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Dose dense carboplatin paclitaxel improves progression free survival in patients with endometrial cancer

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HIGHLIGHTS

- Dose dense improves progression-free survival compared to standard chemo.
- Patients with advanced stage had better overall survival in the dose dense cohort.
- Both dose dense and standard protocols are well tolerated.
- Decreased musculoskeletal side effects in the dose dense cohort

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ABSTRACT

Objective. Pilot study to assess the value of weekly paclitaxel plus carboplatin every 3 weeks (dose dense regimen, DD) compared to the standard 3-weekly protocol in the adjuvant setting for endometrial cancer.

Methods. Retrospective cohort study comparing consecutive patients with high and intermediate-high risk endometrial cancer, undergoing DD protocol (from 2011 to 2015) to a non-overlapping historical cohort with similar characteristics who received treatment every three weeks (2008–2011).

Results. 122 patients with endometrial cancer were included in the study, of these, 61 patients received the dose dense protocol and 61 were treated with the standard 3-weekly protocol. After a median follow-up of 61.6 months in the 3-weekly cohort, compared with 41.6 months in the DD cohort, 40 progressions were recorded. 29 progressions were observed in women treated in the standard protocol, with a three years progression free survival (PFS) of 57.4%, compared to 11 progressions observed in patients in the DD schedule, with a three years PFS of 79.5% ($P = 0.03$). Patients who were treated with the DD protocol were less likely to have progression events compared to the standard cohort with a hazard ratio of 0.4 on multivariate analysis (CI 95%, 0.2–0.8, $P = 0.01$), had significantly less distant metastases ($P = 0.01$), and had improved overall survival when diagnosed with advanced stage disease ($P = 0.02$). Complaints of musculoskeletal pain were more frequent in the standard cohort ($n = 17$, 27.9%) compared to the dose dense cohort ($n = 4$, 6.6%), $P = 0.005$.

Conclusion. Preliminary data suggests that dose dense chemotherapy might be a reasonable and superior option for adjuvant treatment of endometrial cancer, compared to standard chemotherapy.

1. Introduction

In contrast to the excellent outcome of the majority of patients who have early stage endometrial cancer (EC) [1], locally advanced uterine cancer (stages III and IVA) represents 15% of all cases of EC, but accounts for 50% of EC-related deaths [2].

Adjuvant treatment is administered in select cases based on clinical and pathologic factors associated with risk for distant and/or vaginal recurrence [3–6]. Studies have shown that the addition of a platinum-

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based combination chemotherapy to radiotherapy (RT) may improve outcomes for women considered to be at high risk of recurrence [7–9]. Cisplatin, doxorubicin, and paclitaxel are active agents used for the treatment of metastatic or recurrent EC [10,11]. Carboplatin and paclitaxel combination treatment has been tested in several phase II studies, with promising results [12]. When compared in a randomized fashion in GOG protocol 209, this regimen was better tolerated and not inferior to triple therapy with cisplatin, doxorubicin, and paclitaxel for progression free survival (PFS) and overall survival (OS) [13]. Based on response rates (RRs) of 47–61% and low toxicity, the standard chemotherapy treatment for EC in many centers is a combination of intravenous carboplatin (area under the plasma concentration-time curve [AUC],5–6) and paclitaxel (175 mg/m^2) in a once every 3 weeks regimen (3-weeks TC) [12,14].

Theoretically, an increase in efficacy of chemotherapy regimens could be achieved by increasing the dose of the chemotherapy agents, or by shortening the interval between treatments [15]. Dose dense (DD) therapy is based on the concept that the cumulative dose remains the same, but the time interval between cycles of treatment is shortened to reduce the opportunity for re-growth of tumor cells [16]. Based on the improved outcome of dose dense regimens in breast cancer [17] and ovarian cancer (JGOG) [18,19], we treated patients with intermediate-high and high risk for recurrence of EC with the DD protocol. The aim of the current study is to compare the OS and PFS of these patients to a non-overlapping historic cohort of patients with EC who were treated with the standard 3-weeks TC protocol.

2. Materials and methods

This retrospective analysis was conducted in the division of Gynecologic Oncology, Segal Cancer Center, Jewish General Hospital, a tertiary care center in Montreal, Canada. The Institutional Review Board (in accordance with the Helsinki declaration) approved the study, protocol #15-070.

Patients who were diagnosed and treated after their surgery for EC between the years 2008–2015 were included in the study. All the patients in both cohorts underwent hysterectomy, bilateral salpingo-oophorectomy and surgical staging. All the patients who underwent surgery between January 2008 and October 2010 underwent complete pelvic lymphadenectomy and from October 2010, patients underwent sentinel lymph node mapping in addition to complete pelvic LND.

Gynecologic Oncology Group (GOG) criteria were used to define a high intermediate-risk group for recurrence based on age and the following three pathologic factors: the presence of deep myometrial invasion, grade 2 or 3 histology, the presence of lymphovascular space invasion (LVSI) [6]. Women in the high intermediate-risk group, women with serous or clear cell carcinoma with myometrial invasion, and women diagnosed with stages III/IV, were counseled to undergo adjuvant chemotherapy with carboplatin and paclitaxel for six cycles followed by radiation [7,20–24].

Data for the study was collected retrospectively from a prospective electronic medical chart. All patients received adjuvant platinum combination chemotherapy following their surgery. The standard group was composed of all the patients who were treated with carboplatin (AUC 5–6) and paclitaxel (175 mg/m^2) every 3 weeks from January 2008 to September 2011. The DD group included all consecutive patients who received their treatment from September 2011 to January 2015. The treatment protocol was carboplatin (AUC 5–6) every 3 weeks and paclitaxel 80 mg/m^2 every week. For each patient, the following information was extracted: age; body mass index (BMI); Eastern Cooperative Oncology Group (ECOG) performance status; pre-surgical American Society of Anesthesiologists (ASA) score; type of surgery and pathological findings including histologic type; grade and stage (FIGO 2009); type of chemotherapy; radiation therapy (RT) utilized; and data regarding crossovers, dose reductions, response to treatment, as well as side effects and allergic responses. The surgical management of patients did not change between the two groups.

Adjuvant RT consisted of vaginal cuff brachytherapy, external beam radiation therapy, or both, in function of tumor extent according to a standardized protocol that was not changed during the study period. Patients with stage IB grade 3 tumors underwent brachytherapy to the vaginal vault following chemotherapy. Patients with stages II, IIIA and IIIB underwent pelvic radiotherapy and vaginal brachytherapy, whereas patients with stage IIIC or IVB underwent teletherapy to the pelvis and the para-aortic area and vaginal brachytherapy. The dose of external beam radiation was 45 Gy given in 25 fractions over 5 weeks with concomitant boosts to 55 Gy to any areas of gross disease remaining after adjuvant chemotherapy. Brachytherapy was given in one or two sessions of 6 Gy depending on the presence of cervical stroma invasion. During the surveillance period, routine follow-up examinations and laboratory tests, including CA125 levels, were performed every 4 months during the first two years, every 6 months for up to 5 years, and yearly thereafter. Imaging was performed only if clinically indicated. This protocol was the same for both cohorts.

Overall survival (OS) was defined as time from diagnosis to either last follow-up or death. Progression free survival (PFS) was defined as the time from the last cycle of treatment to either diagnosis date of recurrence or death.

Statistical analysis was performed using the STATA 12 (StataCorp, College Station, TX). Statistical significance was calculated using the chi square test for differences in qualitative variables and the Student *t*-test for differences in continuous variables.

Kaplan-Meier survival curves were used to calculate survival estimates (PFS and OS) and the log rank test was used in order to quantify survival differences according to different variables. A multivariate analysis using the Cox proportion hazards model with a propensity score was performed to assess the hazard ratio of the prognostic factors for PFS and OS.

Table 1
Clinical characteristics.

Patient characteristics	Standard treatment every 3 weeks ($n = 61$)	Dose dense treatment Taxol weekly ($n = 61$)	*P*-value
Median age	66(43–85)	67(41–84)	0.90
BMI	28.3(18.7–53.3)	29.3(18.4–45)	0.62
ASA score			0.04
1	15(24.6%)	5 (8.2%)	
2	29(47.5%)	37(60.7%)	
3	15(24.6%)	18(29.5%)	
Missing	2 (3.3%)	1(1.6%)	
Tumor grading			0.69
Well differentiated	2(3.3%)	4(6.6%)	
Moderately differentiated	9(14.7%)	10(16.4%)	
Poorly differentiated	50(82.0%)	47(77.0%)	
Tumor histology			0.27
Endometrioid	27(44.3%)	24(39.3%)	
UPSC/clear cell	32(52.4%)	30(49.2%)	
Carcinosarcoma	2(3.3%)	7(11.5%)	
FIGO 2010 Stage			0.72
Ia	12(19.7%)	14(23.0%)	
Ib	11(18.0%)	8(13.1%)	
II	7(11.5%)	7(11.5%)	
III	26(42.6%)	30(49.2%)	
IV	5(8.2%)	2(3.3%)	
Adjuvant radiation therapy	55(90.2%)	55(90.2%)	1.00
Follow up in months	61.6(2.5–101.5)	41.6(1.9–62.5)	0.008

Data are median (range) or n (%). ASA = American Society of Anesthesiologists. UPSC = Uterine Papillary Serous Carcinomas. FIGO = International Federation of Gynecology and Obstetrics.

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