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Multicenter phase II trial of topotecan, cisplatin and bevacizumab for recurrent or persistent cervical cancer☆

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HIGHLIGHTS

• The experimental regimen is very active for advanced cervical cancer.
• This regimen results in high toxicity.
• Biomarkers of response and regimen modifications to minimize toxicity are needed.

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ABSTRACT

Objective. We evaluated the activity and safety of the combination of topotecan, cisplatin and bevacizumab in patients with recurrent or persistent carcinoma of the cervix.

Methods. Eligible patients had persistent or recurrent cervical cancer not amenable to curative intent treatment. No prior chemotherapy for recurrence was allowed. Treatment consisted of cisplatin 50 mg/m^2 day 1, topotecan 0.75 mg/m^2 days 1, 2 and 3 and bevacizumab 15 mg/kg day 1 every 21 days until disease progression or limiting toxicity. The primary endpoint was progression free survival at 6 months. We explored PET/CT as a potential early indicator of response to therapy.

Results. Twenty-seven eligible patients received a median of 3 treatment cycles (range, 1–19). Median follow-up was 10 months (range, 1.7–33.4). The 6-month PFS was 59% (80% CI: 46–70%). In 26 evaluable patients, we observed 1 CR (4%; 80% CI: 0.4–14%) and 8 PR (31%; 80% CI: 19–45%) lasting a median of 4.4 months. Ten patients had SD (39%; 80% CI: 25–53%) with median duration of 2.2 months. Median PFS was 7.1 months (80% CI: 4.7–10.1) and median OS was 13.2 months (80% CI: 8.0–15.4). All patients were evaluated for toxicity. Grade 3–4 hematologic toxicity was common (thrombocytopenia 82% leukopenia 74%, anemia 63%, neutropenia 56%). Most patients (78%) required unanticipated hospital admissions for supportive care and/or management of toxicities.

Conclusion. The addition of bevacizumab to topotecan and cisplatin results in an active but highly toxic regimen. Future efforts should focus on identification of predictive biomarkers of prolonged response and regimen modifications to minimize toxicity.

Introduction

Cervical cancer remains the third most common and the fourth most lethal cancer in females worldwide [1]. In the United States, it is estimated that 12,170 women were diagnosed and 4,220 women died from cervical cancer in 2012 [2].

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Despite survival improvement since the introduction of chemoradiation, the prognosis for patients with cervical cancer remains poor. Failure rates approach 15–30% for patients with stage I–II disease and increases to 40–60% for those with stage III tumors [3–6]. Only 10% of patients with recurrent disease respond to therapy and are alive at 5 years [3,7].

Cisplatin is considered the most active single agent in the setting of recurrent cervical cancer [8]. The Gynecologic Oncology Group (GOG) protocol 179 was the first study to demonstrate a survival benefit with combination therapy. The combination of cisplatin and topotecan was superior to single-agent cisplatin, with the former showing progression free survival (PFS) of 4.6 months, overall survival (OS) of 9.4 months, and a 27% objective response rate [9]. Recent evaluation of other cisplatin-containing combinations has demonstrated comparable survival figures [10].

Angiogenesis plays a key role in cervical carcinogenesis and progression [11–14]. VEGF expression has been associated with deep tumor invasion, pelvic node metastases, pelvic and distant failures as well as impaired survival [14,15]. VEGF inhibition represents an attractive therapeutic strategy for this disease. The GOG conducted a phase II study of bevacizumab for the treatment of persistent or recurrent cervical cancer. The drug was well tolerated and 24% of patients survived progression free for at least 6 months with an objective response rate of 11% [16]. We previously reported on six patients with heavily pre-treated cervical cancer managed with bevacizumab in combination with cytotoxic chemotherapy. One complete and one partial response were observed and two patients had stable (estimated clinical benefit rate of 67%) [17].

While the anti-tumor activity of these agents is promising, there is a critical need to identify biomarkers of therapeutic response. Positron emission tomography-computed tomography (PET/CT) has emerged as an important tool for the management of patients with cervical cancer [18,19]. Interestingly, there is emerging data on the potential role of PET/CT as a clinically useful biomarker for early prediction of therapeutic oncologic responses [20,21].

We sought to evaluate the activity and safety of the combination of topotecan, cisplatin and bevacizumab in patients with incurable recurrent or persistent carcinoma of the cervix. In addition, we explored the potential role of PET-CT with [^{18} F]-fluorodeoxyglucose (FDG) as an early indicator of response to therapy.

Patients and methods

Patient eligibility

Patients with histologically proven recurrent or persistent squamous, adenosquamous or adenocarcinoma of the uterine cervix not amenable to curative treatment were enrolled. Eligibility criteria included age ≥18 years, disease measurable by Response Evaluation Criteria in Solid Tumors (RECIST Version 1.0) [22]; no prior therapy for recurrence and no prior chemotherapy or biologic therapy other than adjuvant cisplatin; GOG performance status of 0 or 1; adequate bone marrow function (defined as absolute neutrophil count (ANC) ≥1,500/μL, and platelets ≥100,000/μL); adequate renal function (defined as creatinine ≤1.5× the institutional upper limit normal [ULN] or creatinine clearance >60 mL/minute); normal hepatic function (defined as bilirubin ≤1.5 × ULN and AST and alkaline phosphatase ≤2.5 × ULN); normal coagulation parameters (defined as prothrombin time [PT] such that the international normalized ratio [INR] <1.5 [INR between 2 and 3 allowed if a patient was on stable dose of therapeutic warfarin] and a PTT <1.2 X control). Minimal peripheral neuropathy was allowed (sensory and/or motor ≤grade 1).

Patients with severe infection; non-healing wound, ulcer or bone fracture, active bleeding, coagulopathy, significant cardiovascular disease, proteinuria (urine protein–creatinine ratio [UPCR] >1.0), active central nervous system disease, abdominal fistula or abscess, recent surgery and/or history of other malignancy within 5 years of enrollment were ineligible.

The study was reviewed and approved by the institutional review board of each participating institution and all patients gave informed consent prior to enrollment according to local institutional and federal guidelines (registered under ClinicalTrials.gov under identifier: NCT00548418).

Protocol treatment and evaluation

Patients received topotecan 0.75 mg/m^2 intravenously (IV) on days 1, 2 and 3; cisplatin 50 mg/m^2 IV on day 1 and bevacizumab 15 mg/kg IV on day 1, every 21 days until disease progression or cumulative adverse effects dictating cessation of therapy. Dose modifications were allowed in cases of >10% change in body weight. Cytokine support was permitted at the treating physician's discretion. G-CSF was indicated by protocol for subsequent cycles in patients who developed grade 3 or 4 neutropenia despite protocol mandated dose reductions.

Toxicity was monitored clinically and by laboratory assessment before each cycle. The National Cancer Institute's Common Toxicity Criteria, version 3.0 was used to characterize toxicity [23]. Patients were required to have ANC ≥1,500/μL, platelet count ≥100,000/μL, and creatinine <2.0 mg/dL (or <1.5 mg/dL if prior grade 2 or higher renal toxicity) on the day of re-treatment. There was no dose modification of bevacizumab. Cisplatin dose reductions of 25% in 2 level increments and topotecan dose reduction (to 0.5 mg/m^2) were indicated for specific toxicities defined by protocol.

PET/CT scans were performed at study entry and within 7 days prior to third cycle of therapy. Acquisition and analysis of FDG-PET/CT scans were performed according to accepted NCI guidelines [21]. FDG was dosed at 0.14–0.21 mCi/kg (actual dose 10–20 mCi) and image acquisition was started 60 ± 10 minutes after FDG injection. A low-dose CT scan was acquired for anatomic localization and attenuation correction using standard parameters. PET data were corrected for dead time, scatter, random and attenuation using standard algorithms. All images were qualitatively and quantitatively interpreted by a single experienced nuclear medicine physician (F.D.). Results from second PET/CT were not provided to the patient or the treating oncologist. For PET/CT interpretation, up to a maximum of 3 lesions (≥1.5 cm in smallest dimension) having the highest intensity uptake were identified as target lesions on the baseline FDG PET/CT study. Standardized uptake values (SUV) based on the patient's total body weight were measured on each target lesion using 3-dimensional ellipsoidal volumes of interest (VOIs) surrounding the tumor. Maximum SUV (SUV_{max}) was recorded for each VOI.

Results of the PET/CT scan performed prior to cycle 3 were compared to those of the baseline FDG-PET/CT study. Complete metabolic response (CMR) was defined as complete resolution of all metabolically active target and non-target lesions, and no interval development of new lesions. Partial metabolic response (PMR) was recorded when one or both of the following occurred: 1. 20% or greater decrease in maximum SUV from baseline at target lesion with no unequivocal metabolic progression of non-target disease, and no unequivocal new lesions or 2. decrease in total number of non-target lesions, without complete resolution of metabolically active disease, or unequivocal decrease in degree of FDG activity within >50% of the lesions and unequivocal new lesions. Metabolic progression (MP) was defined as: unequivocal development of one or more new metabolically active lesion(s) or 20% or greater increase in maximum SUV from baseline at target lesion(s) or unequivocal increase in FDG activity within non-target lesions or unequivocal increase in size of target or non-target lesions. Other cases were defined as metabolically stable (MS).

Imaging studies for disease evaluation were obtained at study entry and prior to every other treatment cycle. Best response as defined according to RECIST was recorded for each patient based on