Gynecologic Oncology 132 (2014) 50–54

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Phase II trial of vaginal cuff brachytherapy followed by chemotherapy in early stage endometrial cancer patients with high-intermediate risk factors

Lisa M. Landrum [a,*], Elizabeth K. Nugent [a], Rosemary E. Zuna [b], Elizabeth Syzek [c], Robert S. Mannel [a], Kathleen N. Moore [a], Joan L. Walker [a], D. Scott McMeekin [a]

[a] Section of Gynecology Oncology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA
[b] Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA
[c] Department of Radiation Oncology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA

HIGHLIGHTS

- Combined VCB and chemotherapy is a promising form of adjuvant therapy for H-IR endometrial cancer.
- Combined VCB and platinum-based chemotherapy is well tolerated adjuvant therapy.

ARTICLE INFO

Article history:
Received 26 September 2013
Accepted 4 November 2013
Available online 9 November 2013

Keywords:
Carboplatin
Paclitaxel
Uterine cancer
Radiation
Chemotherapy
Serous carcinoma

ABSTRACT

Objective. To determine the progression free survival (PFS), toxicity, and patterns of failure for early stage, high-intermediate risk (H-IR) patients in a phase II trial with adjuvant vaginal cuff brachytherapy (VCB) and three cycles of carboplatin and paclitaxel.

Methods. Surgically staged patients with stage I-IIb endometrial cancer with H-IR factors were treated with VCB (2100 cGy) followed by three cycles of carboplatin (AUC 6) and paclitaxel (175 mg/m^2). The primary endpoint was PFS at 2 years, with toxicity and sites of failure as secondary endpoints. Toxicity was assessed by patient report (CTCAE v. 3) as well as by delays or dose modifications in treatment.

Results. All patients completed VCB and 19/23 (83%) completed both VCB and 3 cycles of chemotherapy. Mean time to complete VCB was 14.5 days with minimal acute toxicity noted. At 6 months, all toxicity related to VCB had resolved. In total 60 cycles of chemotherapy were given, with one dose reduction (1.6%) for grade 2 neuropathy and seven delays (11.6%) in treatment due to hematologic toxicity. At a median follow-up of 44.5 months, 91% of patients remained progression free at 2 years. Four patients experienced a recurrence; they recurred both locally and distant.

Conclusions. Adjuvant therapy with VCB and chemotherapy is well tolerated in a population of patients with H-IR endometrial carcinoma and provides 2 year PFS of 91%. A randomized trial is currently underway to assess whether combined VCB and chemotherapy reduces the rate of recurrence compared to external beam radiation therapy (EBRT) in this patient population.

Introduction

Each year more than 49,000 women in the United States will be diagnosed with endometrial cancer with 8190 deaths projected in 2013 [1,2]. In general, the prognosis for patients diagnosed with endometrial cancer is excellent with the majority of cases diagnosed with stage I disease. However, some patients within this group will have risk factors such as tumor grade, depth of myometrial invasion, and lymphovascular space invasion that will place recurrence risk as high as 30% despite being diagnosed at an early stage [3,4]. For patients with early stage endometrial cancer, post-operative adjuvant therapy may have some benefit. Two large cooperative-group trials, Gynecologic Oncology Group (GOG) 99 and the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC-1) demonstrated a reduction in local recurrence for patients with stage 1 endometrial cancer having intermediate risk factors that were treated with adjuvant external beam pelvic

* Corresponding author at: Stephenson Oklahoma Cancer Center, 800 NE 13th St, Oklahoma City, OK 73104, USA. Fax: +1 405 271 2976.
E-mail address: Lisa-landrum@ouhsc.edu (L.M. Landrum).

0090-8258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ygyno.2013.11.005

radiation therapy (EBRT) compared to those who were only observed [5,6]. While local recurrences were reduced in both studies, it is important to note that there were no improvements in the overall survival with adjuvant radiation therapy. Within GOG 99 a smaller subset of patients with high-intermediate risk (H-IR) factors was identified. This group represented only 1/3 of patients (n = 132), but 66% of recurrences occurred in this group. In fact, for patients with H-IR factors, the recurrence rate at 2 years was 26% for patients with no therapy and 6% for patients receiving EBRT (relative hazard 0.42, p = 0.007) [4].

A subgroup of 99 patients with stage IC grade 3 endometrial cancer was evaluated with PORTEC-1 patients, but was deemed too high risk to undergo random assignment between EBRT and observation [7]. As such, this group was excluded from the trial and all patients received adjuvant EBRT. Despite this, the stage IC grade 3 population was noted to have very poor outcomes with a 5 year overall survival of 58% compared to patients randomized to EBRT (81%) or observation (85%) on PORTEC-1. In addition, analysis of patterns of failure revealed a striking number of distant relapses in this subgroup, prompting questions regarding the role of systemic therapy. Likewise, in GOG 99, patients with H-IR features that randomized to observation had a 19% rate of distant failure at 48 months suggesting that systemic therapy could benefit at least some node negative patients. Furthermore, approximately 10% of endometrial cancer diagnoses are uterine papillary serous carcinoma (UPSC) and clear cell carcinoma (CC). These are considerably more aggressive variants of endometrial cancer with higher rates of both local and distant relapses [8,9]. It is uncertain how to best treat patients with early stage UPSC and CC tumors but a role for chemotherapy has been queried by a number of investigators due to the biologic behavior of these histologic subtypes [10–13]. Ideally, a role for both local control and systemic control in adjuvant therapy is desirable. We conducted a phase II trial to determine the progression free survival, toxicity, and patterns of failure for surgically staged patients with early stage endometrial cancer and H-IR factors treated with adjuvant VCB and systemic chemotherapy.

Materials and methods

Patient eligibility

This IRB-approved phase II study recruited patients at the University of Oklahoma Health Sciences Center from July 2007 to June 2009. Patients underwent surgical staging to include hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and pelvic washing. Patients with H-IR factors as defined by GOG 99 were eligible if enrolled within 4 weeks of surgery. Recurrence risk was stratified by patient age based on the presence of grade 2–3 tumor, positive lymphovascular space invasion, and invasion of the outer 50% of the myometrium. Patients aged 70 and older needed to have only one additional risk factor to meet the H-IR criteria, while patients aged 50 and older needed to have two additional risk factors. In addition, we included all patients with stage IIb endometrial cancer and patients with stage I-IIb serous and clear cell cancers. Adequate hematologic (absolute neutrophil count >2000/mm^3 and platelets >100,000/mm), renal (creatinine ≤1.5 mg/dl), and hepatic (bilirubin ≤1.5 × laboratory normal and SGOT ≤3 × laboratory normal) function and GOG performance status of ≤2 were required.

Radiation therapy

All patients received HDR vaginal brachytherapy within 4 weeks of surgery to avoid a delay in initiating systemic therapy. Three fractions of 700 cGy were delivered to a depth of 0.5 cm for a total dose of 2100 cGy. The target of treatment was the proximal 3–5 cm of the vagina with no more than 2/3 of the length of the vagina included in the treatment volume. Brachytherapy fractions were separated by at least 72 h and delivered using a cylinder with ^{192}Iridium source. Complications were assessed in terms of acute (≤30 days from completion of treatment) and chronic (>30 days from completion of treatment) GI, GU and vaginal toxicity.

Chemotherapy

Chemotherapy was initiated within 2 weeks of completing radiation therapy and consisted of 3 cycles of IV paclitaxel at 175 mg/m^2 administered over 3 h followed by carboplatin AUC = 6 every 21 days. Chemotherapy doses were calculated based on surface area and creatinine clearance was calculated by the Jelliffe formula for each cycle. Oral dexamethasone (20 mg PO at 12 and 6 h prior to treatment), diphenhydramine (50 mg IV) and famotidine (20 mg IV) were given prior to the administration of paclitaxel to reduce the incidence of hypersensitivity reactions. Ondansetron (16 mg IV) was given 30 min prior to chemotherapy for prophylaxis of nausea and vomiting.

Toxicity was classified according to the Common Terminology Criteria for Adverse Events, version 3 (CTCAE, v. 3) guidelines. Dose reductions for both carboplatin (AUC 5) and paclitaxel (135 mg/m^2) were implemented for febrile neutropenia or sepsis requiring IV antibiotics or treatment delays of ≥2 weeks for neutropenia <1500 cell/mm^3. Patients with delays of >3 weeks were removed from the study. Carboplatin alone was dose reduced for patients with grade 4 thrombocytopenia. Treatment was delayed for patients with ≥grade 2 neuropathy until toxicity resolved to ≤grade 1 with a subsequent dose reduction in paclitaxel at next cycle. Patients with delay of >2 weeks for neuropathy were removed from the study. Frequency and duration of treatment interruptions due to toxicity were assessed.

Patient follow-up

Patients were evaluated weekly during radiation therapy. Before each chemotherapy cycle the patients underwent physical examination, toxicity assessment, CA 125, complete blood count and comprehensive metabolic profile. All toxicity and adverse events were assessed and reported. Toxicity was assessed using self-reported toxicity assessment sheets that patients completed at each evaluation during the first two years of surveillance. Once treatment was completed, the patient was assessed every 3 months for the first 2 years and then every 6 months for the next 3 years for recurrence of disease or toxicity from therapy.

Statistical analysis

The study was designed to determine the PFS at 2 years as the primary endpoint. This was calculated from date of study entry to date of relapse or death or censored at last contact date for patients with no evidence of disease. To determine a sample size, it was anticipated that 30 patients per year could be enrolled in the study. Using an estimated recurrence rate of 30% for historic controls, a relative decrease in the recurrence/death hazard of 50% translated into an increase in PFS at 2 years to 85% for patients treated with the intervention. This difference required observing at least 35 failures to provide 90% statistical power when type I error is limited to 0.05 (two-tailed test). The sample size necessary to observe 35 recurrences under these conditions was estimated to be 120 patients. This study was intended to collect pilot data within our institution prior to the opening of GOG 249. Once this cooperative group study was open for enrollment, we discontinued our institutional study in favor of participating in GOG 249. Secondary endpoints were overall survival, sites of relapse, and toxicity of therapy. Patient baseline demographic and clinical characteristics were collected and summarized. Kaplan–Meier methods were used to estimate survival curves.