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A Phase I Study of Concurrent Weekly Topotecan and Cisplatin Chemotherapy with Whole Pelvic Radiation Therapy in Locally Advanced Cervical Cancer: a Gynecologic Oncology Group Study

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Abstract

Purpose—To determine the maximum tolerated dose (MTD) and acute dose-limiting toxicities (DLT) of intravenous topotecan administered with weekly cisplatin during pelvic radiation therapy in patients with locally advanced cervical cancer.

Methods—Patients were treated at one of two dose levels receiving intravenous topotecan at 0.5 mg/m² and cisplatin at either 30 or 40 mg/m² given weekly for 6 weeks concurrently with pelvic radiation and intracavitary brachytherapy. The primary endpoint for the escalation study was acute dose-limiting toxicities occurring within 30 days of completing radiation therapy.

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Conflict of Interest Statement

The authors wish to report that there are no conflicts of interest.

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Results—Eleven patients were enrolled. Dose-limiting toxicity consisting of Grade 3 nausea and vomiting lasting > 24 hours in one patient and grade 3 febrile neutropenia in another patient occurred at the first dose level of weekly topotecan 0.5 mg/m² and cisplatin 40 mg/m². This necessitated de-escalation to weekly cisplatin 30 mg/m² in combination with topotecan 0.5 mg/m² and pelvic radiation. This dose level was tolerable in 6 evaluable patients with only one DLT consisting of grade 4 thrombocytopenia, grade 3 abdominal pain and grade 3 elevated gamma glutamyl transpeptidase (GGT).

Conclusions—In women with locally advanced cervical cancer, intravenous topotecan 0.5 mg/m² and cisplatin 30 mg/m² given weekly for 6 weeks with concurrent pelvic radiation and intracavitary brachytherapy was tolerable. Further expansion of the feasibility cohort of this study was suspended based on the results of a phase 3 trial comparing the efficacy of platinum combinations in advanced and recurrent cervical cancer.

Introduction

Cisplatin-based chemoradiation has been demonstrated to be superior to radiation therapy alone in five randomized trials.^{1–6} In 1999, cisplatin-based chemoradiation therapy was formally recommended by the NCI as a new standard for cervical cancer.⁷ However, despite concurrent cisplatin-based radiation, failure of tumor control within the radiation field continues to represent a therapeutic problem. A randomized trial by the Gynecologic Oncology Group (GOG) compared weekly cisplatin with infusional 5-fluorouracil. The study was stopped during the interim analysis when the risk of disease progression was greater in the infusional 5-fluorouracil arm with a hazard ratio of 1.33, and it was evident that this regimen would not be superior to cisplatin.⁸ The GOG is intent on developing new chemoradiation regimens that will include cisplatin to further build on the current success of cisplatin chemoradiation.

Topotecan, a specific inhibitor of topoisomerase-I, has demonstrated activity in recurrent cervical cancer.⁹ The combination of topotecan and cisplatin demonstrates schedule dependent synergy in preclinical models.¹⁰ Clinical trials of the combination have found a schedule dependent increase in myelosuppression when cisplatin precedes topotecan.¹¹ However, the myelosuppressive effects of topotecan are decreased when it is administered on a weekly schedule.¹² In cervical cancer, the combination of cisplatin and topotecan is active¹³. Specifically, the combination of cisplatin and topotecan improved the response rate, progression-free survival and overall survival compared to cisplatin alone.¹⁴ Since cisplatin-based combination therapy has demonstrated increased efficacy in cervical cancer patients with advanced or recurrent cervical cancer^{14,15}, it seems reasonable to see if these combinations can be delivered with concurrent radiation therapy.

Topotecan is a chemotherapeutic agent that has demonstrated efficacy as a radiation sensitizer.^{16–18} A number of phase II trials utilizing topotecan have been completed or are underway.^{19,20} At ASCO 2005 a phase I trial of weekly cisplatin and continuous infusion topotecan was reported. The continuous infusion of topotecan 0.15 mg/m²/d daily for 5 days each week during radiation therapy in combination with cisplatin 20 mg/m² weekly was well tolerated and clinically active with a 94% complete response rate and disease free

survival at 6 months among stage IB₂–IVA.²¹ One of the more serious adverse events found when using this combination was thromboembolic complications. Some of the other adverse events reported on this trial included lymphopenia, leukopenia, neutropenia, lymphocysts, coagulation difficulties, fatigue, gastrointestinal problems, and non-neutropenic fever. Some patients also required blood transfusions during treatment.

This current study was planned as both a dose finding study and a feasibility study. In the Phase I dose finding study, the maximum tolerated dose and dose-limiting toxicities of topotecan that can be administered weekly with cisplatin during pelvic radiation therapy would be estimated. If there was sufficient interest in pursuing a phase III study, a feasibility study would be conducted to further assess acute and chronic treatment toxicity as well as the progression-free survival and overall survival at the established MTD.

Methods

Eligibility criteria

Patients 18 years of age were eligible if they had primary, previously untreated, histologically confirmed by original institution, invasive carcinoma of the uterine cervix. Patients were required to have a Clinical Stage IB₂, IIA, IIB, IIIB, or IVA cancer with negative para-aortic lymph nodes by radiologic evaluation or biopsy. Patients must have had adequate bone marrow, renal and hepatic function defined as; absolute neutrophil count 1,500/mcl; platelet count 100,000/mcl; creatinine 1.5 times upper institutional normal; bilirubin 1.5 times upper limit of normal; and SGOT and alkaline phosphatase 2.5 times upper limit of normal. Patients with ureteral obstruction must have been treated with stent or nephrostomy tube to maximize renal function before enrollment. Additionally, patients were required to have a GOG Performance Status of 0, 1, or 2 and no history of prior malignancy evident within the last 5 years. Patients with severe infection, pregnant patients who did not wish pregnancy termination prior to treatment, patients with renal abnormalities, such as pelvic kidney, horseshoe kidney, or renal transplantation, that would require modification of radiation fields, and patients whose circumstances would not permit completion of this study or the required follow-up were ineligible. All patients gave written informed consent before study entry in compliance with institutional, state, and federal regulations.

Staging was performed by standard FIGO criteria although cystoscopy, proctoscopy, and barium enema were optional. Additionally, all patients were required to undergo an abdominal and pelvic CT scan with intravenous contrast, while lymphangiography or ultrasound was considered optional. Those patients who have positive or suspicious para-aortic nodes on lymphangiography, CT scan, or ultrasound examinations were required to undergo a fine needle aspiration (FNA) or extraperitoneal lymph node biopsy. Those patients with negative radiologic evaluation for para-aortic adenopathy were not required to have cytologic or histologic confirmation.

Treatment

Radiation therapy consisted of both external and intracavitary radiation therapy which was to be completed within 8 weeks. External radiation therapy consisted of 45 Gy external

beam delivered homogeneously to the pelvis in 25 fractions of 180 cGy utilizing a four-field box technique. Either low dose rate or high dose rate brachytherapy was allowed and had to be specified upon enrollment. For patients receiving low dose rate brachytherapy a dose of 40.0 Gy to Point A by intracavitary implant with radium or its equivalent in one or two applications was planned. The first implant was to be performed immediately following external radiation therapy, and if two implants were used, the second implant must have been completed within three weeks of the completion of external radiation therapy. High dose rate brachytherapy consisted of five fractions of 600cGy per fraction for a total dose of 30 Gy to Point A. High dose rate brachytherapy was scheduled to begin on week 4 with at least one implant per week with no external radiation therapy given on the day of the insertion. Two implants per week could be performed but must have been separated by at least 72 hours. If intracavitary RT could not be performed, shrinking field technique was performed to bring gross tumor volume with adequate margins to a minimum of 65 Gy. Interstitial brachytherapy was not permitted and if delivered was considered a major treatment deviation.

Chemotherapy was planned on days 1, 8, 15, 22, 29 and 36 of external radiation therapy (preferably Mondays), approximately four hours prior to radiation. Weekly topotecan (Hycamtin®, GlaxoSmithKline) at 0.5 mg/m² was administered as a 30 minute infusion for 6 weeks. Topotecan was to be dose escalated by 0.5 mg/m² increments to 3.0 mg/m² if tolerated with cisplatin. Weekly intravenous cisplatin at 40 mg/m² (maximum total dose 70 mg/week) was administered at a rate of 1 mg/min immediately after topotecan. Due to dose limiting toxicity at the dose level 1 (topotecan 0.5 mg/m² and cisplatin 40 mg/m²), cisplatin was dose reduced to 30 mg/m² (maximum total dose 60 mg/week) with topotecan 0.5 mg/m² for dose level 2, and no further escalation of topotecan was performed.

Evaluation of toxicity, dose modifications, and assessment of response

Patients were eligible to continue treatment unless there was evidence of unacceptable toxicity or progressive disease. Toxicities were graded in accordance with the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. Dose-limiting toxicities were identified by certain toxicities considered severe and observed during any of the six treatment cycles or within four weeks following completion of treatment. Dose-limiting toxicities were defined as grade 4 neutropenia (ANC < 500/mcL) lasting > 7 days, grade 3 or 4 neutropenia (ANC <1,000/mcL) of any duration associated with fever (≥ 38.5°C) requiring antibiotics, grade 4 thrombocytopenia (platelets < 20,000/mcL), grade 3 or 4 thrombocytopenia (platelets < 50,000/mcL) associated with bleeding requiring platelet transfusion, any grade 3 or higher non-hematological toxicity (excluding grade 3 nausea and vomiting ≥ 24 hours or grade 3 diarrhea leading to a cumulative treatment delay of ≥ 6 days, and grade 3 hypokalemia, hypomagnesemia, hypocalcemia, hypophosphatemia, and hyponatremia), or any treatment-related toxicity causing a delay in radiation more than 1 week or causing the radiation treatment to extend more than 8 weeks.

A complete blood count was obtained weekly during treatment, and twice weekly if the ANC <1,000/mcL or platelet count <50,000/mcL. On the day of treatment, chemotherapy was held if the ANC < 500/mcL and the platelet count < 50,000/mcL. If withholding the

chemotherapy for one week did not resolve the neutropenia and thrombocytopenia, then radiation was held until the ANC > 500/mcL and platelet count >50,000. Both chemotherapy (at a dose level reduction) and radiotherapy were able to resume with the ANC >500/mcL and the platelet count >50,000/mcL. In addition, both chemotherapy and radiotherapy were interrupted for grade 3 or 4 neutropenia associated with fever ($>38.5^{\circ}\text{C}$) requiring antibiotics, grade 3 or 4 platelet count with bleeding, and any grade 3 non-hematologic toxicities excluding nausea and vomiting except when requiring hospitalization for intravenous fluids. Treatment delays of up to one week were allowed for recovery of toxicities.

Antitumor response was evaluated by physical examination and/or imaging pre-study, one-month post-treatment. Responses were defined by Response Evaluation Criteria in Solid Tumors (RECIST) [19].

Statistical considerations

The primary objective of this dose finding study was to estimate the maximum tolerated dose (MTD) and its associated acute toxicities of weekly topotecan and cisplatin with concurrent radiation therapy. Acute toxicity was defined by events having onset during or within 30 days of completing therapy. A cohort of three patients was to be treated at each dose level of topotecan and cisplatin and if they successfully completed radiation therapy and 6 weekly treatments of chemotherapy followed by four weeks of follow-up without a DLT, dose escalation continued. If a dose-limiting toxicity occurred in one of the three patients treated at a given dose level, up to three additional patients were treated at that dose level. If two patients at any dose level experienced a DLT, enrollment at this dose level would be terminated; in this case, an additional three patients would be entered at the previous dose if only three patients had previously been entered at that dose level to be sure that no more than one patient in six experiences a DLT. If two or more patients experience a DLT, de-escalation would continue. The maximum tolerated dose (MTD) of weekly topotecan, cisplatin, and concurrent pelvic radiation was estimated by the highest dose level where less than two out of six patients experienced a dose-limiting toxicity. It was anticipated that the primary dose-limiting toxicities would be hematologic, with modifications in chemotherapy dose considered when dose-limiting events became apparent as described above.

Results

Patient characteristics

Eleven eligible patients were enrolled from October 2007 to March 2010 and their characteristics are summarized in Table 1.

Treatment, toxicities, and response

Eleven patients received sixty-three doses of the topotecan/cisplatin combination therapy (median of 6 cycles), and all were evaluable for toxicity. Nine patients were evaluable for dose-limiting toxicities over the full course of treatment (3 in dose level 1 and 6 in dose level 2). Two patients in dose level 2 received the wrong dose of cisplatin.

From October to December 2007, three patients were treated on dose level 1 (topotecan 5 mg/m² and cisplatin 40 mg/m²). Two of the three patients had dose limiting toxicities. One patient had grade 3 nausea and vomiting >24 hours on week 4. The other patient had grade 3 neutropenic fever (DLT). Because it was felt that the nausea and vomiting may have been related to a cisplatin toxicity, the decision was made to decrease the dose of cisplatin to 30 mg/m² and to reopen the study.

Eight patients were enrolled on dose level 2 (topotecan 5 mg/m² and cisplatin 30 mg/m²) from May 2009 to March 2010. Two patients received the wrong dose of cisplatin (40 mg/m²) for 5 of the 6 weekly treatments, and because of this, they were not considered evaluable. While one of the patients had no significant toxicities, the other patient was hospitalized with grade 4 hypokalemia, grade 3 abdominal pain and grade 3 infection (urinary tract) with grade 4 neutrophils. A third patient received the wrong dose of cisplatin (40 mg/m²) for only the first week of the 6 weekly treatments. After the third weekly treatment of cisplatin, this patient had a DLT consisting of grade 4 thrombocytopenia, grade 3 abdominal pain, and grade 3 gamma glutamyl transpeptidase (GGT). The remaining 5 patients were treated at the appropriate cisplatin dose and completed the 6 weeks of chemotherapy in combination with radiotherapy without a DLT. Since 5 of 6 patients were treated at this dose level without a DLT, the MTD was declared.

A complete response rate and durable local control was seen in 9/11 (82%) with 7/11 (64%) currently disease-free and at a median follow up of 24 months (range 16–46). In view of the results of a phase III study comparing four platinum-based combinations in advanced and recurrent cervical cancer, in which a trend in response rate, progression-free and overall survival favored cisplatin and paclitaxel, we decided not to proceed to the feasibility phase of the study.²²

Discussion

This study was undertaken to determine the maximum dose of topotecan that could be administered before cisplatin weekly with concurrent pelvic radiation therapy. Although a dose intensive schedule of topotecan up to 3.0 mg/m² weekly was planned, dose limiting toxicity occurred at the lowest dose level 0.5 mg/m² weekly. In fact, this topotecan dose could only be delivered with cisplatin after decreasing the dose of cisplatin from 40 mg/m² to 30 mg/m² weekly. Additionally, despite the less myelosuppressive sequence of the drug administration, topotecan followed by cisplatin, hematologic toxicity was still the dominant toxicity.

Since the design and conduct of this trial, three studies have been published which are relevant to our study and the future trials of chemoradiation. The first is a phase II feasibility trial of the same combination with pelvic radiation for locally advanced cervical cancer conducted at University of California at Irvine.²³ This trial of 12 patients delivered cisplatin 40 mg/m² weekly followed by topotecan 2.0 mg/m². Only one patient was able to complete all 6 cycles of therapy. Treatment delays were reported in 54% of patients, with all patients receiving four cycles and 82% receiving five of the intended six cycles. Dose delays were most common in cycles 4 and 5 (84% of all delays). At least one-third of the patients had

radiation delayed for more than 8 weeks, and 17% of patients were delayed more than 10 weeks. This may be relevant since delays in radiation treatment are associated with decreased cure rates when radiation alone is given for cervical cancer.²⁴ In the current GOG study, radiation treatment was to be completed by 8 weeks and delays of greater than 1 week beyond that point precluded planned dose escalation.

The second study is the randomized four arm study of cisplatin based combinations in advanced and recurrent cervical cancer.²² This trial was closed for futility when on interim analysis of 513 patients it was evident that trends in response rate, progression-free survival and overall survival favored the cisplatin/paclitaxel combination. Furthermore, the percentage of patients who had received prior chemoradiation with cisplatin in GOG 169 which studied the combination of cisplatin and paclitaxel and GOG 179 which studied the combination of cisplatin and topotecan was 40% and 56%, respectively. In GOG 179, the response rate in the control arm of cisplatin alone was 8% for patients who had prior cisplatin-based chemoradiation and 20% for patients who were chemoradiation naïve. The reason the cisplatin and topotecan was statistically better in all measures of antitumor activity is because the control group of cisplatin alone performed so badly in this heavily cisplatin pre-exposed population. When comparing experimental combinations in GOG 179 to 169 the response rate (26% vs 37%), progression-free survival (4.6 months vs 4.8 months) and overall survival (9.2 months vs 9.7 months) are all inferior with the cisplatin and topotecan combination. With this finding, our interest of developing the cisplatin/topotecan in combination for further phase III development diminished. The GOG had already completed two trials with concurrent cisplatin and paclitaxel for patients with pelvic radiation therapy only or pelvic and extended field radiation therapy (GOG 9803 & 9804). This regimen was tolerable and appeared efficacious.^{25,26}

The third major study that is relevant is the trial of concurrent chemoradiation with cisplatin and gemcitabine followed by adjuvant cisplatin and gemcitabine compared to chemoradiation with weekly cisplatin alone.²⁷ This large multinational trial demonstrated significant improvement in PFS and survival with statistically significant hazard ratios that are as impressive as those originally reported with cisplatin-based chemoradiation. However, the toxicity of the cisplatin/gemcitabine combination was noted to be unacceptably high by two American studies and confirmation of this important trial is awaited.^{28,29} Whether the benefit seen in this trial was due to the combination of cisplatin/gemcitabine chemotherapy as a radiation sensitizer or due to the adjuvant cisplatin/gemcitabine chemotherapy following radiation is indiscernible. To address the role of adjuvant chemotherapy a large trial of cisplatin chemoradiation with randomization to 6 cycles of adjuvant chemotherapy with cisplatin and paclitaxel is planned.

The phase III randomized GOG trial of weekly cisplatin chemoradiation versus cisplatin/tirapazamine for women with newly diagnosed locally advanced cervical cancer was closed due to shortages of tirapazamine and the replacement study has not yet been initiated. The role of biologic therapy is being evaluated in a phase II trial of cisplatin and cetuximab with concurrent radiation with results awaited. Additionally, bevacizumab which has demonstrated activity in metastatic cervical cancer has not been evaluated with concurrent radiation therapy. The current study demonstrates that the combination of weekly cisplatin

30 mg/m² and topotecan 0.5 mg/m² with concurrent pelvic radiation therapy has acceptable toxicity. Given our experience with non-cisplatin regimens and the impressive efficacy of the cisplatin/gemcitabine combination further efforts to develop cisplatin-based combinations seem warranted.

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Research Highlights

- A phase I study was conducted of intravenous topotecan and intravenous cisplatin administered weekly with radiation for locally advanced cervical cancer.
- Hematologic toxicity was dose limiting.

Table 1

Patient characteristics.

Characteristic	No. patients (<i>n</i> = 11)
Age (y)	
Median (range)	42 (25–65)
GOG performance status	
0	10
1	1
Race	
American Indian or Alaska Native	2
Black or African-American	1
White	8
Histology	
Squamous cell	11
Stage	
IB2	1
IIB	7
IIIB	3
Grade	
1	1
2	7
3	3

Abbreviation: GOG, Gynecologic Oncology Group.

Table 2

Incidence of hematological and non-hematologic toxicity.

Adverse event Grade of adverse event	Dose Level									
	1 (n = 3)					2 (n = 8)				
	1	2	3	4	1	2	3	4	1	2
Blood/Bone Marrow										
Hemoglobin					2	1			7	1
Neutrophils					1	1	1 [^]	1	2	3 [†]
Platelets	1				1	1		1	1	2 ^{##}
Constitutional Symptoms										
Fatigue					1			4	3	
Fever	1							2	1	
Gastrointestinal										
Constipation								4	1	
Diarrhea	1	1						3	4	
Nausea/vomiting						2 [*]		6	2	
Infection/Febrile Neutropenia										
Febrile neutropenia					1 [^]					
Infection with Gr. 3/4 neutrophils – urinary tract								1	1 [†]	
Metabolic/Laboratory										
Albumin, serum-low	1	2						3		
ALT, SGPT	1							1	1	
AST, SGOT	1							1	1	
Calcium, serum-low	1	2						2	2	
GGT								1	1 [#]	
Magnesium, serum-low	1							3		
Potassium, serum-low	1							2	1	1 [†]
Sodium, serum-low	2							1	3	
Neurology										
Neuropathy - sensory					1			4		
Pain										

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Adverse event Grade of adverse event	Dose Level									
	1 (n = 3)			2 (n = 8)			2 ^{#†}			
Abdomen, NOS	1	2	3	4	1	2	3	4		

Dose level 1: DLTs - *one patient with grade 3 nausea/vomiting and ^one patient with grade 3 febrile neutropenia.
Dose level 2: DLT- #one patient with grade 4 thrombocytopenia, grade 3 abdominal pain, and grade 3 GGT.
No DLT- [†]one patient with grade 4 thrombocytopenia, grade 4 hypokalemia, grade 3 infection (urinary tract) with grade 4 neutrophils, and grade 3 abdominal pain (see text).