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Phase 1/2 Study of Atrasentan Combined with Pegylated Liposomal Doxorubicin in Platinum-Resistant Recurrent Ovarian Cancer[1]

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Abstract

BACKGROUND: Ovarian cancer overexpresses ET-1, and *in vitro* studies have shown that ET-1 confers resistance to anthracycline-containing chemotherapy. Atrasentan has been developed as an oral selective endothelin-A receptor antagonist. The objective of the study was to investigate the feasibility and toxicity of adding increasing doses of atrasentan (to a maximum of 10 mg/d) and liposomal doxorubicin in patients with progressive ovarian cancer, refractory for platinum and paclitaxel. *METHODS:* Patients with platinum-resistant ovarian cancer were treated with pegylated liposomal doxorubicin (PLD) 50 mg/m^2 on day 1 (and repeated every 4 weeks) in combination with escalating doses of atrasentan once daily. The starting dose was 2.5 mg and escalated in cohorts of three patients from 5 to 10 mg. *RESULTS:* Twenty-six patients (mean age = 60 years, range = 42-74 years) were treated at the three dose levels. Atrasentan could be safely administered in combination at a dose of 10 mg. All patients were evaluable for toxicity, and 19 patients, included in the phase 2 period, were evaluable for response. Adverse events included nausea, vomiting, mucositis, skin toxicity, and rhinitis. Clinical cardiac toxicity, intensively monitored, was not observed, although two patients had a decrease in cardiac ejection fraction. Three objective responses were observed and another six patients had stable disease with a median time to progression of 14 weeks and an overall survival of 13.1 months. *CONCLUSIONS:* The addition of atrasentan to standard dose PLD in platinum-resistant ovarian cancer is feasible with some suggestion of prolonged survival.

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Introduction

Ovarian cancer is the fifth most common cancer among women and also the leading cause of gynecologic cancer–related deaths [1]. Despite advances in cytoreductive surgery and chemotherapy, only slight improvements in long-term survival have been observed. The current standard first-line chemotherapy consists of a platinum compound combined with paclitaxel [2]. With interventions, most patients attain complete clinical remission. Most patients, however, eventually relapse and die of progressive drug-resistant disease [3]. When platinum- and taxane-resistant disease is reached, agents that lack cross-resistance with platinum compounds are required. On the basis of survival and toxicity advantages and a once-a-month administration schedule, pegylated liposomal doxorubicin (PLD) is the first-choice nonplatinum agent for relapsed disease [4,5]. However, the effect on survival is modest, and the development of new treatment modalities to obtain more prolonged survival is therefore highly needed.

The endothelin family of peptides (ET) is identified as contributing to the pathophysiology of cancer. Its role in the modulation of mitogenesis, apoptosis, angiogenesis, tumor invasion, and development of metastases makes it an attractive target for therapy [6]. Elevated levels of ET-1 have been demonstrated in a variety of human tumors, including ovarian cancer and several other endocrine-responsive malignancies including prostate and cervical cancer [7–10].

ET-1, the most important isoform in cancer among the three ETs, is produced by many epithelial cells and binds to its cognate G protein–coupled receptor. There are two receptor subtypes; ET_A and ET_B, the

Abbreviations: PLD, pegylated liposomal doxorubicin

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ET_AR being the one that binds to ET-1 with the highest affinity. The increased expression of both ET-1 and ET_AR in human tumors suggests an autocrine or paracrine mechanism of tumoral growth promotion or maintenance [7].

The ET_AR is therefore an attractive potential target for anticancer therapy. In this light, ABT-627 (atrasentan), an orally bioavailable selective ET_AR antagonist, was developed to interrupt ET_AR signaling. Numerous preclinical studies have confirmed the importance of the ET/ET_AR pathway and its validity as an anticancer target. Successful data of *in vitro* and *in vivo* inhibition of proliferation, angiogenesis, and invasion with single agent therapy were further improved through combination with cytotoxic agents, in particular the taxanes [8,9]. In phase 1 dose-escalation studies, the pharmacokinetics of atrasentan were linear, dose-proportional, and time independent over a 2.5- to 95-mg daily dose range, with steady-state plasma concentrations reaching biologically relevant levels (mean unbound C_{min} for the 10-mg daily dose was eight-fold greater than that of ET_ARKi) [8]. Atrasentan was well tolerated with a safety profile reflective of its vasodilator properties through ET_AR antagonism. The most common adverse effects were attributable to the vasoactive nature, including rhinitis, headache, peripheral edema, and anemia (caused by hemodilution) [9,11–13].

In a randomized, placebo-controlled phase 2 study with atrasentan in prostate cancer prolongation of time to progression (TTP) was seen [14]; however, in the following phase 3 study, atrasentan did not delay disease progression in men with metastatic prostate cancer despite evidence of biologic effects on markers of disease burden [13]. A phase 1/2 study of atrasentan plus paclitaxel-carboplatin in advanced non–small cell lung carcinoma was safe and well tolerated, with no apparent paclitaxel-atrasentan pharmacokinetic interaction. Efficacy and survival were comparable with studies of chemotherapy alone [15]. A phase 2 study with another endothelin A antagonist in melanoma showed benefit in disease stabilization when given as monotherapy [16].

We performed a phase 1/2 trial combining PLD and atrasentan. The primary objectives of the phase 1 period was to establish the safety profile and determine a safe dose for phase 2 testing of atrasentan combined with PLD when administered simultaneously. The primary objective of the phase 2 period of this trial in patients with refractory ovarian carcinoma was to determine the response rate of the combination according to a conventional study design. Secondary end points were progression-free survival (PFS) and overall survival (OS).

Patients and Methods

All patients were assigned in the University Medical Center Utrecht, The Netherlands. Before performance of study-specific procedures, patients gave signed informed consent. The clinical protocol, any protocol amendments, the informed consent, and other necessary documents were reviewed and approved by the institutional review board/independent ethics committee before initiation of the study. Blinding of investigational products or study data was not performed.

Assessments

Adverse events, laboratory profiles, electrocardiograms, left ventricular ejection fraction (LVEF) by multigated acquisition (MUGA) scan, physical examinations, and vital signs were assessed throughout the study. If a single patient in the phase 1 period within a cohort experienced a dose-limiting toxicity (DLT), escalation of any subsequent cohorts did not continue until an additional three patients had been enrolled and dosed at the same dose level, and these three new patients did not exhibit a DLT. Toxicities (both acute and intermediate) were measured each visit using the CTC, version 2.0 (National Cancer Institute, Bethesda, MD). If any of the additional three patients exhibited any grade 3 or 4 toxicity, then this dose was considered the maximum tolerable dose.

Efficacy variables used were response rate using RECIST criteria, OS as measured from study registration, PFS as measured from study registration until progressive disease or death, and response duration as measured from the first moment a response, either complete or partial response, was noted till progression. Duration of stable disease was measured from start of study registration. Tumor measurements were performed before start of treatment and after every two cycles thereafter. Patients were followed until progressive disease.

Eligibility Criteria

All patients were required to have histologically confirmed epithelial ovarian cancer that was resistant to platinum (progression during platinum therapy or in the following 6 months). Further entry criteria were as follows age older than 18 years; World Health Organization performance status 0 to 2; measurable disease according to the RECIST criteria; adequate renal, hepatic, and bone marrow functions; and adequate cardiac function to tolerate treatment and controllable hypertension. The life expectancy had to be at least 3 months.

Exclusion criteria were as follows: another previous or present malignancy other than ovarian cancer, except cured stage I cervical cancer and nonmelanoma skin cancer; radiation therapy less than 4 weeks before start of study treatment; previous chemotherapy less than 3 weeks before start of study treatment; presence of disease with immune etiology that might exacerbate because of study treatment and/or active infection; known positive testing for human immunodeficiency virus; clinical neurologic examination suggesting cerebral metastasis; known history of cardiovascular disability status of New York Heart Association class 2 or higher; and allergy for medication to be used. The LVEF, as determined by MUGA, had to be greater than 50%. An LVEF was determined during screening, within 14 days of the beginning of study treatment. Thereafter, it was determined on weeks 8 and 16 and when clinically indicated or when the patient had reached a withdrawal criterion.

Treatment Regimen

PLD is a doxorubicin HCl encapsulated in stealth liposomes. All patients started treatment with a regimen of PLD in a fixed schedule of 50 mg/m^2 intravenously once every 4 weeks. Prophylactic premedication with 10 mg of dexamethasone, 50 mg of ranitidine, and 2 mg of tavegil was administered. In addition, supportive treatment with standard antiemetic therapy was provided. The PLD dose was reduced by 25% in patients with hematologic or skin toxicity (grade 3 or 4) or mucositis. A phase 1 cohort consisted of a minimum of three and a maximum of six evaluable patients. Atrasentan was administered from day 1 in a dose-escalation manner. The starting dose was 2.5 mg and escalated to 5 mg and later to a maximum of 10 mg when no DLT were observed. On the basis of the single-agent phase 1 study of atrasentan, a dose of 10 mg was chosen as the dose for further development. No escalations beyond this dose were included in the protocol.

Atrasentan was supplied as capsules for oral use by Abbott Laboratories (Chicago, IL) and was taken once daily on all days of the week. The patients entered in the phase 1 period at the maximum tolerable dose level were included in the analysis of the phase 2 end points.

Statistics

Duration of response was measured from the time of initial documented response to the first sign of disease progression. TTP was measured from the date of inclusion until the time progressive disease was documented.

The Gehan two-stage design was applied to the total study cohort, to reject a treatment which has no success observed in the first group of $n = 14$ patients (with $\alpha = 0.05$ and β error < 01.0), with a predetermined level of activity of 20%. The number of patients in the second stage depends on the number of responders observed during the first stage [17].

TTP and OS analyses were performed using the Kaplan-Meier method. For all statistical analyses, SPSS (version 15.0; IBM, Armonk, NY) was used with a defined significance level of $P < .005$.

Results

The phase 1 and 2 studies were performed as a single-center study. Patients were included between April 2003 and march 2007. Mean age of the patients was 59 years (range = 43-74 years). More than half of the patients had received more than one period of platinum therapy before they became platinum-resistant. Only seven patients received only one period of platinum therapy because of recurrent disease within 6 months after the first treatment. All patients had received taxanes as part of their primary treatment. Patient demographics and disease characteristics are presented in Table 1.

Phase 1

Ten patients were included in the phase 1 period of the study. The combination of PLD and atrasentan was well tolerated at all three atrasentan dose levels. In the first cohort, an additional patient was included because one patient withdrew informed consent a few days after the first administration of PLD. No dose-limiting toxicities were assessed during the phase 1 period of the study, and atrasentan 10 mg was selected as the dose for the phase 2 period.

Toxicity in Phase 1. All 10 patients were evaluable for the safety analysis. Hematologic toxicity did not exceed grade 2, but grades 1 and 2 anemia were observed in almost all patients. In one patient, the dose of PLD was reduced because of grade 4 mucositis. Other nonhematologic toxicity included grade 3 to 4 nausea and vomiting observed in 20% of patients in the phase 1 period. No deaths due to toxicity occurred. The complete data on toxicity are presented in Table 2.

Table 1. Patients' Characteristics.

	Phase 1	Phase 2*
No. patients enrolled	10	19
Age, mean (range), years	64 (46-74)	60 (43-74)
Previous chemotherapy lines, *n* (%)		
1	3 (30)	7 (37)
2	5 (50)	9 (47)
3	2 (20)	2 (11)
4	—	1 (5)
Dose (mg)		
2.5	4	
5	3	
10	3	19
Initial FIGO stage		
III	9	13
IV	1	6
World Health Organization performance, *n* (%)		
0	2 (20)	6 (32)
1	5 (50)	11 (58)
Missing	3 (30)	2 (10)
LVEF, mean (range), %	65 (52-74)	64 (57-75)

FIGO indicates International Federation of Gynecology and Obstetrics.
*Including three patients on a 10-mg dose in phase 1.

Clinical response in Phase 1. Patients in the 2.5- and 5-mg cohorts did not show any objective responses; however, stable disease was observed in two patients for a period of 3.7 and 5.5 months, respectively.

Phase 2

Twenty-two patients were included in the phase 2 analysis of the study, including the three patients from the 10-mg cohort of the phase 1 period. Two patients did not meet the entry criteria (screenings failures). Both patients had slightly decreased EF assessments at the start of treatment. A third patient withdrew consent at day 5 of treatment and was lost to follow-up. Nineteen patients were evaluable for assessment of response. Three patients were only evaluable for toxicity because they did not complete two courses of combination therapy; one patient stopped after the first course because of early progression. Two patients stopped treatment with atrasentan 10 mg during the first course because of toxicity.

Toxicity in Phase 2. All 19 patients were evaluable for the safety analysis. As in the phase 1 part, hematologic toxicity did not exceed grade 2, but grades 1 and 2 anemia were observed in almost all patients.

Other nonhematologic toxicity included grade 3 to 4 nausea and vomiting observed in 18% of the patients.

Headache, a known adverse effect of atrasentan, was observed in one patient, and this did not diminish after reducing the dose of atrasentan to 5 mg. After stopping atrasentan the headache resolved completely, and this patient continued on PLD monotherapy. In another patient, the dose of atrasentan was reduced to 5 mg because of congestive rhinitis, and the patient was able to continue with combination treatment. One patient stopped atrasentan after 2 weeks because of increasing ascites and peripheral edema. This patient was found to have progressive metastatic disease. During the phase 2 period of the study, 6 of 19 patients had a 25% dose reduction of PLD, 2 because of mucositis, and 4 because of handfoot syndrome (palmar-plantar erythrodysesthesia [PPE]). In two patients, combination therapy was stopped per protocol due to decreased EF. In the first patient, a grade 2 decrease in EF was observed after two courses of therapy, and tumor evaluation showed progressive disease. In the second patient, the EF decreased from 57% at the start of the study to 49% after four courses of therapy, and she had stable disease on evaluation. Neither of the two patients had clinical signs of congestive heart failure. A third patient with dyspnea and a grade 1 decrease in LVEF was diagnosed with pericardial effusion as the first sign of progressive metastatic disease. No deaths due to toxicity occurred. The complete data on toxicity are presented in Table 3.

Clinical response in Phase 2. In the 19 patients who received atrasentan 10 mg, a complete response was demonstrated in 1 patient and a partial response was seen in 2 patients. An additional six patients showed stable disease. This corresponds to an overall response rate of 16% and demonstrable clinical benefit in 9 (46%) of 19 patients. The three patients with objective response were all heavily pretreated with more than one line of platinum therapy.

CA-125 response in Phase 2. All 19 patients included in the phase 2 study population were evaluable for CA-125 response. Four

Table 2. Adverse Events.

Adverse Event	Phase 1 (n = 10)				Phase 2 (n = 19)*			
	All grades (n)	All grades (%)	Grade 3/4 (n)	Grade 3/4 (%)	All grades (n)	All grades (%)	Grade 3/4 (n)	Grade 3/4 (%)
Hematologic								
Anemia	7	70	1	10	15	88	0	
Leukopenia	4	40	1	10	6	35	0	
Thrombocytopenia	2	20	0		5	29	0	
Nonhematologic								
Nausea and vomiting	8	80	2	20	18	95	3	16
Mucositis	6	60	1	10	12	63	1	5
Anorexia	3	30	0		7	41	0	
Headache	1	10	0		7	41	1	6
Peripheral edema	3	30	0		7	41	0	
Rhinitis	1	10	0		8	47	0	
PPE	0		0		6	35	0	
Metabolic								
Hyponatremia	7	70	1	10	5	29	1	6
Hypokalemia	4	40	1	10	16	94	0	
Hypoalbuminemia	6	60	1	10	7	41	0	
Creatinine	2	20	0		1	6	0	

*Including three patients on a 10-mg dose in phase 1.

patients (21%) had confirmed CA-125 responses, including the three patients with an objective response and one patient with stable disease.

TTP and overall survival in Phase 2. The maximum duration of follow-up was 64 months after the start of study treatment with a median follow-up of 13 months. A median TTP of 14 weeks (range = 0.7-45 weeks) was observed with a median OS of 13.1 months (range = 3.0-63+ months). At the time of the analysis, one patient was still alive (OS = 63 months; Figure W1).

Discussion

Although most patients had previously received multiple lines of platinum-containing chemotherapy, the regimen of PLD and atrasentan was generally well tolerated. Hematologic toxicity was easily managed, and no febrile neutropenia was observed. Dose reduction of PLD was necessary because of handfoot syndrome (PPE) and mucositis. Handfoot syndrome (PPE) of any grade was not observed in the phase 1 part of the study and in 32% of the patients in the phase 2 part, resulting in a total incidence of 23% (6/26 patients), without any grade 3 or 4 events. This incidence in PPE is comparable to other studies with PLD where total incidences of up to 40% are reported with grade 3 and 4 events ranging from 12% to 23% [9,11–13].

Table 3. Response and Response Duration.

Response	
RECIST response (n = 19), n (%)	
CR	1 (5)
PR	2 (11)
SD	6 (32)
PD	10 (52)
CA-125 response (n = 19), n (%)	
Response	4 (21%)
No response	15 (79%)
TTP (n = 22), weeks	
Median (range)	14 (0.7-45)
Overall survival (n = 22), months	
Median (range)	13.1 (3-63+)

PD indicates progressive disease; SD, stable disease.

Cardiac assessments by MUGA scan were done repeatedly (every two cycles), and this intensive monitoring showed a grade 1 and 2 decrease in cardiac EFs in two patients, without any clinical symptoms of heart failure. Rhinitis and headache, well-recognized adverse effects of ET receptor antagonists, were observed in 42% and 37%, respectively, of the patients receiving a daily dose of atrasentan 10 mg. Safety studies performed with atrasentan 10 mg demonstrated incidences between 0% and 100% for headaches and between 0% and 67% for rhinitis. Across all doses of atrasentan, headaches were experienced by more than 60% of patients, and rhinitis was reported for 50% to 100% of the patients. The incidence of headaches and rhinitis was dose-dependent, with the highest incidence seen in the higher-dose cohorts (>60 mg). In the current study, one patient discontinued because of headaches even after lowering the atrasentan dose to 5 mg.

Overall, the addition of atrasentan did not seem to increase the toxicity of PLD. PLD is a well-known, non–cross-resistant drug available for patients with platinum-paclitaxel–resistant ovarian cancer. Gordon et al. [18] showed in a phase 2 study of monotherapy PLD a response rate of 18.3% for platinum- and paclitaxel-refractory patients. In a phase 3 study in 474 patients, in which PLD was compared with topotecan, the response rate for PLD was 12.3% [19]. The response rate observed in this study was 16% and therefore similar to that observed in previous studies with PLD. In the aforementioned phase 3 study, the median TTP was 9.1 weeks, with a median OS of 35 weeks. In our study, median TTP was 14 weeks and median OS was 57 weeks (13.1 months). Although one cannot compare phase 2 and 3 data, there is some suggestion of increased survival in our patient population, possibly due to the addition of atrasentan.

Several other non–cross-resistant agents have demonstrated activity after failure of platinum-paclitaxel regimens, although in some studies, platinum-sensitive and platinum-resistant patients were combined. In phase 2 studies of monotherapy of gemcitabine in patients with advanced ovarian cancer after platinum and paclitaxel, response rates of 13% and 13.9% were observed [20]. In the study of Shapiro et al. [21], 29% of the patients were still considered to be potentially platinum-sensitive, and no data on TTP or OS were given. In the study by Friedlander et al. [22] 16 of 38 patients were still platinum-sensitive. In this study, an OS of 6.7 months was observed. Rose et al. [23] studied prolonged oral etoposide in platinum-resistant

and platinum-sensitive ovarian cancer and observed in the platinum-resistant group a response rate of 26.8% with a PFS of 5.7 months and an OS of 10.8 months. Topotecan is another currently used drug in advanced ovarian cancer. In a phase 2 study by Bookman et al. [24], a group of 139 patients of whom 81% were platinum-resistant received intravenous topotecan as second-line treatment. In the group with platinum-resistant disease, a response rate of 12.4% was observed, with a TTP of 11 weeks and an OS of 45 weeks.

In conclusion, the addition of atrasentan to PLD can be done safely in platinum-pretreated patients with resistant ovarian cancer. The combination has an antitumor activity similar to that reported for other chemotherapeutics in this patient population, although the TTP was relatively long. Further studies with endothelin receptor antagonists in platinum-refractory ovarian cancer patients are therefore warranted.

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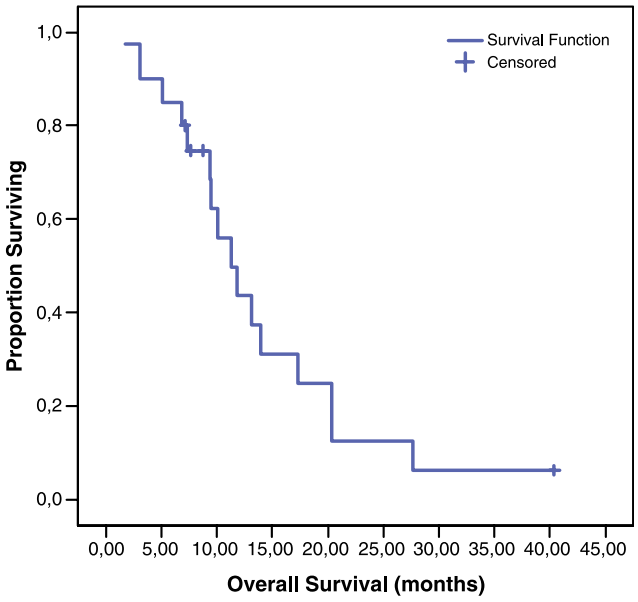

Figure W1. Overall Survival in 19 Eligible Patients.