Phase I Trial of Paclitaxel Plus Megestrol Acetate in Patients with Paclitaxel-refractory Ovarian Cancer

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ABSTRACT

Increased expression of P-glycoprotein has been proposed as one important mechanism for inherent or acquired drug resistance of malignant disease to cytotoxic chemotherapy. In experimental systems, hormonal agents, including megestrol acetate (MA), have been shown to be capable of reversing P-glycoprotein-mediated multidrug resistance to natural products, including paclitaxel. Because paclitaxel is one of the most active cytotoxic agents in ovarian cancer (OC), we sought to determine whether retreating patients with well-defined paclitaxel-resistant OC with a combination of paclitaxel and MA would result in clinically relevant reversal of that resistant state.

In this Phase I trial, 44 patients with OC or primary peritoneal carcinoma received paclitaxel (135–175 mg/m² over 3 h) plus an oral loading dose (800–9600 mg over 24 h) and subsequent maintenance dose (800–3200 mg/day × 3 days) of micronized MA. Both the loading dose and maintenance therapy were delivered in four equal daily doses. Therapy was repeated every 21 days, assuming recovery from the toxicity of the prior course. There were no intrapatient dose escalations.

The major toxicity of the regimen was peripheral neuropathy (32% of patients; 11% grade 2–3), although four individuals developed major venous blood clots and one suffered a stroke. Four patients exhibited biological evidence of antineoplastic effects, although only one patient experienced improvement in clinically relevant symptoms. Al though pharmacokineti studies were not performed as a component of this study, prior evaluation of MA pharma colokinetics and in vitro data examining the concentrations of the agent required to reverse P-glycoprotein-mediated paclitaxel resistance suggest that the majority of our patient population achieved levels of MA theoretically capable of producing this desired effect.

We conclude that the level of activity and toxicity pattern observed in this trial, associated with the combination of paclitaxel and MA, does not provide strong support for further exploration of the regimen as a treatment strategy to overcome paclitaxel resistance in OC.

INTRODUCTION

Despite the high objective response rate of OC to platinum/paclitaxel-containing chemotherapy, the majority of women with advanced disease at presentation will ultimately recur and be found to have developed resistant disease (1). Thus, the development of effective means to overcome this resistance has become a high priority among OC investigators.

One proposed mechanism for the establishment of resistance is through increased expression of P-glycoprotein, a transmembrane energy-dependent drug efflux pump that is responsible for the transport of certain substances (including natural products like paclitaxel) from inside to outside the cell (2, 3). This enhanced expression of P-glycoprotein has been suggested to be responsible for development of multidrug resistance in a number of human cancers.

Over the past decade, investigators have devoted considerable laboratory and clinical research efforts to develop successful strategies to inhibit this drug efflux pump and reverse resistance to cytotoxic agents including doxorubicin, vincristine, and paclitaxel (2–4). Although laboratory studies have been relatively successful in documenting the ability to inhibit the multidrug resistance phenotype in vitro, translating this work into the clinic has been problematic. A particularly difficult problem has been finding a pharmacological agent capable of inhibiting the efflux pump without itself causing significant side effects (5, 6).

In experimental systems, hormonal agents, including progestosterone and MA, have been demonstrated to be capable of reversing P-glycoprotein mediated multidrug resistance to natural product cytotoxic chemotherapeutic drugs at concentrations of the modulating agents achievable in vivo in humans (7–12). To explore the potential for this therapeutic strategy to reverse paclitaxel resistance in patients with advanced OC, we conducted a trial of MA in combination with this cytotoxic drug in women with well-defined paclitaxel-resistant disease. We report here the results of this Phase I study.

MATERIALS AND METHODS

Patient Eligibility. To be eligible for entry into this trial, patients had to meet the following criteria: (a) histologically

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2 The abbreviations used are: OC, ovarian cancer; MA, megestrol acetate.
confirmed diagnosis of ovarian cancer, fallopian tube cancer, or primary carcinoma of the peritoneum; (b) patients must have received prior therapy with paclitaxel as a component of initial or second-line therapy for the disease) and either failed to respond or, if a response was observed and the cancer recurred >3 months after the completion of this therapy, the individual was required to be retreated with paclitaxel to document resistance; (c) Gynecological Oncology Group performance status of 0–2; (d) life expectancy ≥2 months; (e) laboratory parameters: WBC ≥2,500/mm$^3$, neutrophils ≥1,500/mm$^3$, platelets ≥100,000/mm$^3$, serum creatinine ≤2 mg%, serum bilirubin ≤1.5 mg%; serum aspartate aminotransferase/alanine aminotransferase ≤2 times normal; (f) age ≥18 years of age; and (g) sign an informed consent document stating they understood the investigational nature of the proposed treatment program.

Individuals with serious medical conditions, including heart failure, poorly controlled hypertension, history of serious thromboembolic disease, poorly controlled diabetes mellitus, evidence of severe peripheral neuropathy, history of cirrhosis or severe hepatic dysfunction, or history of allergy to Cremophor were not eligible for entry into this trial.

Measurable or evaluable disease was not required, but all efforts were made to assess patients for evidence of response to this therapeutic program, including monitoring changes in the serum level of the CA-125 antigen.

**Treatment Plan.** The basic therapeutic concept was to administer MA prior to paclitaxel to achieve adequate serum concentrations of the hormone during delivery of the cytotoxic agent and for at least an additional 72-h period after the completion of the chemotherapy infusion. Because MA is an oral preparation, it was felt necessary to give a loading dose the day prior to delivery of paclitaxel to achieve adequate steady-state concentrations in the systemic circulation at the time of delivery of the cytotoxic agent.

The trial was designed as a Phase I dose escalation study. The initial three patients on the trial were treated with paclitaxel at a dose of 135 mg/m$^2$ (administered over 3 h), with all subsequent patients treated with the agent at a dose of 175 mg/m$^2$ (delivered over 3 h). The dose escalation schema for MA is shown in Table 1.

Three patients were planned to be treated at each dose level before further dose escalation was permitted. This conservative MA dose escalation schedule (Table 1) was used because of concerns that paclitaxel-associated toxicity might be markedly enhanced secondary to inhibition of the P-glycoprotein pump. For example, data published previously had revealed increased bone marrow suppression when doxorubicin was administered in combination with i.v. progesterone (13).

Both the initial loading dose of MA and maintenance therapy were delivered in four equally divided doses in a 24-h period. There was no intrapatient dose escalation of the MA in the trial.

MA (Megace Oral Suspension) was administered as an oral suspension containing 40 mg of micronized MA per milliliter. Patients were provided a bottle of the oral suspension with detailed instructions describing exactly how the medication should be taken both before and after each treatment with paclitaxel.

Paclitaxel was delivered as a 3-h infusion ~24 h after the oral MA was initiated. Treatment was to be repeated on a 21-day schedule in responding patients or those with stable disease, assuming recovering at that point from any treatment-related toxic effects. Standard prophylaxis for paclitaxel-associated hypersensitivity reactions was used with each treatment course. If the required baseline hematological parameters were not satisfied at the time of scheduled retreatment, further therapy was to be withheld until necessary bone marrow recovery. An individual patient experiencing a mandated delay in receiving subsequent courses of therapy would have treatment continued with a paclitaxel dose reduction to 135 mg/m$^2$.

**Monitoring for Response to the Treatment Program.** Standard response criteria for measurable disease (by physical examination or radiographic evaluation) were used in this trial. In addition, patients whose disease was only evaluable by changes in the serum CA-125 antigen level were followed for evidence of response by this tumor marker. For this purpose, two “CA-125 response categories” were considered (14), including a ≥50 and ≥90% reduction in the level of the antigen, compared with a baseline determination prior to the initiation of this experimental treatment program. The reduction in CA-125 levels had to persist for ≥2 months for a patient to be considered to have achieved a response by these CA-125 criteria.

In this trial it was believed appropriate to evaluate CA-125 as an indication of response, because a major aim of the study was to determine whether there was evidence of sufficient biological activity to warrant further clinical investigation. There was no intent to compare response by CA-125 to changes in measurable masses, either in this study or in other published trials.

**RESULTS**

**Patient Characteristics.** A total of 44 patients (median age, 59 years; range, 33–80 years) were entered into this Phase I trial. Additional characteristics of the treated population are outlined in Table 2.

**Toxicity.** In general, this two-drug treatment program was reasonably well tolerated. The most common side effect was peripheral neuropathy (32% incidence; Table 3). Bone marrow toxicity was mild, with only one patient experiencing grade 3 neutropenia and two individuals developing grade 3 anemia. There were no grade 4 toxicities encountered in this

### Table 1 MA dose escalation schema

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<th>Level</th>
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<th>Daily maintenance dose</th>
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trial. Four patients experienced noticeable fluid retention, most likely secondary to the use of high-dose MA. Two patients developed radiographically confirmed pulmonary emboli while being treated with the combination regimen of paclitaxel and MA. Three additional patients experienced major vascular events (one patient each a portal vein thrombosis, superior mesenteric vein thrombosis, or stroke). We were unable to correlate the development of these events with particular MA dose levels used in this Phase I trial.

**Antineoplastic Activity.** Of the 44 patients entered into this Phase I-II trial, 4 exhibited evidence of an antineoplastic effect. This included a decline of the CA-125 antigen level of >50% in 2 patients (duration, 5 and 4 months), >90% in 1 patient (duration, 5 months), and a disappearance of malignant ascites (previously requiring regular paracentesis; duration, 5 months). Of these 4 individuals demonstrating evidence of a biological response to the treatment program, 2 were among the 25 patients who received a maintenance dose of MA of ≥1600 mg/day. No patient achieved an objective response (partial response or complete response) of measurable disease.

**DISCUSSION**

In this Phase I trial, we have shown that it is possible to administer oral MA in combination with paclitaxel with an overall acceptable toxicity profile. Bone marrow suppression was limited, and hypersensitivity reactions in this population treated previously with paclitaxel were not observed.

Although several patients demonstrated evidence of hypercoagulability, it is unknown whether these events were a direct result of the 4 days of treatment with high doses of the hormonal agent every 3 weeks, was related to the natural history of disease in a group of individuals with advanced cancer (e.g., reduced mobility, cancer-induced hypercoagulable state) or a combination of these factors.

We also observed patients who developed worsening of a preexisting platinum or paclitaxel-associated peripheral neuropathy after initiation of therapy on this regimen. Although the neuropathy in these individuals may have worsened independently of the specific subsequent treatment program used, it is reasonable to speculate that the combination of MA with paclitaxel potentiates this toxicity, possibly because of an enhanced concentration of the cytotoxic agent within the peripheral nerves.

Although we did not perform formal pharmacokinetic studies of systemic blood levels of MA achieved in this trial, for several reasons it is reasonable to suggest we achieved serum concentrations that had the potential to modulate the P-glycoprotein efflux pump:

(a) Prior pharmacokinetic studies examining the bioavailability of the micronized megestrol material have demonstrated serum levels of ~0.5 µM associated with a daily dose of 160 mg (15) and 2 µM observed with a daily dose of 800 mg (11). With the 24-h loading dose and maintenance strategy used in this trial, serum levels were likely to equal or exceed these concentrations.

(b) Preclinical *in vitro* models have demonstrated concentrations of MA or progesterone of the order of 2-5 µM are capable of at least partially reversing the resistance of susceptible cancer cells to several natural cytotoxic agents, including paclitaxel (9, 11, 12).

However, definitive conclusions regarding *in vivo* interactions between paclitaxel and MA will require direct laboratory correlation, which was not obtained in this study. Unfortunately, while we noted objective evidence of a biological effect of this regimen and limited data suggesting possible clinical benefit, the modest level of activity observed was actually not consistent with responses being secondary to an effect of the hormonal agent itself in this patient population (16). In addition, although paclitaxel was easily administered in the outpatient setting and the MA is an oral medication that can be administered at home, the treatment regimen used in this trial requiring a large oral loading dose and oral maintenance therapy for several days is complex and inconvenient for patients.

Thus, our data, both the observed worrisome toxicity profile and limited evidence of antineoplastic activity, do not provide strong support for further clinical exploration of the combination of MA and paclitaxel as a therapeutic strategy to overcome paclitaxel resistance in OC. A role for the inhibition of P-glycoprotein activity in enhancing the effectiveness of the treatment of solid tumors remains to be defined (17).

**REFERENCES**

1. McGuire, W. P., Hoskins, W. J., Brady, M. F., Kucera, P. R., Partridge, E. E., Look, K. Y., Clarke-Pearson, D. L., and Davidson, M. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin...


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