Available online at www.sciencedirect.com
SCIENCE DIRECT
Gynecologic Oncology 100 (2006) 385 – 388
Gynecologic Oncology
www.elsevier.com/locate/ygyno

Cisplatin plus gemcitabine in previously treated squamous cell carcinoma of the cervix: A phase II study of the Gynecologic Oncology Group

Cheryl A. Brewer [a,b,*], John A. Blessing [c], Robert A. Nagourney [d], D. Scott McMeekin [e], Shashikant Lele [f], Susan L. Zweizig [g]

[a] Division of Gynecologic Oncology, University of California Irvine Medical Center, Orange, CA 92868, USA
[b] Division of Gynecologic Oncology, University of Mississippi Medical Center, Jackson, MS 39216, USA
[c] Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY 14263, USA
[d] Malcolm C. Todd Cancer Institute, Memorial Medical Center of Long Beach, Long Beach, CA 90806, USA
[e] Division of Gynecologic Oncology, University of Oklahoma, Oklahoma City, OK 73190, USA
[f] Division of Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, NY 14263, USA
[g] Division of Gynecologic Oncology, University of Massachusetts Memorial Medical Center, Worcester, MA 01605, USA

Received 27 April 2005
Available online 4 November 2005

Abstract

Objectives. This trial was conducted to evaluate the safety and efficacy of cisplatin plus gemcitabine in previously treated squamous cell carcinoma of the cervix.

Subjects and methods. All women had measurable histologically confirmed squamous cell cervical cancer and a GOG performance status less than or equal to 2. The women were to receive cisplatin at 30 mg/m^2 plus gemcitabine at 800 mg/m^2 day 1 and day 8 every 28 days.

Results. Between February 2001 and May 2002, 32 eligible patients were entered. All women had received prior chemotherapy and 29 had received radiation. Twenty patients received platinum previously twice. The median time from primary treatment to recurrence was 21 months, but the median time from last prior chemotherapy was less than 2 months. A second phase of accrual was not indicated per the established stopping rules.

There were 7 (21.9%) partial responses and median response duration was 2.1 months. Twelve additional women (37.5%) had stable disease. Nine women (28.1%) had increasing disease. Median time to progression was 3.5 months. There were no treatment-related deaths. Six women had grade 4 neutropenia, three had grade 4 anemia, and two had grade 4 thrombocytopenia. Grade 4 gastrointestinal toxicity occurred in two women and grade 4 anorexia occurred in one.

Conclusions. This study suggests modest activity for the gemcitabine plus cisplatin doublet in previously treated squamous cell carcinoma of the cervix. The objective response rate of 22% is comparable to that of other active agents and combinations tested in this setting. Toxicities were primarily hematologic and generally manageable with dose reductions.

Keywords: Recurrent; Squamous; Cervical; GOG; Cisplatin; Gemcitabine

Introduction

Cervical cancer is a leading cause of cancer death in women worldwide; advanced persistent or recurrent disease remains a difficult target for effective chemotherapy [1]. Response rates are greater than 60% for neoadjuvant chemotherapy in the chemonaive population, but lower in the recurrent setting after women have received chemoradiation [1–3]. While prior chemotherapy and radiation are clearly adverse determinants of response, a number of other factors may also be influential. These include the patient performance status, sites of recurrence, and the treatment-free interval [4–6]. However, prior exposure to radiation and chemotherapy remain dominant determinants of subsequent response.

The Gynecologic Oncology Group (GOG) established a phase II trial series to evaluate therapeutic intervention for the treatment of advanced and recurrent cervical cancer. Initial

* Corresponding author. Division of Gynecologic Oncology, The University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216-4505, USA. Fax: +1 309 677 6931.
E-mail address: brewer@peoriago.com (C.A. Brewer).

0090-8258/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2005.09.009

treatment strategies such as chemoradiation have now shifted more and more chemotherapy subjects toward the chemoresistant state. Most patients with recurrent disease have now received platinum as part of their initial treatment.

The combination of cisplatin and gemcitabine provides a biologically plausible mechanism to address platinum resistance. The ability of gemcitabine to alter established platinum resistance and also synergize with platinum has been previously described [7–9]. Analyses in human tumor primary cultures indicate activity for the gemcitabine/cisplatin combination for multiple tumor types and clinical responses in platinum refractory patients have now also been assessed [8–10]. Cisplatin resistant cells up-regulate nucleotide excision repair enzyme complexes ERCC1, ERCC2, and XPA and provide a potential target for gemcitabine. Gemcitabine when directly incorporated into DNA as a triphosphate dFdCTP results in "masked" chain termination. The diphosphate, dFdCDP, inhibits ribonucleotide reductase and concurrently depletes cells of needed deoxynucleoside pools [11–14].

Based on these scientific findings, the present trial was conducted to assess the activity of a gemcitabine and cisplatin combination in a population of previously treated, presumably chemoresistant patients.

Materials and methods

Women with persistent or recurrent squamous cell carcinoma of the cervix were entered. Those with no more than one chemotherapy regimen, outside that administered in conjunction with primary radiation as a radiosensitizer, were eligible. Women could not have received prior gemcitabine. Histological confirmation of the original primary tumor by the GOG Pathology Committee was required. Women were required to be at least 18 years of age with a GOG performance status of 0, 1, or 2. Women must have failed local therapeutic measures. They must not have received radiation to more than 25% of marrow-bearing areas. At least 3 weeks must have elapsed since any prior treatment directed at the malignant tumor. All women had bi-dimensional disease measurable by physical exam or medical imaging including CXR, CT, or MRI. Women with concomitant or prior malignancy other than a nonmelanoma skin cancer within the preceding 5 years were not eligible. Subjects who met protocol criteria and had adequate hematologic, renal, hepatic, pulmonary, and cardiac function with no active infections were accrued. Patients provided written informed consent consistent with federal, state, and local requirements.

Patients were assessed prior to each cycle of treatment. Disease measurements were required every other course of treatment and standard GOG response criteria were used. A complete response was defined as the disappearance of all measurable disease for at least 4 weeks. A partial response was defined as a 50% or greater reduction in the products of each measurable lesion for at least 4 weeks duration. Increasing disease was defined as a 50% or more increase in the product of any indicated lesion or the appearance of any new lesions within 8 weeks of study entry. Stable disease was defined as any condition not meeting any of the above criteria. Survival is the observed length of life from initiation of treatment to death or the date of last contact. Progression-free survival is the period from study entry until disease progression or the last date of contact. Patients who received one or more cycles of drug and lived at least 4 weeks were evaluable for response. However, patients deemed inevaluable for response (intent to treat group) were also utilized in calculation of response rates. Women who received one or more cycles of drug were considered evaluable for adverse effects.

The treatment consisted of cisplatin 30 mg/m^2 followed by gemcitabine 800 mg/m^2 given day 1 and day 8 every 28 days. The scheduled administration of chemotherapy on day 8 could be adjusted ±1 day. The minimal treatment period was considered to be one cycle. Two treatment weeks with a 2-week rest period constituted one cycle. A cycle of therapy was not administered unless the absolute neutrophil count was ≥1500l and platelets were ≥ to the institutional lower limit of normal (CTC Grade 0). Creatinine was required to be ≤ to 2.0 mg%. Sensory and motor neuropathy for each patient was required to be ≤ to CTC grade 1.

Dose adjustments were based on the absolute neutrophil count. Treatment delays of up to 14 days were permitted. No dose modifications were made for uncomplicated granulocyte nadirs lasting less than 7 days. For the first occurrence of febrile neutropenia, and/or documented grade 4 neutropenia persisting ≥7 days, the gemcitabine was reduced one dose level in subsequent cycles. Only women who experienced recurrent febrile neutropenia or recurrent documented grade 4 neutropenia, persisting ≥7 days after dose reduction were allowed to receive growth factor support. Women with further episodes of febrile neutropenia or recurrent documented grade 4 neutropenia persisting ≥7 days (after dose reduction and the addition of growth factors) underwent an additional dose reduction of gemcitabine. Treatment modifications applied equally for day 1 and day 8, with the day 8 treatment held if the ANC was <1000 cells/μl or platelets were <75,000. Those subjects who failed to recover adequate counts within a 2-week delay were removed from study. Women were allowed to receive erythropoetin after documentation of hemoglobin less than 10. Prophylactic thrombopoetic agents could only be given for recurrent thrombocytopenia after treatment modifications. Grade 3 elevations in liver enzymes, alkaline phosphatase, or bilirubin also required a dose reduction of one level in gemcitabine and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1. Recurrent grade 3 nausea and vomiting despite adequate antiemetic therapy required a dose reduction of cisplatin to 20 mg/m^2. Grade 2 or greater peripheral neuropathy or grade 2 or greater renal toxicity required a dose reduction in cisplatin and a delay in subsequent therapy for up to 2 weeks. Amifostine or other protective agents were not allowed.

Women were removed from study if they requested it or if they were unable to tolerate the lowest doses. Dose escalations were given of one dose level gemcitabine to 1000 mg/m^2 after one complete cycle or 4 weeks of therapy in those with less than grade 3 nausea and vomiting, less than grade 2 other nonhematologic toxicity, and less than grade 2 hematologic toxicity. All dose reductions were permanent without re-escalation. A patient could remain on the study until progression or unacceptable toxicity and all were to be followed until death.

The study employed a two-stage accrual design with an early stopping rule in the event of insufficient activity. During the first stage of accrual, 28–35 patients were to be entered and evaluated. If at least seven responses were observed among the first 28–31 patients, or at least eight responses were observed among 32–35 patients, a second phase would be initiated. The regimen would be considered active if at least 16 responses were observed among 62 patients, or at least 17 responses were observed among 63–65 patients, or at least 18 responses were observed among 66–68 patients, or at least 19 responses were observed out of 69 patients. If the true response rate was 20%, the average probability of designating the treatment as active was 10% and the probability of stopping the trial after the first stage of accrual was 64%. Conversely, if the true response rate was 35%, then the probability of correctly classifying the treatment as active was 90%.

Results

Thirty-three women were accrued between 2/2001 and 5/2002. One subject was deemed ineligible due to inadequate pathology. The patient characteristics are presented in Table 1. All women had received prior chemotherapy and 29 had received prior radiation. The median time to recurrence was 21 months (range 2–130 months). Twenty-five of the women had received another regimen of chemotherapy in addition to initial radiosensitizing treatment. Prior chemotherapy included methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) in two patients, cisplatin plus topotecan, taxanes, carboplatin, xeloda, 5-flurouracil, and bleomycin, etoposide plus cisplatin. Twenty patients received two prior platinum regimens if initial radiation sensitizing chemotherapy is counted. Both mean