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Feasibility study of dose dense Epirubicin/Carboplatin followed by Paclitaxel/ Carboplatin in advanced, recurrent or metastatic endometrial carcinoma

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Abstract

Purpose: To develop a potentially superior chemotherapy regimen, we conducted a feasibility study of dose dense sequential Epirubicin/Carboplatin followed by Paclitaxel/Carboplatin. The primary objective was to determine the feasibility and toxicity of the regimen; the secondary objective was to estimate the progression-free and overall survival.

Experimental Design: Chemo naive patients with stage III, IV, or recurrent endometrial cancer were studied. Treatment consisted of six cycles of Epirubicin (75 mg/m2) /Carboplatin (area under the curve [AUC] 3) [EC], followed by 6 cycles of Paclitaxel (135 mg/m2) /Carboplatin (AUC3) [PC] with each cycle administered at 14-day intervals. Granulocyte colony stimulating factor (G-CSF) was given routinely on day 2.

Results: Between November 2007 and October 2009, 29 patients were enrolled. About 23 of 29 patients (79.4%) have completed all chemotherapy as planned; 3 patients (10.3%) had disease progression during treatment. Excluding three patients who did not complete treatment for non-drug-related causes, 89.6% completed all planned treatment. Overall median PFS and overall survival were 17.3 months and 43 months respectively. Common Toxicity Criteria grade 3/4 haematological toxic effects, particularly neutropenia and thrombocytopenia, were the predominant cause of treatment delays and dose reductions. A low incidence of grade 3 neurotoxicity and no cardiac toxicity were observed.

Conclusion: Dose-dense every-2-week EC × 6 → PC × 6 with pegfilgrastim is feasible based on our prospective definition.

Introduction

Carcinoma of the epithelial lining (endometrium) of the uterine corpus is the most common female pelvic malignancy. Factors influencing its prominence are the declining incidence of cervical cancer, longer life expectancy, and earlier diagnosis. Adenocarcinoma of the endometrium, the most prevalent histologic subtype, is currently the fourth most common cancer in women, ranking behind breast, lung, and bowel cancers. Endometrial adenocarcinoma is the eighth leading cause of death from malignancy in women (1). Clinical outcome is often favourable as the majority of women present with early-stage disease and can consequently be treated with radical surgery and/or radiotherapy (RT). However, the prognosis is not so favourable for those patients with recurrent or advanced (stage III/ IV) disease (2).

Patients who have advanced or recurrent endometrial carcinoma should be considered for systemic therapy. According to current evidence, patients who have a grade 1 tumor and/or known progesterone receptor-positive disease clearly benefit from treatment with progestins (response rate, 40%; median progression-free interval, 9 months; overall median survival, 14 months) and should be so treated (3). Tamoxifen has a 0% to 13% response rate, is not as active as progestins, and is of little value as second-line therapy in patients who do not respond to progestins. Other hormonal agents, such as gonadotropin-releasing hormone analogs (LHRH) do not appear to have sufficient activity to warrant further study (3).Those with grade 2 to 3 tumor, and/or known progesterone receptor-negative disease, other histological subtypes such as papillary serous or clear carcinomas and for patients with visceral metastases do not well with progestins therapy (response rate, 12%; median progression-free interval, 3 months; overall median survival, 10 months) and should be considered for initial treatment with single-agent or a combination chemotherapy regimen (4). Chemotherapy should also be considered for patients who do not respond to initial hormonal treatment. Although platinum based chemotherapy would be a standard of care in most centres, However there is no consensus as to the best regimen (5).

Single agent trials focus on three groups with demonstrated activity: anthracyclines, platinum compounds and taxanes. The anthracyclines studies include doxorubicin and epirubicin. Doxorubicin produced a 27% response rate. Epirubicin yielded a 26% response rate. Two platinum compounds have activity. Cisplatin elicited response in 29%. The use of carboplatin instead of cisplatin has been suggested to improve tolerability with the same efficacy. Paclitaxel, in two Gynecologic Oncology Group (GOG) studies, yielded responses in 36% of chemotherapy-naïve and 27% of previously treated patients. Other single agents with modest activity in endometrial cancer include ifosfamide and topotecan (6-8).

Combination chemotherapy has produced superior clinical outcomes compared with single-agent therapy. A number of phase II trials of combination regimens have been conducted. The combination of carboplatin and paclitaxel has been demonstrated to be active in advanced endometrial cancer (50% to 60%

response rate) (9). A trial of circadian timed administration of cisplatin and doxorubicin found no significant benefit (10). Following encouraging phase II results, a phase III randomized trial of cisplatin and doxorubicin with or without paclitaxel following surgery and radiation therapy did not show any improvement in recurrence-free survival but did have more toxicity (11). A Gynecological Oncology Group (GOG) then compared this two-drug (cisplatin [50 mg/m2]/ doxorubicin [60 mg/m2]) regimen with a three-drug combination of cisplatin (50 mg/m2), doxorubicin (45 mg/m2), and paclitaxel 160 mg/m2 as a 3-hour infusion), with G-CSF (granulocyte colony-stimulating factor, filgrastin [Neupogen] support (GOG 177). The three-drug combination of the paclitaxel-containing program produced higher response rate (57% vs 35%) and an improved progression-free survival (8.3 months vs 5.3 months). 0verall survival was also modestly (15,3 months vs 12.3 months; P = .037) with the three drug program but with considerably greater toxicity, particularly peripheral neuropathy (grade 3, 12% vs 1%) (12).

As a triplet combination may be superior to a doublet, achieving adequate dose intensities was problematic in the former as the concurrent administration of these agents requires frequent dose reductions and treatment interruption due to toxic effects and may render the regimen less effective (13–15). The use of non-cross-resistant agents, i.e. Epirubicin and Paclitaxel, on a carboplatin backbone in sequential manner could not only overcome this problem but also minimise the likelihood of emergence of resistant clones as predicted by the Goldie–Coldman model (16). To develop a potentially superior chemotherapy regimen with acceptable toxicity, we planned this study to test a regimen of an epirubicin/carboplatin × 6 followed by paclitaxel/carboplatin × 6, all given in a dose-dense fashion every 2 weeks with pegfilgrastim. The objectives of this trial were to determine the feasibility and safety of this regimen and to evaluate response rate, DSF and OS.

Patients and Methods

Eligible patients had histologically confirmed stage III or IV advanced, recurrent, or metastatic endometrial cancer requiring systemic chemotherapy. In addition, patients with high risk endometrial histologies (papillary serous and clear cell carcinoma) were also eligible. At least one measurable lesion that could be assessed according to the response evaluation criteria in solid tumors (RECIST), performance status (PS) of 0-2 according to the Eastern Co-operative Oncology Group (ECOG), should be fulfilled in all the patients.

Absolute neutrophil count ≥1,500/μL and platelet count ≥100,000/ μL; normal total bilirubin; serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase ≤ 2.5 upper limit of normal, adequate kidney function (creatinine clearance (CrCl) >60mL/min and serum creatinine level of <1.5mg/dl). In addition, normal cardiac function was required as demonstrated by echocardiogram. Patients with known history of unstable angina, myocardial infarction, congestive heart failure, previous chemotherapy, or serious medical illnesses were excluded. All patients were required to provide written informed consent before joining the study, and the protocol was approved by the institutional ethics committee.

Treatment Plan

Six cycles of Epirubicin (75 mg/m2) /Carboplatin (area under the curve [AUC] 3), followed by 6 cycles of Paclitaxel (135 mg/m2) /Carboplatin (AUC3) with each cycle administered at 14-day intervals were planned. Carboplatin dose was calculated following others (17). Granulcyte colony stimulating factor (pegfilgrastim 6 mg SC) was given routinely on day 2. Epirubicin was administered as a rapid i.v. infusion in 250 ml of 0.9% sodium chloride, paclitaxel was given as a 3-h i.v. infusion in 500 ml of 0.9% sodium chloride and carboplatin was given as an i.v. infusion in 500 ml of 5% glucose over 1 h. Standard premedication consisting of 5HT3 antagonists, dexamethasone, antihistamines, and rantidine was used.

Due to obesity and overweight, patients who were >40% above their ideal body weight were dosed using the corrected body weight (actual weight plus the ideal body weight divided by 2). A complete blood count with leukocyte differential, liver, and renal functions were performed before each treatment of chemotherapy. Patients were seen every 2 weeks during treatments for history and physical examination and assessment of performance status and toxicity. Before the first cycle of therapy, a computed tomography (CT) study of the thorax, abdomen and pelvis was carried out; this was repeated following six and twelve cycles of chemotherapy or earlier if clinically indicated.

When patients required RT, either external beam and/or brachytherapy to the vaginal vault, in addition to chemotherapy; RT was administered at the end of chemotherapy.

Dose Modifications

Patients experiencing neutropenic fever (ANC < 1000/μL and body temperature ≥ 38.5°C) and/or grade 3 or 4 nonhematologic toxicity had day 1 doses in subsequent cycles reduced by 25% of the dose administered in the current cycle. A maximum of 2 dose reductions were allowed. If on the day that chemotherapy in subsequent cycles of treatment was due, platelet counts were < 100,000 cells/μL and/or ANC < 1000 cells/μL and/or nonhematologic toxicities (excluding alopecia) had not recovered to ≤ grade 1, treatment was delayed by ≤ 1 week, and CBC and toxicity grading were repeated weekly. If a treatment delay of > 2 consecutive weeks was required, the patient would be taken off study.

Evaluation criteria

Tumor assessments were performed at baseline and during follow up according to RECIST. Response had to be reconfirmed at least 4 weeks after first being noted. Should progressive disease be documented, treatment was stopped. Chemotherapy-related toxicities were recorded according to the National Cancer Institute Common Toxicity Criteria version 3.0 (18).

Study endpoints

The primary objective was to determine the feasibility and toxicity of the regimen; the secondary objective was to estimate median survival, median progression free survival and toxicity. The 2-year survival and 2-year progression free survival (PFS) were estimated using the Kaplan-Meier method. Survival was estimated from the date of first treatment day to death or last follow-up visit. PFS was estimated from the date of first treatment day to first evidence of disease progression.

Results

Between November 2007 and October 2009, 29 patients were treated with this regimen in ASUH and private centers; Table 1 lists the characteristics of the evaluable patients who entered the study. Of 29 patients, 14 had stage III (IIIA in six, IIIB in two and IIIC in six cases) and six had metastatic disease (lung

in four, liver in one and distant nodes in one case). Nine patients, six of whom had previously been irradiated, presented recurrence in either the retroperitoneal nodes (five cases) or the pelvis (four cases).

Table 1: Patient characteristics

Characteristics	No of patients (%)
Age	
Median (range)	57 (34-71)
Performance status	
0	4
1	23
2	2
Pathology	
Endometroid carcinoma	18
Papillary serous carcinoma	9
Clear cell carcinoma	1
Adenocarcinoma	1
Grade	
1	2
2	17
3	10
Stage	
III	14
IV	6
Recurrent	9

About 23 of 29 patients (79.4%) have completed all chemotherapy as planned; 3 patients (10.3%) had disease progression during treatment. the remaining 3 of 29 patients (10.3%) had modified treatments. Of these 3 patients, 1 completed only EC × 5 because of grade 3 fatigue and proceeded to complete PC × 6, 1 completed EC × 6 and only PC × 4 because of grade 3 nail changes, and 1 completed only EC × 5 because of grade 3 fatigue and completed only 1 cycle of PC and was changed to weekly P because of grade 3 bone pain. Excluding the patients who did not complete their treatment due to disease progression (three patients), 89.6% of patients completed their cycles of treatment. A total of 348 cycles of chemotherapy were planned and 321 were administered (92.2%); of the administered treatments, 45 cycles were delayed and hence, 86% of treatments occurred on time.

There were 9 hospitalizations in 6 of 29 patients (24.1%) enrolled; 3 patients had 2 hospitalizations each for FN. seven admissions were related to EC treatments as follows: 5 FN, 1 headache, and 1 hypertension shortly after the completion of all chemotherapy. One hospitalization (herpes zoster) occurred during the paclitaxel phase.

During EC treatment, 6 of 29 patients (24.1%) had treatment reductions, all because of FN. During PC treatment, 2 of 29 patients (6.8%) had a dose reduction because of grade 3 nail changes and grade 3 neuropathy.

For the 29 patients, eleven demonstrated CRs, 14 achieved PRs, three had progression of disease (PD) and one had stable disease. The overall RR (CR and PR) of the patients was therefore 86.2%. A median follow-up period of 24 months was reached. Overall median PFS was 17.3 months [95% confidence interval (CI) 13.1–21.1] as illustrated in Figure 1. The median OS was 43 months (95% CI 34.6–50.5) as shown in Figure 2.

All 29 patients underwent toxicity assessment. Hematologic and nonhematologic evidence of toxicities is summarized in Table 2. Four (13.7%) patients experienced grade 3-4 anemia. Grade 3 and grade 4 neutropenia occurred in 6 (24.1%). Nonhematologic toxicity was mild. The major symptom being fatigue, observed in 4 (13.7%) of patients. Grade 3 nausea and vomiting occurred in 10.3%. No treatment-related deaths occurred.

Table 2: The occurrence of Grade 3-4 adverse events

Adverse event	No (%)
Haematological	
Neutropenia	6 (24.1%)
Thrombocytopenia	5 (17.2%)
Anaemia	4 (13.7%)
Gastrointestinal	
Nausea	2 (6.8%)
Vomiting	1 (3.4%)
Diarrhoea	1 (3.4%)
Constipation	1 (3.4%)
Neurological	
Neuropathy	3 (10.3%)
Hearing loss	0
Hepatotoxicity	2 (6.8%)
Renal toxicity	2 (6.8%)
Skeletal	
Arthalgia	1 (3.4%)
Myalgia	3 (10.3%)
Fatigue	4 (13.7%)
Mucositis	1 (3.4%)
Alopecia	3 (10.3%)

Discussion

Relapse of disease may be due to relative or absolute drug resistance (19). Inherent or acquired drug resistance and variable drug sensitivity among subclones could contribute to resistance as well (19). To overcome this limitation on the effectiveness of chemotherapy, various strategies, including the use of non-cross-resistant drugs and manipulations of dose and schedule, have been investigated.

The Norton-Simon model predicts that the optimal treatment of a heterogeneous mix of cells (in terms of chemotherapy sensitivity) is to eradicate the numerically dominant, fastergrowing cells first, followed by eradication of the more slowgrowing, resistant cells (20). This is termed sequential therapy and is superior to alternating therapy in a randomized clinical trial (21). Sequential therapy may be more effective because it increases the frequency ("density") of treatments as compared with alternating therapy, thereby minimizing the time during which sensitive cells can regrow before retreatment (19).

One of the objectives of this study was to evaluate the feasibility of the experimental regimen and assess its toxicity, because one of the main risks of adding a third drug to standard doublet chemotherapy is a predictable increase in adverse events. Overall, the combinations used in this phase II clinical trial showed good feasibility and acceptable tolerability and toxicity, using the three drugs under investigation at relatively high doses and in sequential

manner. In total, 79.4% of all patients completed all twelve cycles of treatment and 89.6% of all administered treatments occurred on time. In other published studies, the proportions of patients completing six or more cycles of 3-weekly carboplatin AUC5/paclitaxel 175 mg/m2 and 4-weekly carboplatin AUC6/ pegylated liposomal doxorubicin (PLD) 40 mg/m2 were 83% [20] and 56% [11], respectively. In all, 10.3% of all patients discontinued treatment due to drug-related toxic effects in this study. It is also interesting to note that the proportions of patients discontinuing treatments due to drug-related toxic effects were 7% and 24% in the doxorubicin–paclitaxel (AP) and paclitaxel,
doxorubicin and cisplatin (TAP) arms, respectively, of the study by Fleming et al. (22)

In a similar work, Ang et al, (23) used sequential doublet chemotherapy comprising carboplatin/doxorubicin ×4 and carboplatin/paclitaxel × 4 to treat 52 advanced or recurrent endometrial cancer patients. They reported a RR of 82.1% in comparison to 86.4% in our study. Also, PFS and overall survival were 15.3 and 38.5 months in comparison to 17.4 and 43 months in our study respectively. In this work, we chose 6 cycles of Carboplatin/epirubicin and 6 cycles of carboplatin/paclitaxel because of the controversy regarding the efficacy of 4 cycles of any chemotherapy agent.

In this study, the incidence of grade 3 or 4 sensory neuropathy was low at 10.3% with nonhaematological toxicity was mild. No treatment-related deaths occurred. No patient developed clinically significant deterioration in cardiac function. These rates of treatment-related toxic effects compare favorably with results of other trials involving various combinations of these three agents, especially when they were administered concurrently. For instance, while the incidence of sensory neuropathy was about 7% to 9% in studies involving doublets of doxorubicin and paclitaxel or cisplatin, it was 39% when TAP was administered concurrently (22, 24]. It could be argued that the low incidence of neurotoxicity observed in our series was partly due to the fact that carboplatin instead of cisplatin was used. However, we note that the proportion of our patients who developed either grade 3 or 4 neutropenia was 24.1% (with routine use of G-CSF) and this is less than reported from other published studies, including the TAP combination with G-CSF support where it was 59% (22,24). The incidence of grade 3 and 4 thrombocytopenia in our series was 17.3% and is comparable to the 22% in the TAP series; however, there were no cases of related bleeding.

Although preliminary, the results of this study confirm initial reports of a significant antitumour activity of platinum compounds, anthracyclines and taxenes in endometrial carcinoma. Notwithstanding the brief follow-up period, the small size of this series and the different characteristics of the patients evaluated, it appears that the use of dose dense sequential doublet of Epirubicin/ Carboplatin followed by Paclitaxel/Carboplatin produce better OS and DFS with lesser toxicity than concurrent administration of these drugs.

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Figures

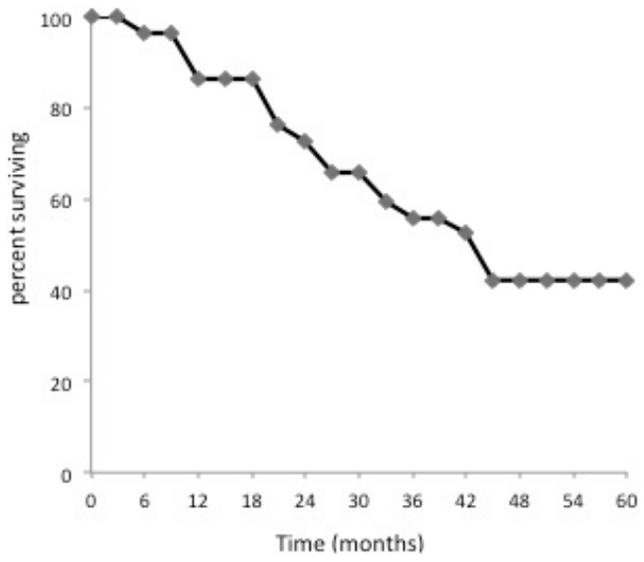

Fig 1: Overall survival.

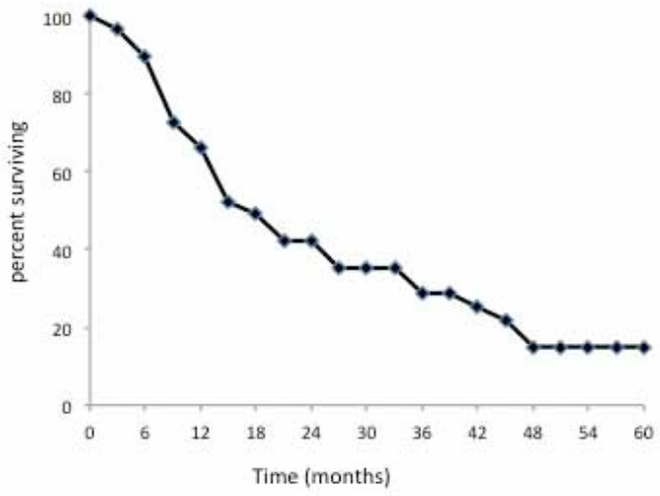

Fig 2: Progression-free survival.