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Concomitant chemotherapy and radiation for the treatment of advanced-stage endometrial cancer

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HIGHLIGHTS

- Concomitant chemotherapy and radiation shortens treatment time.
- Toxicity and survival are comparable to sequential and "sandwich" treatments.

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ABSTRACT

Introduction. Ccombination chemotherapy and radiation therapy is used for adjuvant treatment of stage III–IV endometrial cancer. The goal of this study was to review the treatment duration, toxicity, and survival for patients treated with concomitant chemotherapy and radiation.

Methods. Women with stage III–IV endometrial cancer treated with concurrent chemotherapy and radiation between 2006 and 2013 were included. Toxicities were classified per CTCAE v3.0 and RTOG/EORTC late radiation morbidity scoring. Descriptive statistics were used to quantify treatment and toxicities. Kaplan–Meier method was used to estimate survival.

Results. Fifty-one patients met our inclusion criteria. Median age was 60 (range 33–85). Thirty-six patients (70.6%) had endometrioid histology, 13 patients (25.5%) had serous, clear cell, or mixed histology, and 2 women (3.9%) had carcinosarcoma. Forty-eight patients had stage III disease and three patients were stage IVB. Mean treatment duration was 107 ± 19 days. Forty-two patients received all planned chemotherapy, and 16 patients required a dose reduction. Thirty-four patients (66.7%) experienced grade 3–4 toxicities, the majority of which were hematologic. There were no deaths related to therapy. Eighty-six percent of patients received leukocyte growth factors, and 25% of patients received a blood transfusion. Seven late grade 3–4 complications occurred: four gastrointestinal and two genitourinary, and one patient had ongoing neuropathy. Median progression-free survival was 42.8 months (range 4.4–81.5 months) and median overall survival was 44.9 months (range 5.1–82.6 months). Three-year overall survival was 80%.

Conclusion. Concomitant chemotherapy and radiation is an adequately tolerated treatment modality that allows for shorter treatment duration.

Introduction

Endometrial cancer remains the most common cancer of the female genital tract in the developed world with over 142,000 cases per year and 33,000 deaths [1]. Approximately 70% of women in the United States with endometrial cancer are diagnosed with stage I or II disease; the remainder of women will have advanced-stage disease, which carries an estimated 5-year-survival of 21%–56% [2]. Current treatment recommendations for advanced-stage endometrial cancer consist of chemotherapy, radiation or multimodality therapy [3]. Initial randomized trials comparing treatment modalities for high-risk endometrial cancer patients have shown either lower rates of local recurrence with radiation alone or lower rates of distant recurrence with systemic chemotherapy [4–6]. Subsequent studies and standard treatment today have thus focused on multimodality therapy. In 2010, Hogberg et al. [7] evaluated two protocols that randomized patients with high-risk endometrial cancer to sequential radiation and chemotherapy versus radiation alone and showed a significant improvement in progression-free

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survival (PFS) and disease-specific survival for women receiving radiation and chemotherapy. Additional retrospective and phase II studies have shown favorable results for sequential therapy of radiation and chemotherapy [8–11] or those treated with "sandwich" therapy consisting of chemotherapy, interval radiation, and further chemotherapy [12–14].

The ideal sequence of chemotherapy and radiation has not yet been determined for the treatment of endometrial cancer. Concomitant chemotherapy and radiation has been used in other cancers such as lung and head and neck malignancy to shorten treatment times and improve efficacy [15,16]. In a study by Nagar et al. [17], vaginal brachytherapy during chemotherapy was well tolerated and significantly shortened treatment by 4 weeks for women with endometrial cancer. The goal of this study was to evaluate toxicity and treatment duration for women with stage III–IV endometrial cancer who received concomitant chemotherapy and external beam radiation with brachytherapy boost.

Methods

This retrospective study was conducted at a single academic institution. After approval from the Human Studies Committee at Washington University, women diagnosed with stage III–IV endometrial cancer between January 2006 and March 2013 were identified from a database maintained within the division of gynecologic oncology. All women underwent at least hysterectomy and salpingo-oophorectomy. Nodal dissection was performed in women with tumors containing high-risk features. Women who received concurrent chemotherapy and external beam radiation were included in the study. Women treated with overlapping chemotherapy and brachytherapy but no overlap in chemotherapy and external beam radiation were excluded.

Chemotherapy regimens were administered at the discretion of the treating gynecologic oncologist. Women with advanced-stage endometrioid, serous, clear cell or mixed endometrial carcinoma were treated with carboplatin (AUC 5–6) and paclitaxel (175 mg/m^2) for 4–6 cycles of adjuvant therapy. Women with carcinosarcoma are treated with carboplatin and paclitaxel or ifosfamide (1200–1600 mg/m^2 on days 1, 2, and 3 of a day cycle) and paclitaxel (135 mg/m^2 when combined with ifosfamide) as inpatients at our institution. Radiation was started during cycles 1–3 of chemotherapy at the discretion of the treating physician and radiation oncology team. Growth factors were given in the setting of leukopenia or neutropenia. Treatment time was calculated as the number of days between the first and last day of treatment. Completion of therapy was based on the intended treatment doses and regimen described by the treating physician at the initiation of therapy.

External radiation therapy was given via intensity-modulated radiation therapy (IMRT). Following computed tomography simulation, IMRT was planned to be delivered in once-daily fractions of 160–180 cGy, 5 days per week over a 6-week period for a total IMRT dose of 4800–5120 cGy. Patients with positive para-aortic lymph nodes received treatment to both pelvic and para-aortic nodal beds. Vaginal brachytherapy was given weekly for six doses to boost the radiation dose to the vagina. Brachytherapy doses were estimated at 0.5 cm deep to the vaginal surface.

Demographic and tumor data were extracted as well as treatment dosing, duration of treatment, complications and disease course. Tumor stage was determined based on FIGO 2009 guidelines. Toxicities were classified per Common Terminology Criteria for Adverse Events (CTCAE) v3.0 and Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) late radiation morbidity scoring schema. Descriptive statistics were used to quantify treatment characteristics and toxicities. Kaplan–Meier method was used to estimate overall and progression-free survival.

Results

Seventy-six patients were treated for stage III–IV endometrial cancer with adjuvant chemotherapy and radiation, 16 of which received sequential therapy and 9 of which received sandwich therapy. We identified 51 patients who received concomitant chemotherapy and radiation. Among women who received concomitant therapy, the median age at diagnosis was 60 years (range 33–85). Forty-six patients (90.2%) underwent complete surgical staging with pelvic and para-aortic lymphadenectomy. A median of 16 pelvic lymph nodes (range 2–55) and 6 para-aortic lymph nodes (range 0–11) were sampled from patients who underwent staging. Five patients (9.8%) were thought to have benign or low-risk disease at the time of surgery and did not undergo lymphadenectomy. Thirty-six patients (70.6%) had endometrioid histology, 13 patients (25.5%) had serous, clear cell, or mixed histology, and 2 patients (3.9%) had carcinosarcoma. Ten patients (19.6%) had stage IIIA disease, two patients (3.9%) had stage IIIB disease, and 36 (70.6%) women had stage IIIC cancer (29 IIIC1 and 7 IIIC2). The remaining three patients (5.9%) had stage IVB cancer. Women with positive pelvic lymph nodes had a median of 1 positive node (range 1–30) and women with positive para-aortic lymph nodes had a median of 2 positive para-aortic nodes (range 1–4). Forty-three patients (84.3%) had lymph-vascular space invasion and five patients (9.8%) had malignant cells identified in pelvic washings. Table 1 outlines demographic data and tumor characteristics.

Patients were treated for an average of 107 ± 19 days. Forty-nine patients were treated with full-dose doublet therapy of carboplatin and paclitaxel. One patient with adenocarcinoma received triplet therapy with doxorubicin, cisplatin, and docetaxel. One patient with carcinosarcoma received four cycles of carboplatin and paclitaxel followed by four cycles of paclitaxel and ifosfamide per a phase one protocol (radiation was given during carboplatin and paclitaxel). Patients completed a median of 6 cycles of chemotherapy (range 2–8 cycles). Thirty-seven patients (72.5%) received 6 cycles and three patients (5.9%) received less than 4 cycles of chemotherapy. Two patients (3.9%) received 8 cycles of chemotherapy: one patient with carcinosarcoma per a phase one protocol, and one patient with endometrioid cancer received 8 cycles of chemotherapy because of an incomplete radiologic response after 6 cycles. Two patients were transitioned from paclitaxel to docetaxel; one patient for an allergic reaction and one patient due to neuropathy. Nine patients (17.6%) stopped their chemotherapy prematurely due to toxicity. Sixteen patients (31.3%) required chemotherapy dose reductions because of toxicity. There was no correlation between dose reductions or failure to complete chemotherapy and para-aortic radiation ($P > 0.05$). Thirty-nine patients (76.5%) started radiation within 1 month of initiation of chemotherapy. There was no association between timing of radiation initiation (within 1 month versus after

Table 1
Patient and tumor characteristics.

Age (median(range)	60 (33–85)
Histology, *n* (%)	
Endometrioid	36 (7 0.6)
Serous, clear cell, mixed	13 (25.5)
Carcinosarcoma	2 (3.9)
Grade, *n* (%)	
1	19 (37.3)
2	11 (21.6)
3	21 (41.2)
Stage, *n* (%)	
IIIA	10 (1 9.6)
IIIB	2 (3.9)
IIIC1	28 (54.9)
IIIC2	8 (15.7)
IVB	3 (5.9)
+LVSI[a], *n* (%)	43 (84.3)
+Washings, *n* (%)	5 (9.8)

[a] Lymph-vascular space invasion.