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A prospective feasibility study of radiation and concurrent bevacizumab for recurrent endometrial cancer☆,☆☆,★

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HIGHLIGHTS

- Bevacizumab with concurrent radiation is feasible for patients with recurrent endometrial or ovarian cancer.
- This regimen provides excellent local tumor control and survival with no patients relapsing in the radiated field.
- Toxicities were limited.

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ABSTRACT

Objectives. To determine the toxicity and survival rates in a trial of concurrent bevacizumab and external beam radiation (EB) for patients with recurrent endometrial or ovarian cancer.

Methods. Nineteen women with recurrent endometrial ($n = 15$) or ovarian ($n = 4$) cancer with gross disease involving the vaginal cuff, and/or pelvic nodes and/or para-aortic nodes, cancer were enrolled between 2008 and 2010. All patients received bevacizumab during radiation. Toxicity was assessed at baseline, weekly during treatment and every 3 months for at least 1 year after treatment.

Results. All patients completed EB on schedule. For the 15 patients with recurrent endometrial cancer, the 1- and 3-year progression-free survival (PFS was) 80%/67% and overall survival (OS) was 93%/80%. Patients that had a vaginal cuff recurrence alone had a 1- and 3-year PFS of 75%/63% and OS of 100%/75%. Two patients with pelvic node involvement did not recur throughout the entire follow-up period. The 5 patients with para-aortic node involvement had a 1- and 3-year PFS of 80%/60% and OS of 80%/80%. Of the 4 ovarian cancer patients 3 relapsed with 1- and 3-year PFS of 80%/40% and OS of 100%/60%. Toxicities included thrombosis and 1 embolic event in the setting of metastatic disease. No gastrointestinal perforations were noted.

Conclusions. Delivering bevacizumab with concurrent radiation provides excellent local tumor control and survival for women with recurrent endometrioid endometrial cancer, particularly those with unresectable nodes. Caution must be used in those at highest risk of developing metastatic disease given the increased risk of thromboembolic events. This regimen may be considered for recurrent gynecologic malignancies in future trials.

Introduction

Local and systemic failures remain a significant cause of morbidity and mortality in patients with recurrent endometrial cancer and recurrent ovarian cancer. Patients with recurrent endometrial cancer in the vaginal cuff or the pelvic or para-aortic nodes may be treated with radiation, though survival rates for those with nodal recurrence remain low, with a 10-year survival rate of 18% [1]. Patients with recurrent ovarian cancer are most commonly treated with a combination of surgery if feasible and chemotherapy, with radiation used in patients that are

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unresectable [2,3]. Novel therapies that may further improve outcomes are needed.

Studies have noted that serum vascular endothelial growth factor (VEGF) levels in patients with endometrial cancer are significantly elevated compared with those of controls [4], but levels do not correlate with stage [5]. As endothelial cell proliferation and neovascularization are critical for growth of endometrial cancer, the inhibition of angiogenesis may be critical to halt tumor progression [6]. Antiangiogenic agents sensitize tumors and tumor vasculature to radiotherapy by counteracting VEGF upregulation, which can act to protect tumor blood vessels from the ionizing effects of radiation [7,8]. Antiangiogenic agents may also inhibit the activity of cancer stem cells, which are resistant to the effects of radiation [9]. Furthermore, VEGF may protect endothelial cells from radiation-induced apoptosis [10]. Therefore, use of a VEGF blocker such as bevacizumab, a recombinant humanized version of a murine anti-human VEGF monoclonal antibody, in combination with radiation may result in a synergistic normalization of vasculature. In addition, increased sensitivity of the tumor to the effects of radiation, particularly in the most resistant hypoxic portions of a tumor, may occur [11]. A study of chemo-radiation with bevacizumab in cervical cancer showed feasibility when delivered with weekly cisplatin [12]. A decrease in interstitial fluid pressure due to resumption of normal function of the tumor vasculature was seen in rectal cancer patients after bevacizumab and pelvic radiation [11].

The use of bevacizumab in endometrial cancer is relatively understudied, despite the fact that uterine and gynecologic tissue in general is highly vascular. The use of antiangiogenic agents without radiation in the treatment of patients with recurrent endometrial [13,14] or ovarian [15] cancer, is feasible. The combination of bevacizumab with concurrent radiation in these cancers has not been previously reported. This trial sought to test the concept that bevacizumab and pelvic radiation could be safely and successfully administered in recurrent endometrial and ovarian cancer. The objectives of this prospective study were to determine the toxicities and survival rates of concurrent bevacizumab in patients with recurrent endometrial or ovarian cancer.

Materials/Methods

Twenty women were enrolled in a prospective protocol between 2008 and 2010. Eighteen were treated at Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC) and two were treated at Lowell General Hospital (LGH). One patient was excluded due to supraclavicular lymph-node disease; 19 patients therefore comprised the analysis cohort. Eligible patients were ≥18 years of age, had biopsy-proven recurrent endometrial or ovarian cancer of any histology deemed amenable to EB radiation to a confined pelvic or para-aortic area, had a prior hysterectomy, ECOG performance status 0–1, and a computed tomography (CT) scan of the chest, abdomen and pelvis at baseline. Pelvic magnetic resonance imaging (MRI) could be obtained instead of a pelvic CT. Patients were required to have a serum creatinine ≤1.5 mg/dL, serum total bilirubin ≤1.5 mg/dL, SGOT/SGPT <3 times the upper limit of normal for the reference lab, and an ability to understand and willingness to sign a written informed consent document. Exclusions included a prior history of EB to the same region; a life expectancy <12 weeks; uncontrolled known illness (CNS disease, hypertension, congestive heart failure, myocardial infarction or unstable angina, vascular disease, bleeding diathesis or coagulopathy) within 6 months of enrollment; any surgical procedure requiring an incision; open biopsy or traumatic injury within 28 days prior to study enrollment; history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to enrollment; non-healing wound or bone fracture; proteinuria; known bevacizumab hypersensitivity; and inability to follow study procedures.

This prospective study was listed on ClinicalTrials.gov by the National Institutes of Health (NCT#00545792). The project was reviewed and approved by the Dana-Farber Cancer Institute Institutional Review Board. Consent was obtained in writing from all participants. At inception, the trial was limited to patients with a pelvic (vaginal or nodal) recurrence of endometrial cancer. Due to DF monitoring committee accrual requirements, the trial was expanded to include endometrial cancer that might be present at metastatic sites for which one localized site required radiation for local control, and similarly to include women with recurrent ovarian cancer that required radiation to a single symptomatic region but who may have had disease in other areas. The standard protocol for these patients would have been EB radiation alone without chemotherapy.

Endpoints

The primary endpoint was the toxicity of patients treated with concurrent bevacizumab and daily radiation to the pelvic and/or para-aortic regions. Secondary endpoints were 1-year progression-free survival (PFS) and 1-year overall survival (OS).

Chemotherapy

Bevacizumab was administered at a dose of 10 mg/kg intravenously every 2 weeks for 3 doses during radiation therapy (days 1, 15, and 29). Baseline and weekly laboratory tests included routine complete blood count; chemistries, including electrolytes, kidney and liver function tests; and urinalysis. No other chemotherapy was allowed during the radiation portion of treatment. Patients may have had chemotherapy prior to enrollment. All 4 ovarian-cancer patients had received platinum-based chemotherapy at diagnosis prior to this recurrence. Of the endometrial-cancer patients, four had received chemotherapy prior to enrollment on this trial. One patient with carcinosarcoma initially received 2 cycles of gemcitabine/oxaliplatin but relapsed at the vaginal cuff prior to initiation of the third cycle and was then switched to this protocol. One patient with Stage IIIC1 papillary serous cancer with possible peritoneal carcinomatosis on CT received 6 cycles of carboplatin/taxol, then failed 3.5 months later in the para-aortic region prior to enrollment on this trial. Another patient with enlarged abdominal and para-aortic nodes at diagnosis received 6 cycles of carboplatin/taxol but had disease growth during the chemotherapy. Finally, one patient with a para-aortic node recurrence received 6 cycles of chemotherapy and had a partial response prior to enrollment.

Radiation

All patients underwent simulation using CT scanning. The gross tumor volume (GTV) was defined as all visible regions of the primary tumor (i.e., vaginal mass, nodal enlargement). The clinical target volume (CTV) included the GTV plus the entire region at risk (vagina, pelvic and/or para-aortic nodal chain). Pelvic radiation was delivered using a four-field box technique (anteroposterior, posteroanterior, and two lateral fields) with 15-MV photons to 45 Gy in 25 fractions in 13 patients. The pelvic field extended from the bifurcation of the common iliac vessels or the L5-S1 interspace to the ischial tuberosity, and laterally 1.5 to 2 cm beyond the lateral margins of the bony pelvic wall. For the lateral fields, the anterior border was 1 cm anterior to the pubic symphysis and the posterior border covered the sacrum. Intensity modulated radiation (IMRT) was administered to 6 patients; 1 required treatment to the pelvis with dose escalation for an enlarged pelvic node and 5 required treatment to the para-aortic nodes with dose escalation. For IMRT contouring, the RTOG post-operative endometrial cancer contouring atlas [16] was followed, with the para-aortic nodes drawn contiguous with the pelvic lymph-node chain. IMRT dose constraints were set for the kidneys, spinal cord, liver, and the small bowel. We strove not to exceed a dose of 55 Gy to approximately 5–10 cc of small bowel as is our standard practice [17,18]. The PTV for the vaginal region and vaginal tumor was based on an integrated target volume (ITV) with approximately 2–3 cm added to the CTV to account for organ motion. An additional contour of the enlarged (>1 cm on short axis) lymph node(s) was