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ZD0473 combined with other chemotherapeutic agents for the treatment of solid malignancies

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Abstract

Platinum-based combination chemotherapy regimens are the mainstay of current treatments for advanced solid malignancies. Preclinical *in vitro* studies have shown synergism with ZD0473 in combination with several agents, including vinorelbine and topotecan. This paper reviews the tolerability and activity observed with ZD0473 in combination with vinorelbine or topotecan, in two Phase I dose-escalating studies in patients with advanced, solid, refractory malignancies.

Twenty-four patients were included in the ZD0473 plus vinorelbine trial and were treated with doses of ZD0473 60–150 mg/m^2 and vinorelbine 15–25 mg/m^2. In this trial, dose-limiting toxicity comprised non-haematological events and the most common grade 3/4 toxicities included neutropenia (54.2%), thrombocytopenia (29.2%) and anaemia (20.8%). Eleven patients were included in the ZD0473 plus topotecan trial and were treated with ZD0473 60–90 mg/m^2 and topotecan 0.5 mg/m^2/day for 3 or 5 days. In this trial, dose-limiting toxicity comprised haematological events and the most common grade 3/4 toxicities included thrombocytopenia (63.6%), neutropenia (36.4%) and anaemia (18.2%). No objective responses were observed in either trial, but disease stabilisation occurred in 29.2% and 27.3% of patients in the vinorelbine and topotecan trials, respectively.

Keywords: ZD0473 combination treatment; Topotecan; Vinorelbine; Solid tumours

1. Introduction

Despite the success of modern cancer chemotherapy in selected tumours, half of all cancer patients either fail to respond or relapse during follow-up and die from metastatic disease [1]. For example, although there have been advances in combination treatment for non-small-cell lung (NSCLC) and small-cell lung cancers (SCLC), 5-year survival remains poor at only 15% [2]. The hope for improved treatment outcomes for patients with metastatic disease has led to intensive research to optimise the administration and combination of currently available treatments. Combination chemotherapy accomplishes three important objectives not possible with monotherapy: it provides maximum cell kill within the range of toxicity tolerated by the patient for each drug; it offers broader coverage of resistant cell lines in a heterogeneous tumour population; and it prevents or slows the development of new drug-resistant cell lines. The focus of this paper is platinum-based combination regimens.

2. Platinum agents

Platinum agents (eg cisplatin, carboplatin, oxaliplatin, or ZD0473) act by forming DNA–DNA and DNA–protein crosslinks that interfere with DNA replication and transcription, resulting in cell death. However, the efficacy of platinum agents is limited by both inherent and acquired resistance mechanisms [3], including impaired cellular uptake, intracellular inactivation by thiols, enhanced DNA

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repair and increased tolerance to platinum-DNA adducts. The use of cisplatin in the clinic is also limited by significant neuro- and nephrotoxicity, while carboplatin is associated with myelosuppression [4].

ZD0473 is a new platinum agent that was rationally designed to overcome many of the platinum resistance mechanisms that significantly reduce the success of currently available platinum agents. In preclinical studies, ZD0473 demonstrated activity in a range of tumours, including those resistant to platinums [5,6]. Unlike earlier platinum agents, ZD0473 was not associated with nephro- or neurotoxicity *in vivo*, and no evidence of clinically significant nephro-, neuro-, or ototoxicity has been observed in clinical studies to-date [7,8]. ZD0473 has a manageable toxicity profile in Phase I/II monotherapy studies, with myelosuppression being the main dose-limiting toxicity (DLT) [9]. The antitumour activity of ZD0473 has been demonstrated in a range of tumours [7,8].

2.1. Platinum agents in combination chemotherapy regimens

Platinum agents are commonly combined with plant alkaloids (eg paclitaxel or vinorelbine) in the treatment of patients with advanced solid malignancies. Plant alkaloids prevent cell division by binding to the protein tubulin, but vinorelbine also has more specific antitumour effects that are due to its inhibition of mitosis during metaphase. At present, vinorelbine is often co-administered with platinum agents in the treatment of advanced NSCLC [10–13]. Granulocytopenia is the main DLT associated with vinorelbine and platinum combinations [14,15].

Topotecan, an antitumour drug that inhibits topoisomerase I, has also been studied in combination with platinums. It has shown efficacy in the second-line treatment of advanced ovarian carcinoma [16,17] and relapsed SCLC [18]. The main DLT associated with topotecan treatment is myelosuppression, particularly neutropenia. However, studies combining topotecan with platinum-alkaloid chemotherapy regimens in lung [2] and ovarian cancer [19] have generally led to substantial bone marrow toxicity.

2.2. ZD0473 combination regimens

Preclinical *in vitro* studies have shown synergistic activity with ZD0473 in combination with paclitaxel, gemcitabine, topotecan, or vinorelbine in some tumour cell types [20]. A number of Phase I studies of ZD0473 in combination with other chemotherapeutic agents have been undertaken, and preliminary results from trials of ZD0473 in combination with paclitaxel [21], gemcitabine [22], liposomal doxorubicin [23], docetaxel [24], and vinorelbine [25] have been reported previously. This present paper reviews the tolerability and activity of two combination regimens evaluated in Phase I trials in patients with refractory solid malignancies: ZD0473 plus vinorelbine, and ZD0473 plus topotecan.

3. Methods and Results

These were open-label, dose-escalating Phase I trials to determine the DLT, maximum tolerated dose (MTD), and recommended dose of ZD0473 when given in combination with vinorelbine or topotecan in patients with refractory solid malignancies.

3.1. Patients

Patients with histologically and/or cytologically confirmed refractory solid tumours for which no effective treatment exists were recruited to both the vinorelbine and topotecan trials. The remaining inclusion criteria were similar for the two trials and included patients aged $\geq$18 years with World Health Organization (WHO) performance status of 0 or 1, creatinine clearance of $\geq$60 mL/min and a life expectancy of $\geq$12 weeks. Exclusion criteria included absolute neutrophil count (ANC) $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, haemoglobin <9 g/dL, serum bilirubin $>1.25 \times$ the upper limit of the reference range (ULRR) and alanine transferases (ALT) or aspartate transferases (AST) $>2.5 \times$ ULRR (or $5 \times$ ULRR in the presence of liver metastases). Patients with a body surface area <1.2 m^2, or those with evidence of uncontrolled systemic disease or systemic anticancer therapy within the past 4 weeks, were also excluded from the trial. Written, informed consent was obtained from all participants.

In the ZD0473 plus vinorelbine trial, 24 patients received at least 1 cycle of treatment and comprised the intent-to-treat (ITT) population. In the ZD0473 plus topotecan trial, 11 patients received at least 1 cycle of treatment and comprised the ITT population. Patient demographics for both trials are presented in Table 1.

3.2. ZD0473 plus vinorelbine

Drugs were administered by intravenous infusion on days 1 (ZD0473 and vinorelbine) and 8 (vinorelbine only) of each 3-week cycle. On day 1, vinorelbine was administered over a 6- to 10-min period, followed 30 min later by ZD0473 over a 1- to 2-h period. On day 8, vinorelbine was given alone over a 6- to 10-min period. Treatment was to be continued until the patient experienced unresolved toxicity or disease progression.

Three patients were treated with ZD0473 (day 1) and vinorelbine (days 1 and 8) at each of dose levels 1 (ZD0473 60 mg/m^2, vinorelbine 15 mg/m^2), 2 (ZD0473 90 mg/m^2, vinorelbine 15 mg/m^2), 3 (ZD0473 120 mg/m^2, vinorelbine 15 mg/m^2) and 4 (ZD0473 120 mg/m^2, vinorelbine 20 mg/m^2). Six patients were treated at each of dose levels 5 (ZD0473 120 mg/m^2, vinorelbine 25 mg/m^2) and 6

Table 1
Patient demographics

	No. patients	
	ZD0473 plus vinorelbine	ZD0473 plus topotecan
No. patients	24	11
Median age, years (range)	57.5 (42-77)	65.0 (36-77)
Male : female	16 : 8	5 : 6
WHO performance status		
0	10	2
1	14	9
Site of primary tumour		
NSCLC	3	3
SCLC	4	0
colorectal	7	2
liver	6	0
other/not recorded	4	6
Metastatic disease	20	11
Prior treatment [a]		
chemo-/immuno-/ hormonal therapy	20	11
platinum therapy	16	7
radiotherapy	7	6
surgery	15	7

[a] Prior treatments are not mutually exclusive.

(ZD0473 150 mg/m^2, vinorelbine 20 mg/m^2). A total of 54 cycles of treatment were administered, and a median number of 2 cycles was received by each patient (range 1–8).

3.3. ZD0473 plus topotecan

Drugs were initially administered by intravenous infusion on day 1 (ZD0473) and days 1 to 5 (topotecan), but following a protocol amendment, topotecan was administered on days 1 to 3 of each 3-week cycle (amended dose level 1). ZD0473 was administered for 1 h, followed 30 min later by topotecan for 30 min. Up to 6 treatment cycles were planned, unless discontinuation criteria were met (unresolved toxicity or disease progression), but treatment could be continued beyond 6 cycles if it was considered in the best interest of the patient.

Four patients were treated at dose level 1 (ZD0473 60 mg/m^2 [day 1], topotecan 0.5 mg/m^2/day [days 1–5]). Administration of topotecan was reduced to 3 days after myelotoxicity was observed in the first 4 patients treated. Three patients were then treated at the amended dose level 1 (ZD0473 60 mg/m^2 [day 1], topotecan 0.5 mg/m^2/day [days 1–3]). A further 4 patients received treatment at dose level 2 (ZD0473 90 mg/m^2 [day 1], topotecan 0.5 mg/m^2/day [days 1–3]). A total of 28 cycles of treatment were administered and a median number of 2 cycles was received by each patient (range 1–8). One patient treated at the amended dose level 1 received the planned 6 cycles of therapy.

3.4. Tolerability

Toxicities were assessed using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) grading system. In both trials, only adverse events that occurred during the first cycle were assessed in terms of DLT. DLT was defined as ANC $<1.5 \times 10^9$/L associated with CTC grade 2 fever or infection lasting longer than 7 days; platelet count $<25 \times 10^9$/L; grade 3/4 treatment-related non-haematological toxicity (except for alopecia or reversible, transient elevations of ALT or AST, or nausea and vomiting in patients who were not being given optimal antiemetic medication); or treatment delay of >3 weeks because of unresolved toxicity. Prophylactic antiemetic agents were not always used during cycle 1 of treatment in the ZD0473 plus vinorelbine trial. The criteria for dose-escalation and determination of MTD and recommended dose are shown in Table 2.

3.4.1. ZD0473 plus vinorelbine

Dose-limiting, treatment-related, non-haematological toxicity (grade 3 heart failure and peripheral oedema) was observed during cycle 1 in one patient who received dose level 6 (ZD0473 150 mg/m^2 [day 1], vinorelbine 20 mg/m^2 [days 1 and 8]). During the second treatment cycle, a further 2 patients from dose level 6 experienced adverse events meeting the criteria of DLT (grade 4 febrile neutropenia plus grade 4 thrombocytopenia [1 patient], grade 4 thrombocytopenia [1 patient]). Although DLT was only to be assessed during cycle 1 of treatment, these observations indicated that treatment at the next dose level (ZD0473 150 mg/m^2 [day 1], vinorelbine 25 mg/m^2 [days 1 and 8]) would lead to pronounced toxicity. For this reason, the toxicities occurring in cycle 2 were accepted as DLT and the study was stopped because in total, DLT was observed in 3/6 patients who received treatment at dose level 6. Dose level 5 (ZD0473 120 mg/m^2 [day 1], vinorelbine 25 mg/m^2 [days 1 and 8]) meets the protocol definition of DLT, however, both dose level 5 and 6 (ZD0473 150 mg/m^2 [day 1], vinorelbine 20 mg/m^2 [days 1 and 8]) were designated the MTD, as they were assumed to be equitoxic.

The most common treatment-related adverse events were vomiting (19 patients, 79.2%), nausea (18 patients,

Table 2
Criteria for dose escalation and determination of MTD and recommended dose (RD)

No. patients with DLT	Action
0/3	Escalate to next dose
1/3	Recruit 3 additional patients
1/6	Escalate to next dose
2/6	MTD; RD is dose below
≥ 2/3 or 3/6	Toxic dose; MTD is dose below, RD is 2 doses below

Table 3
ZD0473 plus vinorelbine ($n = 24$): all haematological and non-haematological toxicities (all cycles) occurring in >10% patients, irrespective of causality

	No. patients (%)[a]				
	grade 1	grade 2	grade 3	grade 4	all
Haematological					
anaemia	6 (25.0)	13 (54.2)	5 (20.8)	0 (0)	24 (100)
neutropenia	1 (4.2)	1 (4.2)	5 (20.8)	8 (33.3)	15 (62.5)
thrombocytopenia[b]	8 (33.3)	3 (12.5)	3 (12.5)	4 (16.7)	18 (75.0)
Non-haematological					
abdominal pain	3 (12.5)	2 (8.3)	0 (0)	0 (0)	5 (20.8)
anorexia	2 (8.3)	1 (4.2)	1 (4.2)	0 (0)	4 (16.7)
anxiety	2 (8.3)	1 (4.2)	1 (4.2)	0 (0)	4 (16.7)
asthenia	4 (16.7)	8 (33.3)	2 (8.3)	1 (4.2)	15 (62.5)
bilirubinemia	2 (8.3)	2 (8.3)	1 (4.2)	0 (0)	5 (20.8)
cachexia	0 (0)	1 (4.2)	1 (4.2)	2 (8.3)	4 (16.7)
chest pain	1 (4.2)	0 (0)	1 (4.2)	1 (4.2)	3 (12.5)
constipation	5 (20.8)	3 (12.5)	0 (0)	0 (0)	8 (33.3)
diarrhoea	5 (20.8)	1 (4.2)	1 (4.2)	0 (0)	7 (29.2)
dyspnoea	0 (0)	3 (12.5)	4 (16.7)	0 (0)	7 (29.2)
fever	5 (20.8)	2 (8.3)	0 (0)	0 (0)	7 (29.2)
increased cough	2 (8.3)	2 (8.3)	0 (0)	0 (0)	4 (16.7)
increased SGOT/SGPT	0 (0)	3 (12.5)	3 (12.5)	0 (0)	6 (25.0)
insomnia	1 (4.2)	2 (8.3)	0 (0)	0 (0)	3 (12.5)
mucous membrane disorder	4 (16.7)	2 (8.3)	0 (0)	0 (0)	6 (25.0)
nausea[c]	15 (62.5)	4 (16.7)	0 (0)	0 (0)	19 (79.2)
pain	2 (8.3)	1 (4.2)	0 (0)	0 (0)	3 (12.5)
peripheral oedema	1 (4.2)	3 (12.5)	1 (4.2)	0 (0)	5 (20.8)
vomiting[c]	14 (58.3)	5 (20.8)	0 (0)	0 (0)	19 (79.2)
weight loss	3 (12.5)	0 (0)	0 (0)	0 (0)	3 (12.5)

[a]Patients may have experienced >1 grade 3/4 adverse event; [b]The CTC definition of grade 4 thrombocytopenia is platelets $< 10 \times 10^9$/L but, in this study, platelets $< 25 \times 10^9$/L was recorded as grade 4; [c]Prophylactic antiemetic agents were not always used during cycle 1.
AP; alkaline phosphatase; GGT, γ-glutamyl transpeptidase; SGOT, serum glutamic-oxaloacetic transaminase.

75.0%), thrombocytopenia (17 patients, 70.8%), leucopenia (15 patients, 62.5%), anaemia (13 patients, 54.2%), constipation (8 patients, 33.3%), and asthenia (7 patients, 29.2%). Most treatment-related adverse events were mild-to-moderate (grade 1–2) in nature. No clinically significant neuro-, nephro- or ototoxicity was observed during this study. All haematological and non-haematological adverse events occurring in more than 10% of patients are presented in Table 3.

All 24 patients eventually withdrew from treatment: 2 patients withdrew due to treatment-related adverse events (heart failure and pancytopenia, respectively); 3 patients withdrew because of cachexia (non-treatment-related); 16 patients had disease progression; 1 patient received 8 cycles of treatment but was later withdrawn (investigator's decision); and 2 patients withdrew for other reasons (investigator's decision). At the end of the trial, 19 patients (79.2%) were still alive, and 5 patients (20.8%) had died from cancer.

3.4.2. ZD0473 plus topotecan

DLT was observed in 4 patients and was primarily haematological. Haematological DLT was observed in 2/4 patients who received dose level 1 (ZD0473 60 mg/m^2 [day 1], topotecan 0.5 mg/m^2/day [days 1–5]); 1 patient had neutropenia and grade 2 fever/infection and 1 patient had thrombocytopenia. One patient at dose level 2 (ZD0473 90 mg/m^2 [day 1], topotecan 0.5 mg/m^2/day [days 1–3]) also experienced DLT of thrombocytopenia, and a second patient at this dose level experienced non-haematological DLT (grade 3 treatment-related asthenia). This study failed to identify the MTD of the ZD0473 plus topotecan combination. As no patients experienced DLT at the amended dose level 1 (ZD0473 60 mg/m^2 [day 1], topotecan 0.5 mg/m^2 [days 1–3]), this dose level meets the protocol definition for the recommended dose. However, the doses of each agent in this combination are too low to recommend further usage.

All patients experienced at least one treatment-related adverse event, the most common being nausea (9 patients, 81.8%), thrombocytopenia (9 patients, 81.8%), asthenia (8 patients, 72.7%), anaemia (6 patients, 54.5%), anorexia (5 patients, 45.4%), vomiting (5 patients, 45.5%), and leucopenia (4 patients, 36.4%). All haematological and non-haematological toxicities occurring in more than 10% of patients are reported in Table 4.

All 11 patients eventually withdrew from treatment: 4 patients withdrew due to treatment-related adverse events (asthenia [2 patients], asthenia and nausea [1 patient],

Table 4
ZD0473 plus topotecan (n = 11): all haematological and non-haematological toxicities (all cycles) occurring in > 10% patients, irrespective of causality

	No. patients (%)[a]				
	grade 1	grade 2	grade 3	grade 4	all
Haematological					
anaemia	4 (36.4)	5 (45.4)	2 (18.2)	0 (0)	11 (100)
neutropenia	2 (18.2)	3 (27.3)	0 (0)	4 (36.4)	9 (81.8)
thrombocytopenia	0 (0)	4 (36.4)	5 (45.4)	2 (18.2)	11 (100)
Non-haematological					
anorexia	3 (27.3)	2 (18.2)	0 (0)	0 (0)	5 (45.4)
asthenia	4 (36.4)	3 (27.3)	2 (18.2)	0 (0)	9 (81.8)
chest pain	0 (0)	2 (18.2)	0 (0)	0 (0)	2 (18.2)
dyspnoea	1 (9.1)	2 (18.2)	0 (0)	1 (9.1)	4 (36.4)
nausea	5 (45.4)	5 (45.4)	0 (0)	0 (0)	10 (90.9)
neuropathy	1 (9.1)	1 (9.1)	0 (0)	0 (0)	2 (18.2)
pain	1 (9.1)	1 (9.1)	0 (0)	0 (0)	2 (18.2)
pelvic pain	1 (9.1)	1 (9.1)	0 (0)	0 (0)	2 (18.2)
pharyngitis	1 (9.1)	1 (9.1)	0 (0)	0 (0)	2 (18.2)
pneumonia	0 (0)	2 (18.2)	0 (0)	0 (0)	2 (18.2)
sinusitis	0 (0)	2 (18.2)	0 (0)	0 (0)	2 (18.2)
vomiting	2 (18.2)	3 (27.3)	0 (0)	0 (0)	5 (45.4)

[a]Patients may have experienced more than 1 grade 3/4 adverse event.

neuropathy and tinnitus [1 patient]), 4 patients had disease progression, 1 patient died (thrombocytopenia and lung haemorrhage), 1 patient received 8 cycles of treatment but was later withdrawn (investigator's decision) and 1 patient had a treatment delay of >3 weeks due to unresolved haematological toxicity.

3.5. Antitumour activity

The antitumour activity of each combination regimen was assessed by objective measurement of ≤10 measurable lesions (lesions with a diameter >20 mm) using computed tomography scans. Tumour response was defined according to the NCI Response Evaluation Criteria in Solid Tumors. Tumour response was assessed at baseline, after every 2 cycles of treatment, and at withdrawal.

There were no complete or partial responses in either of the two ZD0473 combination studies. In the ZD0473 plus vinorelbine trial, 7 patients (29.2%) had a best overall objective response of stable disease, 12 patients (50.0%) had disease progression, 2 patients (8.3%) had symptomatic deterioration, and 3 patients were not evaluable for tumour response. In the ZD0473 plus topotecan trial, 3 patients (27.3%) had a best overall objective response of stable disease and 6 patients (54.5%) had disease progression. One patient died and the remaining patient was not evaluable for tumour response.

4. Discussion

Vinorelbine has proven efficacy in the treatment of solid tumours, and the combination of cisplatin or carboplatin plus vinorelbine has become a standard treatment for advanced NSCLC. In Phase I trials of cisplatin/carboplatin plus vinorelbine in patients with untreated NSCLC, myelosuppression (especially neutropenia) was the main DLT [14,15,26,27]. Similarly in this study, ZD0473 combined with vinorelbine was associated with myelosuppression, although it did not become dose-limiting. The recommended dose of this combination is yet to be established, however, the present study identified the MTD to be two equitoxic dose levels: dose level 5 (120 mg/m^2 ZD0473, 25 mg/m^2 vinorelbine) and 6 (150 mg/m^2 ZD0473, 20 mg/m^2 vinorelbine).

Response rates associated with cisplatin/carboplatin plus vinorelbine treatment in untreated NSCLC are in the range of 15–33% [14,15,26]. In our study, no objective responses were observed; however, this study included a heterogeneous population of patients, all of which were pretreated, so a lower level of response may be expected. Furthermore, the use of granulocyte colony-stimulating factor support in one of the trials alleviated haematological toxicity, which allowed treatment with higher vinorelbine doses that may, in turn, be expected to lead to increased efficacy [26]. The vinorelbine doses used in the literature (generally 20 or 30 mg/m^2) are similar to those employed in this study.

The DLT associated with single-agent topotecan in patients with refractory solid tumours is primarily myelosuppression, especially neutropenia and anaemia [28–30]. Likewise, when given in combination with ZD0473, patients experienced DLTs of neutropenia and thrombocytopenia. The main toxicities in Phase I trials of carboplatin in combination with topotecan in relapsed solid malignancies were also similar to this study (neutropenia, thrombocytopenia and anaemia) [31–33]. Comparable toxicities were also observed in Phase I/II trials of cisplatin plus

topotecan in both minimally pretreated patients [34–36] and heavily pretreated patients [37]. Topotecan doses in the combination trials were similar to those planned in the present study, ranging between 0.3–2.0 mg/m^2, and the recommended dose for topotecan monotherapy is 1.5 mg/m^2 for 5 consecutive days [38].

Response rates reported for topotecan monotherapy in patients with refractory solid tumours are low, being in the range of 0–6% [28,30]. Although response rates in platinum plus topotecan combination trials are slightly higher than those seen with topotecan alone, they remain low (in the region of 9–14%) [33,34,36,37]. In this study, no objective responses were observed, but as only 11 patients received treatment, higher patient numbers may be required for objective responses to be observed. The high levels of haematological toxicity observed also meant that this combination was too toxic for use at dose levels that might be expected to demonstrate efficacy.

In general, high levels of haematological toxicity are seen with combinations of cisplatin or carboplatin plus topotecan [35–37], especially when the platinum agent is given prior to topotecan [34]. Cisplatin plus topotecan is not a feasible option for the treatment of solid refractory tumours, although some studies recommend further evaluation of the sequence-dependence of this combination [34,35]. Generally, combinations containing carboplatin and topotecan have slightly less haematological toxicity, and are slightly more active than cisplatin-based regimens [31,32]. Therefore, treatment with topotecan followed by carboplatin is a more promising therapeutic option, although this may be more feasible in minimally pretreated patients [31,32]. Consequently, the high levels of haematological toxicity and low levels of activity of ZD0473 in combination with topotecan are in overall agreement with similar published studies, especially those in which the platinum agent was administered prior to topotecan. Furthermore, as the topotecan dose had to be reduced due to myelosuppression, the dose used in this study (0.5 mg/m^2 over 3 days) was only a fraction of the recommended single agent dose [38]. Similarly, the ZD0473 dose that had to be used in the present study (60 mg/m^2) was only half that of the recommended single agent dose for ZD0473 (120–150 mg/m^2) [9]. Therefore, because the ZD0473 plus topotecan combination would have to use approximately 1/3–1/2 of the respective single agent doses, this combination was judged too myelosuppressive for further development.

5. Conclusions

ZD0473 combined with vinorelbine has a manageable tolerability profile in a range of solid, refractory tumours. However, ZD0473 combined with vinorelbine appears to be no more effective in the treatment of advanced, solid, refractory tumours than current platinum-based combination regimens, although no recommended dose has been established for this regimen. The high levels of haematological toxicity that occurred in the ZD0473 plus topotecan trial meant that the doses of both topotecan and ZD0473 were reduced to such a level that this combination regimen is not a feasible option for the treatment of refractory solid malignancies.

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