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Phase II trial of bryostatin-1 in combination with cisplatin in patients with recurrent or persistent epithelial ovarian cancer: a California cancer consortium study

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Summary

Background—The California Cancer Consortium has performed a Phase II trial of infusional bryostatin, a protein kinase C inhibitor isolated from the marine invertebrate bryozoan, Bugula Neritina, a member of the phylum Ectoprocta, in combination with cisplatin, in patients (pts) with recurrent platinum-sensitive or resistant ovarian cancer (OC).

Methods—Pts received bryostatin 45 mcg/m^2 as a 72 h continuous infusion followed by cisplatin 50 mg/m^2. Cycles were repeated every 3 weeks. Dosages were chosen based on phase I data obtained by the CCC in a population of pts with mixed tumor types.

Results—Eight pts with recurrent or persistent epithelial OC received 23 cycles of treatment. All pts had received previous platinum-based chemotherapy; two pts had received one prior course, five had received two prior courses, and one had received three prior courses of chemotherapy.

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The median age was 64 (range 32–72), and Karnofsky performance status 90 (range 80–100). A median of 3 cycles of chemotherapy were delivered (range: 1–5). The median progression-free and overall survivals were 3 and 8.2 months respectively. Best responses included two partial responses (one in a platinum-resistant pt), three pts with stable disease, and three progressions. All pts experienced Grade 3 or 4 toxicities including severe myalgias/pain/fatigue/asthenia in six pts, and severe nausea/ vomiting/constipation in two other pts. One pt experienced a seizure and liver function tests were elevated in one other.

Conclusions—A modest response rate is observed in pts with recurrent or persistent ovarian cancer treated with the combination of bryostatin and cisplatin. The toxicity profile, however, observed in this pt population (primarily severe myalgias), precludes tolerability and prevents this combination from further investigation at this dose and schedule. It is possible that platinum pre-exposure in OC patients exacerbates observed toxicity. Phase II dosages of investigational agents in OC pts that are determined by phase I trials in pts with other tumor types should be chosen cautiously.

Keywords

Chemomodulation; Chemotherapy; Phase II; Bryostatin; Cisplatin

Introduction

Advanced cancer of the ovary is the fifth most common malignancy in women and the fourth leading cause of cancer-related death [1], ranking first in overall mortality among gynecologic cancers. The standard initial therapeutic approach to advanced ovarian cancer includes debulking surgery followed by chemotherapy [2] which results in a disease-free survival rate of approximately 15–25% in optimally debulked stage 3 patients [3]. The optimal treatment for patients having residual disease or who relapse after initial therapy remains unclear and many chemotherapeutic approaches have been tried with variable results. As of yet, there is no second-line chemotherapeutic regimen that is considered standard for these patients [4].

Bryostatin-1 is a natural product isolated from the marine invertebrate Bryozoan, Bugula Neritina, a member of the phylum Ectoprocta. The drug has a complex macrocyclic lactone structure with a molecular weight of 904 Da. It has both antitumor and immunomodulatory activity. Proposed mechanisms of action are through modulation of protein kinase C (PKC) activity [5-8], enhancement of drug-induced apoptosis, and sensitization of tumor cells to cisplatin (cDDP) [9-12].

Based on these preclinical and clinical data we performed a phase II study of Bryostatin-1 and cisplatin (cDDP) in patients with persistent or recurrent epithelial ovarian carcinoma. Because of the dose and time response effect of Bryostatin-1 in animal models and preliminary data from phase I trials using continuous infusion, we employed a schedule consisting of a 72 h continuous infusion of Bryostatin-1 immediately followed by cDDP. This strategy allowed optimal synergistic effects of the two agents. We report here the results of that study.

Patients and methods

Patient selection

Eight patients with residual or recurrent ovarian cancer were enrolled on this trial. All patients had an estimated survival of at least 2 months. Adequate renal and bone marrow function were defined as creatinine ≤1.5 mg/dl or measured creatinine clearance ≥60 ml/min, platelets ≥150,000/μl, or absolute granulocyte count of ≥500/μl. In addition, the

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bilirubin was required to be ≤1.5 mg/dl, and SGOT was required to be less than twice the institutional upper limit of normal. Patients must have recovered from the toxicity of any previous chemotherapy. All patients gave their voluntary, informed consent and signed an informed consent document approved by the Clinical Protocol Review and Monitoring Committees and the Institutional Review Boards of the City of Hope National Medical Center, University of California, Davis, or the University of Southern California.

Pre-treatment evaluation

Pre-treatment evaluation included a complete history and physical examination, complete blood count with differential, chemistry panel including liver function tests and serum creatinine, urinalysis, 24 h urine creatinine clearance, electrocardiogram, chest x-ray, serum magnesium, and radiographic examinations for tumor measurements with baseline evaluations within 2 weeks prior to the first course of treatment. Serum chemistries and blood counts were repeated weekly. CA-125 levels were repeated prior to each cycle of chemotherapy. Repeat radiographic evaluations were performed after every two cycles of therapy.

Treatment plan

Patients received Bryostatin-1, 15 μg/m^2/d (45 μg/m^2), as a 72-hour infusion immediately followed by a 1-hour infusion of cDDP, 50 mg/m^2 at hour 73.

For subsequent cycles the dose of cisplatin was to be decreased by 25% if the creatinine clearance decreased by 26–50% of baseline, and by 50% for a >50% decrease. Cisplatin was held for a creatinine clearance value of <60 ml/min, for persistent grade 3 or 4 paresthesia or vestibular toxicity, and for hematologic parameters which had not recovered to levels consistent with study eligibility. A 1-week delay was allowed for hematologic recovery or cisplatin was withheld for that cycle. A 20% dose reduction of cisplatin was required for an absolute granulocyte count 500–999 or platelets <50,000 and a 30% dose reduction for AGC <500 or platelets <25,000. Other components of therapy continued as per their adjustment parameters.

Dosage adjustments of Bryostatin-1 were made for hematologic toxicity, liver function abnormalities and myalgias. A 25% dose reduction was made for AGC 500–999 or platelets 25–50,000. It was held for AGC <500 or platelets <25,000. Patients with transaminase elevation must have returned to levels consistent with protocol entry requirements prior to retreatment. For peak transaminases 2–4 times normal a 10% dosage reduction was required for retreatment. For peak levels 3–6, or 6–8 times the upper limit of normal were to have dose reductions of 20% and 30% respectively. For peak levels >8 times normal the Bryostatin-1 was to have been withheld. Dosage adjustments due to myalgia included no dosage escalation for grade 1, a 25% dose reduction for grade 2, a 50% dose reduction for grade 3. Patients experiencing grade 4 myalgias were to have the Bryostatin-1 held. Single agent cisplatin was to be administered in this situation. Gastrointestinal toxicity including constipation, nausea, vomiting and headache required that the symptoms resolve after which patients were retreated without dose adjustments.

Study design and statistical considerations

This multi-centered Phase II study was coordinated by the California Cancer Consortium with the collaboration of the University of Chicago Phase II Consortium. The proposed sample size was 32 evaluable patients using a modification of Simon's Two-Stage minimax Phase II design [13]. The assumptions presumed that a true response rate of 20% would warrant further study, while a true response rate of less than 5% would not warrant any further study of this regimen. In the first stage, accrual of 18 evaluable patients was planned.

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If no responses were seen, then accrual would stop, with the conclusion that the regimen is not promising for further study. If one or more responses were observed in the first 18 evaluable patients, continuation of the trial would be re-evaluated in light of relative numbers of platinum sensitive and platinum refractory patients. If continuation was deemed warranted, an additional 14 evaluable patients would be accrued during the second stage of accrual. Four or more responses out of the 32 patients would be considered evidence that the regimen warranted further study, provided that other factors such as toxicity and survival also appeared to be favorable. Using this design, the probability of correctly declaring that an agent with a true response rate of 20% warranted further study is 0.90 (power), and the probability of falsely declaring that an agent with only a 5% true response rate warrants further study is 0.10 (alpha). The use of the minimax design, as opposed to an optimal design, limits the impact of the first stage monitoring, so that the study may be analyzed as a fixed sample study when judging the impact of platinum sensitivity and other prognostic factors on the overall evidence of efficacy.

The probability of falsely declaring an agent with a 5% response probability as warranting further study is 0.04 (alpha) and the probability of correctly declaring an agent with a 20% response probability as warranting further study is 0.82 (power). With 27 patients (the planned accrual) the true probability of response could be estimated with a maximum standard error equal to 0.10. Durations of survival were to be estimated using the product-limit method of Kaplan and Meier [14].

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria v2.0 [(the NCI Myalgia toxicity grading scale is included in the common toxicity criteria under musculoskeletal/pain) CTEP home page: http://CTEP.info.nih.gov]. Standard Southwest Oncology Group criteria were used [15] to assess response. Although measurable disease was not per se a requirement for protocol entry, an increase of CA-125 alone did not define progression in any circumstance; in patients with a CA-125 increase to >125% of baseline for two successive measurements, a diligent search for clinical or radiologic progression was performed; however, patients without unequivocal evidence of progression were to be treated with a subsequent cycle of therapy. The study was closed early when unexpected severe toxicity (primarily severe myalgias) led to poor accrual and it became apparent that the accrual goals would not be met. Additionally, the 72-hour infusion was poorly tolerated and patient acceptance of this modality was minimal.

Results

Patient characteristics

Eight patients received 23 cycles of cisplatin and Bryostatin-1 chemotherapy (median 3, range 1–5) (Table 1). The patient characteristics are summarized in Table 2. All patients were female having a median age of 64 years (range 32–72). The median Karnofsky performance score was 90% (range 70–100%), and the tumor types included endometrioid carcinoma (1), papillary serous carcinoma (6), and mixed papillary serous/endometrioid carcinoma (1). All patients were Caucasian. All patients had received prior treatment that included various combinations of surgery, hormonal therapy, radiation, and/or chemotherapy [median number of prior chemotherapy regimens: 2 (range 0–5)].

Toxicities of therapy

Primary toxicity—Toxicities of therapy are summarized in Table 3. The primary toxicity that was observed in this study was myalgia that was seen in all patients. Grade 3 or 4 myalgia occurred in 11/23 cycles administered and persisted for approximately 1 week.

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Gastrointestinal toxicity was also observed, including grade 3 constipation occurring in 3/23 cycles. Grade 3 fatigue was noted in three patients.

Other toxicities—Other observed grade 3 or 4 toxicities included one instance each of: lymphopenia, infection without neutropenia, hypophosphatemia, seizure, hypotension, diarrhea, and dehydration. One patient required a red cell transfusion. Two instances of nausea/emesis and self-limited elevations of SGOT and alkaline phosphatase were noted.

Numbers of cycles administered, therapeutic responses, and reasons for treatment discontinuation

Patients received a median of 3 cycles of combination therapy (range 1–5). All receiving more than two cycles required dosage reductions due to toxicity. Therapeutic responses are summarized in Table 1. Two partial responses were observed; one in a platinum-resistant patient who received 3 cycles of therapy before progressing, and a second in a platinum-sensitive patient who received 3 cycles of treatment, stopping due to myalgias. Two patients had stable disease for four cycles and stopped due to disease progression. One patient had stable disease for five cycles but discontinued therapy due to myalgia. Three patients progressed at the time of the first response evaluation following one or two cycles of treatment.

Discussion

Chemotherapeutic strategies for the treatment of advanced ovarian cancer result in a small percentage of patients having long-term disease-free survival, however, patients with residual or recurrent disease following up-front therapy continue to have a poor prognosis. Modern efforts to improve control of ovarian cancer include efforts to identify biological targets and develop agents that specifically affect these targets. Bryostatin-1 is one such agent that was identified as a result of the National Cancer Institute effort to screen natural products. This natural product extracted from the marine bryozoan Bugula neritina, has shown in vitro anti-tumor activity against lung, breast, ovarian, and renal carcinomas, melanoma, sarcoma and lymphoma and leukemia cell lines [5, 9, 16, 17] and in vivo activity against lymphoma and melanoma [18, 19]. The range of tumors that respond to Bryostatin-1 in xenograft models is similar to the in vitro tumor types, suggesting a direct mode of action [6].

The mechanism of action of Bryostatin-1 has been proposed to be modulation of activity of protein kinase C the activity of which has been implicated in influencing cellular sensitivity to anticancer drugs [10, 20]. Activators of PKC have been shown to increase the sensitivity of rat Walker carcinoma by inhibition of PKC, whereas in human ovarian cervical carcinoma cells, cDDP sensitization is associated with activation of PKC [10-12, 20]. The complexity of the PKC signal transduction pathway may contribute to these contradictory results. These serine/ threonine kinases represent a family of more than twelve isoforms which have been described as a) the classical (or conventional) PKC isoforms α, βI, βII, γ; (b) the novel PKC isoforms δ, ε, η, θ, and (c) the atypical PKC isoforms λ and ζ. The various isoforms require the presence of differing co-factors including differently charged phospholipids and/or calcium for optimal activity [21, 22]. PKCs are critical transducers of signals that generate diacylglycerol, one of the major intracellular second messengers in cells and thereby have been shown to transduce the mitogenic signaling pathways of platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). PKCs have thus been shown to play an important role in a variety of cellular events, including cell growth, progression in cell cycle, differentiation, drug efflux, apoptosis, and tumor angiogenesis. Down regulation of PKC-α by bryostatin 1 has been described in in

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vitro models [23]. Additionally modulation of PKC eta (η), a PKC isoform that promotes cell proliferation through the mammalian target of rapamycin (mTOR) pathway, by bryostatin-1 was examined by Pavlick et al. [24] in peripheral blood mononuclear cells of patients with non-hematologic malignancies who were treated with continuous infusions of bryostatin in combination with cisplatin. They observed consistent inhibition of this isoform. These observations suggest multi-phasic effects on signaling pathways potentially contributing to malignant phenotypes, and suggesting that PKC isotypes are appropriate targets for anti-neoplastic therapy.

Bryostatin-1 has been shown to exert biphasic effects on cellular PKC activity [10]. Whereas short-term exposure to Bryostatin leads to PKC activation, chronic exposure results in enzyme degradation and down regulation in several cell types [10]. Significantly, concentrations of Bryostatin-1 that potentiate ara-C related apoptosis are associated with substantial PKC down-regulation, which is consistent with previous evidence that PKC activity opposes apoptosis [8]. Furthermore Bryostatin-1 demonstrates a biphasic concentration-dependent effect on cisplatin sensitization, which has been also observed in other cell systems, although the mechanism of this complex regulation is poorly understood [8]. Data from Basu et al. demonstrates that the cellular sensitization to cDDP is associated with an increase in cellular platinum content [10] the magnitude of which is sufficient to explain the elevated sensitivity of the tumor cells to cDDP treatment. The enhanced sensitization to cDDP by Bryostatin-1 is dependent on concentration, time of exposure, and the cell type [10]. These results taken together show that Bryostatin-1 effectively sensitizes tumor cells to cisplatin therapy, suggesting that Bryostatin-1 can be used as a chemo-modulator of cDDP to increase the therapeutic potential.

For chemomodulation to be a clinically useful therapeutic strategy, it must be possible to deliver effective concentrations of the drug resistance modifying agent at an acceptable level of toxicity. While Bryostatin-1 has minimal end-organ toxicity, its severe incidence of myalgias shown in this study limits its ability to be delivered in effective doses. Virtually all patients developed severe pain that required narcotics for control. The appearance of myalgias was the reason for treatment discontinuation in two patients despite partial responses.

The mechanism of myalgia caused by this agent is unclear. It had been proposed that the mechanism of the myalgias was due to direct effects on muscle metabolism. Hickman et al. [25] reported experiments that suggested impaired mitochondrial (oxidative) energy production, possibly due to a direct effect on the mitochondria or secondary to reduced blood flow. They recommended studies utilizing concomitant vasodilators. Thompson et al. [26] subsequently reported a trial in melanoma patients that utilized nifedipine to attempt to abrogate potential vasoconstrive effects. In the presence of nifedipine, two of the effects of bryostatin, impaired reoxygenation rate and reduced proton efflux, were abolished, but the impaired mitochondrial activity remained. Nifedipine counteracted the vasoconstrictive effect of bryostatin 1, however, because nifedipine itself had an unexpected effect on mitochondrial metabolism, it was not possible to assess whether nifedipine modified the effect of bryostatin on this variable. There was no additive detrimental effect of bryostatin on mitochondrial metabolism and nifedipine did not reduce the clinical toxicity of bryostatin 1, which cannot therefore be due to vasoconstriction.

Our dosing decisions in this study were made based on a phase I study completed in the California Cancer Consortium in patients with mixed tumors, primarily gastrointestinal tumors [27]. These doses were tolerable in this group of patients, with only minor myalgias observed at the maximally-tolerated doses. Pavlick et al. observed tolerable toxcities with similar total doses of bryostatin and cisplatin when utilizing 24 h infusions of bryostatin, but

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dose-limiting myalgias with shorter duration infusions in their phase I study [24]. In our study of ovarian cancer patients, the severe myalgias experienced at these doses precluded further patient accrual or treatment on this study. These observations suggest the hypothesis that platinum pre-treated patients may have a different toxicity profile when phase II studies are performed, and PhaseI/II ovarian cancer specific studies should be considered, rather than adopting doses determined in broad phase I studies. This would lead to patient-specific dosing rather than assuming that all patients will tolerate chemotherapy levels regardless of previous treatment cycles.

In conclusion, the combination of Bryostatin-1 and cisplatin is active in a subset of patients with recurrent ovarian cancer. The toxicity profile, however, observed in this patient population (primarily severe myalgias), precludes tolerability and prevents this combination from further investigation at this dose and schedule. It is possible that platinum pre-exposure in OC patients exacerbates observed toxicity. Phase II dosages of investigational agents in OC pts that are determined by phase I trials in pts with other tumor types should be chosen cautiously.

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Table 1

Number of courses completed, best response, and reason for stopping therapy

# of Cycles	# of patients	Best response	Reason for stopping therapy
1	2	Progression (2)	Progression
2	1	Progression	Progression
3	2	PR (2)	Toxicity
4	2	SD (2)	Progression
5	1	SD	Toxicity

PR partial response; *SD* stable disease

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Table 2

Patient characteristics

Gender	
Female	8
Race	
Caucasian	8
Karnofsky	
100	1
90	4
80	3
Histologic Types	
Endometrioid	1
Papillary Serous	6
Mixed Endometrioid/Papillary Serous	1
Age in years (median (range))	64 (32–72)

NOS not otherwise specified

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Table 3

Grade 3 and 4 toxicities (No. of episodes)

Total no. of cycles	**23**
Hematologic	
Lymphopenia	1
Red Cell Transfusion	1
Infection without Neutropenia	1
Myalgia	11
Hypophosphatemia	1
Neurological	
Seizure	1
Hypotension	
Requiring therapy (grade 3)	1
Gastrointestinal	
Diarrhea	1
Constipation	3
SGOT/Alkaline Phosphatase Elevation	2
Nausea/Emesis	2
Dehydration	1
Fatigue	3