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

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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 2.5 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

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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 ≥1500/l 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-fluorouracil, and bleomycin, etoposide plus cisplatin. Twenty patients received two prior platinum regimens if initial radiation sensitizing chemotherapy is counted. Both mean

Table 1
Patient characteristics

Characteristic	
Age	
Median	51.5
Range	28–70
Performance status	No. of cases
0	16
1	14
2	2
Grade	
1	1
2	20
3	11
Prior chemotherapy	32
Prior radiotherapy	29
Courses	
Median	3
Range	1–11

and median times to progression from last prior chemotherapy were less than 2 months (range 1–24 months) and only three women had a chemotherapy-free interval of greater than 6 months. Nearly one half of patients had progressed after GOG 179.

Four women were deemed inevaluable for response with two having hypersensitivity reactions to cisplatin. A third woman was inevaluable due to a pelvic abscess and the fourth electively discontinued study participation. Nevertheless, all eligible patients were included in the response denomination based on intent to treat.

Seven (21.9%) partial responses were seen with median response duration of 2.1 months. An additional 12 women (37.5%) had stable disease. Two stable patients had a greater than 50% decrement in measurable disease outside the radiation fields, including one with complete and prolonged regression of an enlarged supraclavicular lymph node. Overall, however, disease response categories were evenly distributed between radiated and nonradiated areas.

Supraclavicular lymph node disease was more likely to be measured by physical exam. This accounted for just a few cases, but constituted two of seven responses, and another node regressed clinically as above in a stable patient. Mandatory imaging on study to verify or complement the physical exam may be of interest in the future.

Nine women (28.1%) demonstrated increasing disease. The median time to progression was 3.5 months for all patients. Response could not be assessed in 4 patients (12.5%), but these patients were included in the intent to treat analysis.

The most common adverse events were hematologic with the results of all toxicities provided by grade (Table 2). Only 12 patients required a dose reduction (2 in gemcitabine only, 4 in cisplatin only, and 6 in both gemcitabine and cisplatin). Two patients received a dose escalation in gemcitabine. Neutropenia was common, with six women experiencing grade 4 neutropenia. Three women developed grade 4 anemias and two grade 4 thrombocytopenia. One woman required a platelet transfusion. Additionally, there were two grade 4 GI toxicities and one episode of grade 4 anorexia. Little cumulative neurotoxicity was noted at this cisplatin dose and there were no treatment-related deaths.

Discussion

In 1999, five large randomized trials for the treatment of cervical cancer were summarized in a NCI Clinical Announcement [15]. These trials showed a reduction in the risk of recurrence and death with the addition of chemotherapy to primary radiation treatment [16–20]. This has resulted in an increasing exposure to cisplatin and other chemotherapy initially and more platinum resistance. Reversal of drug resistance, and in particular platinum resistance, is of increasing importance in the recurrent setting. The GOG experience with cisplatin in a previous study yielded only 2/40 responses after cisplatin plus concurrent radiotherapy, and the GOG experience with gemcitabine in previously treated patients was only 2/25 responses [21,22]. Clearly, historic response rates of 23% for cisplatin as a single agent cannot be extrapolated to the existing recurrent population.

In the current study, the combination of gemcitabine and cisplatin provided a clinical objective response rate of 22%. This rate is comparable to the most active agents in the recurrent setting when only measurable disease is considered. Clear decrement in tumor size outside of radiation fields was also noted in patients who did not meet formal criteria for response but were considered stable. Improved time to progression and palliation of symptoms are also indicative of

Table 2
Adverse events ($n = 32$)

Patient adverse events	Grade	
	3	4
Leukopenia	7	3
Neutropenia	7	6
Thrombocytopenia	16	2
Platelet transfusion	1	0
Anemia	9	3
RBC transfusion	16	0
Nausea/vomiting	2	1
Gastrointestinal	3	1
Genitourinary	2	0
Fatigue/weakness	7	0
Pain	7	0
Metabolic	4	0
Hepatic	3	0
Dyspnea	3	0
Cardiovascular	1	0
Infection	2	0
Fever	1	0
Allergy	1	0
Syncope	1	0
Depression	1	0
Hypertension	1	0
Hyponatremia	1	0
Hematuria	1	0
Anorexia	0	1

The median WBC nadir for those 27 patients experiencing leukopenia was 2100 (range: 700–3780). The median platelet nadir for those 26 patients experiencing thrombocytopenia was 34,500 (range: 4000–138,000). No treatment-related deaths have been reported.

overall therapeutic benefit and represent additional endpoints worthy of future study.

The main toxicities with this regimen were hematologic. Colony stimulating factors and erythropoetin should be considered, particularly in patients having received prior radiotherapy. Sensitization reactions to platinum are rare, but should be anticipated and carefully treated. Aggressive attention to the prevention of nausea and vomiting is warranted. Based on the stopping rules in force, the response rate did not qualify for a second phase of accrual. However, the goal may have been too high for this heavily pretreated population. In the absence of a randomized trial, no firm conclusions can be drawn; however, additional study of this combination is warranted and would best be conducted in patients less heavily pretreated. An ongoing randomized Gynecologic Oncology Group study is evaluating this combination in such a population, in comparison with three other doublets.

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References

[1] Thigpen T. The role of chemotherapy in the management of carcinoma of the cervix. Cancer J 2003;9:425–32.
[2] Stehman FB, Rose PG, Greer BE, Roy M, Plante M, Penalver M, et al. Innovations in the treatment of invasive cervical cancer. Cancer 2003; 98:2052–63.
[3] Rose PG. Stage IIB–IVA cancer of the cervix. Cancer J 2003;9:404–14.
[4] Stehman FB, Bundy BN, DiSaia PJ, Keys HM, Larson JE, Fowler WC. Carcinoma of the cervix treated with radiation therapy: I. A multi-variate analysis of prognostic variables in the Gynecologic Oncology Group. Cancer 1991;67:2776–85.
[5] Stock RJ, Zion R, Bundy BN, Askin FB, Woodward J, Fetter B, et al. Evaluation and comparison of histopathologic grading systems of epithelial carcinoma of the uterine cervix: Gynecologic Oncology Group studies. Int J Gynecol Pathol 1994;13:99–108.
[6] Eralp Y, Saip P, Sakar B, Kucucuk S, Aydiner A, Dincer M, et al. Prognostic factors and survival in patients with metastatic or recurrent carcinoma of the uterine cervix. Int J Gynecol Cancer 2003;4: 497–504.
[7] Nagourney RA, Link JS, Blitzer JB, Forsthoff C, Evans SS. Gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed breast cancer patients. J Clin Oncol 2000;18:2245–9.
[8] Nagourney RA, Brewer CA, Radecki S, DiSaia P. Phase II trial of gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed ovarian cancer subjects. Gynecol Oncol 2003;88:35–9.
[9] Rose PG, Mossbruger K, Fusco N, Smrekar M, Eaton S, Rodriguez M. Gemcitabine reverses cisplatin resistance: demonstration of activity in platinum and multidrug-resistant ovarian and peritoneal carcinoma. Gynecol Oncol 2003;88:17–21.
[10] Emmanouilides C, Coloves C, Pinter-Brown L, Hernandez L, Schiller G, Territo M, et al. Pilot study of fixed-infusion rate gemcitabine with cisplatin and dexamethasone in patients with relapsed of refractory lymphoma. Clin Lymphoma 2004;5:45–9.
[11] Lee KB, Parker RJ, Bohr V, Cornelison T, Reed E. Cisplatin sensitivity/resistance in UV repair-deficient Chinese hamster ovary cells of complementation groups 1 and 3. Carcinogenesis 1993;14:2177–80.
[12] Dabholkar M, Bostick-Bruton F, Weber C, Bohr VA, Egwuagu C, Reed E. ERCC1 and ERCC2 expression in malignant tissues from ovarian cancer patients. J Natl Cancer Inst 1992;84:1512–7.
[13] Dabholkar M, Thornton K, Vionnet J, Bostick-Bruton F, Yu JJ, Reed E. Increased mRNA levels of xeroderma pigmentosum complementation group B (XPB) and cockayne's syndrome complementation group B (CSB) without increased mRNA levels of multidrug-resistance gene (MDR1) or metallothionein-II (MT-II) in platinum-resistant human ovarian cancer tissues. Biochem Pharmacol 2000;60:1611–9.
[14] Fichtinger-Schepman AMJ, van Oosterom AT, Lohman PHM, Berends F. Cis-diamminedichloroplatinum (II) induced adducts in peripheral leukocytes from seven cancer patients: quantitative immunochemical detection of the adduct induction and removal after a single dose of cis-diamminedichloroplatinum (II). Cancer Res 1987;47:3000–4.
[15] National Cancer Institute. Digest page: NCI clinical announcement on cervical cancer. Available from URL: http://www.cancer.gov/clinicaltrials/digestpage/cervical-cancer-announcement.
[16] Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler J. WC, et al. A randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in Stages IIB–IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 1999;17:1339–48.
[17] Peters III WA, Liu PY, Barrent II RJ, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606–13.
[18] Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340:1144–53.
[19] Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340:1137–43.
[20] Keys HM, Bundy BN, Stehman FB, Muderspach LI, Hafe WE, Suggs III CL, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky Stage IB cervical carcinoma. N Engl J Med 1999;340:1154–61.
[21] Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 2004;22(15):3113–9.
[22] Schilder RJ, Blessing JA, Morgan M, Mangan CE, Rader JS. Evaluation of gemcitabine in patients with squamous cell carcinoma of the cervix: a Phase II study of the Gynecologic Oncology Group. Gynecol Oncol 2000;76:204–7.