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ORIGINAL ARTICLE

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A phase I study of paclitaxel and altretamine as second-line therapy to cisplatin regimens for ovarian cancer

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Abstract *Purpose*: The efficacy and pharmacokinetics of paclitaxel when combined with altretamine for ovarian cancer were studied. *Methods*: A group of 30 patients, whose only chemotherapy was one or more cisplatin-based non-paclitaxel-containing regimens and whose ovarian cancer failed to respond or had relapsed within 6 months of their last platinum regimen, received paclitaxel as a 3-h intravenous infusion and altretamine given orally in four divided doses daily for 14 days repeated every 28 days. Doses were escalated from paclitaxel/altretamine 135/150 mg/m^2 to 250/300 mg/m^2 in cohorts of three patients. *Results*: The dose-limiting toxicities at 250/300 mg/m^2 were WHO grade 3 myalgias and arthralgias in two patients and grade 3 lethargy, stomach cramps, peripheral neuropathy and vomiting in single patients. Considering all dose levels in cycle 1, 16 patients had grade 3 or 4 neutropenia but there was only one episode of febrile neutropenia. Other grade 3 toxicities were vomiting in four patients, myalgias in three, peripheral neuropathy in two and lethargy in two. Grade 3 alopecia occurred in 23 patients. Three patients achieved a complete response and 12 achieved a partial response for an overall objective response rate of 50%. Responses occurred at all dose levels of 175/150 mg/m^2 and higher. The median freedom from progression was 35 weeks, with a median survival of 55 weeks. Altretamine did not alter the pharmacokinetics of paclitaxel and there were no consistent differences in paclitaxel pharmacokinetic parameters or toxicities between course 1 and 2. No dose-response relationships were evident above paclitaxel/altretamine 175/150 mg/m^2. *Conclusion*: Paclitaxel and altretamine can be safely combined and with a high response rate in relapsed ovarian cancer, justifying further studies with this combination.

Keywords Paclitaxel · Altretamine · Ovarian cancer · Pharmacokinetics

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Introduction

Platinum combinations have been the mainstay of the treatment of chemotherapy-naive ovarian cancer. In the United States since the Gynecologic Oncology Group (GOG 111) study demonstrating a survival advantage for the combination of cisplatin and paclitaxel over cisplatin and cyclophosphamide, platinum/taxane combinations have become the standard treatment [16]. A confirmatory European/Canadian study has been completed [25]. The analysis of GOG 132 did not suggest a survival advantage for the paclitaxel combination over a higher dose of cisplatin, but a high crossover in this trial has been postulated as a possible reason for this result [18, 24]. The Third International Collaborative Ovarian Neoplasm Study (ICON3) comparing carboplatin and paclitaxel with either single-agent carboplatin or cisplatin, doxorubicin and cyclophosphamide is still in progress, not yet having shown superiority for the paclitaxel/carboplatin arm [9]. Further data would be useful comparing concomitant versus sequential use of paclitaxel and platinum agents.

Despite encouraging response rates to first-line chemotherapy, the outcome of second-line therapy has been disappointing. Favourable prognostic factors for

response to second-line therapy include whether the patient exhibits de novo or acquired resistance to cisplatin and carboplatin, the duration of the freedom from progression and the bulk of disease at relapse [13, 20, 27].

Potentially useful drugs in treating cisplatin-refractory ovarian cancer include paclitaxel, if it has not been used first-line, altretamine, etoposide, gemcitabine, topotecan and liposomal doxorubicin [7, 10, 12, 14, 17, 26]. A distinction must be made between previously cisplatin-sensitive and cisplatin-resistant disease. For example, response rates of 40–50% to single-agent paclitaxel have been recorded in cisplatin-sensitive patients and 20–30% in patients with cisplatin-resistant disease [2, 26]. The duration of remission, however, has been disappointingly short, ranging from 5 to 9 months [6, 26]. Altretamine has shown high response rates in combination chemotherapy (hexaCAF) in chemotherapy-naive ovarian cancer and a 10% response rate in cisplatin-resistant disease in GOG studies [2, 23].

Many doublets of the available active drugs that have different mechanisms of action could be studied to develop combinations that may show improved efficacy. This trial was a dose-finding study and a pharmacokinetic study of the combination of paclitaxel and altretamine. The patient population was a group who were resistant to platinum-based regimens but who had not received paclitaxel first-line and were suitable for salvage therapy. The pharmacokinetic study was designed to detect whether the combination would alter the known pharmacokinetics of paclitaxel as different doses of the drugs were studied in combination.

Patients and methods

Eligibility criteria

Eligibility was limited to female patients who had epithelial carcinoma of the ovary, who had received at least one prior platinum-containing regimen and had either progressed during treatment or relapsed within 6 months of their last chemotherapy regimen. Patients were allowed to have received more than one regimen including cisplatin or carboplatin but no non-platinum chemotherapy regimens and any hormone therapy had to be discontinued. In addition, prior combinations of platinum with taxanes, altretamine, mitomycin, nitrosoureas or melphalan were not permitted. At least 3 weeks must have elapsed since prior chemotherapy and patients must have recovered from all reversible toxicities (Table 1). Prior radiation therapy was acceptable if no more than 25% of the bone marrow volume had been irradiated and 4 weeks had elapsed since completion of the therapy. Measurable, evaluable or marker-only relapse was allowed but patients had to have a performance status of ECOG 0, 1 or 2. Patients were required to have adequate haematological, hepatic and renal function with neutrophils $\geq 2.0\times10^9$/l, platelets $\geq 100\times10^9$/l, bilirubin less than 1.5 times the upper limit of normal, liver transaminases ALT/AST less than 2.5 times the upper limit of normal unless due to hepatic metastases, and a calculated creatinine clearance ≥60 ml/min.

Patients were excluded if they were pregnant or lactating or of childbearing age and not taking adequate contraceptive

Table 1 Patient characteristics (*CR* complete response, *PD* progressive disease, *PR* partial response, *SD* stable disease)

Patient no.	Dose level (mg/m^2)	ECOG performance status	Number of prior regimens	Stage at diagnosis	Months from diagnosis	Prior response to platinum	Response	Months to death from initiation
1	135/150	2	1	IV	9	Refractory	SD	9
2	135/150	1	3	IIIC	34	Sensitive	SD	12
3	135/150	0	2	IIIC	4	Refractory	PD	35
4	175/150	0	2	IC	7	Refractory	PR	14
5	175/150	0	3	IIIA	34	Sensitive	PR	13
6	175/150	1	2	IA	18	Refractory	PD	3
7	175/200	1	2	Unknown	13	Resistant	PR	15
8	175/200	0	3	III	23	Sensitive	PR	18
9	175/200	1	3	IIB	65	Sensitive	CR	22
10	175/250	1	2	IIIC	106	Sensitive	PR	9
11	175/250	1	1	IIIC	5	Refractory	SD	7
12	175/250	0	1	IIIC	16	Resistant	SD	12
13	200/200	2	4	IIIC	64	Sensitive	CR	13
14	200/200	2	1	IV	1	Refractory	SD	10
15	200/200	1	2	IIIC	4	Refractory	SD	12
16	200/250	0	1	IIIC	6	Refractory	PD	10
17	200/250	1	3	IIIC	30	Sensitive	PR	28
18	200/250	1	2	IIIC	30	Sensitive	SD	34
19	225/250	2	2	IIB	69	Sensitive	PD	3
20	225/250	1	1	IIC	4	Refractory	PD	6
21	225/250	0	2	IIC	25	Sensitive	PR	10
22	250/250	2	1	IV	4	Refractory	PD	3
23	250/250	0	3	IIIB	104	Sensitive	PR	33
24	250/250	1	1	III	11	Refractory	CR	40
25	250/300	1	1	IIIC	9	Refractory	PR	13
26	250/300	0	2	IV	29	Resistant	PR	28
27	250/300	1	2	IIIC	30	Sensitive	SD	17
28	250/250	0	2	IIIC	5	Refractory	SD	14
29	250/250	1	1	IIIC	18	Sensitive	PR	30
30	250/250	0	2	IV	47	Sensitive	PR	18

precautions. Patients could not have a past or current history of cancer excluding non-melanoma skin cancer and curatively treated carcinoma of the cervix. A past history of a serious medical illness, particularly cardiac disease or pre-existing peripheral neuropathy, or prior reactions to drugs containing Cremophor EL also made patients ineligible for the study. Patients had to be able to swallow and absorb oral medication. All patients were required to give written informed consent. The study was approved by the institutional ethics committee.

Chemotherapy dosing schedule

Prior to each cycle, patients were premedicated with dexamethasone 20 mg orally at 12 h and 6 h before starting the paclitaxel infusion and diphenhydramine 50 mg and ranitidine 50 mg intravenously (i.v.) 30 min before commencing the paclitaxel infusion. Paclitaxel (Anzatax, Fauldings Pharmaceuticals) was given as a 3-h i.v. infusion. Altretamine (Hexalan, Fauldings Pharmaceuticals) was given orally in four divided daily doses orally, starting after the paclitaxel on day 1 of each cycle and was administered for 14 days. The altretamine dose was rounded to the nearest 50 mg. Cycles were repeated every 28 days. Cohorts of three patients were entered at each dose level, commencing at paclitaxel/altretamine 135/150 mg/m^2 and escalating according to the following schedule: 175/150, 175/200, 175/250, 200/200, 200/250, 225/250, 250/250, 250/300 mg/m^2. It was planned to enter a further three patients at a dose level if one patient experienced a dose-limiting toxicity, and if more than one experienced dose-limiting toxicities, three further patients were to be entered at the dose below. If neutropenia was found to be dose-limiting, doses could be escalated with G-CSF support, but this was not required. If patients experienced grade 3 or 4 toxicities in course 1, subsequent courses could be delayed for up to 3 weeks until the toxicity resolved or doses could be reduced back to the dose level used for the previous cohort of patients. No dose escalations were allowed in individual patients.

Response criteria

Standard response criteria were used with a complete response being the disappearance of all tumour for at least 4 weeks, partial response being a reduction of at least 50% in the sum of the products of all diameters of measured lesions or significant reduction in size of an evaluable lesion for at least 4 weeks. Freedom from progression was measured from the commencement of the study to progression. Overall survival was measured from entry onto the study until death. A dose-limiting toxicity was defined as any grade 3 or 4 nonhaematological toxicity, excluding alopecia, or grade 4 haematological toxicity lasting more than 7 days.

Pharmacokinetic analysis

Blood and urine samples were collected during the first and second cycles of treatment. Blood samples were collected pretreatment then at 2, 3, 4, 6, 8, 12, 24 and 48 h after the completion of the infusion. Urine was collected for 48 h. The blood was immediately centrifuged and the plasma stored at –70°C until analysis. Paclitaxel was assayed using an isocratic reversed-phase HPLC method. Plasma samples were prepared by Cyano solid-phase extraction and separation achieved by injection onto a C_8 4 μm 8 mm×10 cm NovaPak column (Waters Associates, Milford, Mass.) using a mobile phase of acetonitrile/methanol/10% phosphoric acid/water (10:60:1:29) at 1.0 ml/min. Detection was by UV absorbance at 227 nm. Paclitaxel concentrations were calculated from the ratio of the peak height of paclitaxel to internal standard (docetaxel) and comparison with a multipoint standard curve over the concentration range 0.04 to 10.0 μg/ml. A previously described three-compartment nonlinear model was fitted to concentration vs time data using Bayesian estimation as implemented by the ADAPT II program [5, 11]. The potential for enhanced myelosuppression was investigated by using the length of time that the plasma paclitaxel concentrations remained above 0.05 μ*M* in the previously published Hill equation, which describes the relationship between single-agent paclitaxel and the percentage reduction in neutrophil count [11]. Where data were available for each course, parameters were assessed for changes between cycle 1 and cycle 2 with the AUC used to determine any change in clearance from course 1 to course 2. Pharmacokinetic and pharmacodynamic relationships between paclitaxel concentrations and myelosuppression were modelled.

Results

A group of 30 patients, with ages ranging from 37 to 73 years (median 55 years) were entered onto the study. They were treated at nine dose levels ranging from paclitaxel 135 mg/m^2 and altretamine 150 mg/m^2 to paclitaxel 250 mg/m^2 and altretamine 300 mg/m^2, the dose at which dose-limiting toxicities occurred. They received between two and nine cycles of treatment (median seven cycles). Only one patient had an elevated CA 125 as the sole evidence of disease.

In the first cycle, the dose-limiting toxicities at the maximum dose of paclitaxel 250 mg/m^2 and altretamine 300 mg/m^2 included WHO grade 3 myalgias, arthralgias or stomach cramps in two of the three patients. Single patients had grade 3 peripheral neuropathy, grade 3 lethargy and grade 3 vomiting while all three at this dose level experienced grade 3 alopecia. Considering all dose levels for the first cycle, 16 patients had grade 3 or 4 neutropenia and it was seen at all paclitaxel dose levels of 175 mg/m^2 and higher with altretamine 150 mg/m^2. Despite this, only one episode of febrile neutropenia occurred and no G-CSF was used (Table 2). Other nonhaematological grade 3 toxicities were dose-related except for alopecia, which was severe in 23 patients. With repeated doses, although dose reduction was allowed, cumulative glove and stocking peripheral neuropathy was clinically recorded at grade 3 in five patients.

Three patients achieved a complete response and 12 patients achieved a partial response for an overall objective response rate of 50%. One of the complete responders was the patient with marker-only relapse, the only patient with evaluable, nonmeasurable disease. All patients were progressing at the time of study entry. Nine had stable disease recorded as their best response and six patients had progressive disease. Responses occurred at all paclitaxel dose levels of 175 mg/m^2 and higher and altretamine 150 mg/m^2. The median freedom from progression was 35 weeks and the median survival was 55 weeks. Serial CA 125 estimations correlated closely with the clinical assessment of response.

In pharmacokinetic and pharmacodynamic analyses, we demonstrated that the previously described nonlinear three-compartment model for single-agent paclitaxel [12] fitted the data from the current trial well despite concomitant altretamine. Furthermore, there was no observed greater reduction in neutrophil count for the

combination as compared to that calculated for paclitaxel alone using the length of time that paclitaxel concentrations remained above 0.05 μ*M*. In addition there were no consistent differences between any pharmacokinetic parameter in cycle 1 as compared to cycle 2 (Table 3). Finally, there was no cumulative myelosuppression between cycle 1 and cycle 2, when myelosuppression was evaluated as percentage reduction in absolute neutrophil count (Fig. 1).

Discussion

The combination of paclitaxel and altretamine showed a 50% response rate for treating ovarian cancer, second-line to cisplatin regimens, but did not result in survival rates that were any different from those expected for the single agents (Table 1). The response rate was 50% in patients selected for a phase I study but where a large

Table 2 Cycle 1, grade 3 or 4 toxicities

Toxicity	Dose level																	
	Grade 3									Grade 4								
	1	2	3	4	4a	5	6	7	8	1	2	3	4	4a	5	6	7	8
Leucopenia	0	1	2	0	1	1	2	3	0	0	0	0	1	0	0	0	0	0
Neutropenia	0	1	2	0	1	2	2	0	0	0	0	1	1	1	0	1	4	0
Nausea/vomiting	1	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0
Pulmonary	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Peripheral neuropathy	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0
Alopecia	1	2	1	2	3	3	3	5	3	0	0	0	0	0	0	0	0	0
Myalgia/arthralgia	0	0	0	1	0	0	0	0	2	0	0	0	0	0	0	0	0	0
Stomach cramps	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Lethargy	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Sciatic pain	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0

Table 3 Paclitaxel pharmacokinetics

Patient no.	Dose level (mg/m^2)	AUC (μ*M*·h)		t > 0.05 μ*M* [a]		Nadir	
		Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2
1	135/150	11.35	12.48	16.64	20.4	2.1	2.67
2	135/150	11.46	11.05	21.52	22.24	1.4	1.2
3	135/150	17.81	13.27	21.29	34.59	1.776	2.164
4	175/150	17.5	15.47	21.45	22.06	0.703	2.4
5	175/150		15.12		23.1	1.4	0.9
6	175/150	15.96	17.2	25.45	27.16	1.924	2.304
7	175/200					0.589	2.97
8	175/200					0.76	0.289
9	175/200	20.04	18.32	23.82	36.08	0.884	1.085
10	175/250	21.47	15.81	28.19	24.0	1.128	1.091
11	175/250	20.54	20.08	31.21	29.39	1.128	0.415
12	175/250	22.54	25.19	29.86	32.59	0.1	1.114
13	200/200		34.47		42.89	0.572	0.237
14	200/200	18.39	22.23	18.71	28.66	1.757	0.678
15	200/200	21.48	26.53	32.41	24.74	0.259	0.543
16	200/250	18.11		27.09		0.553	0.272
17	200/250	21.28		34.72		0.984	0.998
18	200/250	36.45	38.47	37.44	45.05	1.35	0.43
19	225/250	40.49	44.16	42.37	43.51		
20	225/250	29.01		39.95		0.392	0.8
21	225/250	27.01	26.01	29.71	28.1	0.975	0.504
22	250/250	29.66	29.01	25.92	25.48	2.482	2.292
23	250/250	34.66	40.92	57.31	50.98	1.2	0.3
24	250/250	46.76		49.54		0.186	0.1
25	250/300	36.93		37.47		1.85	0.66
26	250/300	39.2	56.03	50.62	38.44	2.137	2.48
27	250/300	51.06	36.98	41.91	40.79	1.01	0.302
28	250/250	33.41	35.00	50.66	30.53	0.3	0.1
29	250/250	59.65		53.08		0.101	0.057
30	250/250	38.41	42.29	44.64	47.5	0.1	0.121

[a]Length of time (min) concentration of paclitaxel > 0.05 μ*M*

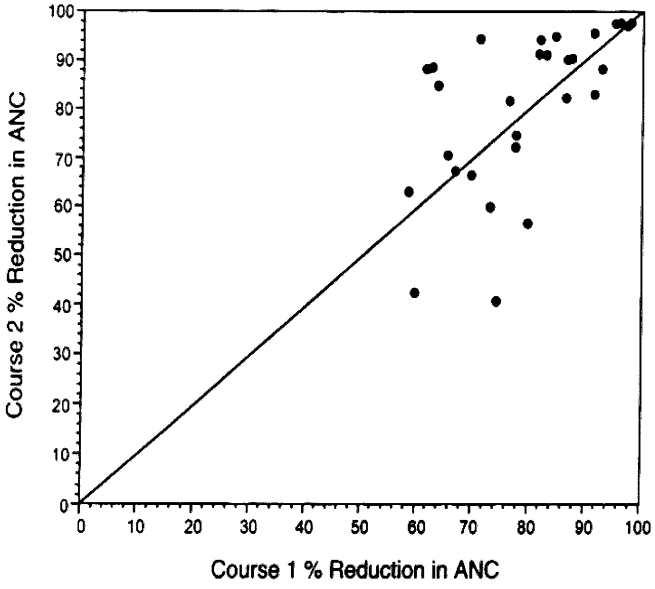

Fig. 1 Comparison of percentage reduction in absolute neutrophil count (ANC) between courses 1 and 2

group of patients were treated in an effective dose range, since additional benefit has not been found in escalating paclitaxel to its maximum tolerated dose [22]. Three of the patients (one complete response and two partial response) were resistant to cisplatin. In a previous Australasian study with a similar population of patients with relapsed ovarian cancer, the response to single-agent paclitaxel was 22% [21]. In platinum-resistant ovarian cancer, as defined as either failing to respond or relapsing within 6 months, response rates of between 7% and 33% have been reported with single-agent paclitaxel [15, 26]. The survival and freedom from progression found in the current study for paclitaxel and altretamine of 55 weeks and 35 weeks, respectively, are similar to those reported for single-agent studies of paclitaxel. In a study by du Bois et al. of paclitaxel as salvage therapy, the progression-free survival was 15 weeks and survival 46 weeks, while in a study by Thigpen et al. the progression-free interval in resistant patients was 16 weeks [6, 27].

The combination of paclitaxel and altretamine was well tolerated and the addition of altretamine did not compromise the dose of paclitaxel that could be administered. Although dose-limiting toxicities occurred when 300 mg/m^2 of altretamine was given with 250 mg/m^2 of paclitaxel, there was no evidence of a therapeutic dose-response relationship, as responses were recorded at all dose levels except for the lowest. Altretamine was a favourable drug to combine with paclitaxel with respect to overlapping toxicities. Hypersensitivity reactions have not been recorded with altretamine [28]. The lack of cumulative marrow suppression reported for paclitaxel was observed clinically and confirmed with pharmacokinetic and pharmacodynamic studies in this trial. Studies of paclitaxel with G-CSF have been performed to test the efficacy of dose escalation [3]. However, neuromuscular toxicities rather than myelosuppression were dose-limiting for the combination used in this trial. The low incidence of febrile neutropenia observed in this trial is consistent with the brief nadir of paclitaxel and again the pharmacokinetic analyses showed that the percentage reduction in absolute neutrophil count was not consistently greater than that expected for single-agent paclitaxel.

Paclitaxel has successfully been incorporated into first-line therapies in combination with cisplatin, and a survival advantage in ovarian cancer has been demonstrated over cisplatin and cyclophosphamide [16]. It is yet to be determined whether concomitant paclitaxel and cisplatin regimens or cisplatin regimens followed by paclitaxel salvage regimens will give the best overall survival result. Paclitaxel and cisplatin sequentially in combination as salvage therapy even after patients' ovarian cancers have failed to respond to single-agent paclitaxel or cisplatin-based therapy has also been reported as active [8]. Other strategies for salvage therapy include high-dose therapy with haematological support, changes in scheduling such as weekly paclitaxel, regimens including intraperitoneal therapy and combinations with a range of other agents including the camptothecin analogues [1, 19].

The marker CA 125 has been studied in many trials to determine its prognostic value and its place in evaluating the response to chemotherapy [4, 15, 23]. In this study CA 125 was measured during the chemotherapy and it was confirmed that the trend in serial concentrations correlated with the course of disease as measured by scans and clinical examination.

The maximum tolerated dose of the combination of paclitaxel and altretamine was 250 mg/m^2 of each drug. However, the lack of evidence of a dose-response relationship for therapeutic response for doses above paclitaxel 175 mg/m^2 and altretamine 150 mg/m^2 and the fact that lower doses are better tolerated, must be considered in planning for phase II trials.

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