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Permalink
https://escholarship.org/uc/item/7877k50b

Journal
Gynecologic Oncology, 112(1)

ISSN
0090-8258

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Publication Date
2009

DOI
10.1016/j.ygyno.2008.09.029

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Peer reviewed
A feasibility study of topotecan with standard-dose cisplatin and concurrent primary radiation therapy in locally advanced cervical cancer

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Received 24 July 2008
Available online 1 November 2008

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/m² plus IV topotecan 2 mg/m² 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
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/m² 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]. Multi-modality 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 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 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/m² for the first 6 patients, with a planned increase to 3 mg/m² 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/m² administered IV, infused at 1 mg/min to a maximum dose of 70 mg/m². 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.
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/m²) 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

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**Table 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tr>
<td>Age—median</td>
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<td>Range</td>
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**Table 2**

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<td>Hematologic</td>
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<tr>
<td>Leukopenia</td>
<td>6(C4) 4(C5) 2(C4) 1(C5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4(C3) 10(C4) 4(C5) 2(C3) 1(C4) 2(C5)</td>
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<tr>
<td>Neutropenia with fever</td>
<td>1(C5)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>1(C5)</td>
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<tr>
<td>Anemia</td>
<td>1(C5) 1(C6)</td>
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<tr>
<td>Hematologic-others</td>
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<tr>
<td>Non-hematologic</td>
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<td>Coagulation</td>
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<tr>
<td>Metabolic</td>
<td>2(C2) 1(C3) 2(C4) 3(C5) 1(C2) 1(C3)</td>
</tr>
<tr>
<td>Pain</td>
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C = cycle.
The authors have no conflicts of interest to declare.

Conflict of interest
The authors have no conflicts of interest to declare.

Acknowledgment
This study was supported by Glaxo Smith Kline.
References


