ZD9331 in combination with topotecan: phase I and II experience

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Background **ZD9331, a novel, direct-acting thymidylate synthase inhibitor, and the topoisomerase inhibitor topotecan have antitumour activity in a range of solid tumours. We report results from two open-label, multicentre, phase I and phase II trials, investigating the pharmacokinetics, tolerability and efficacy of ZD9331, when used in combination with topotecan in patients with relapsed or refractory tumours.**

Patients and methods **Patients in the phase II trial had progressed following first- or second-line treatment with platinum and paclitaxel. The recommended dose (RD) from the phase I study was subsequently used in the phase II trial. ZD9331 was given as a 30-min i.v. infusion on days 1 and 8 combined with a 30-min i.v. infusion of topotecan on days 1–5 of each 3-week cycle.**

Results **Sixteen patients with a selection of solid tumours were recruited to the phase I trial. Forty-one patients were included in the combination therapy arm of the phase II study; 95% of which had ovarian cancer and 5% had peritoneal cancer. Three patients experienced dose-limiting toxicity during the phase I trial, one at dose level 1 (ZD9331 65 mg/m^2, topotecan 0.5 mg/m^2) and two at dose level 2 (ZD9331 65 mg/m^2, topotecan 0.75 mg/m^2). The RD for the phase II study was ZD9331 65 mg/m^2, topotecan 0.5 mg/m^2. In both trials, the most common grade 3 and 4 adverse events were thrombocytopenia (15 of 57 patients, 26.3%), neutropenia (11 of 57 patients, 19.3%) and anaemia (9 of 57 patients, 15.8%). One patient (2.4%) in the phase II trial experienced a complete response and six patients overall experienced a partial response [one (6.3%) in phase I, five (12.2%) in phase II]. Seventeen patients achieved stable disease [three (18.8%) in phase I, 14 (34.1%) in phase II].**

Conclusions **ZD9331, in combination with topotecan, showed manageable toxicity and some evidence of activity in patients with ovarian cancer.** ***Anti-Cancer Drugs*** **14 (suppl 1):S21–S27 © 2003 Lippincott Williams & Wilkins.**

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Introduction

Novel treatments are urgently required to improve the outcome for the large number of patients whose cancer grows, returns or metastasises, even after having received the most effective therapies currently available. For many solid tumours, particularly at an advanced stage, combination chemotherapy offers the best chance of effective treatment. The goal of combination chemotherapy is to maximise tumour cell kill by synergistic antitumour activity, while minimising side effects and the development of resistant tumour cells. This is best achieved by combining agents with non-cross-resistant modes of action and different toxicity profiles.

ZD9331 is a folate analogue and direct-acting thymidylate synthase (TS) inhibitor intended for the treatment of solid tumours. It is actively transported into cells by the reduced folate carrier, which is thought to be expressed to a greater extent by tumour cells than by normal cells [1] and therefore may offer a degree of antitumour selectivity. Furthermore, in contrast to some other TS inhibitors, ZD9331 does not require polyglutamation by the enzyme folylpolyglutamate synthetase to become active and, thus, may show activity against tumour cells with a poor ability to polyglutamate antifolates.

In phase I and II studies, antitumour activity has been observed with i.v. ZD9331 monotherapy in a range of solid tumours including ovarian [2,3], pancreatic [4], gastric [5], non-small cell lung (NSCLC) [6] and colorectal cancer (CRC) [7,8]. These trials have shown ZD9331 to have a manageable toxicity profile with myelosuppression being the main dose-limiting toxicity (DLT).

Topotecan belongs to the family of drugs known as topoisomerase I inhibitors; these agents have a mechanism of action clearly distinct from TS inhibition. Topotecan produces DNA damage in the presence of the nuclear enzyme topoisomerase I, which is involved in the control of DNA topology. In previous phase I and II studies,

topotecan demonstrated activity in a wide range of tumour types, including recurrent ovarian cancer [9,10], relapsed small-cell lung cancer (SCLC) [11,12], CRC [13,14] and breast cancer [15,16], as well as in haematological malignancies [17–19]. The safety of topotecan is well established. Like ZD9331, the principal toxicity is myelosuppression, with non-haematological toxicities being generally mild.

The use of topotecan in combination therapy has shown encouraging results. Dual [20,21] and triple [22–24] topotecan combinations have all demonstrated promising activity in ovarian cancer. A number of topotecan combinations also have been investigated in SCLC including topotecan plus cisplatin and paclitaxel [22], topotecan plus carboplatin and paclitaxel [25], topotecan plus ifosfamide [26] and topotecan plus cyclophosphamide [27].

A phase I study was undertaken to investigate the pharmacokinetics and to determine the maximum tolerated dose (MTD) of ZD9331 when used in combination with topotecan in patients with a range of refractory solid malignancies. The recommended dose (RD) of ZD9331/topotecan identified in the phase I trial was subsequently used in the phase II trial. The phase II trial assessed the efficacy and tolerability of the ZD9331/topotecan combination and ZD9331 monotherapy in patients with relapsed or refractory ovarian cancer. This review presents the key findings from both the phase I and II trials. Results from two ZD9331 monotherapy arms of the phase II trial are presented elsewhere in this supplement.

Patients and methods

Phase I

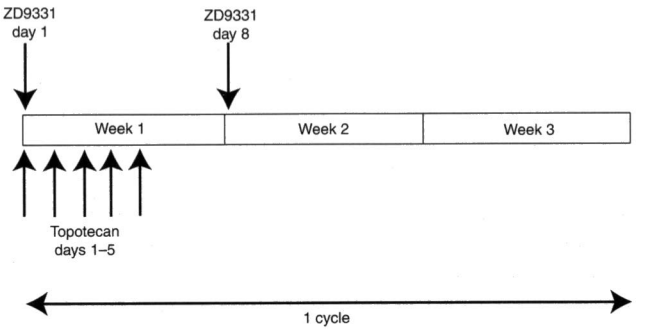
Study design

This was an open-label, non-comparative, multicentre, dose-escalation study in adult patients with histologically or cytologically confirmed solid, malignant tumours, refractory to treatment or for which no effective treatment existed. It was proposed that at least three patients per dose level would be recruited, with nine to 30 patients treated at the MTD.

Treatment

There were seven proposed dose levels for the study. Dose level (DL) 1 was ZD9331 65 mg/m^2 and topotecan 0.5 mg/m^2. The topotecan dose was increased by 0.25 mg/m^2 at each dose level until DL5 of each cycle. The dose of ZD9331 remained the same for each dose level up to DL6 and 7 when it was increased to 97 mg/m^2 and 130 mg/m^2, respectively. ZD9331 was given as a 30-min i.v. infusion on days 1 and 8 of a 3-week cycle combined with a 30-min i.v. infusion of topotecan on days 1–5 (Fig. 1). Patients continued to receive treatment until there was objective evidence of disease progression (PD) or until another event necessitating treatment withdrawal occurred.

Fig. 1



ZD9331 and topotecan were administered as a 30 min intravenous infusion

Treatment schedule–phase I trial.

Assessments

Adverse events (AEs) were monitored throughout the study. Blood samples were collected for pharmacokinetic analysis during the first cycle of treatment. For the analysis of ZD9331 plasma levels, blood samples were taken throughout cycle 1 (days 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15 and 22), whereas blood samples for analysis of topotecan plasma levels were taken on days 1 and 5 of this cycle. Mean pharmacokinetic parameters for cycle 1 overall were calculated for ZD9331, whereas mean pharmacokinetic parameters for topotecan were calculated for both days 1 and 5 of cycle 1.

DLT was defined as any of the following treatment-related events in two or more patients at a given dose level: absolute neutrophil count (ANC) $<0.5 \times 10^9$/l associated with fever or infection, ANC $<0.5 \times 10^9$/l lasting longer than 7 days, platelet count $<25 \times 10^9$/l, grade 3 or 4 non-haematological toxicity that was not ameliorated by symptomatic measures (except for reversible elevations of alanine aminotransferase or aspartate aminotransferase), inability to administer day 8 dose of ZD9331 due to myelosuppression or treatment delay >2 weeks due to unresolved toxicity. The MTD was defined as the dose level at or below the dose level which resulted in DLT in two or more of six patients, and had acceptable, manageable and reversible toxicity. The secondary endpoints of the phase I study included objective tumour response based on a modified version of the 1999 National Cancer Institute Response Evaluation Criteria in Solid Tumours (NCI-RECIST) definitions.

Phase II

Study design

This was an open-label, randomised, multicentre study of ZD9331 plus topotecan and ZD9331 monotherapy in adult women with histologically or cytologically confirmed ovarian, primary peritoneal or fallopian tube cancer, whose disease had progressed following first- or

second-line combination therapy with platinum and paclitaxel. Patients were not eligible for inclusion if they had received previous topotecan treatment. It was intended that approximately 120 patients would be recruited over a period of 10 months with follow-up for at least 2 months.

Treatment

Patients received ZD9331 plus topotecan at the RD determined during the phase I trial [ZD9331 65 mg/m^2 (days 1 and 8) and topotecan 0.5 mg/m^2 (days 1–5), 3-week cycle] (Fig. 1). Patients who received ZD9331 monotherapy in the two other treatment arms of the phase II study are not discussed in this review.

Assessments

The primary endpoint of the phase II study was objective tumour response based on the 1999 NCI-RECIST definitions. Secondary endpoints included time to progression and tolerability.

Results

Patients

Baseline patient characteristics from both the phase I and II trials are summarised in Table 1.

Phase I

The intent-to-treat population comprised 16 patients recruited from two centres in the USA. The most common primary tumour sites were colorectal (five patients, 31.3%), NSCLC (two patients, 12.5%) and pancreas (two patients, 12.5%). All patients had distant metastatic disease and had received prior cancer treatment including chemotherapy/immunotherapy/hormonal therapy (15 patients, 93.8%), surgery (13 patients, 81.3%) and radiotherapy (8 patients, 50.0%). Most patients (12 patients, 75.0%) had received two or more prior courses of chemotherapy, immunotherapy or hormonal therapy.

Fifteen patients had withdrawn from treatment at the time of analysis, the most common reason for which was PD (11 patients, 68.8%). Other reasons for withdrawal included AEs (two patients at DL2, 12.5%) and non-compliance (one patient, 6.3%). One patient (6.3%) was withdrawn at the investigator's discretion. Five patients died during the trial; three patients at DL1 and two patients at DL2. All five patients died from cancer.

Phase II

Patients were recruited from 44 centres in nine countries. Forty-one patients were randomised to the combination treatment arm of the study. Thirty-nine patients (95.1%) had ovarian cancer and the remaining two patients had peritoneal cancer. All the patients had received prior cancer treatment including surgery (41 patients, 100%), chemotherapy/immunotherapy/hormonal therapy (41 patients, 100%) and radiotherapy (1 patient, 6.3%).

Table 1 Patient characteristics at baseline: phase I and phase II trials

	Phase I ($n = 16$)	Phase II ($n = 41$)
Age (years)		
mean	55.5	59.6
range	42–75	37–78
Sex [*n* (%)]		
Male	9 (56.2)	0 (0.0)
Female	7 (43.8)	41 (100.0)
WHO performance status [*n* (%)]		
1 (normal activity)	9 (56.2)	26 (63.4)
2 (restricted activity)	7 (43.8)	15 (36.4)
Primary tumour site [*n* (%)]		
colorectal	5 (31.2)	–
exocrine pancreas	2 (12.5)	–
NSCLC	2 (12.5)	–
ovary	–	39 (95.1)
peritoneum	–	2 (4.9)
other	6 (37.5)	–
not recorded	1 (6.3)	–
Previous cancer therapy [*n* (%)]		
chemotherapy	15 (93.8)[a]	41 (100.0)[b]
1 previous course	5 (31.2)	25 (61.0)
2 previous courses	2 (12.5)	14 (34.1)
3 previous courses	4 (25.1)	2 (4.9)
4 previous courses	5 (31.2)	–
immunotherapy	1 (6.3)	0 (0.0)
hormonal therapy	2 (12.5)	4 (9.8)
surgery	13 (81.2)	41 (100.0)
radiotherapy	8 (50.0)	1 (2.4)

[a]All patients refractory to previous chemotherapy.
[b]Four patients refractory and 37 patients relapsed following previous platinum therapy.

Thirty-seven patients had withdrawn from the trial at the time of analysis, most commonly due to PD (24 patients, 58.5%). Six patients (14.6%) were withdrawn due to AEs, six patients (14.6%) at the investigators' discretion and one patient (6.3%) by withdrawal of informed consent. One patient died during the trial as a result of treatment-related AEs.

Treatment

Phase I and II

In the phase I trial, 20 and 29 cycles of treatment were administered at DL1 and DL2, respectively. The maximum number of cycles received was 8.0 and the mean number of treatment cycles received was 3.1.

A total of 172 cycles of treatment were administered in the phase II trial. The maximum number of cycles received was 13.0 and the mean number of treatment cycles received was 4.2.

Pharmacokinetics

Pharmacokinetic data are available from the 16 patients included in the phase I study.

ZD9331 pharmacokinetics

Mean plasma pharmacokinetic parameters for ZD9331 when given in combination with topotecan are presented in Table 2. ZD9331 plasma concentration data suggest that the pharmacokinetics of ZD9331 are similar when given in combination with topotecan at doses of 0.5 and

Table 2 Plasma pharmacokinetic parameters for ZD9331: phase I trial (cycle 1, days 1–22)

Pharmacokinetic parameter	Dose level received (mg/m²) ZD9331/topotecan 65/0.50 (*n* = 7)	65/0.75 (*n* = 9)	All[a] (*n* = 16)
$AUC_{(0-t)}$ (ng·h/ml)			
n	5	6	11
Gmean	251 000	335 000	294 000
CV (%)	56.9	47.8	51.8
C_{max} (ng/ml)			
n	7	9	16
Gmean	14 000	16 000	15 100
CV (%)	17.9	16.3	17.8
CL (ml/min)			
n	7	8	15
mean	15.3	13.4	14.3
SD	10.0	6.1	7.9
V_{ss} (l)			
n	7	8	15
mean	95.2	84.4	89.4
SD	80.9	55.1	66.0
$t_{1/2}$ (h)			
n	7	8	15
mean	42.1	42.7	42.4
SD	23.1	20.9	21.1

[a]Independent of dose level.
$AUC_{(0-t)}$: area under the plasma concentration–time curve from zero to time, *t*; C_{max}: maximum plasma concentration; CV: coefficient of variation (%); Gmean: geometric mean; CL: clearance; SD: standard deviation; V_{ss}: steady-state volume of distribution; $t_{1/2}$: elimination half-life.

Table 3 Plasma pharmacokinetic parameters for topotecan: phase I trial (cycle 1, days 1 and 5)

Pharmacokinetic parameter	Dose level received (mg/m²) ZD9331/topotecan 65/0.50 (*n* = 7) Day 1	Day 5	65/0.75 (*n* = 9) Day 1	Day 5	All[a] (*n* = 16) Day 1	Day 5
$AUC_{(0-\infty)}$ (ng·h/ml)						
n	7	7	9	8		
Gmean	45.7	43.7	81.7	84.5	NR	NR
CV (%)	75.8	74.9	54.6	43.9		
C_{max} (ng/ml)						
n	7	7	9	8		
Gmean	12.8	13.7	27.1	26.7	NR	NR
CV (%)	27.3	38.0	57.5	104		
CL (ml/min)						
n	7	7	9	8	16	15
mean	408	423	335	321	367	369
SD	196	198	121	124	157	166
CL_R (ml/min/m²)						
n	7	7	9	8	16	15
mean	214	223	167	159	188	189
SD	101.0	104.0	57.8	53.4	80.4	84.5
V_{ss} (l)						
n	7	7	9	8	16	15
mean	91.9	89.2	73.9	75.2	81.8	81.8
SD	28.4	35.9	29.3	40.3	29.5	37.7
$t_{1/2}$ (h)						
n	7	7	9	8	16	15
mean	3.67	3.13	3.22	3.24	3.42	3.19
SD	1.91	1.15	1.51	0.94	1.65	1.00

[a]Independent of dose level.
$AUC_{(0-\infty)}$: area under the plasma concentration-time curve from zero to infinity.
CL_R, renal clearance.

0.75 mg/m², and when given as monotherapy. There was a high degree of interpatient variability with an approximate 4-fold range in area under the concentration–time curve (AUC) values and a 7-fold range in total plasma clearance (CL) values.

Topotecan pharmacokinetics

Mean plasma pharmacokinetic parameters for topotecan when given in combination with ZD9331 are shown in Table 3. Comparison of the pharmacokinetics of topotecan in combination with ZD9331 and the pharmacokinetics of topotecan monotherapy suggests that addition of ZD9331 does not affect overall exposure to topotecan, but may decrease the CL of topotecan. In two patients this reduction in CL gave rise to a much higher AUC. The increased exposure in this group may be associated with higher toxicity as one patient experienced thrombocytopenia and leucopenia, and another patient experienced hepatitis.

Tolerability

Phase I

Overall, the most common AEs were asthenia (15 patients, 93.8%), nausea (12 patients, 75.0%), anaemia (10 patients, 62.5%) and fever (nine patients, 56.3%). Most of the AEs were grade 1 or 2. The most common grade 3 and 4 AEs were thrombocytopenia (two patients at DL1, 12.5%; four patients at DL2, 25.0%), neutropenia (two patients at DL1, 12.5%; three patients at DL2, 18.8%), anaemia (four patients at DL1, 25.0%; one patient at DL2, 6.3%) and infection (three patients at DL1, 18.8%; two patients at DL2, 12.5%) (Table 4).

Three patients experienced DLT; one patient at DL1 on day 14 of cycle 3 of treatment [grade 3 infection, grade 4 thrombocytopenia and grade 4 neutropenia (lasting longer than 7 days)]. Additional patients were recruited at DL2 and this dose level was confirmed as the MTD, with two out of nine patients (22.2%) experiencing DLT [grade 3 thrombocytopenia, day 16 of cycle 2 (one patient) and grade 4 neutropenia (lasting longer than 7 days) on day 9 of cycle 1, febrile neutropenia and thrombocytopenia on day 10 of cycle 1 (one patient)]. DL1 (ZD9331 65 mg/m² and topotecan 0.50 mg/m²) was recommended as the dose for the phase II study.

Two patients were withdrawn as a result of treatment-related AEs: one as a result of hepatitis and one as a result of agitation with confusion. There were no treatment-related deaths during the phase I trial.

Phase II

The most common AEs (all grades) in the phase II trial were anaemia (25 patients, 61.0%) and neutropenia (23 patients, 56.1%). The most frequently occurring grade 3 or 4 AEs were thrombocytopenia (nine patients, 22.0%), neutropenia (eight patients, 19.5%) and asthenia (seven patients, 17.1%) (Table 5).

Six patients were withdrawn from therapy due to different AEs: ascites (one patient), rash (one patient), consti-

Table 4 All grade 3 or 4 haematological and non-haematological AEs (by worst CTC grade): phase I trial

	No. of patients[a]				
	Dose level received (ZD9331/topotecan)				
	65/50 mg/m² (*n* = 7)		65/75 mg/m² (*n* = 9)		
	Grade 3	Grade 4	Grade 3	Grade 4	Total[b] (%)
Haematological					
anaemia	4	0	1	0	5 (31.3)
leucopenia	0	1	1	0	2 (12.5)
neutropenia	0	2	1	2	5 (31.3)
febrile neutropenia	0	0	0	1	1 (6.3)
thrombocytopenia	1	1	3	1	6 (37.5)
lymphocytopenia	0	0	0	1	1 (6.3)
marrow depression	0	0	0	1	1 (6.3)
Non-haematological					
abdominal pain	0	0	1	0	1 (6.3)
anorexia	0	1	0	0	1 (6.3)
bilirubinaemia	2	0	0	0	2 (12.5)
fatigue	1	0	1	0	2 (12.5)
haemorrhage	1	0	0	7	1 (6.3)
hypokalaemia	1	0	0	0	1 (6.3)
hyponatraemia	1	0	0	0	1 (6.3)
hypophosphataemia	1	0	0	0	1 (6.3)
hypoproteinaemia	0	0	1	0	1 (6.3)
infection	3	0	0	2	5 (31.3)
nausea	1	0	0	0	1 (6.3)
neuro-constipation	1	0	0	0	1 (6.3)
neuro-cortical	0	0	0	1	1 (6.3)
pulmonary	2	0	0	1	3 (18.8)
transaminase	2	0	1	0	3 (18.8)
vomiting	1	0	0	0	1 (6.3)

[a]A patient may have had more than one CTC graded AE; a patient was only counted once at the worst CTC grade in each CTC category.
[b]Total number of grade 3 and grade 4 AEs.

pation and hypoproteinaemia (one patient), intestinal obstruction and hypoproteinaemia (one patient), and nausea and vomiting (one patient). The sixth patient experienced eight AEs leading to her withdrawal and subsequent death from treatment-related toxicity. She had acidosis, anaemia, asthenia, diarrhoea, hypoproteinaemia, hypotension, mucous membrane disorder and vomiting. All these events occurred during the first cycle of treatment and she died 18 days after receiving the first dose (ZD9331 on days 1 and 8 and topotecan on days 1–5).

Efficacy

Phase I and II response rates are shown in Table 6.

Phase I

Of the 11 patients evaluated for efficacy, one patient (9.0%) with NSCLC had a partial response (PR) and three patients (27.2%) achieved stable disease (SD) for 4 cycles of therapy; all four patients were treated at DL2.

Phase II

All 41 patients were evaluated for efficacy. One patient (2.4%) had a complete response (CR) and five patients (12.2%) had a PR (all six patients had ovarian cancer). The patient that had a CR was receiving ZD9311 plus topotecan as second-line treatment after having previously experienced a PR to platinum therapy. Three of the patients that had a PR were also receiving ZD9311 plus topotecan as their second-line of treatment after having previously experienced a CR (two patients) or SD (one patient) to platinum therapy. Of the two remaining PRs, one patient was receiving ZD9311 plus topotecan as third-line treatment and one as fourth-line treatment. Both patients had previously experienced a PR and a CR to platinum therapy. Fourteen patients (34.1%) achieved SD, nine of these for 4 cycles or more. The objective tumour response rate was 14.6% and the median time to progression was 92 days.

Table 5 Grade 3 or 4 haematological and non-haematological AEs occurring in one or more patients (by worst CTC grade): phase II trial

	Number of patients[a] (*n* = 41)		
	Grade 3	Grade 4	Total[b] (%)
Haematological			
anaemia	2	2	4 (9.7)
febrile neutropenia	1	2	3 (7.3)
leucopenia	2	1	3 (7.3)
neutropenia	6	2	8 (19.5)
thrombocytopenia	7	2	9 (22.0)
Non-haematological			
abdominal pain	3	0	3 (7.3)
anorexia	1	1	2 (4.9)
ascites	2	0	2 (4.9)
asthenia	7	0	7 (17.1)
constipation	1	1	2 (4.9)
diarrhoea	2	0	2 (4.9)
dyspnoea	2	2	4 (9.7)
intestinal obstruction	0	2	2 (4.9)
mucous membrane disorder	2	0	2 (4.9)
nausea	3	0	3 (7.3)
alanine aminotransferases increased	4	0	4 (9.7)
vomiting	5	0	5 (12.2)

[a]A patient may have had more than one CTC graded AE; a patient was only counted once at the worst CTC grade in each CTC category.
[b]Total number of grade 3 and grade 4 AEs.

Table 6 Phase I/II response rates

	Number of patients (%)	
	Phase I (*n* = 16)	Phase II (*n* = 41)
Best overall objective tumour response		
CR	0 (0.0)	1 (2.4)
PR	1 (6.3)	5 (12.2)
SD	3 (18.8)	14 (34.1)
PD	4 (25.0)	19 (46.3)
SYD	3 (18.8)	–
died within 6 weeks of first dose	–	1 (2.4)
NR[a]	5 (31.3)	1 (2.4)
Objective tumour response		
CR or PR	1 (6.3)	6 (14.6)
Disease control		
CR or PR or SD	4 (25.0)	20 (48.8)

[a]An overall response of 'not recorded' indicates that patients in the analysis population have insufficient information on objective response to make an assessment of best overall response. CR, complete response; PR, partial response; SD, stable disease; PD, disease progression; SYD, symptomatic deterioration; NR, not recorded.

Discussion

ZD9331 plasma concentration data suggest that ZD9331 pharmacokinetics are not affected when combined with

topotecan. Renal clearance is an important route of elimination for both ZD9331 and topotecan, and renal impairment has been shown to increase the toxicity of topotecan treatment leading to a requirement for dose reduction [28]. In this trial, none of the patients experiencing DLT had particularly low clearance, and the link between exposure and toxicity is not clear. It is possible that ZD9331 may have affected the renal clearance of topotecan on both day 1 and day 5; however, conclusions are limited due to the small number of patients recruited.

AEs were consistent with the toxicity profile of each individual drug or the underlying disease, with myelosuppression being the most commonly experienced grade 3 or 4 AE in both the phase I and II studies. The number of patients in the phase I trial was too small to discern any dose-related differences in tolerability.

Four patients in the phase I trial experienced disease control (one PR and three SD), but all of these were treated at a higher dose level than was subsequently recommended for the phase II study (ZD9331 65 mg/m^2 and topotecan 0.5 mg/m^2). In the phase II trial one patient (2.4%) experienced a CR, five patients (12.2%) had a PR and 14 patients (34.1%) achieved SD, some of which for more than 4 cycles of treatment. All six patients who responded to treatment had ovarian cancer. Although both phase I and II studies included second- or third-line patients with few alternative treatment options, ZD9331 in combination with topotecan appears to offer improved response rates over those already demonstrated by ZD9331 monotherapy in a similar patient group (objective response rate 6.8%) [3]. In addition, response rates to second- and third-line topotecan monotherapy range from 13.7 to 32.6% in ovarian cancer patients previously treated with platinum [9,10,29,30].

Conclusions

ZD9331, in combination with topotecan, had a manageable toxicity profile and showed evidence of activity in patients with ovarian cancer. However, the objective tumour response rate showed no improvement over those available with alternative treatment options.

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