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CLINICAL TRIAL REPORT

A phase I-II study of elacytarabine (CP-4055) in the treatment of patients with ovarian cancer resistant or refractory to platinum therapy

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Abstract
Purpose Treatment of patients with recurrent ovarian cancer remains a challenge, and there is a need for new and more effective agents. A phase I-II study was designed to determine the recommended dose (RD) and the anti-tumour effect of a prolonged administration of elacytarabine, the elaidic ester of cytarabine, in patients with refractory/resistant recurrent ovarian cancer.
Experimental design The primary objective of the dose escalation phase I part was to determine the RD for elacytarabine when given twice for five consecutive days in a 4-week schedule, D1-5 and D8(+2)-12(+2) q4w. Three to six patients were to be enrolled at each dose level. The start dose was elacytarabine 75 mg/m^2/day. The phase II part was designed as a two-step study based on response.
Results A total of 28 patients entered the study, 17 patients in the phase I part and 11$^{\#}$ patients in phase II. Three dose levels were tested: 75 mg/m^2/day in 3 patients, 100 mg/m^2/day in 7 + 11$^{\#}$ patients, and 125 mg/m^2/day in 7 patients. Three (17.6%) patients in phase I experienced a dose limiting toxicity (DLT), all at the 125 mg/m^2/day dose level, establishing the lower dose of 100 mg/m^2/day as the RD. The DLTs were neutropenia grade 4 according to the Common Terminology Criteria for Adverse Events (CTCAE) and thrombocytopenia grade 4 (2 patients), and vomiting grade 2 with hospitalisation and hypokalaemia grade 3 (1 patient). The best response was a clinically meaningful stabilization observed in 3 patients. In two of them, the disease stabilization exceeded the previous platinum-free interval (PFI).
Conclusions The RD for elacytarabine was 100 mg/m^2/day, D1-5 and D8-12 q4w. The safety profile was comparable to the safety profiles reported in previous clinical studies with elacytarabine in solid tumours. Despite some longer-lasting disease stabilisations, two of them exceeding the previous progression-free interval, further investigations of elacytarabine in the ovarian cancer indication are not warranted.

Keywords Elacytarabine · CP-4055 · Ovarian cancer · Chemotherapy · Recurrence

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Introduction

The standard initial treatment of patients with advanced ovarian cancer is cytoreductive surgery followed by combination chemotherapy with paclitaxel and carboplatin [1].

Despite the activity of the combination chemotherapy, which gives response rates up to 80%, the majority of patients experience a recurrence and will ultimately die of the disease [2]. Therefore, a large proportion of patients are in need for new treatments. Patients who progress during or relapse within 1 month of first-line platinum therapy are defined as refractory to a platinum re-treatment, while patients responding to primary platinum treatment and relapse within 6 months are defined as platinum resistant. In these patients, pegylated liposomal doxorubicin and topotecan are considered the drugs of choice, and the results remain, however, unsatisfactory with low response rates and short duration of response [3–5]. On the contrary, patients recurring after 6 months are still sensitive to platinum compounds and benefit from re-treatment with a very high response rate. However, platinum resistance emerges and then these patients are usually treated with non-platinum agents, often in a single-agent regimen therapy, with palliative intent [6]. In this setting, agents such as epirubicin [6, 7], topotecan [6, 8], etoposide [6, 9], pegylated liposomal doxorubicin [6, 10], and gemcitabine [6] show very low response rates, ranging from 5 to 15% [11].

Based on these data, treatment of patients with refractory/resistant recurrent ovarian cancer remains a challenge, and there is a need for new and more effective agents.

Cytarabine (ara-C), a well-known anti-metabolite drug, is routinely used in combination with other chemotherapeutics to treat acute myeloid leukaemia [12], acute lymphoblastic leukaemia and non-Hodgkin's lymphoma [13–15]. In solid tumours, the cytotoxicity of ara-C is limited [16–18]. This may be due to a poor penetration into the tumour cells [18], a minimal accumulation in tumour cells [19], a limited intracellular phosphorylation into the active ara-CTP (ara-C triphosphate, the active metabolite), or a rapid deamination and inactivation to ara-U (uracil arabinoside).

Elacytarabine, a fatty acid derivative of ara-C (ara-C-5′-elaidic acid ester), was designed in order to produce an active product that could circumvent some of the mechanisms limiting the activity of ara-C. Unlike ara-C, the cellular uptake of elacytarabine is independent of nucleoside transporters, and elacytarabine is believed to diffuse passively through the cellular membrane or to exploit an alternative internalisation mechanism [20]. Elacytarabine is then hydrolysed intracellularly by esterases to release free ara-C that is subsequently phosphorylated to the active ara-CTP. Interestingly, in contrast to ara-C described solely as a potent inhibitor of DNA synthesis [21], elacytarabine also transiently inhibits RNA synthesis [22]. Moreover, elacytarabine is not a substrate for deoxycytidine deaminase [23].

Elacytarabine has demonstrated cytotoxicity in solid tumour and leukaemia cells in vitro and in vivo [20–23]. Repeated treatment with elacytarabine in human leukaemia and in solid tumour models in vivo enhanced the anti-tumour effect [20]. The data from the first-in-man clinical study in patients with melanoma, ovarian cancer, and lung cancer showed that elacytarabine has a safety profile characterised by transient haematological suppression that was predictable and easily manageable. The RD for further development was 200 mg/m^2/day. The infusion time did not seem to influence the safety profile and anti-tumour activity was limited, possibly due to the infrequent dosing [24, 25].

Based on the above preclinical and clinical data, a phase I-II study with a more frequent schedule of dosing was designed. The phase I part was to determine the RD for elacytarabine given twice for five consecutive days every 4 weeks [D1-5 and D8(+2)-12(+2) q4w], and the phase II part to evaluate anti-tumour effects in patients with platinum refractory or resistant ovarian cancer. The starting dose was set at 75 mg/m^2/day based on the previous clinical experience while considering also a safety margin.

Methods

Patient eligibility

The main inclusion criteria were as follows: histologically or cytologically documented advanced epithelial ovarian cancer (FIGO stages III and IV) measurable with CT and/or MRI, excluding mixed mullerian tumours (MMT) carcinosarcomas; prior chemotherapy regimen(s) for ovarian cancer at least one being a platinum-based therapy. The last dose of prior chemotherapy should have been given at least 6 weeks before the start of elacytarabine treatment; evidence of platinum-resistant or refractory disease (resistant defined as progression according to the Response Evaluation Criteria in Solid Tumors 1.0 (RECIST) [26] or CA-125 within 6 months after completion of PBT (platinum-based therapy)); refractory defined as progression during first-line chemotherapy or progressing within 1 month); ECOG Performance Status 0–1; age 18 years or more. The study was performed in accordance with good clinical practices (GCP) and complied with requirements established by the Declaration of Helsinki. The study protocol was approved by local Ethics Committees. All patients gave their written informed consent.

Experimental design

This was an international multicentre (four centres in Italy and one in Belgium) study planned to be conducted in two successive phases.

The primary objective of the phase I was to determine, based on the emergence of DLTs, the RD for elacytarabine when given D1-5 and D8(+2)-12(+2) q4w. Three to

six patients were to be enrolled at each dose level (DL). The start dose was elacytarabine 75 mg/m^2/day. The IV infusion time was 2 h. Anti-emetic pre-medication was given according to the centre practice. The patients would receive elacytarabine at increasing DLs until ≥2 DLTs were found when dose escalation had to be stopped and the lower dose level was declared the RD for the phase II part.

DLTs were defined during cycle 1 as treatment related in the following situations: non-haematological toxicity CTCAE grade ≥3, excluding alopecia (nausea and vomiting were considered DLTs only after adequate systemic anti-emetic medication had been administered in standard doses according to the study centre routines); neutropenia CTCAE grade 4 (febrile neutropenia); thrombocytopenia CTCAE grade 4, treatment delay on day 8 by >2 days due to treatment-related toxicity; treatment delay >2 weeks of cycle 2 due to treatment-related toxicity.

The primary objective of the phase II part was to evaluate the objective tumour response rate (RR) and had a 2-step design. In the step 1, patients were to be enrolled at the RD until there were a maximum of 16 evaluable patients at this dose level including those from the dose escalation part. An objective RR of 15% was the lowest rate considered to be of such magnitude to justify further investigation in this indication. The rationale behind this choice was that the probability of detecting at least one responder among 16 patients was 93% when the "true" RR is 15%. Consequently, the probability for wrongly rejecting a promising treatment was 7%, which was considered to be on an acceptable level. The aim of step 2 was to confirm the RR, and the plan was to enrol 26 patients.

Patient evaluation

Pre-treatment staging of the patients was performed within 14 days before starting therapy and included a complete medical history and physical examination, blood cell counts and serum chemistries, urinalysis, serum CA-125, ECG, computerised axial tomography, or nuclear magnetic resonance of the abdomen and pelvis.

Response evaluation was performed every 2 cycles in accordance with RECIST; CA-125 was assessed at baseline and at the end of each cycle.

Toxicity was graded according to CTCAE version 3.0.

Time to progression (TTP) was described by the Kaplan–Meier product limit method.

Plasma concentrations of elacytarabine and its metabolites, ara-C and ara-U, were assayed by a tandem mass spectrometric, liquid chromatographic method by York Bioanalytical Solutions (York, England) of samples obtained at days 1 and 11 of the first cycle.

Results

A total of 28 patients entered the study, 17 patients in the phase I part and 11 patients in the phase II part. Three dose levels were tested: 75 (3 patients), 100 (7 + 11 patients), and 125 mg/m^2/day (7 patients). The mean age of the patients was 59.5 years. All patients were Caucasian/white.

All patients were platinum resistant. The patients' ovarian cancer history varied in length from less than 1–12 years (1 patient), the majority with a history of less than 4 years. The number of previous treatment regimens varied between one and nine; most had two to five lines and all included platinum. All patients were in progression at the time of inclusion in the study.

All 28 patients received at least one dose of elacytarabine (See Table 1). The median number of cycles given and completed was two for the two lower dose groups and 1.5 cycles in the 125 mg/m^2/day dose group. The range was between 0.5 and 6 cycles. The mean dose intensity and cumulative doses across the dose groups seems representative of the allocated doses. There was some variation in the mean duration of exposure across the dose groups, the highest being 63.7 days in the 75 mg/m^2/day dose group. A total of 18 patients (64.3%) underwent a dose adjustment. The majority of patients had adverse event (AE) (14 patients in total) as the reason for dose adjustment (See Table 1).

All patients experienced at least one AE (See Table 2). A total of 85.7% of patients had an AE of CTCAE grade 3 or higher and 64.3% patients had an AE of grade 3 or higher which was related to elacytarabine. The most common reported AEs were anaemia, nausea, thrombocytopenia, vomiting, neutropenia, and pyrexia. The majority were of grades 1–2, except for neutropenia with as many grade 3 as the grades 1–2 and thrombocytopenia with the majority of grades 3 and 4. The total per cent of patients who discontinued due to an AE was 21.4. No patients discontinued because of AEs in the 75 mg/m^2/day dose group; 16.7% in the 100 mg/m^2/day dose group and 42.9% in the 125 mg/m^2/day dose group discontinued due to AE.

A total of 3 (17.6%) patients in phase I experienced a DLT, all at the 125 mg/m^2/day, establishing the lower dose level of 100 mg/m^2/day as the RD. The DLTs were neutropenia (grade 4) and thrombocytopenia (grade 4) in 2 patients, vomiting (grade 2) with hospitalisation, and hypokalaemia (CTCAE grade 3) in one patient.

Twenty-two patients (78.6%) who received at least one dose of elacytarabine and had an initial CA-125 level of at least twice the upper limit of normal were included in the efficacy analysis. Twenty-four patients (85.7%) completed at least one cycle of treatment. The majority of patients (78.6%) discontinued elacytarabine treatment due to disease progression; additionally, two patients (7.1%)

Table 1 Patient exposure by dose level

	Total	75 mg/m^2/day	100 mg/m^2/day	125 mg/m^2/day MTD
Elacytarabine dose level				
Number of patients (*N*)	28	3	18	7
Patients with at least one cycle of treatment completed *N* (%)	24 (85.7)	3 (100)	15 (83.3)	6 (85.7)
Number of cycles: entered (*N*)	61	8	35	18
Completed (median)	2.0	2.0	2.0	1.5
Cumulative dose (median mg)	3145.0	2386.0	3145.0	4014.0
Dose intensity (median mg/week)	533.3	368.8	539.1	597.8
Duration of exposure[a] (median days)	40.0	41.0	40.0	43.0
Number of patients having at least one dose adjustment, *N* (%)	18 (64.3)	2 (66.7)	11 (61.1)	5 (71.4)
Reason for adjustment of study dose[b]				
Adverse events (*N*)	14	1	9	4
Other (*N*)	8	2	4	2
Primary reason for discontinuing study treatment[c], *N* (%)				
Disease progression	22 (78.6)	3 (100)	13 (72.2)	6 (85.7)
Adverse event	2 (7.1)	0	1 (5.6)	1 (14.3)
Death	2 (7.1)	0	2 (11.1)	0
Investigator decision	1 (3.6)	0	1 (5.6)	0
Missing	1 (3.6)	0	1 (5.6)	0

[a] Exposure duration is calculated as last dose date—start dose date +1

[b] Patients can have more than one dose adjustment

[c] Percentages are based on the number of patients in the safety population

Table 2 Overall summary of adverse events by dose level

	Total	75 mg/m^2/day	100 mg/m^2/day	125 mg/m^2/day MTD
All enrolled patients				
Elacytarabine dose level				
Number of patients, *N* (%)	28	3	18	7
At least one AE	28 (100)	3 (100)	18 (100)	7 (100)
Severity grades 1–2	28 (100)	3 (100)	18 (100)	7 (100)
Severity grade ≥3	24 (85.7)	2 (66.7)	15 (83.3)	7 (100)
Related to study drug[a]	27 (96.4)	3 (100)	17 (94.4)	7 (100)
Severity grades 1–2	27 (96.4)	3 (100)	17 (94.4)	7 (100)
Severity grade ≥3	18 (64.3)	2 (66.7)	10 (55.6)	6 (85.7)
Serious AE	17 (60.7)	0	11 (61.1)	6 (85.7)
AE leading to study discontinuation	6 (21.4)	0	3 (16.7)	3 (42.9)

[a] Includes AEs possibly, probably, or definitely related to study drug or relationship is unknown

discontinued due to AEs, two patients (7.1%) died while on study, one patient (3.6%) was discontinued by the investigator, and one patient (3.6%) had an unknown reason for discontinuation.

Table 3 presents the response rate according to RECIST criteria. No complete or partial response (CR or PR) was recorded, while a clinically meaningful stabilization was observed in 3 cases at the dose 100 mg/m^2/day. In two of the patients, the stabilization exceeded the previous PFI. The median TTP was 50 days (95% CI 35–52 days). The assessment of response rate to elacytarabine was also recorded using the CA-125 criteria. The assessments were made at baseline, at the end of every cycle, and at study end. No patient treated met the criteria for CA-125 response. Two patients (9.1%), both at the 100 mg/m^2/day level, experienced stable disease.

Table 3 Overall tumour response rate by dose level based on RECIST criteria

Elacytarabine, dose level	Response	*N* (%)
Total, *N* = 28	Complete response (CR)	0
	Partial response (PR)	0
	Stable disease (SD)	8 (42.1)
	Progressive disease (PD)	11 (57.9)
75 mg/m^2/day, *N* = 3	Complete response	0
	Partial response	0
	Stable disease	1 (33.3)
	Progressive disease	2 (66.7)
100 mg/m^2/day, *N* = 18	Complete response	0
	Partial response	0
	Stable disease	3 (30.0)
	Progressive disease	7 (70.0)
125 mg/m^2/day, *N* = 7	Complete response	0
	Partial response	0
	Stable disease	4 (66.7)
	Progressive disease	2 (33.3)

Pharmacokinetic analyses

Blood plasma samples were taken from a total of 22 patients, 3 patients on 75 mg/m^2/day, 18 patients on 100 mg/m^2/day, and 1 patient on 125 mg/m^2/day. The blood for PK analysis was to be taken at a maximum of eight different time points during day 1 (0, 1, 2, 2.5, 3, 4, 5, and 24 h) and day 11(+2) or day 12(+2) in cycle 1. Very few patients had a full set of PK data, and the results were therefore difficult to interpret. A summary of the results is given in Table 4. There seems to be a slight increase in C_{max} for elacytarabine and metabolites when the dose is increased from 75 to 100 mg/m^2/day. Sampling for PK was only taken from one patient at 125 mg/m^2/day, and any comparison is therefore difficult to make. Concentration versus time for all metabolites at the three dose levels is shown in Fig. 1.

Discussion

The percentage of patients diagnosed with metastatic ovarian cancer who relapse after a first line of therapy is about 70. Nevertheless, the period up to first relapse varies widely, from a few months to more than 5 years. Patients with progression during platinum treatment or those having less than 3 months of PFI are defined as refractory or resistant, respectively. These patients have very little chance to respond to second-line chemotherapy; many phase II studies of single agents for these patients show at the most a 5–10% response rate. Thus, the search for more effective second-line treatments with new drugs is an urgent priority in ovarian cancer.

The aims of this phase I-II study in patients with resistant ovarian cancer were to determine the RD for elacytarabine when given in a 4-week schedule (D1-5 and D8-12q4w) and to evaluate the anti-tumour effect of this prolonged administration of elacytarabine.

The majority of the patients were heavily pre-treated with several prior chemotherapy lines. The median number of cycles of elacytarabine received was two, and the range was between 0.5 and 6 cycles. Data indicate that the RD of elacytarabine is 100 mg/m^2/day when given by the study schedule. This dose had a manageable safety profile with reversible and generally easily manageable anaemia, nausea, thrombocytopenia, vomiting, neutropenia, and pyrexia. The DLTs at the 125 mg/m^2/day level were neutropenia

Table 4 Pharmacokinetics; elacytarabine, ara-C and ara-U on 75, 100, and 125 mg/m^2/day dose

Dose, mg/m^2/day	C_{max} Elacytarabine, μM	T_{max}, h	$t_{1/2\alpha}$ Elacytarabine, h	AUC Elacytarabine, μMh	Cl, L/h/m^2	Vss, L/m^2
75	5.41	2.0	0.22	12.10	12.10	13.80
100	12.44	2.0	0.50	37.40	2.93	109.20
125	9.92	1.0	0.42	26.20	9.36	14.40

Dose, mg/m^2/day	C_{max} ara-C, μM	T_{max}, h	$t_{1/2}$ ara-C, h	AUC ara-C, μMh
75	0.55	2.0	1.12	1.24
100	0.75	2.0	0.78	1.76
125	0.97	3.0	0.60	2.62

Dose, mg/m^2/day	C_{max} ara-U, μM	T_{max}, h	$t_{1/2}$ ara-U, h	AUC ara-U, μMh
75	4.82	2.0	6.45	60.92
100	6.41	3.0	22.10	98.20
125	6.34	4.0	6.56	86.52

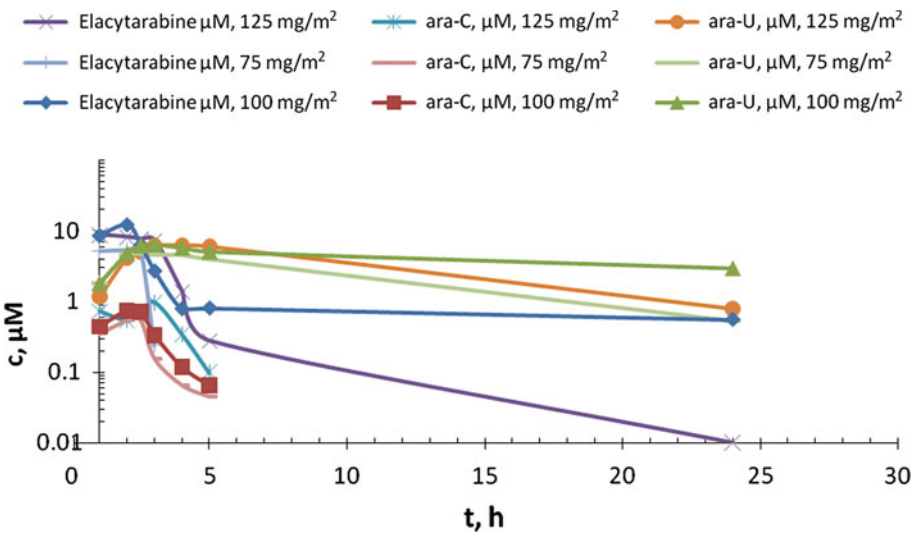

Fig. 1 Concentrations versus time; elacytarabine, ara-C and ara-U

(grade 4) and thrombocytopenia (grade 4) in 2 patients and vomiting (grade 2) with hospitalisation and hypokalaemia (grade 3) in one patients. The majority of the adverse events recorded were of grades 1–2, except for neutropenia with as many grade 3 as the grades 1–2 and thrombocytopenia with the majority of grade 3 or 4. The safety profile was comparable to the safety profiles reported in previous clinical studies with elacytarabine in solid tumours [24].

The phase II part of the clinical study was planned with a two-step design. In step 1, 18 patients, including the phase I patients, were treated at the RD of 100 mg/m^2/day, the best response was stable disease (3 patients), and no patients achieved a PR or CR. Hence, step 2 was not started, and the study was terminated. Our data are in agreement with those reported in a previous study in solid tumours by Dueland et al. [24]; no response was observed in the eight heavily pre-treated patients with ovarian cancer treated with elacytarabine, with two out of eight patients showing stable disease after 2 cycles.

Although there were some long-lasting disease stabilisations, two of which exceeded the previous PFI, further studies of elacytarabine in the ovarian cancer indication are not warranted, also in patients with platinum-sensitive disease, and the clinical development of elacytarabine is currently focussed on haematological malignancies.

Conflict of interest The co-authors Kjell Hernes and Wenche Rasch are employees at the company Clavis Pharma ASA. F. Amant is Sr. Clinical Investigator for the Research Fund-Flanders (FWO). The other co-authors have no conflict of interest.

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