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A Phase I Evaluation of Extended Field Radiation Therapy with Concomitant Cisplatin Chemotherapy Followed by Paclitaxel and Carboplatin Chemotherapy in Women with Cervical Carcinoma Metastatic to the Para-aortic Lymph Nodes: An NRG Oncology/ Gynecologic Oncology Group study

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AUTHOR CONTRIBUTIONS

All authors provided data, were involved in writing, revision, and approved the final manuscript. Dr. Brady performed the statistical analyses of this study.

CONFLICTS OF INTEREST

Dr. Don Dizon reports other from Pfizer, Fuji Pharm, outside the submitted work. Dr. Kathleen Moore reports other from Astra Zeneca, Clovis, Tesaro, Immunogen, and Genentech/Roche, outside of the submitted work. Dr. Aghajanian reports personal fees from Oxigene Steering Committee Meetings, Cerulean Advisory Board, Bayer Advisory Board, and Oxigene Advisory Board. Dr. Aghajanian also reports other from AbbVie as well as travel for investigator meetings x 2, outside of the submitted work. Dr. Fracasso reports that she became an employee of Bristol-Myers Squibb Company (BMS) as of May 1, 2014 and, as such, has stock with the company. Prior to her employment with BMS, she was Professor of Medicine and Obstetrics and Gynecology. This clinical study was done while she was a Professor of Virginia and no activities in this work have any relationship to her work at BMS. All other coauthors have nothing to disclose.

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Abstract

Background: Chemo-radiation (chemoRT) has improved the overall survival for locally advanced cervical cancer (LACC) though women whose disease involves the para-aortic nodes (PAN) experience recurrence rates and worse survival outcomes compared to those without PAN involvement. This Phase I study determined if additional cycles of systemic chemotherapy could be safely added to extended field chemoRT in this population of patients.

Methods: Women with LACC and documented positive PAN were eligible for treatment. All women were treated with extended field radiation and brachytherapy and concurrent cisplatin 40 mg/m² weekly for six weeks. Four to six weeks after completion of chemoRT, patients were treated with four cycles of paclitaxel 135 mg/m² and escalating doses of carboplatin (Dose Level (DL) 1= AUC 4, DL2 = AUC 5).

Results: Eleven women were entered on study and 9 were evaluable for dose limiting toxicities (DLT). Two women (1 in each of 2 DLs) did not complete chemoRT and so were not evaluable for DLT. Three women completed all 10 cycles at DL 1 with no DLTs. Six women were then treated at DL 2. For the 10 patients evaluable for response, the ORR was 60% (CR+PR). PFS and OS at 12 months were 60% and 90%, respectively. The predominant grade 3 or 4 acute toxicities were hematologic. There were no grade 5 events.

Conclusion: Extended field chemoRT followed by paclitaxel 135mg/m² and carboplatin AUC 5 is feasible in women with LACC and positive PAN.

Keywords

cervical cancer; para-aortic nodes; extended field radiation

INTRODUCTION

Despite the introduction of the HPV vaccine in 2006, cervical cancer continues to be a problem in the US, with 12,820 women projected to be diagnosed in the United States in 2017, and 4,210 projected deaths from disease. With the addition of chemotherapy to radiation (chemoRT), progress has been made in the primary therapy of women with locally advanced cervical cancer (LACC).

Of these patients, positive para-aortic node (PAN) involvement is seen in 17%, which represent a small but challenging cohort to treat. In addition, compared to women without PAN involvement, these women have poor outcomes despite definitive chemoradiation, with a high likelihood of recurrence and death from disease. Kim et al reported a compromised 5 year disease free survival rate of 42% versus 73% and a compromised distant failure free survival rate of 47% vs 82% in PAN patients. For PAN patients treated on GOG-0125 with extended field radiation and concomitant 5-FU and cisplatin as radiosensitization, there was a 33% diseasefree survival and a 39% overall survival at 3 years. In RTOG 90-01 the addition of cisplatin and 5-FU to extended field RT alone resulted in an overall reduction in disease recurrence of 51% and improved survival outcomes (41% vs 67%) at 8 years. While

encouraging, both of these studies still demonstrate a high rate of disease recurrence in these high risk women.

Additionally, primary therapy for these women has been felt to carry significant toxicity, either with extended field radiation alone or with concomitant chemotherapy.⁷ In the study by Kim et al, grade 2–4 hematologic toxicity was reported in 52% of patients who received extended field radiation with chemotherapy as compared to 17% in patients treated with radiation alone. In GOG 0125, grade 3–4 acute gastrointestinal toxicity and hematologic toxicity was seen in 18.6% and 15.1% of patients, respectively. Late morbidity at 4 years was seen in 14%. Acute grade 3–4 hematologic and GI toxicity was seen in 39% and 9% respectively of patients receiving chemo-radiation in RT-OG 90–01 as compared to 1.5% and 1% respectively grade 3 toxicity in the extended field radiation alone patients. Long term grade 3–4 GI toxicity was similar in both arms, 13% versus 12%.

Because patients with positive PAN are at significant risk of systemic progression despite standard chemo radiation, the administration of systemic chemotherapy after chemo radiation may improve outcomes. The safety of such a regimen has been supported by several Gynecologic Oncology Group (GOG) trials, albeit not in this precise population. For example, in GOG-9804, extended-field radiation plus paclitaxel and cisplatin (during RT) was found to be tolerable. For women with recurrent cervical cancer (who predominantly had received prior chemo radiation), GOG-0169 and GOG-0179 established the superiority of combination chemotherapy over cisplatin alone. Finally, GOG-0204 established paclitaxel and cisplatin as the standard comparator arm for the subsequently treated randomized trial, GOG-0240, which enrolled a population of women with recurrent, advanced, or metastatic cervical cancer. GOG 240 assessed the addition of bevacizumab both to the standard paclitaxel cisplatin combination as well as to a non-platinum based doublet (paclitaxel plus topotecan) and at the addition of bevacizumab to both chemotherapy regimens. Data from several studies support the use of carboplatin rather than cisplatin in combination with paclitaxel.⁸

Building on these data, we evaluated the safety and efficacy of additional chemotherapy immediately following primary chemoRT in women with newly diagnosed cervical cancer that involved the PAN. We therefore performed a Phase I feasibility study of extended field radiation with weekly cisplatin followed by four cycles of paclitaxel and carboplatin, in a dose-finding design.

MATERIALS AND METHODS

Patients

Women with histologically confirmed cervical cancer (squamous, adenocarcinoma, or adenosquamous) including those FIGO clinical stages IB-IVA were eligible. All participants underwent clinical staging as permitted by FIGO rules. An abdominal and pelvic CT scan with intravenous contrast was required, as was radiologic assessment of the chest with either chest CT or chest x-ray. All patients were required to undergo PET/CT, fine needle aspiration (FNA), or surgical assessment of the para-aortic nodes for confirmation of involvement. Patients were required to have GOG performance status of 0–2; adequate bone

marrow function (absolute neutrophil count (ANC) $\geq 1500/\mu\text{L}$, and platelets $\geq 100,000/\mu\text{L}$); renal function (creatinine $\leq 1.5 \times$ institutional upper limit of normal (ULN) or if ULN, creatinine clearance had to be $>50 \text{ mL/min}$); hepatic function (bilirubin $\leq 1.5 \times$ institutional ULN, and AST, ALT and alkaline phosphatase $\leq 2.5 \times$ institutional ULN); and neurologic function (baseline sensory and/or motor neuropathy) Common Toxicity Criteria grade 1). HIV status was not specifically determined at enrollment.

Patients with ureteral obstruction were allowed but required to undergo stent or nephrostomy tube placement prior to study entry. All patients were required to have an audiogram at baseline, and patients with pre-existing hearing loss or hearing loss during treatment required frequent assessment. Patients were not allowed to receive any previous pelvic or abdominal radiation or any cytotoxic chemotherapy. Patients must have been enrolled prior to chemoRT and were not allowed to enroll in the study for the adjuvant chemotherapy portion only.

All patients signed written, informed consent before study entry in compliance with institutional, state, and federal guidelines.

Treatment plan

Patients received extended field radiation (i.e., a continuous radiation treatment portal encompassing pelvic nodes and para-aortic nodes), for 5 consecutive weeks. The total dose delivered was 4500 cGy in 30 fractions. A five consecutive day parametrial boost was given in the sixth week to boost the parametria to 5400 cGy. Six once weekly cisplatin infusions were coadministered with extended field and parametrial boost radiation. Brachytherapy was completed within three weeks of completion of external beam irradiation. Either LDR or HDR was allowed based on institutional preference. All radiation was required to be completed within 56 ± 3 days of initiation. Adjuvant chemotherapy was administered 4–6 weeks after completion of chemoRT.

Radiation therapy—External beam radiation was delivered using a linear accelerator with a photon energy of 10 MV or greater. Source-to-axis distance (SAD) of 100cm was required. Intracavitary low dose rate (LDR) brachytherapy was delivered using $^{137}\text{cesium}$. Intracavitary high dose rate (HDR) brachytherapy was an allowed alternative and was delivered with $^{192}\text{iridium}$. Intensity modulated radiation therapy (IMRT) and helical tomotherapy (TOMO) were not permitted on this study. All patients were also treated with extended field radiation. Treatment to the extended fields was delivered using a half-beam technique. All fields were treated each day.

Concurrent chemotherapy—Patients received cisplatin treatments as an IV infusion over 1 hour during the radiation therapy at a dose of 40 mg/m^2 (maximum dose of 70 mg) weekly for 6 weeks. Cisplatin infusions were preferably given on Mondays. Dose reductions for toxicity were specified.

Adjuvant chemotherapy—Four to six weeks following completion of chemoRT, patients initiated combination chemotherapy with four cycles of paclitaxel 135 mg/m^2 over 3 hours

and escalating doses of carboplatin AUC 4 (DL 1) or AUC 5 (DL 2) administered every 3 weeks.

Evaluation of toxicity, dose modifications, and assessment of response:

Toxicities throughout the study were graded according to National Cancer Institute Common Toxicity Criteria Adverse Events version 4.0 (CTCAE v4.0). Dose limiting toxicities (DLTs) were determined in the first cycle of adjuvant chemotherapy (after completion of chemoRT). Dose limiting hematologic toxicities were defined as the following: dose delay > 3 weeks due to failure to recover counts, febrile neutropenia, grade 4 neutropenia for greater than 7 days, and grade 4 thrombocytopenia or clinically significant bleeding associated with grade 3 thrombocytopenia. Dose limiting non-hematologic toxicities were defined as non-hematologic grade 3 or 4 toxicity with the exception of grade 3–4 allergic/hypersensitivity reaction and grade 3 anorexia, constipation, fatigue, nausea and/or vomiting lasting <48 hours, dehydration or electrolyte abnormalities resulting from nausea and vomiting lasting <48 hours, and UTI with a normal ANC. Additional toxicity data was collected up to one year from enrollment.

Dose modifications during adjuvant chemotherapy included delays in treatment and/or dose reductions in chemotherapy. Chemotherapy was held if the ANC <1,500/mcl and the platelet count <100,000/mcl for a maximum of 3 weeks. Patients with dose delays for hematologic toxicity greater than 3 weeks were removed from study. Dose reductions for the most common hematologic toxicities such as febrile neutropenia, ANC <500/mcl lasting >7 days associated with grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding, carboplatin was reduced from AUC 5 to 4 for the first occurrence. On the second occurrence, paclitaxel was reduced to 110 mg/m² and G-CSF was added and following the third occurrence, therapy was discontinued. For grade 4 uncomplicated neutropenia lasting < 7 days, there was no dose modifications. For grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding, carboplatin was reduced from AUC 5 to 4. On the second occurrence, paclitaxel was reduced to 110 mg/m², and following the third occurrence, therapy was discontinued. For grade 3 or 4 neurotoxicity, paclitaxel and carboplatin were dose reduced and therapy was delayed until recovery to grade 1. If the neurotoxicity did not recover to grade 1 in 21 days, therapy was discontinued.

Antitumor response was evaluated by physical examination and imaging by CT scans. CT scans were obtained following completion of treatment and then every 6 months for 1 year. Responses were defined by Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1). Responses (CR and PR) required confirmation at greater than or equal to 4 weeks from initial documentation

Statistical design

This study was designed to evaluate the maximum tolerated dose (MTD) and feasibility of the study regimens by assessing the tolerability through dose limiting toxicities (DLTs). The study had two phases: a dose-escalation phase to determine the MTD of carboplatin in combination with paclitaxel given as adjuvant chemotherapy based on DLTs in the first cycle, and a feasibility phase in which the feasibility of the regimen was examined by

evaluating DLTs over four cycles. The primary parameters employed to assess toxicity and efficacy was: adjuvant chemotherapy first-cycle DLTs in the dose escalation phase for evaluation of the MTD and toxicities. Secondary endpoints included response rates in patients enrolled with measurable disease, progression free survival and overall survival, and chronic toxicities experienced within one year of study entry.

RESULTS

Patient characteristics

Baseline characteristics for the study patients are shown in Table 1. The majority of patients were under 50 years old (8/11, 73%) and white (10/11, 91%). All patients but one had squamous cell carcinoma.

Eleven patients were accrued to the study, and of these, two did not complete chemoRT and are therefore not evaluable for DLT. Of the remaining 9 women, three were treated at DL1 and six were treated on DL2. One patient in DL1 discontinued study treatment in the chemoRT portion after receiving three cycles of cisplatin due to a decline in performance status (PS=3) after suffering a traumatic stroke. She did complete radiation and is included in response assessment data. One patient in DL2 never received any study treatment and withdrew consent for study participation shortly after enrolling. She was lost to follow up and is not included in response assessment.

At DL1, all three patients completed four cycles of systemic chemotherapy as planned without a DLT. At DL 2, three of six patients completed all planned cycles of systemic therapy while one patient came off study due to a DLT after one cycle of carboplatin and paclitaxel, one declined further treatment after two cycles, and one came off treatment after three cycles due to thrombocytopenia that resulted in a >3 week delay. One DLT was seen consisting of a dose delay for greater than 3 weeks due to grade 3 thrombocytopenia and leukopenia after the first cycle of carboplatin and paclitaxel. As five patients completed the first cycle of chemotherapy, this was the MTD. Higher dose levels were not planned as higher doses of carboplatin and/or paclitaxel were felt not to be feasible after extended field chemoRT.

Acute treatment related grade 3–4 adverse events by dose level are shown in Table 2. The majority of the adverse events were hematologic and grade 3. Chronic toxicities related to treatment were assessed up to one year following study entry. There were no grade 3 or 4 chronic adverse events recorded. There were no grade 5 acute or chronic adverse events.

Objective tumor response by dose level is summarized in Table 3. In the ten patients with measurable disease, the ORR was 60% (CR+PR). The ORR in DL1 was 75% and 50% in DL2. Progression-free survival (PFS) and overall survival (OS) at 12 months are summarized in Table 4 and shown in Figure 1. Two patients died of disease and one died of other causes.

DISCUSSION

Despite effective screening and the advent of HPV vaccination, there is still an appreciable incidence of LACC. Women with para-aortic node positive LACC present a special

challenge with respect to treatment: the extended field radiation required for treatment is more toxic and they are more likely to experience recurrent disease. Because of this, these women are often specifically excluded from clinical trials designed to improve outcomes with respect to primary therapy in LACC. The addition of chemotherapy to radiation in the late 1990's improved overall survival rates considerably, but a significant proportion of women with cervical cancer still die of disease.

The concept of adjuvant or “outback” chemotherapy, with systemic chemotherapy given following completion of chemoRT, is aimed at improving disease control and cure rates. Introducing additional chemotherapeutics during primary radiotherapy as well as after completion of chemo-radiation may reduce the risk of development of drug resistance and therefore improve disease control. Duenas-Gonzalez and colleagues have published the results of an international trial utilizing this approach. Five hundred fifteen women with Stages IIB-IVA cervical carcinoma were randomized to standard chemo radiation using cisplatin versus an experimental regimen of cisplatin 40 mg/m² and gemcitabine 125 mg/m² during radiotherapy followed by two further cycles of cisplatin 50 mg/m² and gemcitabine 1,000 mg/m² on Days 1 and 8, every 21 days. There was a statistically significant improvement in progression-free survival at 3 years with the experimental treatment compared to standard cisplatin-based chemo radiation (74.4% vs. 65%, $p=0.029$), which was coupled with a 32% improvement in overall survival ($p=0.0224$). When rates of local and distant failures were reported, the benefit of the more aggressive regimen was seen in a statistically significant reduction in distant failures, 8% in the experimental arm versus 16% in standard arm ($p=0.005$); the differences in the local failure rate were not statistically significant, 11% versus 16%, respectively ($p=0.097$). The ongoing ANZGOG-0902/GOG-0274/RTOG-1174 trial is also a randomized trial that is randomizing women with LACC to receive standard chemoRT versus standard chemoRT with an additional 4 cycles of systemic chemotherapy. However, as with previous studies, both of these studies exclude patients who are para-aortic node positive due to toxicity concerns, specifically the lack of phase I data in this patient population. Nevertheless, these are the women who are expected to benefit the most from this additional post chemoRT therapy.

ANZGOG-0902/GOG-0274/RTOG-1174, a phase III randomized trial that considers a regimen similar to the one in the current study, although notably extended field radiation is not permitted. Patients on this trial are randomized to receive chemoRT versus chemoRT plus adjuvant paclitaxel and carboplatin for four cycles. They are treated with cisplatin IV for 5 weeks (not 6). Beginning 4 weeks following completion of radiation, patients are prescribed adjuvant chemotherapy (so-called outback chemotherapy) consisting of paclitaxel IV over 3 hours at a dose of 155 mg/m² and carboplatin IV over 1 hour at an AUC 5, every 21 days for 4 courses. This study has completed accrual; results are eagerly anticipated. This phase III randomized trial will establish the role (or lack thereof) of adjuvant chemotherapy in this patient population. It will not, however, answer the question of whether this regimen is tolerable in patients who receive extended field radiation, the subjects of the current study.

The primary concern of the adjuvant chemotherapy in the population of patients that require extended field radiation is toxicity, especially hematologic toxicity. The extended field exposes a greater percentage of bone marrow to radiation, thus potentially limiting a

patients' ability to tolerate further adjuvant cytotoxic chemotherapy. Additionally, more healthy tissue, especially the small bowel, is included in the radiation treatment field and therefore at risk for more gastro-intestinal (GI) toxicity. Thus, we anticipated that the treatment of these patients would be limited by both hematologic and GI toxicity.

The primary objectives of the current study were to determine the MTD and DLT of adjuvant carboplatin and paclitaxel chemotherapy following chemoRT with extended field radiation in women with LACC and positive para-aortic nodes, to determine feasibility of this regimen once the MTD was determined, and to assess the toxicities of the regimen. The study was designed with two dose levels of carboplatin given with a fixed dose of paclitaxel, chosen based on likelihood of tolerability after extended field chemoRT. No DLTs were observed at the first dose level and only one was observed at the second dose level. The observed toxicities were consistent those with expected. The regimen was determined to be tolerable. No grade 3–5 adverse events were observed at 1 year of follow-up. Data on late (>1 year) manifestations of extended field radiation plus chemotherapy toxicity was not collected so we are unable to comment on the long term risks of this approach. While our current study was not designed to determine response rate, PFS, or OS as primary endpoints, we saw evidence of efficacy in this small group of women who are at very high risk for disease recurrence with a CR of 50% and a PR of 10% for and ORR of 60%.

Treatment of para-aortic node positive cervical cancer patients remains challenging. Currently available treatment with extended field chemoRT has significant toxicity and is not always completely efficacious, as we observed. The addition of adjuvant chemotherapy can be safely tolerated as demonstrated in this study. However, this approach is not sufficient for all patients, with an ORR of 60%. This study was designed to be a companion study to the ANZGOG-0902/GOG-0274/RTOG-1174 study to specifically address the PA node positive patients. A lower dose of adjuvant paclitaxel was chosen due to the expectation that this cohort would experience greater hematologic toxicity. A more thoughtful commentary on the efficacy of this approach in the front line setting awaits the mature data from the PA node negative study. Studies in Stage IVb and recurrent cervical cancer have shown benefit of the addition of novel approaches such as biological therapies in this patient population. GOG 240 established that the addition of bevacizumab to chemotherapy doublets in Stage IVb and recurrent disease improved overall survival. Pembrolizumab has shown activity in PDL1 positive recurrent cervical cancer and was recently granted FDA approval. Certainly, the benefit of these novel approaches in recurrent disease brings the hope that, if incorporated into the front line setting, these high risk patients may benefit even further with higher response rates. While not the subject of this study, certainly further evaluation of the addition of biological therapies that achieve better systemic consolidation may allow for treatment with more tailored and smaller radiation fields or even perhaps with the omission of radiation entirely in order to mitigate toxicity. Ultimately, continued exploration of novel approaches to achieve better consolidation of systemic risk with novel agents with more tolerable side effect profiles in the front line setting is needed.

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The following Gynecologic Oncology Group member institutions participated in the primary treatment studies: University of Oklahoma Health Sciences Center, Case Western Reserve University, Women and Infants Hospital, and the Hospital of Central Connecticut.

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RESEARH HIGHLIGHTS

- Phase I Study of sequential Extended Field ChemoRT and combination chemotherapy
- Phase I study for primary therapy of Para-aortic Node Positive Cervical Cancer
- Adjuvant chemotherapy in the primary management of advanced cervical cancer
- Safety and feasibility of Paclitaxel and Carboplatin after extended field RT

Figure 1:
Progression-free Survival (PFS) and Overall Survival (OS)

Table 1.

Patient demographics

	All n (%) (N=11)
Age (years)	
Mean	42
Minimum - maximum	26 – 67
Age (years), n (%)	
20–29	3 (27%)
30–39	3 (27%)
40–49	2 (18%)
50–59	1 (9%)
60–69	2 (18%)
Ethnicity, n (%)	
Hispanic or Latino	1 (9%)
Non-Hispanic	9 (82%)
Unknown/Not specified	1 (9%)
Race, n (%)	
White	10 (91%)
Unknown	1 (9%)
Performance Status, n (%)	
0	8 (73%)
1	3 (27%)
Cell Type, n (%)	
Adenocarcinoma, Unsp.	1 (9%)
Squamous Cell Carcinoma	10 (91%)
Measurable Disease, n (%)	
No	1 (9%)
Yes	10 (91%)

Table 2.

Treatment related grade 3–4 events.

System Organ Class/Term	Treatment/Adverse Carboplatin AUC 4 + Paclitaxel 135 mg/m2		Event Grade Carboplatin AUC 5 + Paclitaxel 135 mg/m2	
	G3	G4	G3	G4
Anemia	1	0	3	0
Fatigue	2	0	0	0
Neutrophil count decreased	1	1	3	1
Platelet count decreased	0	0	2	0
White blood cell decreased	2	1	4	1
Anorexia	1	0	0	0
Hypokalemia	0	0	0	1
Back pain	1	0	0	0
Peripheral sensory neuropathy	1	0	0	0

Table 3.

Objective tumor response in measurable disease patients (N=10)

Objective Tumor Response	All n (%) (N=10)	Dose Level	
		Carboplatin AUC 4 + Paclitaxel 135 mg/m ² n (%) (N=4)	Carboplatin AUC 5 + Paclitaxel 135 mg/m ² n (%) (N=6)
Complete Response	5 (50%)	3 (75%)	2 (33%)
Partial Response	1 (10%)	0 (0%)	1 (17%)
Stable	2 (20%)	0 (0%)	2 (33%)
Indeterminate	2 (20%)	1 (25%)	1 (17%)

Table 4.

Progression-Free Survival and Overall Survival

Endpoint	Median (95% CI) (months)	12-Month Percentage (95% CI)
Progression-Free Survival	>46 (5.7, >46)	60% (25%, 83%)
Overall Survival	>46 (8.4, >46)	90% (47%, 99%)