VOLUME 32 · NUMBER 25 · SEPTEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pemetrexed and Cisplatin for the Treatment of Advanced, Persistent, or Recurrent Carcinoma of the Cervix: A Limited Access Phase II Trial of the Gynecologic Oncology Group

David Scott Miller, John A. Blessing, Lois M. Ramondetta, Huyen Q. Pham, Krishnansu S. Tewari, Lisa M. Landrum, Jubilee Brown, and Robert S. Mannel

See accompanying article on page 2687

David Scott Miller, University of Texas Southwestern Medical Center, Dallas; Lois M. Ramondetta and Jubilee Brown, MD Anderson Cancer Center, Houston, TX; John A. Blessing, Roswell Park Cancer Institute, Buffalo, NY; Huyen Q. Pham, University of Southern California, Los Angeles; Krishnansu S. Tewari, University of California Medical Center at Irvine, Orange, CA; and Lisa M. Landrum and Robert S. Mannel, University of Oklahoma, Oklahoma City, OK.

Published online ahead of print at www.jco.org on July 28, 2014.

Supported by National Cancer Institute Grants No. CA 27469 (Gynecologic Oncology Group) and CA 37517 (Gynecologic Oncology Group Statistical and Data Center).

Presented at the 49th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 4, 2013.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00691301

Corresponding author: David Scott Miller, MD, Division of Gynecologic Oncology, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Rm J7-124, Dallas, TX 75390-9032; e-mail: david.miller@utsouthwestern.edu.

0732-183X/14/3225w-2744w/$20.00

DOI: 10.1200/JCO.2013.54.7448

ABSTRACT

Purpose
To estimate the antitumor activity of pemetrexed and cisplatin with objective tumor response (partial and complete) in patients with advanced, persistent, or recurrent carcinoma of the cervix and to determine the nature and degree of toxicity of this regimen. Secondarily, this study will determine the effects of this regimen on progression-free survival and overall survival.

Patients and Methods
Eligible, consenting patients received pemetrexed 500 mg/m^2 and cisplatin 50 mg/m^2 intravenously repeated every 21 days until disease progression or adverse events prohibited further therapy. Patients received no prior therapeutic chemotherapy, except when administered concurrently with primary radiation therapy. Subsequent doses were adjusted according to observed toxicity and protocol guidelines. Adverse events were assessed with Common Terminology Criteria for Adverse Events v 3.0. The primary measure of efficacy was tumor response according to Response Evaluation Criteria in Solid Tumors. The study was stratified by prior radiation therapy.

Results
From September 2008 to November 2011, 55 patients were enrolled by five Gynecologic Oncology Group member institutions; of those, 54 patients were eligible and assessable. The regimen was well tolerated with 26% receiving more than nine cycles. The most common greater than grade 2 toxicities were neutropenia 35%, leukopenia 28%, and metabolic 28%. The overall response rate was 31% (one complete and 16 partial). The median progression-free survival was 5.7 months, and overall survival was 12.3 months.

Conclusion
Pemetrexed in combination with cisplatin demonstrates activity in the treatment of advanced, persistent, or recurrent carcinoma of the cervix.

J Clin Oncol 32:2744-2749. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Cancer of the uterine cervix that has metastasized or recurred at sites not amenable to treatment by surgery or radiation portends a grim prognosis.[1] No potentially curative therapy yet exists. The focus of treatment has been palliation with chemotherapy.[2] The Gynecologic Oncology Group (GOG) has conducted multiple phase II trials in search of active agents against cervical cancer. To date, cisplatin, ifosfamide, paclitaxel, topotecan, vinorelbine, gemcitabine, pemetrexed, and bevacizumab have been found to have activity of interest as single agents or in combinations.[3-15] Combinations of these agents have been compared with improvements in response rates.[16] However, only recently has an improvement in survival been seen with cisplatin and topotecan over cisplatin alone and with the addition of bevacizumab to cisplatin and paclitaxel.[17,18]

Pemetrexed (Alimta, LY231514; Eli Lilly, Indianapolis, IN) is an antifolate, antineoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. Pemetrexed targets thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), all folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides.[19] Pemetrexed has demonstrated activity in multiple tumor types, including mesothelioma, non–small-cell lung cancer, and breast, colorectal, pancreas, bladder, ovarian, and head and neck cancers. A prior

single-institution trial in chemotherapy-naive patients with cervical cancer and two trials in previously treated patients suggested possible activity for pemetrexed alone.[15,20,21]

The objectives of this trial (Pemetrexed and Cisplatin in Treating Patients With Advanced, Persistent, or Recurrent Cervical Cancer [GOG-0076GG]) were to estimate the antitumor activity of pemetrexed and cisplatin with objective tumor response (partial response [PR] and complete response [CR]) in patients with advanced, persistent, or recurrent carcinoma of the cervix; to determine the nature and degree of toxicity of pemetrexed and cisplatin in this cohort of patients; and to determine the effects of this regimen on progression-free survival (PFS) and overall survival (OS).

PATIENTS AND METHODS

Eligibility

To be eligible for the trial, patients must have had advanced, persistent, or recurrent squamous or nonsquamous cell carcinoma of the cervix not amenable to curative therapy. Patients who had prior therapy with cytotoxic drugs for advanced and/or recurrent cervical carcinoma were ineligible. Patients who had prior cisplatin as a radiosensitizer for primary treatment of disease were eligible. Histologic documentation of the original primary tumor was required via the pathology report. All patients must have had measurable disease defined as at least one lesion that could be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must have been $\geq$ 20 mm when measured by conventional techniques, including palpation, plain x-ray, computed tomography, and magnetic resonance imaging, or $\geq$ 10 mm when measured by spiral computed tomography. Patients must have had at least one target lesion that was used to assess response on this protocol as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v 1.0.[22] Tumors within a previously irradiated field were designated as "nontarget" lesions unless progression was documented or a biopsy was obtained to confirm persistence at least 90 days after completion of radiotherapy (RT). Patients must have had a GOG performance status (PS) of 0, 1, or 2 and must have been free of active infection requiring antibiotics (with the exception of uncomplicated urinary tract infections). Any hormonal therapy directed at the malignant tumor must have been discontinued at least 1 week before registration. Continuation of hormone replacement therapy was permitted. Any prior RT must have been discontinued at least 4 weeks before registration. Female patients of childbearing age must have had a negative serum pregnancy test before the study entry and be practicing an effective form of contraception. All patients provided signed informed consent consistent with all local, state, and federal guidelines; the institutional review board at each participating institution provided approval.

Pemetrexed at a dose of 500 mg/m^2 was to be administered as an intravenous (IV) infusion over 10 minutes immediately followed by cisplatin as an IV infusion at less than 1 mg/min over less than 4 hours at a dose of 50 mg/m^2 every 21 days. Seven days before initiation of pemetrexed, patients were to begin taking folic acid at a dose of 350 to 600 mcg daily and to receive an intramuscular injection of 1,000 mcg of vitamin B_{12} to be repeated every 3 months during therapy. Dexamethasone 4 mg by mouth twice per day was taken the day prior to, day of, and day after each dose of pemetrexed. Nonsteroidal anti-inflammatory drugs were held for the 2 days before and after pemetrexed administration. Complete blood counts were obtained once per week. Cycles were to be repeated every 21 days pending an absolute neutrophil count more than 1,500/mL, platelet count more than 100,000/mL, and resolution of nonhematologic toxicities. Weekly delays in therapy were prescribed to allow resolution of persistent hematologic and nonhematologic toxicity. However, patients were removed from study for delays in excess of 2 weeks. This study used the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for defining and grading specific adverse events (AEs).[23] Dose reduction was required for febrile neutropenia and/or grade 4 neutropenia persisting more than 7 days, grade 4 thrombocytopenia, or grade 2 bleeding, and peripheral neuropathy greater than grade 2. Prophylactic growth factors were not allowed unless patients experienced recurrent neutropenic complications after prescribed treatment delays. Use of erythropoietin was allowed. If AEs were not severe, patients remained on pemetrexed until evidence of disease progression or unacceptable toxicity. Cisplatin was continued up to a maximum of six cycles. Patients with continued response or with stable disease (SD) could continue receiving cisplatin beyond the six cycles with the consent of the study chair.

Statistical Design

The protocol used a two-stage group sequential design with stratification on prior cisplatin as a radiation sensitizer. On the basis of prior GOG studies,[16,17,24] the response rate of interest was 40% for those patients who had not received prior *cis*-RT (stratum 1), whereas it was only 25% in those patients who had received prior *cis*-RT (stratum 2). This study involved a mixture of these two strata. Therefore, a two-stage stratified design as proposed by London and Chiang was used.[23] This design uses the marginal number of responses across all strata while factoring differing probabilities of response within each stratum. The null hypothesis of no treatment effect is H_0: $p_1 = 0.20$ and $p_2 = 0.10$. The alternative hypothesis is H_1: $p_1 = 0.40$ and $p_2 = 0.25$. The targeted accrual for the first stage of accrual was 26 patients. The distribution of the two strata could not be determined beforehand; therefore, the required number of responses to proceed with the second stage varied with the realized distribution. Tables were generated for all contingencies. If the study proceeded to the second stage of accrual, at least 49 cumulative patients would be entered. Again, the distribution of the two responses necessitated multiple decision rules. The probabilities of type 1 and type 2 errors were approximately 0.10. Of note, response rates in the individual strata are not the focus of the decision rule. Rather, it is based on the observed responses in the overall sample.

RESULTS

From September 2008 to November 2011, 55 patients were entered onto this limited access trial by five member institutions of the GOG. One patient did not receive any treatment and was inevaluable (Fig 1). The characteristics of the 54 evaluable patients are presented in Table 1. The median age of patients treated was 46 years. Most patients had a PS of 0 (63%), were white (54%), and had squamous histology (80%). No patients had received prior tumor-directed chemotherapy, and 65% had prior RT with 77% of those receiving chemoradiotherapy. A total of 333 cycles (average per patient, 6.2 cycles; range, one to 20 cycles) of chemotherapy were administered with 29% of patients receiving nine or more cycles.

Toxicities for all patients are listed in Table 2. Overall, the treatment was well tolerated with the most common toxicities being anemia, GI, constitutional, and nausea. More serious toxicities (grade 3 and 4) included neutropenia 35%, leukopenia 28%, and metabolic 28%. Dose reduction of both cisplatin and pemetrexed as a result of toxicity was required in five patients (9%) and of cisplatin in only three patients (6%). No treatment-related deaths were reported.

In the first stage of accrual, there were 19 patients from stratum 1 and 10 from stratum 2. We observed nine responses, and the study proceeded to the second stage. The overall response rate was 31% (one CR and 16 PRs; 95% CI, 19.5% to 45.6%) for a median duration of response of 7.6 months (Table 3). All 17 of the responses were seen in the 45 patients with measurable tumor in nonradiated disease sites; no responses were seen in the nine patients with measurable tumor in irradiated disease sites. The response rate for nonradiated disease sites was 38% (95% CI, 23.8% to 53.5%; 17 of 45). There were 14 responses (33%) seen in the 43 patients with squamous histology and three

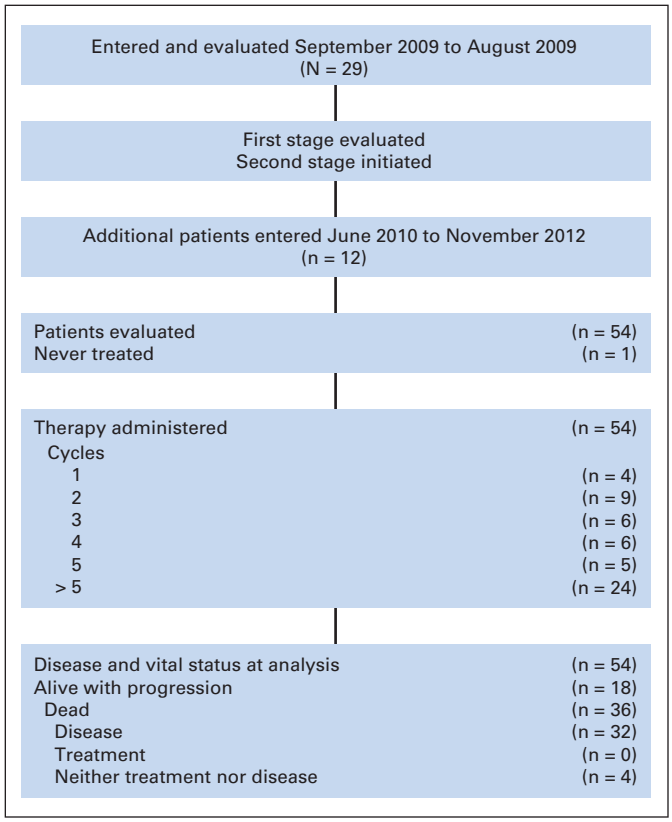

Fig 1. CONSORT diagram.

Table 1. Patient Characteristics

Characteristic	No. of Patients
Age, years	
< 30	3
30-39	10
40-49	23
50-59	15
≥ 60	3
Performance status	
0	34
1	14
2	6
Race/ethnicity	
Hispanic	13
Non-Hispanic	
White	29
Black	9
Asian	2
American Indian	1
Cell type	
Squamous	43
Adenocarcinoma	11
Prior chemotherapy	0
Prior radiotherapy	35
Prior chemoradiation	27
No. of courses	
1	4
2	9
3	6
4	6
5	5
6	2
7	1
8	4
9	3
10	6
> 10	8

(27%) in the 11 patients with adenocarcinoma. Seven responses (26%) were seen in the 27 patients who had received cisplatin with their RT and 10 (37%) responses were seen in 27 patients who had not. SD was seen in 44% for a median of 5.1 months (range, 2.3 to 18.6 months), and increasing disease was seen in 15%. Response could not be assessed in five patients (9%). Median PFS was 5.7 months (range, 0.3 to 38.6 months) and median OS was 12.3 months (range, 0.3 to 38.6 months; Fig 2).

DISCUSSION

Cisplatin and pemetrexed is an active first-line regimen against advanced, recurrent, or persistent cervical carcinoma. The treatment was well tolerated.

Early phase II trials by the GOG had identified several potentially active agents including cisplatin and ifosfamide.[3-5] Several of these drugs were combined and, in some cases, showed increased activity.[26] Although some progress was made toward palliating patients, the search for active agents continued. The GOG then embarked on a series of phase II protocols (GOG-0127 and GOG-0128) evaluating new agents or novel combinations of agents in patients with advanced or recurrent cervical cancer for whom prior chemotherapy had failed. Several potentially active agents were identified, including topotecan, cisplatin plus gemcitabine, and vinorelbine.[7-9,11,27] In addition, potentially active agents and combinations were tested in the first-line setting in the GOG-0076 series. Ifosfamide, paclitaxel, topotecan, paclitaxel plus cisplatin, and cisplatin plus vinorelbine showed activity of interest.[12-14,28,29] Several of the agents and combinations found to have activity of interest in the GOG-0076, GOG-0127, and GOG-0128 series of protocols were compared in phase III trials. Cisplatin plus paclitaxel was superior to cisplatin alone with respect to response rate and PFS with sustained quality of life.[16] Cisplatin plus topotecan was used in the first randomized phase III trial to demonstrate a survival advantage for combination chemotherapy over cisplatin alone in advanced cervical cancer.[17,30,31] Paclitaxel, topotecan, gemcitabine, and vinorelbine were each combined with cisplatin in a randomized first-line trial (GOG-0204). None of the other combinations were superior to cisplatin plus paclitaxel.[24]

Pemetrexed is a third-generation antifolate-containing pyrrolopyrimidine-based nucleus that exerts its antineoplastic activity by disrupting folate-dependent metabolic processes essential for cell replication.[19,32] Unlike older agents that target a single enzyme, pemetrexed targets multiple enzymes: thymidylate synthase (TS), glycinamide ribonucleotide formyltransferase (GARFT), 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (AICARFT), and dihydrofolate reductase (DHFR).[33] Pemetrexed enters the cell through the reduced folate carrier, which is the major

Table 2. Adverse Events (N = 54)

Adverse Event	Grade 0	1	2	3	4
Leukopenia	16	8	15	12	3
Thrombocytopenia	32	11	5	3	3
Neutropenia	20	5	10	12	7
Anemia	2	17	22	6	7
Other hematologic	49	0	3	1	1
Allergy/immunology	49	3	0	1	1
Auditory/ear	39	0	14	1	0
Cardiac	47	5	2	0	0
Coagulation	53	0	0	1	0
Constitutional	6	12	23	12	1
Dermatologic	24	20	9	1	0
Endocrine	53	1	0	0	0
Nausea	7	19	22	6	0
Vomiting	19	11	17	7	0
GI	4	15	24	10	1
Genitourinary/renal	43	6	4	1	0
Hemorrhage	44	7	0	2	1
Infection	37	0	11	6	0
Lymphatics	42	5	7	0	0
Metabolic	10	19	10	10	5
Musculoskeletal	50	3	0	1	0
Neurosensory	31	15	6	2	0
Other neurological	42	8	3	1	0
Ocular/visual	44	6	2	2	0
Pain	18	11	13	12	0
Pulmonary	37	9	6	2	0
Sexual/reproductive	53	1	0	0	0
Syndromes	52	1	1	0	0
Vascular	50	0	3	1	0

NOTE. No treatment-related deaths were reported.

transporter for folates and is also a substrate for the folate receptor-alpha (FR-α).[34] A low-pH transporter may also be involved in pemetrexed internalization.[35] Pemetrexed is activated intracellularly to a polyglutamated form, with the pentaglutamated form being most active.[33] Pentaglutamated pemetrexed potently inhibits TS and also inhibits GARFT and AICARFT but has a low affinity for DHFR.[32,33] Enhanced expression of TS mediates resistance of uterine cervical cancer cells to radiation and has been associated with a poor prognosis in patients with cervical cancer.[36,37] Pemetrexed enhanced radiation-induced cell inactivation in cervical cancer cell lines (HeLa cells).[38]

On the basis of multivariable analyses of toxicities observed in early pemetrexed trials, plasma levels of homocysteine and methylmalonic acid were identified as predictive variables for pemetrexed-associated toxicity.[39] Folic acid and vitamin B_{12} supplementation caused a statistically significant reduction in plasma homocysteine concentrations over time and a significant reduction in the frequencies of severe hematologic toxicities and nonhematologic toxicities, such as mucositis, in patients receiving pemetrexed therapy.[40]

Table 3. Responses

Response Category	No. of Patients	%
Complete response	1	1.9
Partial response	16	29.5
Stable disease	24	44.5
Increasing disease	8	14.8
Inevaluable	5	9.3
Total	54	100.0

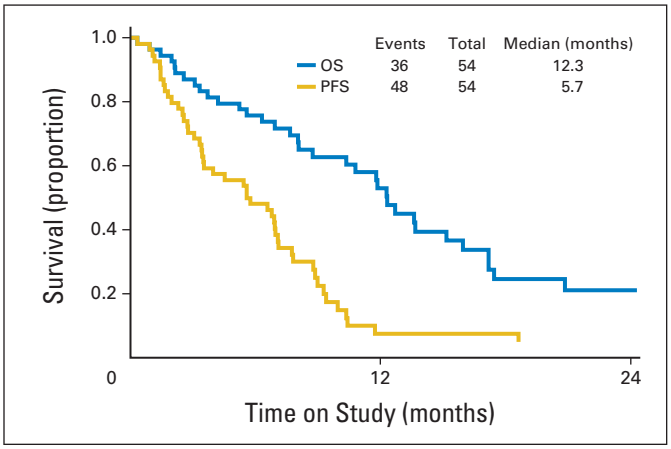

Fig 2. Progression-free survival (PFS) and overall survival (OS).

On the basis of the biologic rationale as well as its activity in other squamous cell cancers, pemetrexed has been tested in three single-arm phase II trials in patients with cervical cancer. One trial involved chemotherapy-naive patients, and two trials investigated the agent as second-line therapy.

Goedhals et al[20] treated 35 chemotherapy-naive patients with stages III and IV cervical squamous cell carcinoma. Patients received pemetrexed 600 mg/m^2 every 21 days, without vitamins, but the dose was subsequently reduced to 500 mg/m^2. Responses were reported in 18% of the patients with a median duration of 4 months.

The GOG evaluated pemetrexed (900 mg/m^2 every 21 days with folic acid and vitamin B_{12}) as second-line therapy in patients with persistent or recurrent carcinoma of the cervix (GOG-0127T). Prior platinum-based chemotherapy was received by all, and prior RT was received by most patients (85%). Patients received a median of four (range, one to 10) cycles, with 37% of patients receiving six or more cycles. Four patients (15%; 95% CI, 4.2% to 33.7%) experienced a PR with a median duration of 4.4 months. The rate for SD was 59%. The response rates for irradiated and nonirradiated disease sites were 7% and 25%, respectively. The median PFS was 3.1 months (range, 0.9 to 23.7 months), and the median OS was 7.4 months (range, 1.4 to 23.7 months). Grade 3 and 4 AEs included anemia (41%), leukopenia (30%), neutropenia (26%), constitutional (26%), and infection (22%). There were no treatment-related deaths. Pemetrexed was well tolerated and demonstrated moderate activity with responses seen in 15% of patients with recurrent carcinoma of the cervix for whom prior chemotherapy had failed.[15] That response rate was similar to the response rate of other agents that have been incorporated into first-line randomized trials.

Lorusso et al[21] evaluated second-line pemetrexed 500 mg/m^2 once every 21 days with folic acid and vitamin B_{12} in patients with advanced or recurrent squamous or nonsquamous cervical carcinoma. All patients received prior platinum-based chemotherapy, and most received prior RT (63%). Patients received a median of two cycles (range, one to nine cycles) of pemetrexed. Six patients (14%)

experienced a PR with a median duration of 7 weeks (range, 3 to 27 weeks). The median PFS and median OS were 10 weeks and 35 weeks, respectively. Hematologic grade 3 and 4 AEs included anemia (12%), leukopenia (28%), neutropenia (30%), and thrombocytopenia (9%). There were no treatment-related deaths.

Data from other tumor sites have suggested synergy between pemetrexed and cisplatin, an active agent in cervical cancer.[41,42] Thus, further study of pemetrexed combined with cisplatin was indicated in patients with advanced or recurrent cervical cancer not previously treated with chemotherapy. GOG-0043 found that cisplatin doses higher than 50 mg/m^2 produced no appreciable differences in CR rate, response duration, progression-free interval, or OS as first-line therapy in cervical cancer.[43] Two trials in breast cancer and non–small-cell lung cancer found no response advantage for pemetrexed doses higher than 500 mg/m^2.[44,45] A trial in relapsed ovarian cancer with pemetrexed 500 mg/m^2 versus 900 mg/m^2 also supported a dose of 500 mg/m^2.[46] Therefore, cisplatin 50 mg/m^2 and pemetrexed 500 mg/m^2 IV once every 21 days was selected for this trial.

Pemetrexed in combination with cisplatin has demonstrated activity in the treatment of advanced, persistent, or recurrent carcinoma of the cervix. Could cisplatin plus pemetrexed be considered as an alternative to cisplatin plus paclitaxel? The response rate, PFS, and OS reported for the cisplatin doublets tested in GOG-0204, which included a group of patients with better prognosis (PS 0 to 1 only) were cisplatin plus paclitaxel 29%, 6 months, 13 months; cisplatin plus vinorelbine 26%, 4 months, 10 months; cisplatin plus gemcitabine 22%, 5 months, 10 months; and cisplatin plus topotecan 23%, 5 months, 10 months.[24] For cisplatin plus pemetrexed in this study, the response rate was 31%, PFS was 7 months, and OS was 12 months. The toxicity profile for cisplatin plus pemetrexed may be more favorable, with the more serious toxicities (grade 3 and above) being neutropenia 35%, leukopenia 28%, and metabolic 28%. For cisplatin plus paclitaxel, neutropenia 78%, leukopenia 63%, and other hematologic 36% were reported in GOG-0204.[24]

The final results of GOG-0240, which also included a group of patients with better prognosis, were recently published. The addition of bevacizumab to cisplatin plus paclitaxel significantly increased response rate from 36% to 48%, PFS from a mean of 5.9 to 8.2 months, and OS from 13.3 to 17 months.[18] Data from other disease sites suggest that bevacizumab can also be combined with cisplatin plus pemetrexed.[47]

After it was recognized that the addition of cisplatin to RT increased survival in patients with locally advanced cervical cancer, it was noted that in subsequent recurrences, responses to cisplatin-based chemotherapy were diminished (odds ratio, 0.52; 95% CI, 0.32 to 0.85; $P = .009$).[48] The substitution of topotecan for cisplatin in combination with paclitaxel was also tested in GOG-0240. Unfortunately, topotecan plus paclitaxel was not superior to cisplatin plus paclitaxel.[49] With cisplatin plus pemetrexed, in this study, responses were noted in 27% of the patients who were previously treated with cisplatin-based chemoradiotherapy and 37% in those who were not.

Pemetrexed combined with cisplatin is an active and tolerable treatment for advanced, persistent, or recurrent carcinoma of the cervix. This combination should be further developed in the treatment of cervical cancer. Given that it may be less toxic than and as active as cisplatin plus paclitaxel and that it can be combined with bevacizumab, comparison of cisplatin-pemetrexed plus bevacizumab with cisplatin-paclitaxel plus bevacizumab would be appropriate. Expression of TS predicts clinical outcomes of pemetrexed-containing chemotherapy for non–small-cell lung cancers and could be evaluated as a biomarker in a cervical cancer trial.[50,51] In addition, the feasibility and safety of concurrent pemetrexed-cisplatin-thoracic RT followed by consolidation pemetrexed-cisplatin for unresectable stage IIIA/B non–small-cell lung cancer has been shown.[52] Thus, it could be tested in cervical cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: David Scott Miller
Provision of study materials or patients: David Scott Miller, Lois M. Ramondetta, Lisa M. Landrum, Robert S. Mannel
Collection and assembly of data: David Scott Miller, Lois M. Ramondetta, Huyen Q. Pham, Lisa M. Landrum, Jubilee Brown, Robert S. Mannel
Data analysis and interpretation: David Scott Miller, John A. Blessing, Krishnansu S. Tewari, Jubilee Brown, Robert S. Mannel
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Phippen NT, Leath CA 3rd, Miller CR, et al: Are supportive care-based treatment strategies preferable to standard chemotherapy in recurrent cervical cancer? Gynecol Oncol 130:317-322, 2013
2. Leath CA 3rd, Straughn JM Jr: Chemotherapy for advanced and recurrent cervical carcinoma: Results from cooperative group trials. Gynecol Oncol 129:251-257, 2013
3. Thigpen T, Shingleton H, Homesley H, et al: Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: A phase II study of the Gynecologic Oncology Group. Cancer 48:899-903, 1981
4. Sutton GP, Blessing JA, Adcock L, et al: Phase II study of ifosfamide and mesna in patients with previously-treated carcinoma of the cervix: A Gynecologic Oncology Group study. Invest New Drugs 7:341-343, 1989
5. Sutton GP, Blessing JA, DiSaia PJ, et al: Phase II study of ifosfamide and mesna in nonsquamous carcinoma of the cervix: A Gynecologic Oncology Group study. Gynecol Oncol 49:48-50, 1993
6. Schilder RJ, Blessing JA, Morgan M, et al: Evaluation of gemcitabine in patients with squamous cell carcinoma of the cervix: A Phase II study of the Gynecologic Oncology Group. Gynecol Oncol 76:204-207, 2000
7. Bookman MA, Blessing JA, Hanjani P, et al: Topotecan in squamous cell carcinoma of the cervix: A Phase II study of the Gynecologic Oncology Group. Gynecol Oncol 77:446-449, 2000
8. Curtin JP, Blessing JA, Webster KD, et al: Paclitaxel, an active agent in nonsquamous carcinomas of the uterine cervix: A Gynecologic Oncology Group Study. J Clin Oncol 19:1275-1278, 2001
9. Muggia FM, Blessing JA, Method M, et al: Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study. Gynecol Oncol 92:639-643, 2004
10. Schilder RJ, Blessing J, Cohn DE: Evaluation of gemcitabine in previously treated patients with non-squamous cell carcinoma of the cervix: A phase II study of the Gynecologic Oncology Group. Gynecol Oncol 96:103-107, 2005
11. Muggia FM, Blessing JA, Waggoner S, et al: Evaluation of vinorelbine in persistent or recurrent nonsquamous carcinoma of the cervix: A Gynecologic Oncology Group study. Gynecol Oncol 96:108-111, 2005
12. Sutton GP, Blessing JA, McGuire WP, et al: Phase II trial of ifosfamide and mesna in patients with advanced or recurrent squamous carcinoma of

the cervix who had never received chemotherapy: A Gynecologic Oncology Group study. Am J Obstet Gynecol 168:805-807, 1993

13. McGuire WP, Blessing JA, Moore D, et al: Paclitaxel has moderate activity in squamous cervix cancer: A Gynecologic Oncology Group study. J Clin Oncol 14:792-795, 1996

14. Muderspach LI, Blessing JA, Levenback C, et al: A Phase II study of topotecan in patients with squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study. Gynecol Oncol 81:213-215, 2001

15. Miller DS, Blessing JA, Bodurka DC, et al: Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: A phase II study of the Gynecologic Oncology Group. Gynecol Oncol 110: 65-70, 2008

16. Moore DH, Blessing JA, McQuellon RP, 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 22:3113-3119, 2004

17. Long HJ 3rd, Bundy BN, Grendys EC Jr, et al: Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: A Gynecologic Oncology Group study. J Clin Oncol 23:4626-4633, 2005

18. Tewari KS, Sill MW, Long HJ 3rd, et al: Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 370:734-743, 2014

19. Miller DS, Tai DF, Obasaju C, et al: Safety and efficacy of pemetrexed in gynecologic cancers: A systematic literature review. Mod Chemother 2:19-32, 2013

20. Goedhals L, van Wiyk AL, Smith BL, et al: Pemetrexed (Alimta, LY231514) demonstrates clinical activity in chemonaive patients with cervical cancer in a phase II single-agent trial. Int J Gynecol Cancer 16:1172-1178, 2006

21. Lorusso D, Ferrandina G, Pignata S, et al: Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or recurrent carcinoma of the cervix: The CERVIX 1 study of the MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. Ann Oncol 21:61-66, 2010

22. Monk BJ, Sill MW, McMeekin DS, et al: Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: A Gynecologic Oncology Group study. J Clin Oncol 27:4649-4655, 2009

23. London WB, Chang MN: One- and two-stage designs for stratified phase II clinical trials. Stat Med 24:2597-2611, 2005

24. Bloss JD, Blessing JA, Behrens BC, et al: Randomized trial of cisplatin and ifosfamide with or without bleomycin in squamous carcinoma of the cervix: A Gynecologic Oncology Group study. J Clin Oncol 20:1832-1837, 2002

25. Brewer CA, Blessing JA, Nagourney RA, et al: Cisplatin plus gemcitabine in previously treated squamous cell carcinoma of the cervix: A phase II study of the Gynecologic Oncology Group. Gynecol Oncol 100:385-388, 2006

26. Plaxe SC, Blessing JA, Lucci JA, et al: Phase II trial of pyrazoloacridine (PZA) in squamous carcinoma of the cervix: A Gynecologic Oncology Group study. Invest New Drugs 19:77-80, 2001

27. Morris M, Blessing JA, Monk BJ, et al: Phase II study of cisplatin and vinorelbine in squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study. J Clin Oncol 22:3340-3344, 2004

28. Monk BJ, Huang HQ, Cella D, et al: Quality of life outcomes from a randomized phase III trial of cisplatin with or without topotecan in advanced carcinoma of the cervix: A Gynecologic Oncology Group study. J Clin Oncol 23:4617-4625, 2005

29. Long HJ 3rd, Monk BJ, Huang HQ, et al: Clinical results and quality of life analysis for the MVAC combination (methotrexate, vinblastine, doxorubicin, and cisplatin) in carcinoma of the uterine cervix: A Gynecologic Oncology Group study. Gynecol Oncol 100:537-543, 2006

30. Rollins KD, Lindley C: Pemetrexed: A multitargeted antifolate. Clin Ther 27:1343-1382, 2005

31. Shih C, Chen VJ, Gossett LS, et al: LY231514, a pyrrolo[2,3-d]pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. Cancer Res 57:1116-1123, 1997

32. Zhao R, Babani S, Gao F, et al: The mechanism of transport of the multitargeted antifolate (MTA) and its cross-resistance pattern in cells with markedly impaired transport of methotrexate. Clin Cancer Res 6:3687-3695, 2000

33. Wang Y, Zhao R, Goldman ID: Characterization of a folate transporter in HeLa cells with a low pH optimum and high affinity for pemetrexed distinct from the reduced folate carrier. Clin Cancer Res 10:6256-6264, 2004

34. Niyikiza C, Baker SD, Seitz DE, et al: Homocysteine and methylmalonic acid: Markers to predict and avoid toxicity from pemetrexed therapy. Mol Cancer Ther 1:545-552, 2002

35. Bunn P, Paoletti P, Niyikiza C, et al: Vitamin B12 and folate reduce toxicity of ALIMTA (pemetrexed disodium, LY231514, MTA), a novel antifolate/antimetabolite. Proc Am Soc Clin Oncol 20:76a, 2001 (abstr 300)

36. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al: Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 21: 2636-2644, 2003

37. Manegold C, Symanowski J, Gatzemeier U, et al: Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma. Ann Oncol 16:923-927, 2005

38. Bonomi P, Blessing JA, Stehman FB, et al: Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: A Gynecologic Oncology Group study. J Clin Oncol 3:1079-1085, 1985

39. Llombart-Cussac A, Martin M, Harbeck N, et al: A randomized, double-blind, phase II study of two doses of pemetrexed as first-line chemotherapy for advanced breast cancer. Clin Cancer Res 13:3652-3659, 2007

40. Cullen MH, Zatloukal P, Sörenson S, et al: A randomized phase III trial comparing standard and high-dose pemetrexed as second-line treatment in patients with locally advanced or metastatic non-small-cell lung cancer. Ann Oncol 19:939-945, 2008

41. Vergote I, Calvert H, Kania M, et al: A randomised, double-blind, phase II study of two doses of pemetrexed in the treatment of platinum-resistant, epithelial ovarian or primary peritoneal cancer. Eur J Cancer 45:1415-1423, 2009

42. Dowell JE, Dunphy FR, Taub RN, et al: A multicenter phase II study of cisplatin, pemetrexed, and bevacizumab in patients with advanced malignant mesothelioma. Lung Cancer 77:567-571, 2012

43. Moore DH, Tian C, Monk BJ, et al: Prognostic factors for response to cisplatin-based chemotherapy in advanced cervical carcinoma: A Gynecologic Oncology Group study. Gynecol Oncol 116:44-49, 2010

44. Tewari K, Sill M, Monk B, et al: Phase III randomized clinical trial of cisplatin plus paclitaxel vs the non-platinum chemotherapy doublet of topotecan plus paclitaxel in women with recurrent, persistent, or advanced cervical carcinoma: A Gynecologic Oncology Group study. Gynecol Oncol S5, 2013 (suppl; abstr SGO#1)

45. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-216, 2000

46. Cancer Therapy Evaluation Program: Common Terminology Criteria for Adverse Events, Version 3.0, August 9, 2006. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

47. Suzuki M, Tsukagoshi S, Saga Y, et al: Enhanced expression of thymidylate synthase may be of prognostic importance in advanced cervical cancer. Oncology 57:50-54, 1999

48. Saga Y, Suzuki M, Mizukami H, et al: Enhanced expression of thymidylate synthase mediates resistance of uterine cervical cancer cells to radiation. Oncology 63:185-191, 2002

49. Bischof M, Weber KJ, Blatter J, et al: Interaction of pemetrexed disodium (ALIMTA, multitargeted antifolate) and irradiation in vitro. Int J Radiat Oncol Biol Phys 52:1381-1388, 2002

50. Liu Y, Yin TJ, Zhou R, et al: Expression of thymidylate synthase predicts clinical outcomes of pemetrexed-containing chemotherapy for non-small-cell lung cancer: A systemic review and meta-analysis. Cancer Chemother Pharmacol 72:1125-1132, 2013

51. Lee SH, Noh KB, Lee JS, et al: Thymidylate synthase and ERCC1 as predictive markers in patients with pulmonary adenocarcinoma treated with pemetrexed and cisplatin. Lung Cancer 81:102-108, 2013

52. Brade A, Bezjak A, MacRae R, et al: Phase I trial of radiation with concurrent and consolidation pemetrexed and cisplatin in patients with unresectable stage IIIA/B non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 79:1395-1401, 2011

Acknowledgment

The following Gynecologic Oncology Group member institutions participated in this protocol: University of Mississippi, University of Texas Southwestern Medical Center, University of California Medical Center at Irvine, MD Anderson Cancer Center, and University of Oklahoma.