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A Phase II Evaluation of Elesclomol Sodium and Weekly Paclitaxel in the Treatment of Recurrent or Persistent Platinum-Resistant Ovarian, Fallopian Tube or Primary Peritoneal Cancer: an NRG Oncology/Gynecologic Oncology Group Study

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AUTHOR CONTRIBUTIONS

All authors provided data, were involved in writing, revision, and approved the final manuscript. James Kauderer performed the statistical analyses of this study.

CONFLICT OF INTEREST

Dr. Angeles Secord received clinical trial grants to her institution from Astra Zeneca, Eisai, Bristol Myers Squibb, Incyte, Amgen, Genentech, Endocyte, Exelixis, Boerhinger Ingelheim, Astex Pharmaceuticals Inc., Prima Biomed, Abbie-Vie, Astellas Pharma Inc., Tesaro, PharmaMar and Merck. She also served on the Advisory Board for Janssen, Clovis, Genentech, Astra Zeneca, Astex, Tesaro, Alexion, Boerhinger Ingelheim, Myriad and Arivave.

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All other co-authors have no conflicts of interest to declare.

Abstract

OBJECTIVE: Preclinical data suggest elesclomol increases oxidative stress and enhances sensitivity to cytotoxic agents. The objective of this prospective multicenter phase 2 trial was to estimate the activity of IV elesclomol plus weekly paclitaxel in patients with platinum-resistant recurrent ovarian, tubal or peritoneal cancer through the frequency of objective tumor responses (ORR).

METHODS: Patients with measurable disease, acceptable organ function, performance status ≤2, and one prior platinum containing regimen were eligible. A two-stage design was utilized with a target sample size of 22 and 30 subjects, respectively. Prior Gynecologic Oncology Group studies within the same population involving single agent taxanes showed an ORR of approximately (20%) and served as a historical control for direct comparison. The present study was designed to determine if the regimen had an ORR of ≥40% with 90% power.

RESULTS: Fifty-eight patients were enrolled, of whom 2 received no study treatment and were inevaluable. The median number of cycles was 3 (268 total cycles, range 1-18). The number of patients responding was 11 (19.6%; 90% CI 11.4% to 30.4%) with one complete response. The median progression-free survival and overall survival was 3.6 months and 13.3 months, respectively. The median ORR duration was 9.2 months. Percentages of subjects with grade 3 toxicity included: Neutropenia 9%; anemia 5%; metabolic 5%; nausea 4%; infection 4%; neurologic (mostly neuropathy) 4%; and vascular (mostly thromboembolism) 4%. There were no grade 4 toxicities reported.

CONCLUSIONS: This combination was well tolerated but is unworthy of further investigation based on the proportion responding [ClinicalTrials.gov Identifier: NCT00888615].

Keywords

Ovarian cancer; clinical trial; Elesclomol

INTRODUCTION

The treatment of recurrent epithelial ovarian, primary peritoneal, and fallopian tube cancer (EOC) after front-line platinum based therapy has revolved around the use of single agent chemotherapy when the platinum-free interval (PFI) is less than 6 months. Typically referred to as platinum-resistant disease, liposomal doxorubicin, topotecan and retreatment with a taxane are common. When the PFI is greater than 6 months, doublet chemotherapy is generally recommended for those women with platinum-sensitive recurrences [1].

For four decades, the Gynecologic Oncology Group (GOG) has searched for novel agents and unique combinations in recurrent ovarian cancer. Only four agents have shown overall response rates (ORR) greater than 20% in "platinum-resistant" studies: Docetaxel ORR=22%, weekly paclitaxel ORR=21%, pemetrexed ORR=21%, and nab-paclitaxel ORR=23% [2-5]. Clearly, given these unsatisfactory results, new agents in treating recurrent EOC are sorely needed [6].

Elesclomol (previously known as STA-4783, N-malonyl-bis (N'-methyl-N'-thiobenzoylhydrazide), is a novel, injectable, small molecule. It has been in development as a sodium salt formulation (elesclomol sodium) for single-agent use or for combination use with other anti-cancer drugs. The free acid form of elesclomol is the active ingredient in both elesclomol and elesclomol sodium. While in the bloodstream, elesclomol binds to copper ions (Cu++) present in the serum. Cancer cells efficiently take up this complex, unlike free elesclomol. Once inside the cell, the copper in the complex undergoes a redox reaction whereby Cu++ is reduced to Cu+. This reaction, which is mediated by elesclomol, creates reactive oxygen species (ROS) and oxidative stress in the cell. The anti-cancer activity of elesclomol is attributed to its ability to directly increase this oxidative stress [7]. Cancer cells already have an elevated level of oxidative stress relative to most normal cells. It was proposed/It was hypothesized that the further increase in ROS induced by elesclomol would exceed a critical threshold in cancer cells, enhancing the sensitivity to traditional cytotoxic chemotherapeutic agents and triggering tumor cell death while sparing most normal cells.

Elesclomol exerts its activity by disrupting the metabolism of mitochondria in cancer cells. This activity requires the presence of oxygen that results in energy metabolism being driven primarily through oxidative phosphorylation in mitochondria. Under hypoxic conditions energy metabolism occurs through glycolysis in cytoplasm, rather than in mitochondria. Under hypoxic conditions, often associated with elevated LDH levels, elesclomol's activity is diminished. These observations are consistent with findings in a Phase 3 metastatic melanoma study, where elesclomol activity was found only in subjects with normal baseline LDH levels [8].

In preclinical models, elesclomol has demonstrated synergistic anti-tumor activity with both paclitaxel and docetaxel, as well as single-agent activity [9]. In a Phase 1 study of elesclomol administered in combination with paclitaxel, a 57-year-old woman with refractory ovarian cancer achieved a partial response (PR) by RECIST (Response Evaluation Criteria In Solid Tumors) [10]. This patient was heavily pretreated with carboplatin \paclitaxel, intraperitoneal cisplatin, a sargramostim tumor vaccine, trabectedin, and liposomal doxorubicin. The combination was well tolerated and elesclomol has not been associated with any specific adverse events.

More than 1,500 subjects have been enrolled in elesclomol clinical trials, and more than 600 subjects have received elesclomol either as a single agent, or in combination with paclitaxel or docetaxel. More than 500 subjects were administered the elesclomol/paclitaxel combination at or above a dose of 213 mg/m^2 given weekly for 3 weeks of a 4-week cycle. A Phase 3 study in metastatic melanoma has also been conducted which enrolled 651 subjects, in which 325 subjects received an elesclomol dose of 213 mg/m^2 plus 80 mg/m^2 of paclitaxel given weekly for 3 weeks of a 4-week cycle. This study was unblinded and terminated in February 2009 as a result of the study Data Monitoring Committee confirming an imbalance of deaths in the elesclomol/paclitaxel arm compared with the paclitaxel alone arm. Upon further analysis of the data, the increased risk of death for the elesclomol/paclitaxel combination was confined to the subgroup of subjects with elevated lactose dehydrogenase (LDH), and it was not attributable to any adverse events. The risk of death in

the normal LDH subgroup was not increased in the combination arm. Progression-free survival (PFS) for the overall intent to treat population showed a trend in favor of elesclomol in combination with paclitaxel as compared to paclitaxel alone (3.4 vs. 1.9 months, HR=0.89, p=0.2076). The normal LDH population, 68% of subjects, experienced a significant improvement in median PFS (3.7 vs. 2.1 months, HR=0.76, p=0.0264) and an increase in ORR from to 8.4% vs. 3.9%. In contrast, the high LDH population, 32% of subjects, showed no benefit (1.8 vs. 1.9 months, HR=1.13, p=0.4229; ORR 5.3 vs 5.4%) [8]. Based on the results of this study, the current protocol only enrolled subjects with a baseline LDH level ≤0.8 x institutional upper limit of normal (ULN). Additionally, a stopping rule for elevated LDH (LDH ≥1.2 x ULN) post-baseline was included.

Based on the results of the aforementioned preclinical and clinical studies suggesting favorable tolerability, anti-tumor interactions with the combination of elesclomol and paclitaxel, as well as the sub-results of analysis of the melanoma study, the GOG launched a study of this doublet called Protocol 260 [ClinicalTrials.gov Identifier: NCT00888615].

MATERIALS AND METHODS

Study Design and Objectives

The primary objectives were: 1) to estimate the anti-tumor activity of elesclomol and paclitaxel in patients with persistent or recurrent ovarian, fallopian tube or primary peritoneal cancer through the frequency of objective tumor responses, and 2) to determine the nature and degree of toxicity of elesclomol and paclitaxel in this cohort of patients. The secondary objectives were to estimate the PFS and overall survival (OS).

Study Population

Eligibility requirements included the following: ≥18 years of age; non-pregnant or lactating; platinum-resistant, recurrent or persistent EOC (histologic documentation of the original primary ovarian, tubal or peritoneal tumor was only required via the pathology report); measurable disease as defined by RECIST 1.1 [11]; GOG performance status (PS) of 0, 1,or 2; normal end organ function as demonstrated by platelet count ≥100,000/mcl, absolute neutrophil count ≥1,500/mcl, hemoglobin >9 g/dl, serum creatinine ≤ to1.5 x ULN, bilirubin ≤1.5 x to ULN, AST and ALT ≤3 × ULN, alkaline phosphatase ≤2.5 ULN, neuropathy (sensory and motor) less than or equal to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) grade 1 [12]; and a signed IRB approved informed consent and authorization permitting release of personal health information. Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease and were allowed but not required to have received one additional non-cytotoxic regimen such as hormonal therapy or an antibody. This initial treatment may have included intraperitoneal therapy, high-dose therapy, or consolidation.

Ineligible patients included those with a history of other invasive malignancies except for nonmelanoma skin cancer, prior abdominal or pelvic radiation, or having received two prior chemotherapeutic regimens.

Drug Administration

Paclitaxel 80 mg/m^2 and elesclomol sodium 200 mg/m^2 (equivalent of free elesclomol) were administered as two separate 1 hour IV infusions weekly x 3 with a one-week rest (Cycle = 4 weeks) until disease progression, patient refusal or adverse effects prohibit further therapy. Standard antiemetic and premedication (dexamethasone, antihistamine such as Benadryl and H2 blocker) were highly recommended. A maximum body surface area of 2.0 m^2 was used. Filgrastim, pegfilgrastim or sargramostim were not allowed but patients were allowed erythropoietin, iron supplements, and/or transfusions as clinically indicated for management of anemia.

Dose reductions for paclitaxel were 70 and 60 mg/m^2, respectively. Dose reductions for elesclomol were 160 and 120 mg/m^2, respectively. Dose escalations or re-escalations were not allowed on this study. Dose reductions depended on the observation of febrile neutropenia, grade 4 neutropenia ≥7 days, grade 4 thrombocytopenia, grade 3 (or worse), and metabolic toxicities of grade 2 or worse.

Subsequent cycles of therapy began when the ANC was ≥1500 cells/mm^3 and the platelet count was ≥100,000/mm^3. Therapy was delayed for a maximum of 2 weeks until these values were achieved and toxicity levels were adequately resolved. Patients who failed to recover within the 2-week delay were removed from study. For days 8 and 15 treatment, ANC of ≥1000 cells/mm^3, and platelet count must of ≥75,000 cells/mm^3 were required. If these parameters were not met, doses were omitted (and not made up). For first occurrences, doses were maintained at the time of the next treatment. For second and third occurrences, dose reductions (one level of both agents) occurred at the time of the next treatment.

Grade 2 (or greater) non-hematologic toxicity required reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1. There were no dose modifications for alopecia or fatigue.

LDH levels were measured prior to each cycle. If a patient's LDH levels rose above 1.2x ULN at any time during the study, treatment with elesclomol sodium was discontinued. LDH determination occurred based on at least two consecutive measurements on two days.

Study Assessments

Pre-treatment laboratory tests were obtained before each cycle to assess the safety of administering the next cycle of the regimen including: CBC/differential/platelets, electrolytes, BUN, creatinine, Ca, Mg, PO4, urinalysis, bilirubin, AST, ALT, alkaline phosphatase, and CA125. CBC/differential/platelets were monitored weekly and if grade 4 neutropenia was documented (ANC <500/mcl), then twice per week until resolved to grade 3. CT scan or MRI were used to follow measurable lesions every other cycle (8 weeks) for the first 6 months; then every 3 months thereafter and at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease or rising serum tumor marker levels (e.g. CA125). Measurable lesions examined by physical exam were followed every cycle. The same technique (e.g. CT, MRI or physical exam) to evaluate response at baseline was used throughout the study and best response was assessed using RECIST 1.1 [11]. Duration of response was the period from achievement of an objective

response until disease progression or death. Toxicity was documented each cycle using CTCAE v4.0 [12].

Statistics

The purpose of this study was to identify a potentially efficacious combination involving paclitaxel. Ordinarily, the proportion of patients responding to therapy for classifying a regimen as worthy of further investigation in platinum-resistant recurrent EOC has been 20-25% (typical power for these studies has been 90%). However, because this study investigated a doublet, a true response rate of 40% would warrant further investigation. This study utilized prior phase II studies of single agent taxanes in treating platinum-resistant recurrent EOC as historical controls and utilized a two stage design [13, 14]. We targeted an accrual of 22 eligible and evaluable patients in the first stage of this study, but in practice permitted accrual to range from 18 to 25 patients due to administrative coordination. If there were more than 4 responses out of 18-20, more than 5 responses out of 21-24, or more than 6 responses out of 25 patients (complete or PR) and medical judgment indicated, accrual to the second stage of the trial was to be initiated. Otherwise, the study would have been stopped and the treatment regimen classified as clinically uninteresting. As the study advanced to the second stage, an overall study accrual of 52 eligible and evaluable patients was targeted, but permitted to range from 48 to 55 patients for administrative reasons. If more than 13 of 48, 14 of 49-51, or more than 15 of 52-55 patients responded then the regimen would have been considered worthy for additional investigation.

If the true response rate was 20% (H1), these decision rules limited the average probability of designating the treatment as active to 5% and the average probability of stopping after completing only the first stage of accrual at 71%. On the other hand, if the true response rate had been 40% (H2), then the average probability of correctly classifying the treatment as active would be 90%. These average probabilities are computed from the individual probabilities averaged over all permitted accrual combinations and assuming each combination is equally likely. Limited investigations have indicated that the type I and type II errors are fairly insensitive to variations in the true probability distribution of accrual combinations.

RESULTS

The study opened December of 2010 and completed enrollment in March of 2015. Fifty-eight patients were enrolled, 2 of which received no study treatment, leaving 56 eligible and evaluable subjects. Patient characteristics are outlined in Table 1. The median age was 64 years and the majority of patients was non-Hispanic white, PS 0 and had high-grade serous cancers.

The median number of cycles was 3 (268 total cycles, range 1-18) and the predominate reason for treatment discontinuation was progression of disease. The number of patients responding was 11 (19.6%; 90% CI 11.4% to 30.4%) with one complete response. The median PFS and OS was 3.6 months and 13.3 months, respectively, and shown in Figure 1. The median ORR duration was 9.2 months.

Adverse events are summarized in Table 2. Percentages of subjects with grade 3 toxicity included: Neutropenia 9%; anemia 5%; metabolic 5%; nausea 4%; infection 4%; neurologic (mostly neuropathy) 4%; and vascular (mostly thromboembolism) 4%. There were no grade 4 toxicities reported.

DISCUSSION

Oxidative stress is a phenomenon caused by an imbalance between production and detoxification of ROS leading to the accumulation of ROS in cells and tissues. A precise level of ROS is central to several physiological roles (i.e., cell signaling) and homeostasis. High or low levels of ROS lead to cellular dysfunction and potentially cell death. While we tend to describe oxidative stress as harmful, it can be exploited as a therapeutic approach to treat clinical conditions such as cancer. One such approach involves the candidate agent elesclomol. Elesclomol is a novel, injectable, small molecule that binds copper, enters cancer cells and induces oxidative stress through disrupting mitochondrial metabolism. Hypothetically, this induced increase in ROS exceeds the critical threshold in tumor cells, enhancing the sensitivity to traditional cytotoxic chemotherapeutic agents and triggers cell death while sparing most normal cells.

Although encouraging in preclinical models, the current prospective multicenter phase 2 trial did not show any added clinical benefit as measured by an objective increase in ORR when elesclomol was added to weekly paclitaxel in treating platinum-resistant recurrent EOC.

The pharmacokinetics of elesclomol has been extensively investigated in many studies. The peak and total exposure of elesclomol increases linearly over the dose ranges used in human trials (44 to 438 mg/m^2). Additionally, neither elesclomol or elesclomol sodium metabolism nor paclitaxel exposure is impacted when these agents are administered in combination. Importantly though, elesclomol is rapidly eliminated from plasma with mean half-life values ranging from 0.79 to 1.06 hours and the mean clearance of elesclomol ranges from 28.6 to 38.7 L/h/m^2. This short half-life and rapid elimination, in addition to the tightly regulated ROS levels in cells, likely explains the lack of clinical benefit, as well as the absence of toxicity, attributable to elesclomol in the current study.

As this study is analyzed, we are reminded that preclinical models are poorly predictive of activity in human studies. Many agents appear promising in pre-clinical models but ultimately fail in the clinic. This is probably related to the complex mechanisms of drug resistance, immune surveillance, drug delivery, and the poorly understood tumor microenvironment.

Finally, the ad hoc analysis of the phase III SYMMETRY study (randomized, double-blind trial of elesclomol plus paclitaxel versus paclitaxel alone as treatment for chemotherapy-naive patients with advanced melanoma) that suggested baseline LDH levels could be used as a predictive factor in clinical trials with this combination was probably spurious. Unplanned post hoc analyses can be valuable in generating hypotheses but are fraught with hazard. Clearly, however, biomarkers are key to enhancing the efficiency of drug discovery and improving the therapeutic ratio between efficacy and toxicity.

Although the current study did not yield positive results, and the future study of elesclomol at this dose and schedule cannot be recommended, this clinical trial illustrates that the GOG (now NRG Oncology) can efficiently evaluate new agents in single arm clinical trials. Generally, randomized studies are needed to screen compounds but the GOG's extensive historical database contextualizes single arm trials and allows appropriate interpretation.

It remains controversial if combinations rather than sequential single agents are optimal in treating "chemotherapy-resistant/platinum-resistant" tumors. Combinations help combat drug resistance and create important synergies between and among agents. However, combinations also almost always increase toxicity. Nevertheless, as more active agents are identified in treating recurrent ovarian cancer, it is possible that doublets or even triplets, as in "chemotherapy-sensitive" disease, will provide superior disease control compared to standard single agent therapy. The recent approval and adoption of the bevacizumab combinations as seen in the AURELIA trial is an encouraging example [15]. More rationally designed trials investigating novel agents and the superiority of combinations compared to existing medicines in the "resistant" setting are needed.

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RESEARCH HIGHLIGHTS

- Elesclomol increases reactive oxygen species and enhances the efficacy of chemotherapy in preclinical models
- There is no added clinical benefit to paclitaxel when elesclomol is added to treatment of recurrent ovarian cancer
- The combination of paclitaxel and elesclomol is well tolerated

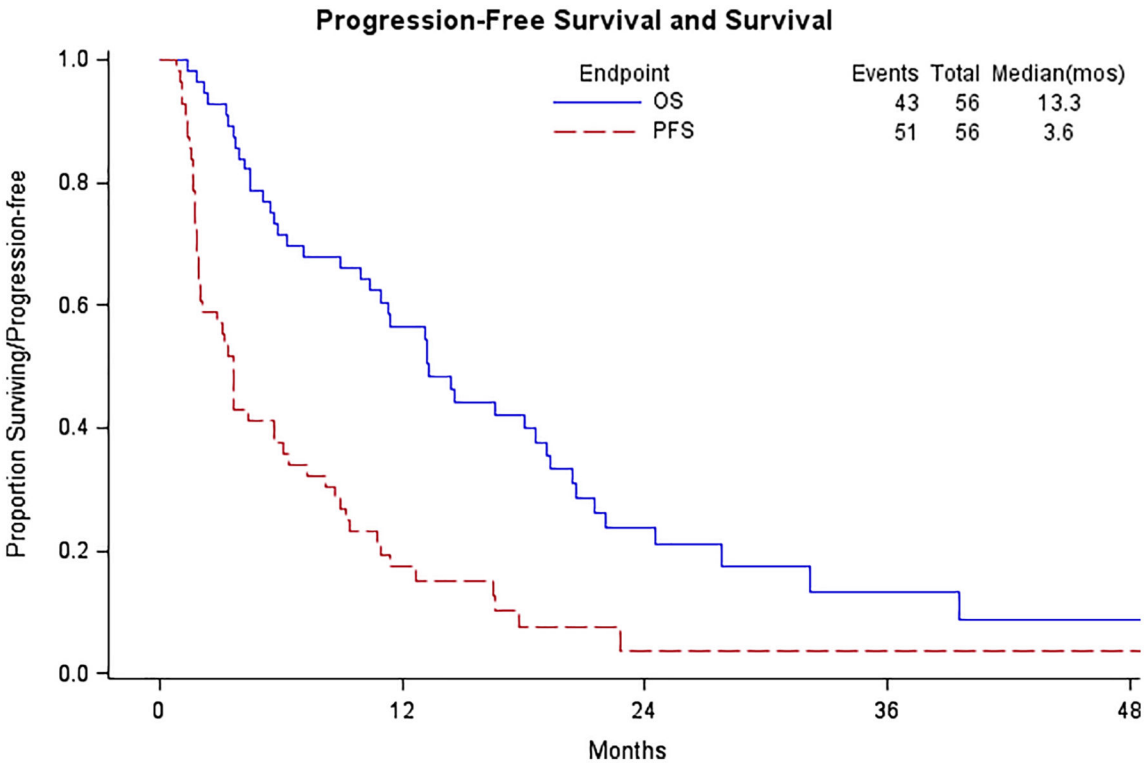

Figure 1:
Progression-Free Survival and Survival

Table 1.

Patient Characteristics (N=56)

Characteristic	Paclitaxel + Elesclomol	
	N	%
Age Group		
40-49	6	10.7
50-59	12	21.4
60-69	22	39.3
70-79	14	25.0
80-89	2	3.6
Ethnicity		
Hispanic or Latino	4	7.1
Non-Hispanic	49	87.5
Unknown/Not specified	3	5.4
Race		
Race unknown	1	1.8
Asian	2	3.6
Black/African American	2	3.6
White	51	91.1
Performance Status		
0	35	62.5
1	18	32.1
2	3	5.4
Cell Type		
Adenocarcinoma, nos	8	14.3
Clear Cell	2	3.6
Endometrioid	2	3.6
Serous	44	78.6
Response		
Partial response	10	17.9
Complete response	1	1.8
Stable disease	19	33.9
Increasing disease	23	41.1
Not evaluable	3	5.4
Number of Courses		
1	6	10.7
2	20	35.7
3	3	5.4
4	8	14.3
5	2	3.6
6	4	7.1
7	1	1.8

Characteristic	Paclitaxel + Elesclomol	
	N	%
8	2	3.6
10	3	5.4
11	2	3.6
12	1	1.8
13	2	3.6
16	1	1.8
18	1	1.8

Table 2:

Adverse Events (N=56)

AE Category	0	1	2	3	4	5	Total
Anemia	4	32	17	3	0	0	56
Dermatologic	25	15	16	0	0	0	56
Fatigue	16	21	18	1	0	0	56
Gastrointestinal	19	23	10	4	0	0	56
Genitourinary/Renal	49	5	2	0	0	0	56
Infection	50	4	2	0	0	0	56
Leukopenia	17	21	14	1	0	0	56
Metabolic	28	18	10	3	0	0	56
Musculoskeletal	45	7	3	1	0	0	56
Nausea	30	19	5	2	0	0	56
Neurosensory	28	16	11	1	0	0	56
Neutropenia	29	14	8	5	0	0	56
Psychiatric	48	4	4	0	0	0	56
Thrombocytopenia	47	7	1	1	0	0	56
Vascular	49	2	3	2	0	0	56
Vomiting	46	7	2	1	0	0	56