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Phase I/II study of weekly paclitaxel plus carboplatin and gemcitabine as first-line treatment of advanced-stage ovarian cancer: Pathologic complete response and longitudinal assessment of impact on cognitive functioning ☆

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Abstract

Background. To determine the pathologic complete response rate of advanced ovarian cancer to weekly paclitaxel plus gemcitabine and carboplatin with filgrastim, and assess the longitudinal impact of this regimen on quality-of-life and cognitive functioning.

Methods. Fourteen patients with advanced ovarian, peritoneal, or fallopian tube cancer were treated in the phase I portion of the study. Initial doses were paclitaxel: 60 mg/m^2 days 1, 8, and 15; gemcitabine: 800 mg/m^2 days 1 and 8; and carboplatin: area under the curve (AUC) 5 day 1, every 21 days for 6 cycles with filgrastim. Twenty-seven patients were treated at the phase II dose. Pathologic response was assessed by second-look laparoscopy in patients with complete response. Patients completed longitudinal assessments of quality-of-life and cognitive functioning.

Results. Maximally tolerated doses were paclitaxel: 80 mg/m^2 days 1 and 8; gemcitabine: 800 mg/m^2 days 1 and 8; and carboplatin: AUC 5 day 1, every 21 days. Forty-eight percent of patients (13/27) experienced at least 1 grade 3 nonhematologic toxicity. Fifty percent (95% confidence interval [CI], 31–69%) of assessable patients achieved pathologic complete response. Median progression-free survival was 27.3 months (95% CI, 17.7 months to not reached), and overall survival 43.6 months (95% CI, 42 months to not reached). Cognitive functioning did not decline during or after chemotherapy. More highly educated women reported a perceived decline in concentration and memory while on chemotherapy. Quality-of-life scores were maintained during therapy.

Conclusions. Fifty percent of patients with advanced-stage ovarian cancer achieved pathologic complete response to weekly paclitaxel plus gemcitabine and carboplatin. Cognitive functioning did not decline by objective measures, although highly educated women reported subjective impairment.

Keywords: Ovarian; Neoplasms; First-line treatment; Chemotherapy; Advanced disease; Paclitaxel; Gemcitabine; Carboplatin; Quality-of-life; Cognitive functioning

Introduction

An estimated 22,220 cases of ovarian cancer will be diagnosed in the US in 2005, and there will be over 16,000 deaths [1]. Standard treatment for women with advanced ovarian cancer includes cytoreductive surgery followed by taxane plus platinum chemotherapy [2]. Paclitaxel plus cisplatin treatment increased overall survival from 24 months to 38

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months compared to cyclophosphamide plus cisplatin [3], and paclitaxel plus carboplatin achieves similar survival rates with less toxicity compared to paclitaxel plus cisplatin [4,5]. Pathologic complete responses may be achieved in 26–50% of patients treated with taxane-platinum therapy [3,4]. Although 60–80% of women will respond to front-line therapy, over 70% will relapse. Long-term survival among women with advanced-stage ovarian cancer remains approximately 30%.

One strategy to improve ovarian cancer outcomes is to optimize front-line therapy by altering drug schedules and/or adding noncross-resistant agents. A potential limitation to an additional cytotoxic in the front-line setting is myelosuppression [6], which might limit delivery of adequate doses of paclitaxel plus carboplatin. Paclitaxel given weekly can maintain dose intensity with acceptable levels of myelosuppression, making this an attractive dosing schedule for combination with carboplatin plus a third cytotoxic.

A number of nonplatinum agents, including gemcitabine [7], topotecan [8], liposomal doxorubicin [9], and oral etoposide [10], have activity in platinum-sensitive and platinum-resistant ovarian cancer. Gemcitabine is synergistic with cisplatin in preclinical models [11]. In one study, gemcitabine was combined with carboplatin plus paclitaxel given once every 3 weeks. Among 20 patients with measurable disease and four with elevated CA-125 only, clinical response was observed in all patients (complete in 14 patients, partial in 10) [12].

Given the promising clinical response rates to gemcitabine, paclitaxel, plus carboplatin, we aimed to determine the maximally tolerated dosing for this triplet with paclitaxel delivered weekly. Then, in the phase II study, we sought to determine the pathologic complete response rate. Our hypothesis was that the weekly paclitaxel–carboplatin–gemcitabine triplet would achieve a pathologic complete response rate higher than that reported with the paclitaxel–carboplatin doublet.

We also sought to determine the impact of this regimen on quality-of-life and cognitive functioning in this potentially curable population through prospective, longitudinal assessments. Cognitive dysfunction has been reported among women who have received chemotherapy [13–16]. However, there are no studies in which cognitive functioning has been measured objectively before, during, and after chemotherapy among women with ovarian cancer.

Patients and methods

Patient population

Inclusion criteria

Epithelial ovarian, fallopian tube, or primary peritoneal cancer, stage IIC, III, or IV, after optimal (defined as <1 cm gross residual disease) or suboptimal debulking; Karnofsky performance status >70%; creatinine <1.6 mg/dL; bilirubin <1.5 mg/dL; no prior chemotherapy or radiation; no active infection; neuropathy <grade 2.

Pretreatment evaluations

History and physical examination; chest X-ray, electrocardiogram, CT scan; complete blood count (CBC), serum chemistry profile; and CA-125 measurement.

Treatment regimen

Planned dosing schedule

Paclitaxel over 1 h days 1, 8, and 15; carboplatin day 1; gemcitabine days 1 and 8. Carboplatin dose was calculated using the Jelliffe formula for creatinine clearance [17], and Calvert formula for area-under-the-curve (AUC) [18]. Standard premedications and anti-emetics were given and could be altered for subsequent doses at the discretion of the treating physician. Granulocyte-colony stimulating factor (G-CSF), 300 or 480 μg, was given days 3–6 and 10–13. Day 1 treatment was given if the absolute neutrophil count (ANC) was >1000/μL and the platelet count was >100,000/μL; day 8 and 15 treatment was given if the ANC was >500 and the platelet count was >50,000/μL. Each cycle was 21 days.

Patients achieving complete clinical response, defined as no evidence of disease on CT and normal CA-125, underwent second-look laparoscopy to assess pathologic response.

Quality-of-life and cognition assessments

Women in the phase II study completed quality-of-life, depression, and cognitive functioning evaluations. Quality-of-life was measured using the Functional Assessment of Cancer Treatment-Ovarian (FACT-O) [19] at baseline and after cycles 3 and 6 of chemotherapy. Cognitive functioning, using the Trails A and B tests (cognitive flexibility and psychomotor speed) [20] and the Wechsler Adult Intelligence Scale-R Digit Span subtest (attention and concentration) [21], and depressive symptomatology, using the Center for Disease Studies-Depression (CES-D) scale [22], were assessed at baseline, after cycles 3 and 6, and at 6 months after completion of chemotherapy. Raw cognitive test scores were compared with published normative values according to age, and when available, to education, and subsequently converted into *z* scores (mean, 0; standard deviation, 1). Each participant reported her personal perception of whether she was having trouble with memory or concentration, and whether she felt that such difficulties interfered with her usual functioning, on a Likert scale query. Assessments were completed prior to delivery of chemotherapy and premedications.

Statistical analyses

The phase I primary endpoint was to determine the maximum-tolerated dose (MTD) of weekly paclitaxel, gemcitabine, and carboplatin. Dose-limiting toxicity (DLT) was defined as any grade 3 or 4 nonhematologic toxicity (excluding alopecia), or >7 days treatment delay between doses within a cycle, or >21 days between cycles, due to failure to meet hematologic parameters for re-treatment. Treatment toxicities were graded using National Cancer Institute Common Toxicity Criteria version 2.0.

Patients were enrolled in groups of 3. If DLT was observed in 0 of 3 patients, dose escalation proceeded. If 1 of 3 patients in a cohort developed DLT, 3 additional patients were enrolled at that dose. MTD was defined as the dose and schedule at which no more than 2 of 6 patients experienced a DLT.

The phase II primary endpoint was pathologic complete response, defined as all pathologic specimens negative for tumor at second-look laparoscopy. Sample size was chosen based on the hypothesis that the triplet would yield a pathologic CR rate of >50%. With 25 patients treated at the phase II dose, the 95% confidence interval (CI) for this estimate of the pathologic CR rate would be ±20%.

Clinical response definitions

Complete response (CR)—disappearance of all clinical evidence of tumor for at least 4 weeks, and CA-125 <35 units/mL; partial response (PR)—50% or greater reduction in the sum of the products of all measurable disease for at least 4 weeks, with no increase in size of any lesion and new lesions, or failure to normalize serum CA-125.

Quality-of-life and cognition analyses

Quality-of-life and cognition assessment data were analyzed using longitudinal data techniques and tested for trend. Exploratory analyses were performed to examine potentially important relationships among the following patient factors (age-continuous variable, depression-dichotomized by CES-D score >16, education level-dichotomized at median years of education) and outcomes (perception of cognitive decline, decline in cognition test scores) using repeated measures analysis of covariance. In samples of the size of the current pilot study, the likelihood of comparisons, statistically significant at