml/min)			
mean	79	48[b]	35
range	60–100	40–57[b]	33–36

[a]Two patients received 65.0 mg/m^2/day at entry.
[b]n=8, excludes patients who received 65.0 mg/m^2/day at entry.
Normal renal function=creatinine clearance $\geqslant$60 ml/min. Mildly impaired renal function=creatinine clearance $\geqslant$40 to $<$60 ml/min. Moderately impaired renal function=creatinine clearance $\geqslant$25 to $<$40 ml/min.

patients a reduced dose of 65 mg/m^2. Of these, 20 patients were evaluable for pharmacokinetic analysis and 23 for toxicity assessment. Patient characteristics are listed in Table 1. All patients had received prior chemotherapy; 21 patients had received more than one prior chemotherapy regimen. Ten patients had had prior radiation. Metastatic gastrointestinal cancer was the underlying disease in eight patients; six patients had genitourinary cancers and three patients non-small cell lung cancer. The WHO performance status was 0 or 1 in all but seven patients. A total of 67 cycles were administered (median 2, range 1–9). Treatment was discontinued in six patients due to experienced side effects (n=4 normal renal function, n=1 mildly impaired renal function and n=1 moderately impaired renal function). Toxicity necessitated dose delay or dose reduction in 10 patients (n=2 normal renal function, n=7 mildly impaired renal function and n=1 moderately impaired renal function). In two patients with mildly impaired renal function, the dose of ZD9331 could be escalated.

Pharmacokinetics and pharmacodynamics

Pharmacokinetic sampling was obtained from 20 patients treated with 130 mg/m^2 ZD9331 in the first treatment cycle. Mean pharmacokinetic parameters for total and free ZD9331 are shown in Table 2. The plasma concentration–time profiles of free ZD9331 are presented in Figure 2. A correlation between the clearance of free ZD9331 and the degree of renal impairment could not be discerned (Figure 3). Full recruitment of the study would not have altered these findings. Similarly, no predictive relationship between the percentage of free ZD9331, nor the AUC or C_{max} of free ZD9331 and the degree of renal impairment could be determined. However, in the groups with mildly and moderately impaired renal function, increased variability in the percentage free ZD9331 was observed compared to those with normal renal function. Consequently, given the variability, observed in each group, no apparent differences in either the free or total ZD9331 pharmacokinetic parameters in relation to renal function could be concluded.

Although no correlation between the clearance of free ZD9331 and renal function could be discerned, there did appear to be an increased incidence of toxicity in patients with renal impairment compared to patients with normal renal function (Figure 4). Of the patients in the group with normal renal function, 30% (three of 10) experienced grade 3/4 hematological toxicity and/or grade 3 rash, whilst in the renally impaired patient groups the incidence increased to 80% (eight of 10) of patients with mild renal impairment and 67% (two of three) of patients with moderate renal impairment.

Tolerability

All but two patients started treatment at a dose of 130 mg/m^2 ZD9331. The proportion of patients who were able to maintain treatment at the original dose level from cycle 2 onwards was seven of 10 in those with normal renal function, three of 10 and one of three in the patients with mildly and moderately impaired renal function, respectively. This resulted in a median achieved relative dose intensity of 75% (range 37–100%) in those with normal renal function and 50% (range 25–100%) in patients with impaired renal function. A total of six patients experienced adverse events leading to treatment discontinuation. There was one death on treatment, considered drug related. The patient had a normal renal function and had a medical history of a thrombosis of the lower leg. He was receiving concomitant warfarin as prophylactic treatment and died as a result of an intracerebral hemorrhage. This adverse event was not associated with thrombocytopenia.

Table 2. Percentage free ZD9331 and plasma pharmacokinetic parameters of free and total ZD9331 following a single dose of 130 mg/m^2 infused over 30 min (cycle 1)

Parameter	Normal renal function (n=9)	Mildly impaired renal function (n=8)	Moderately impaired renal function (n=3)
Percent free ZD9331 in the plasma	1.39 ± 0.25	2.35 ± 1.06	1.70 ± 0.83
CL_{free} (ml/min)	1660 ± 1110	915 ± 707	1310 ± 956
AUC_{free} (ng · h/ml) (gmean [CV (%)])	2810 (71.6)	5040 (63.6)	3380 (91.3)
$C_{max,free}$ (ng/ml) (gmean [CV (%)])	427 (35.2)	643 (46.9)	423 (53.7)
CL_{total} (ml/min) (mean)	20.3 ± 12.3	17.5 ± 7.9	17.8 ± 6.7
AUC_{total} (ng · h/ml) (gmean [CV (%)])	221000 (61.4)	237000 (53.2)	214000 (33.7)
$C_{max,\ total}$ (ng/ml) (gmean [CV (%)])	31300 (16.9)	30300 (26.8)	26900 (3.9)
$T_{1/2,\ total}$ (h)	78.5 ± 50.0	114 ± 52.5	119 ± 126
$V_{ss,\ total}$ (l)	37.0 ± 23.0	45.6 ± 22.3	64.0 ± 25.3

gmean=geometric mean.

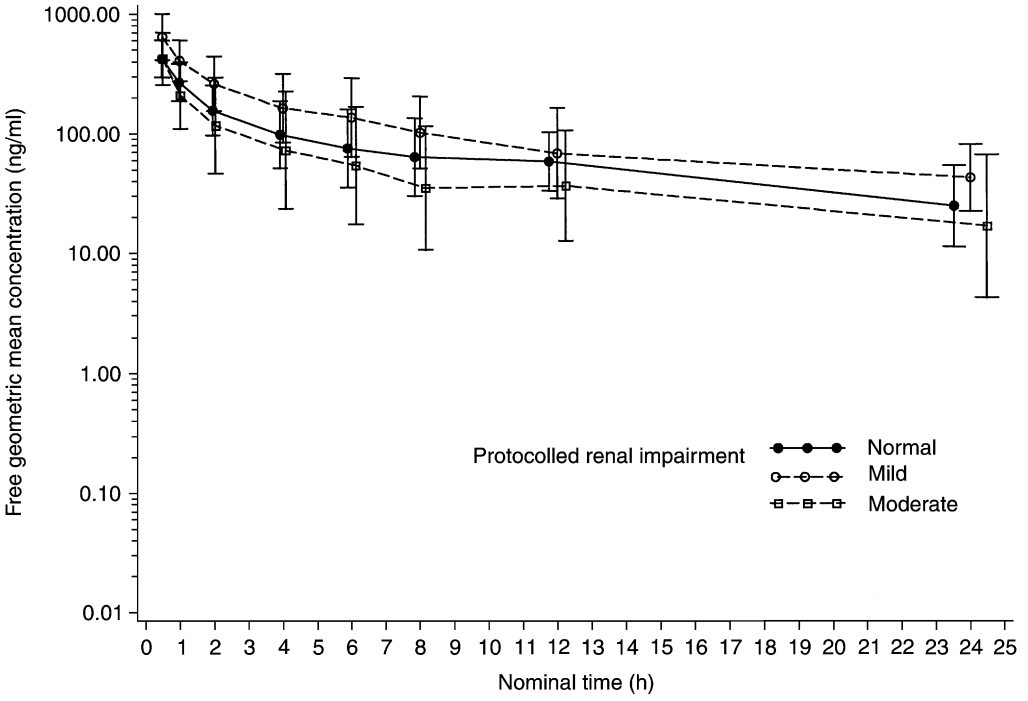

Figure 2. Geometric mean free plasma concentrations of ZD9331 following a single dose of 130 mg/m^2 infused over 30 min (0–24 h post-dose).

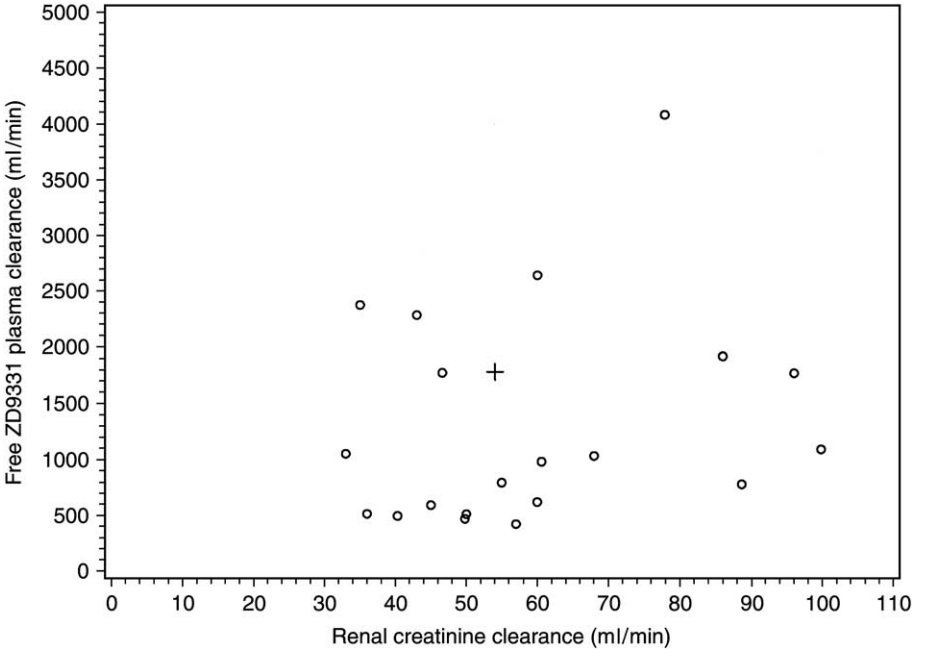

Figure 3. Clearance of free ZD9331 after a single dose of 130 mg/m^2 infused over 30 min compared to baseline creatinine clearance. Open circles: patients at 130 mg/m^2. Cross: patient at 65 mg/m^2.

Myelosuppression was the major toxicity observed (Table 3). Two of 10 patients with normal renal function had grade 3 or 4 thrombocytopenia and/or neutropenia, four of 10 patients with mildly impaired renal function and two of three patients with moderately impaired renal function. Neutropenia was not complicated with fever. Twenty patients developed anemia, which was considered drug related. Grade 1

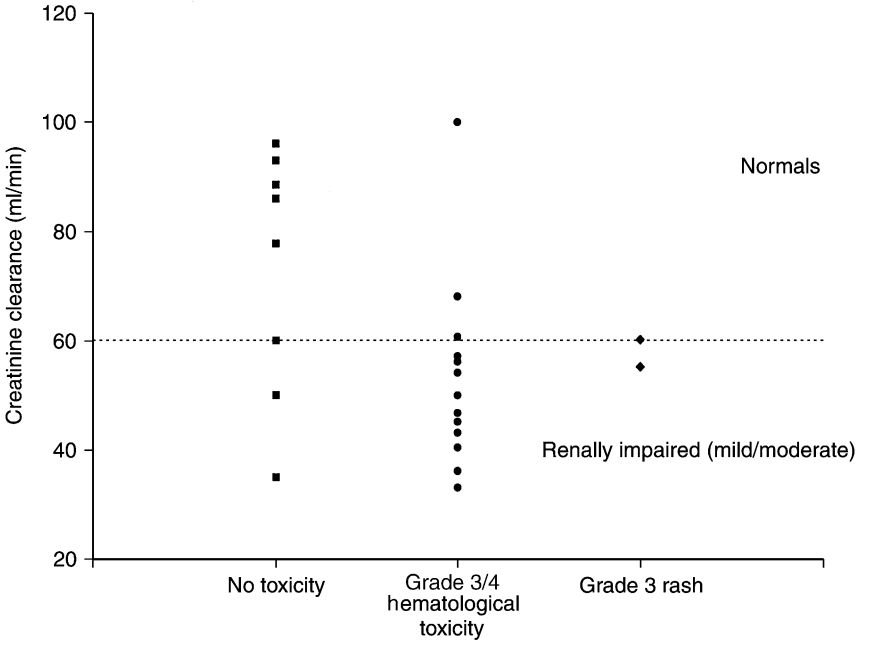

Figure 4. CTC grade 3/4 hematological toxicity and grade 3 rashes compared to creatinine clearance following a single dose of 130 mg/m^2 of ZD9331 infused over 30 min.

Table 3. Worse toxicity per dose level per patient[a]

CTC grade		Dose ZD9331 (mg/m^2)									
		Normal renal function		Mildly impaired renal function						Moderately impaired renal function	
		97.5 (n=2)	130.0 (n=10)	50.0 (n=1)	65.0 (n=3)	95.0 (n=1)	97.5 (n=4)	130.0 (n=8)	162.5 (n=1)	97.5 (n=1)	130.0 (n=3)
Hemoglobin	3	0	0	0	1	0	0	2	0	1	1
	4	0	0	0	0	0	0	1	0	0	0
Neutropenia	3	0	0	0	0	0	0	2	0	0	0
	4	1	0	0	1	0	0	0	0	0	1
Thrombocytopenia	3	0	1	0	0	0	0	2	0	0	1
	4	0	0	0	1	0	1	0	0	0	0
Diarrhea	1/2	0	1	0	0	0	0	3	1	0	1
	3/4	0	1	0	0	0	0	1	0	0	0
Asthenia	1/2	0	3	1	2	0	2	4	0	0	2
	3/4	1	2	0	0	0	0	1	0	0	1
Nausea	1	1	6	0	1	0	1	3	0	0	2
	2	0	0	0	0	0	0	2	0	0	0
	3	0	0	0	0	0	0	0	0	0	0
Vomiting	1	0	1	0	1	0	1	2	0	0	1
	2	0	0	0	0	0	0	1	0	0	2
	3	0	1	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0

[a]Patients who received more than 1 cycle could be counted in more than one column due to dose escalation or dose reduction.

or 2 anemia occurred in 14 patients and grade 3 or 4 in seven patients. Impaired renal function was associated with a greater incidence of hematological toxicity.

The most frequent non-hematological side effects were nausea and asthenia (Table 3). Asthenia may partly be related to the observed anemia. Transient elevation of liver transaminases was observed in eight patients, grade 1 or 2 in two patients and grade 3 or 4 in six patients. Grade 3 or 4 bilirubinemia occurred in conjunction with raised liver transaminases in six

patients; none of these was considered drug related. Two patients experienced grade 3 skin rash. There was no clear evidence to suggest that the incidence of non-hematological toxicity was related to the degree of renal impairment.

Responses

Twenty-one patients were evaluable for response. No major responses were observed. However, six patients showed disease stabilization for more than 42 days. Of these, three patients (colorectal, ovarian and hepatocellular cancer) experienced disease stabilization for at least 13 weeks.

Discussion

New chemotherapeutic agents are first studied in patients with normal organ function. Although renal and hepatic dysfunction is relatively common in patients with metastatic solid tumors, the dosing of cytotoxic agents in patients with organ dysfunction has long been based on empiric data and knowledge of the metabolism of the drug. Only a limited number of prospective studies have addressed the dosing of cytotoxic agents in patients with organ dysfunction, including carboplatin, paclitaxel, etoposide, gemcitabine and capecitabine.[21–24] Pharmacokinetic data derived from phase I studies on ZD9331 showed that a significant amount of the drug was cleared by the renal route. Calculated creatinine clearance was a significant covariate in a multiple linear regression analysis using ZD9331 clearance as the dependent variable.[15] Impairment of renal function therefore may have clinical relevance in determining the recommended dose of ZD9331 in this patient subset.

The primary objective of this study was to investigate the influence of renal impairment, as assessed by creatinine clearance, on the pharmacokinetics of free and total ZD9331, and to study the toxicity profile of ZD9331 in patients with normal and mildly or moderately impaired renal function in order to define any dose reductions required for ZD9331 in patients with renal impairment.

No predictive correlation was found between the clearance of free ZD9331 and the degree of renal impairment as assessed by their creatinine clearance nor between either the AUC of free ZD9331 or C_{max}. The inter-patient variability in the clearance of ZD9331 was high and might have obscured any effect of a reduction in renal function. In addition, 24-h creatinine clearance might not be the most accurate method to assess renal function. Also, in previous phase I studies, ZD9331 showed non-linear pharmacokinetics consistent with excretion through the renal route and saturable tubular reabsorption.[15,17] Reduced renal function might have resulted in a reduction of this active tubular reabsorption of the drug, resulting in a relative increase in clearance of ZD9331 with decreasing renal function. This also might have been an additional factor that might have obscured a relationship between ZD9331 pharmacokinetics and the pharmacodynamic consequences.

The pharmacokinetics of ZD9331 observed in this study corresponded with results from previous phase I studies on the i.v. administration of ZD9331. The terminal elimination half-life was long, with values ranging from 78.5 to 119 h.

The toxicity observed in this study is consistent with the toxicity described in previous phase I studies on ZD9331.[14–17] Myelosuppression and skin toxicity were the dose-limiting toxicities in all treatment schedules studied. However, in the present study even in the group with normal renal function four out of 10 patients were withdrawn from treatment due to adverse events. The median dose intensity achieved for subsequent courses, being 75% of the intended dose intensity (range 37–100%), might suggest that even for patients with normal renal function, the recommended dose of 130 mg/m^2 on days 1 and 8 every 3 weeks is not feasible for multiple courses.

Conclusion

Although no alteration in the pharmacokinetics of free ZD9331 could be discerned in the patient groups with impaired renal function and recent information derived from a single-dose administration study of [^{14}C]ZD9331 revealed that the urinary excretion of ZD9331 accounted for only 22.3% of the dosed radioactivity,[25] the incidence of grade 3 and 4 hematological toxicity and/or skin toxicity increased with renal dysfunction. The mechanism for this apparent effect is unclear. However, these results in combination with the fact that in patients with impaired renal function the median dose intensity achieved from cycle 2 onwards was only 50%, indicate that it may be necessary to administer a reduced dose of ZD9331 to patients with impaired renal function.

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