Carboplatin plus Paclitaxel in the First Line Therapy of Recurrent and Advances Endometrial Cancer

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Abstract

Introduction: To evaluate the efficacy and safety of Carboplatin plus Paclitaxel in patients with advanced locoregional recurrence and metastatic endometrial cancer.

Patient and Method: 32 eligible patients (median age 62, range 41-72) with measurable endometrial cancer were treated with Carboplatin (AUC= 6) and Paclitaxel (175 mg/m^3) every 4 weeks for 6 cycles, or, until disease progression or severe toxicity.

Result: The ORR was 54% (16 out of 30), CR in 4 and PR in 12.

The median progression free survival was 8.2 months. The 6 months overall survival was seen in 80% of trhe patients. The toxicity was generally tolerable.

Conclusion: The combination of Carboplatin plus Paclitaxel was well tolerated in this trial. This regimen demonstrated feasible success in curing advanced endometrial cancer compared to other combination therapies used before (in terms of RR and toxicity).

Keywords: Endometrial cancer, Carboplatin, Paclitaxel.

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Introduction

Endometrial cancer is the most common gynecologic cancer. Most patients are cured with surgery or radiation therapy. The high risk patient population represents a group with a high rate of pelvic recurrence and increased distant dissemination.(1) For those who present relapse or metastases, definitive treatment options are limited.(2) Cisplatin plus doxorubicin was the standard of care for many years but the response has been mostly only partial with short duration.(3) Because of the low benefit of prior treatments, trials with new combinations are strongly needed.

Cisplatin could be substituted by Carboplatin with the same objective response to this disease but has a greater tolerable toxicity profile, especially when it is given in combination with taxens.(4)

RTOG 9708 Greven K, et al. tested radiation combined with cisplatin plus taxol followed by surgery for patients with high risk endometrial cancer. The disease-free survival was 4 years in 81% of the patients.(5)

Paclitaxel is an active cytotoxic product against endometrial adenocarcinoma used as a single agent; therefore, it seems reasonable if it is combined with a platinum agent.(6)

The response rate for a combination of doxorubicin and cisplatin has been 30-35%. This phase II study has been designed to show the feasibility and efficacy of the combination of Carboplatin and Paclitaxel in advanced and recurrent endometrial cancer, and the other objective of this trial was to evaluate the safety and toxicity of this combination chemotherapy.

Materials and Methods

Between September, 2004 and September, 2007, 32 patients with advanced and recurrent endometrial carcinoma were enrolled in this study.

The inclusion criteria: The cases were histologically proven as advanced or recurrent epithelial endometrial carcinoma which could not be cured by surgery or radiation therapy. The performance status was ECOG: 0-2, no prior history of chemotherapy, no prior history of invasive

Table- 1. Patient Characteristics

Age	41-72	
Median (age)	62	
Race	White, Iranian	
Histology	Endometrioid Carcinoma	15
	Adeno Squamous	6
	Papillary Serous	4
	Clear Cell	3
	Papillary Villous	2
Grade	II	13
	III	17
Prior Surgery	+	21
	–	9
Stage	Advanced Locoregional	11
	Metastatic	19
Status	Recurrence	14
	Advanced in First Visit	16

cancer, no renal or liver abnormal function, cell blood counts within normal limits, being fully-informed patients before enrolment.

Treatment Protocol: Paclitaxel at a dose of 175 mg/m2 given over 3 hours, followed by Carboplatin at an AUC of 6 (400 mg/m3) given over 30 minutes.

Dexamethasone, kytril, metochlopramide and ranitidine were administered as standard premedications. Treatment was given on an outpatient basis every 3 weeks for 6 cycles or until tumors progressed, there was severe toxicity or patient withdrawal. The next cycle was delayed until the granulocyte count was at least 1500/ml and the platelet count at least 100,000/ml. If patients experienced severe sensitivity on two occasions, the patient was removed from the study.

Response was evaluated every 3 cycles according to standard criteria. A complete response (CR) was the disappearance of all measurable and evaluable disease. A partial response (PR) represented a greater than 50% decrease in all measurable lesions with no new ones. “Stable disease” was defined as steady state of response either less than a partial response or progression of less than 25%. “Progressive disease” was defined as increase of measurable lesions or a clear worsening of any evaluable disease, or the appearance of any new lesions.

“Overall survival” (OS) was defined from the date of registration to death from any cause. The analysis included the assessment of the patient’s characteristics and the evaluation of toxicity. Progression free survival (PFS) was the primary endpoint for this trial.

Results

A total of 32 patients were enrolled into this study. Of those, two were ineligible due to incorrect pathology and inadequate documentation. A description of 30 eligible patients is summarized in Table-1. The 6-cycle plan was completed in 22 out of 30 patients (77%). Six patients developed progressive disease during the treatment and were taken off the study. Two patients were removed from the study because of severe side effects.

Toxicities were generally mild; fourteen patients showed grade 1-2 sensory neuropathy or neuropathic pain but no one showed grade 4 neuropathy.

Gastrointestinal toxicity including: diarrhea, nausea, vomiting developed in 4 patients that were simply controlled by symptomatic treatment. We did not have any other major side effects, for example, Thromboembolism or cardiac or metabolic toxicities.

Fifteen patients developed grade 4 neutropenia, 4 of them were admitted due to febrile neutropenic conditions. These 15 patients were put on G-CSF for the next courses.

Two patients developed grade III thrombocytopenia and anemia, non needed transfusion.

The overall response rate was 54% (16 out of 30). A complete response (CR) was noted in 4 of the 30 patients (14%); two of these were confirmed pathologically. The PR rate was 40% (12 out of 30). The median progression-free survival rate (PFS) was 8.2 months. The 6 months overall survival (OS) was seen in 80% of patients and the median OS was 15 months.

At the time of this report, three are still living with a follow-up period of more than 30 months. Except for one patient, all deaths were due to disease progression.

Discussion

Studies with single agents and combination chemotherapy have shown encouraging response rates in patients with recurrent and metastatic endometrial adenocarcinoma. There have been a few prospective trials designed to study the feasibility and efficacy of systemic chemotherapy in advanced cases of endometrial cancer (7).

Duska, et al, reported an acceptable feasibility for treatment with 3 cycles of Paclitaxel, doxorubicin and carboplatin in high risk endometrial cancer (8).

Mundt, et al, reviewed 44 patients treated at the University of Chicago with systemic chemotherapy alone which showed a reasonable outcome (9).

Randall, et al, published data from GOG122 demonstrated outcomes for patients with stage IV disease who were randomized to chemotherapy alone with cisplatin and adriamycin or whole

abdominal radiation that were 58% versus 46% in favor of chemotherapy (10).

Katsumata N, et al, in Japan (in 2005) conducted a trial with a combination of docetaxel plus carboplatin in 33 patients with advanced and metastatic endometrial cancer and the RR was 31% (11).

In our study, in spite of a 54% ORR and an acceptable 14% CR, toxicity was tolerable and primarily hematologic. Years of experience using this combination (Carboplatin+Paclitaxel) in epithelial ovarian cancer made it possible to use an outpatient setting with acceptable tolerability for the patients.

Sidney A. Scudder, et al, (in 2004) used this combination plus amifostine and reported a 40% RR with an 8% CR with 79% hematologic toxicity (12).

Conclusion

The feasible activity of carboplatin and paclitaxel in this trial and many similar trials before, as well as generally non-serious toxicity profiles, lead to the conclusion that Taxol plus Carboplatin combination is a reasonable therapeutic option in carefully selected patients with recurrent or metastatic endometrial cancer.

Because the locally advanced, recurrent and metastatic cases of endometrial cancer are uncommon, cooperation of many centers is needed to evaluate the effect of any suggestive trial and assessment of possible promising benefit of them. The possible role of biologic and targeted therapy in advanced endometrial cancers remains to be investigated.

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References

1. Jemal A, Murray T, Samuels A, et al. Cancer Statistics CA Cancer. J Clin Oncol, 2000; 53:5-26.

2. Thigpen JT, Brady MF, Homesley HD, et al. Phase III Trial of Doxorubicin with or without Cisplatin in Advanced Endometrial Carcinoma: A Gynecologic Oncology Group Study. J clin Oncol, 2004; 22:3902-8.

3. Fleming GF, Brunetto VL, Cella D, et al. Phase III Trial of Doxorubicin plus Cisplatin with or without Paclitaxel plus Filgrastim in Advanced Endometrial Carcinoma: A Gynecologic Oncology Group Study. J clin Oncol, 2004; 22: 2159-66.

4. Ozols RF, Bundy BN, Greer BF, et al. Phase III Trial of Carboplatin and Paclitaxel Compared with Cisplatin and Paclitaxel in Patients with Optimally Resected Stage III Ovarian Cancer: A Gynecologic Oncology Group Study. J clin Oncol, 2003; 21:3194-200.

5. Greven KM, Winter K, Underhill K, et al. Radiation Therapy Oncology Group. Preliminary Analysis of RTOG 9708: Adjuvant Postoperative Radiotherapy Combined with Cisplatin/Paclitaxel Chemotherapy after Surgery for Patients with High-risk Endometrial Cancer. Int J Radiat Oncol Biol Phys, 2004; 1 59 (1):168-73.

6. Lincoln S, Blessing JA, Lee RB, e al. Activity of Paclitaxel as Second-line Chemotherapy in Endometrial Carcinoma: A Gynecologic Oncology Group Study. Gynecol Oncol, 2003; 88: 277-81.

7. Marrow PC, Bundy BN, Homesley HD, et al. Doxorubicin as an Adjuvant Following Surgery and Radiation Therapy in Patients with High-risk Endometrial Carcinoma, Stage I and Occult Stage II: A Gynecologic Oncology Group Study. Gynecol Oncol, 1990; 36: 166-71.

8. Duska LR, Berkowitz R, Matulonis U, et al. A Pilot Trial of TAC Chemotherapy with Filgastrin Support Followed by Radiotherapy in Patients with High-risk Endometrial Cancer. Gynecol Oncol, 2005; 96(1): 198-203.

9. Mundt A, McBride R, Rotmensch J, et al. Significant Pelvic Recurrence in High-risk Pathologic Stage I-IV Endometrial Carcinoma Patients after Adjuvant Chemotherapy Alone: Implications for Adjuvant Radiation Therapy. Int J Radiat Oncol Biol Phys, 2001; 50: 1145-53.

10. Randall ME, Filiaci VL, Muss H, et al. Randomized Phase III Trial of Whole-Abdominal Irradiation versus Doxorubicin and Cisplatin Chemotherapy in Advanced Endometrial Carcinoma: A Gynecologic Oncology Group Study. JCO 2006; 24: 36-44.

11. Katsumata N, Noda K, Nozawa S, et al. Phase II Trial of Docetaxel in Advanced or Metastatic Endometrial Cancer: A Japanese Cooperative Study. Br J Cancer. 2005; 93(9): 999-1004.

12. Scudder SA, Liu RY, Wilczynski SP, et al. Southwest Oncology Group. Paclitaxel and Carboplatin with Amifostine in Advanced, Recurrent, or Refractory Endometrial Adenocarcinoma: A Phase II Study of the Southwest Oncology Group.