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# A feasibility study of topotecan with standard-dose cisplatin and concurrent primary radiation therapy in locally advanced cervical cancer<sup>☆</sup>

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## Abstract

**Objectives.** Topotecan improves response rate (RR), progression-free survival (PFS) and overall survival (OS) when added to cisplatin in treating metastatic and recurrent cervical cancer. The objective of this study was to assess the feasibility of adding weekly topotecan to cisplatin in patients with *primary*, locally advanced carcinoma of the cervix receiving pelvic irradiation.

**Methods.** Patients with primary, previously untreated, histologically confirmed invasive squamous cell, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix, stages IB2–IVA were treated with external beam pelvic radiotherapy (45 Gy), intracavitary low dose rate brachytherapy (40 Gy) and a parametrial boost (5.4–9 Gy) with overall treatment time not to exceed 8 weeks. Concurrent chemotherapy was IV cisplatin 40 mg/m<sup>2</sup> plus IV topotecan 2 mg/m<sup>2</sup> on days 1, 8, 15, 22, 29 and once during parametrial boost for 6 cycles. Patients were monitored with history, physical examination, tumor measurement and laboratory evaluation before entering the study, before each cycle of chemotherapy, at study termination and every three months thereafter.

**Results.** The study met its accrual goal of 12 patients. With a median follow-up of 22 months, eleven patients completed treatment and ten are in long term follow up without evidence of recurrent disease. The 12th patient developed progressive disease during therapy. All patients completed at least 4 cycles of chemotherapy, with the majority (82%) completing 5 or more. Grade 2 or higher neutropenia delayed treatment in 54% of cycles. The median treatment delay was 1.5 cycles (range: 1 to 5 cycles). Median treatment time was 59 days (range 46 to 81 days). The complete RR was 92% (95% confidence interval, 55%–100%).

**Conclusions.** The addition of weekly topotecan to cisplatin at this dose and schedule during pelvic irradiation for locally advanced cervical cancer appears to be feasible. Based on this primary treatment data and the activity of cisplatin–topotecan in the recurrent disease setting, phase II and III studies of this combination are warranted.

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**Keywords:** Topotecan; Cisplatin; Cervical cancer; Radiation therapy

## Introduction

There will be approximately 11,070 cases of invasive cervical cancer expected in the United States in 2008, with an estimated 3870 deaths [1]. In developing countries, cervical cancer is the leading cause of cancer-related mortality causing over 272,000 deaths in 2007 [2]. Between 1988 and 2001, there were 95,353 registered cases of cervical carcinoma in the

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Surveillance Epidemiology and End Results (SEER) database, of which approximately 55% were locally advanced disease diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IB2-IVA [3]. A new standard for the treatment of locally advanced cervical cancer was established in 1999 [4,5]. The addition of weekly cisplatin at 40 mg/m<sup>2</sup> for 6 weeks in combination with radiation (RT) reduces the relative risk of death from cervical cancer by approximately 50% by decreasing local failure and distant metastases [6–10]. This combination was favored because Gynecologic Oncology Group (GOG) Protocol 120 showed it to be less toxic and as equally efficacious when compared with other combinations using hydroxyurea and/or 5-fluorouracil (5-FU) [8]. Multimodality therapy is now the standard of care for locally advanced cervical carcinoma [11].

Topotecan acts synergistically with cisplatin and potentiates its cytotoxic activity against cancer cells. The mechanism is thought to occur through DNA repair inhibition [12]. The combination of these two agents was hypothesized to cause greater antitumor activity than might be expected from the additive effects of the two drugs. Clinical trials have since proven this hypothesis in patients with advanced or recurrent cervical cancer [13,14]. Although more hematologically toxic, the combination does not appear to significantly reduce patient quality of life (QOL) when compared with cisplatin alone [15]. GOG Protocol 179 was the first randomized phase III trial to demonstrate a survival advantage for the combination of cisplatin and topotecan over cisplatin alone in recurrent or stage IVB cervical cancer [14]. Topotecan is also a radiosensitizing agent [16] and has been studied at various daily dosing regimens in patients with advanced cervical cancer receiving external beam RT and low-dose rate (LDR) brachytherapy [17,18].

Based on these data, the objective of the present study was to assess the activity, feasibility and toxicity of adding weekly topotecan which is less marrow toxic than the previously studied daily schedules to cisplatin in previously untreated patients with primary, locally advanced (FIGO stage IB2 through IVA) carcinoma of the cervix receiving concurrent pelvic RT.

## Materials and methods

The UCI Institutional Review Board approved the study before any patients were enrolled. All patients provided written informed consent meeting all federal, state and local requirements before receiving any protocol therapy.

Patients with primary, previously untreated, histologically confirmed invasive squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix, Stage IB2, IIB, IIIB and IV-A whose disease was limited to the pelvis were eligible. Negative para-aortic lymphadenopathy was determined by computed tomography (CT), lymphangiogram or magnetic resonance imaging. Additional eligibility criteria included an absolute neutrophil count (ANC) greater than or equal to 1500/μl, platelets ≥ 100,000/μl, and hemoglobin > 10 mg/dl, creatinine ≤ 1.5 mg%, bilirubin ≤ 1.5 times the upper limit of normal, SGOT/alkaline phosphatase ≤ 3 times

the upper limit of normal and a GOG performance status of 0 to 3. Patients of childbearing potential must have had a negative serum pregnancy test and have been using an effective form of contraception. Patients who were not adequately clinically staged, who had lower one-third vaginal involvement, septicemia, severe infection or who were lactating were ineligible as were those with other invasive malignancies (with the exception of non-melanoma skin cancer) within the 5 years prior to protocol entry or whose previous cancer treatment contraindicated protocol therapy.

The study's primary objective was to assess the feasibility and toxicity of administering weekly topotecan among patients with carcinoma of the cervix receiving concurrent pelvic radiation and cisplatin. The secondary objectives were to assess the efficacy of the protocol therapy on progression-free survival, overall survival and local control. The overall treatment time was not to exceed 8 weeks.

Topotecan was administered as a 30 minute continuous intravenous (IV) infusion after cisplatin administration on a weekly basis for 5 cycles with the sixth cycle given concurrent with parametrial boost. The initial topotecan dose was 2 mg/m<sup>2</sup> for the first 6 patients, with a planned increase to 3 mg/m<sup>2</sup> in the subsequent cohort of 6 patients according to predetermined conditions. If none or 1 of the 6 patients in the first stage of accrual finished the prescribed therapy in more than 8 weeks, then the dose of topotecan would increase. If 2 or 3 of the patients in the first stage of accrual finished the prescribed therapy in over 8 weeks, the dose of the topotecan would remain the same in the second stage. If 4 or more of the patients in the first stage of accrual finished the prescribed therapy in over 8 weeks, there would be no second stage of accrual and the regimen would be deemed infeasible. Cisplatin was dosed at 40 mg/m<sup>2</sup> administered IV, infused at 1 mg/min to a maximum dose of 70 mg/m<sup>2</sup>. Pretreatment hydration, steroids and antiemetics were recommended as clinically indicated. Infusions were to be completed approximately 4 h prior to radiation therapy.

Whole pelvic external beam radiation was administered in 25 daily fractions of 1.8 Gy for a total of 45 Gy utilizing a four-field box technique with parallel opposed anterior/posterior (AP/PA) and two opposed lateral fields. Bladder distention and the use of belly boards to exclude the small bowel were encouraged. A parametrial boost of 5.4 to 9.0 Gy in 1.8 Gy fractions utilizing reduced AP/PA fields was given based on the extent of parametrial involvement with the exact boost dose at the discretion of the treating radiation oncologist. CT based treatment planning was required with the superior border of the AP/PA fields at the L4–5 interspace superiorly (the L3–4 interspace allowed only if required by tumor volume) and the inferior border at the obturator foramen or 3 cm margin below the inferior most extent of disease. The lateral borders were 2 cm beyond the lateral margins of the bony pelvis. The anterior border was a horizontal line drawn just anterior to the symphysis pubis, and the posterior border was a vertical line at the posterior border of the sacrum. Superior and inferior borders were the same as for the anterior and posterior fields.

Intracavitary brachytherapy utilizing either high dose rate (HDR) or low dose rate (LDR) techniques was also required.

Table 1  
Patient characteristics

Characteristic	
Age—median	52
Age—range	42–70
Race	
Hispanic	4
White	4
Asian	4
Performance status	
0	7
1	5
Stage	
IB2	2
IIB	8
IIIB	2
Histology	
Squamous	11
Non-squamous	1
Grade	
2	4
3	8
Courses	
Median	5
Range	4–6

Table 2  
Grade 3 or 4 adverse effects (58 cycles)

Toxicity	CTCAE grade	
	Grade 3	Grade 4
<b>Hematologic</b>		
Leukopenia	6(C4) 4(C5)	2(C4) 1(C5)
Neutropenia	4(C3) 10(C4) 4(C5)	2(C3) 1(C4) 2(C5)
Neutropenia with fever	1(C5)	
Thrombocytopenia	1(C5)	
Anemia	1(C5) 1(C6)	
Hematologic-others	4(C5)	
<b>Non-hematologic</b>		
Coagulation	1(C5)	
Gastrointestinal	1(C5)	
Metabolic	2(C2) 1(C3) 2(C4) 3(C5)	1(C2) 1(C3)
Pain	1(C5)	

C = cycle.

HDR brachytherapy was prescribed to deliver 30.0 Gy in 5 fractions beginning in week 4 for a total dose to point A of 30 Gy. LDR brachytherapy was prescribed to deliver 40 Gy to point A in one or two applications at the discretion of the treating radiation oncologist. The total elapsed time for completion of external whole pelvis, intracavitary RT, and parametrial RT was not to exceed eight weeks.

Weekly evaluation during treatment included clinical assessment of toxicity, with complete blood counts and relevant serum chemistry. RT was interrupted (held) for ANC <1000/μl lasting >7 days, platelets <50,000/μl or GI toxicity requiring intravenous hydration or hospitalization. Chemotherapy administration required an ANC ≥ 1500/μl and platelets ≥ 100,000/μl. There were no dose reductions but the topotecan was discontinued for recurrent neutropenia (ANC <1000/μl lasting >7 days) or for neutropenia lasting longer than 14 days. Topotecan was also to be discontinued for grade 4 non-hematologic toxicity felt to be attributed to the drug. Toxicities

were graded according to the NCI Common Toxicity Criteria version 2.0. After protocol completion, assessment for disease status using GOG RECIST criteria and treatment related toxicity occurred every 3 months [19].

**Results**

Enrollment of eligible patients began in February 2004. The twelfth and final patient enrolled on August 3, 2007. The majority of patients enrolled were stage IIB (66%), had squamous cell (92%) and high grade (66%) histology. Clinical characteristics are listed in Table 1. Fifty-eight cycles of chemotherapy, median of 5 per patient, were administered during radiation therapy. Of the six patients in the first stage of accrual, 3 patients finished the prescribed therapy in over 8 weeks. The median length of therapy for this patient cohort was 59 days (range 32 to 81 days). Based on the predetermined requirements for topotecan dose escalation, the dose of topotecan remained the same (2 mg/m<sup>2</sup>) in the second stage of accrual.

There were 25 dose delays during 58 cycles of chemotherapy administered for the entire cohort. Dose delays most often occurred during cycles 4 or 5 (84%). The timing of chemotherapy dose delays is illustrated in Fig. 1. The predominant reported

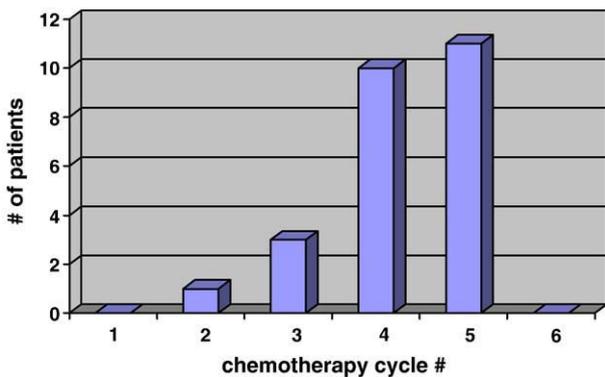


Fig. 1. Timing of dose delays.

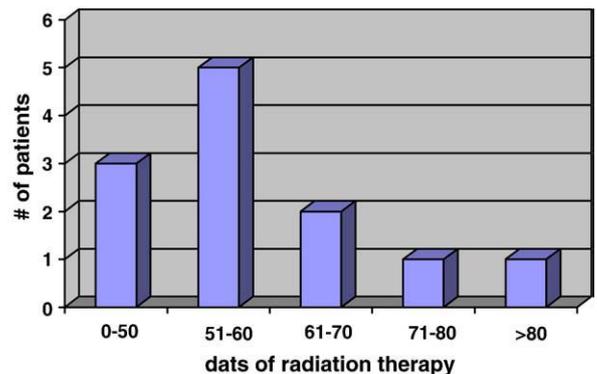


Fig. 2. Length of all radiation therapy.

Table 3  
Response and survival ( $n=12$ )

	No.	%
Clinical response		
Complete response	11	91.7
Partial response	0	0.0
Progression	1	8.3
Clinical status <sup>a</sup>		
No evidence of disease	10	83.3
Alive with disease	0	0.0
Died of disease	2	16.7

<sup>a</sup> Median follow-up: 22 months.

acute toxicities were hematologic in nature, most commonly neutropenia. Grade 2 or higher neutropenia caused 19 of the 25 chemotherapy dose delays (76%). Grade 4 leukopenia and grade 4 hyponatremia caused 2 dose delays with the remaining 4 dose delays (all in the same patient) caused by grade 3 deep venous thrombosis requiring anticoagulation. The frequency and grade of the most common grade 3 or 4 acute adverse events are summarized in Table 2. Eight patients completed 5 cycles of chemotherapy. Three patients completed 4 cycles; two of these (in separate patients) contained cisplatin only. Topotecan was withheld for recurrent unresolved grade 2 neutropenia in one patient after the fourth cycle and for another subject experiencing grade 4 hyponatremia after the fourth cycle. One patient received all six cycles of chemotherapy as planned. Four patients were admitted to the hospital during protocol therapy. Three patients were admitted after cycle 4 of chemotherapy with either small bowel obstruction, neutropenic fever or deep venous thrombosis. The fourth patient was admitted for grade 4 hyponatremia and hyperkalemia.

Eleven patients completed whole pelvic external beam radiation, intracavitary implants and parametrial boosts as planned. One patient with stage IIIB disease and bilateral percutaneous nephrostomy tubes experienced disease progression while on protocol and opted for hospice care prior to completing radiation treatment. Fig. 2 illustrates the length of radiation therapy for the cohort.

For the purposes of survival analysis, data was frozen on March 1, 2008. Median follow up was 22 months with a range of 5 to 39 months. Ten patients (83.3%) were without evidence of disease at the time of last follow up. Eight patients are currently in long term follow up; two patients were lost to follow up after 6 and 22 months. The remaining two patients died of their disease. One patient experienced disease progression as described above and died 10 months after diagnosis. The other patient recurred 7 months after study termination and succumbed 15 months later. The complete RR was 92% (95% confidence interval, 55%–100%). Response and survival data is summarized in Table 3.

## Discussion

These results show that the addition of topotecan to standard dose cisplatin (40 mg/m<sup>2</sup>) and pelvic radiation is feasible at a

dose of 2 mg/m<sup>2</sup>. While this was a pilot study of 12 patients, response data demonstrate a complete response rate of 91.7% (95% CI 55%–100%). With a median follow-up of 22 months, 83.3% of patients were without evidence of disease.

Hematologic toxicity was expected with this combination and lead to delays in therapy. One patient was able to complete 6 courses of combination chemotherapy as planned. Eight of twelve patients were able to complete 5 courses. The major toxicity for these patients was neutropenia, which caused 76% of chemotherapy dose delays. It is important to note that bone marrow support with granulocyte colony stimulating factors (G-CSF) was not part of this study protocol. Treatment delays also occur with cisplatin alone in combination with radiation. The addition of topotecan does not appear to increase this significantly. However, if one were still concerned about the delays in treatment seen in the current study using weekly doses of topotecan at 2 mg/m<sup>2</sup>, one could electively add bone marrow support or reduce the dose of topotecan. Nevertheless, the current data set provides a starting point for clinicians interested in this combination. Excessive treatment delays of chemoradiation beyond 8 weeks is probably associated with poorer PFS and OS although this has never been studied prospectively and the causes of delays in treatment are usually multi-factorial and not just a result of leucopenia [20]. In addition, six doses of chemotherapy may not be required to be beneficial. Based on the survival data available from completed GOG trials, five cycles versus six cycles did not appear to have a negative effect on response or overall survival [20]. In this study, the majority of patients (9/12) were able to complete 5 or more cycles.

Two patients enrolled early in the first stage of accrual received erythropoietin for anemia prevention. Based on early results from GOG 191, subsequent patients received transfusion of packed red blood cells as required. Seven patients required transfusion during chemotherapy [21]. These toxicities and others were well controlled by supportive care. While the combination of cisplatin and topotecan has been shown to be more hematologically toxic than cisplatin alone, there were no long term differences in QOL for patients on this regimen being treated for recurrent cervical cancer [15].

Although there are only 12 patients in the present study, cisplatin and topotecan administered concurrently with radiation therapy for patients with locally advanced cervical cancer appear to be tolerable and possibly efficacious. Hematologic toxicity most frequently caused dose delays but median treatment time (59 days) is acceptable when compared to treatment times for cisplatin–RT alone.

Based on the feasibility of the current regimen and the activity of cisplatin–topotecan in the recurrent disease setting, phase II and III studies to compare this combination to cisplatin alone with radiotherapy are warranted.

## Conflict of interest

The authors have no conflicts of interest to declare.

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