

Combined Chemotherapy Regimen of Carboplatin and Paclitaxel as Adjuvant Treatment for Papillary Serous and Clear Cell Endometrial Cancer

Gil Shechter-Maor, Ilan Bruchim, Zipi Ben-Harim, Marco Altaras, and Ami Fishman

Objective: Uterine papillary serous carcinoma (UPSC) and uterine clear cell carcinoma (UCCC) are highly aggressive variants of endometrial cancer. The optimal adjuvant regimen for these uterine malignant types has not yet been defined. The objective of this study was to evaluate the efficacy and toxicity of a combined chemotherapy regimen of carboplatin and paclitaxel as adjuvant treatment for patients with UPSC and UCCC variants.

Methods: A retrospective analysis of results of adjuvant chemotherapy that was based on 6 cycles of carboplatin (area under the curve, 5–6) and paclitaxel (175 mg/m²) q3 weeks.

Results: Twenty-one patients were eligible for analysis. All patients in this group underwent surgery before chemotherapy, with reported optimal debulking in 90% (n = 19). Fourteen patients (66%) had advanced stage (International Federation of Gynecology and Obstetrics stages III-IV) at the time of diagnosis. Five patients (24%) were treated with pelvic radiotherapy after the chemotherapy regimen. Clinical no-evidence-of-disease status was recorded in 19 patients (90%) at the end of the planned chemotherapy schedule. With a median follow-up of 25 months (8–61 months), 11 patients (58%) had recurrence and all have died of disease. Median progression-free interval was 13 months with a median survival of 27 months. Grade 3 toxicity was recorded in 7 patients (33%). Neutropenia developed in 3 patients (14%), neuropathy in 3 (14%), anaphylaxis in 1 (4.6%), and anemia in 1 (4.6%). Dose reduction was needed in 6 patients (29%), treatment delay in 6 (29%), and treatment cessation in 2 patients (10%).

Conclusions: The regimen of carboplatin and paclitaxel is active in patients with UPSC and UCCC with an acceptable toxicity profile.

Key Words: Uterine papillary serous carcinoma, Uterine clear cell carcinoma, Carboplatin, Paclitaxel

(Int J Gynecol Cancer 2009;19: 662–664)

Uterine papillary serous carcinoma (UPSC) and uterine clear cell carcinoma (UCCC) are highly aggressive variants of endometrial cancer. They represent less than 15% of all endometrial cancers, but account for more than 25% of the disease mortality.¹ The median age of patients with UPSC and UCCC is higher and the 5-year survival rate is significantly lower compared with the more prevalent uterine endometrioid cancer type.^{2–4} Most of these patients (80%–90%) present with extrauterine disease, whereas only 15% to

20% of the endometrioid type were diagnosed with advanced disease.^{5,6} The standard treatment of UPSC and UCCC includes hysterectomy, bilateral salpingo-oophorectomy, and surgical staging. Adjuvant therapy is recommended because of its aggressive behavior; however, there is no consensus regarding the standard approach of this setting. It has been suggested that UPSC responds poorly to radiotherapy, although this modality treatment for patients whose conditions were diagnosed as stages I and II may improve local control.¹ The optimal regimen of chemotherapy in the adjuvant setting has not yet been defined. Based on the similarity of features and pattern of spread between UPSC and epithelial ovarian cancer, there have been attempts to treat this disease with the same chemotherapy regimens that are routinely used in ovarian cases. The use of paclitaxel and carboplatin (PC) as adjuvant treatment of advanced or recurrent endometrial cancer was evaluated in a small series and was reported to be efficacious with low toxicity.^{7–9} The current study evaluates the efficacy and toxicity of combined PC as adjuvant treatment for patients with UPSC and UCCC.

Department of Obstetrics and Gynecology, Meir Medical Center, Kfar-Saba, Israel.

Address correspondence and reprint requests to Shechter-Maor Gil, MD,

Department of Obstetrics and Gynecology, Meir Medical Center, Kfar-Saba, Israel. E-mail: gilshhec@gmail.com.

Copyright © 2009 by IGCS and ESGO

ISSN: 1048-891X

DOI: 10.1111/IGC.0b013e3181a3d626

MATERIALS AND METHODS

This retrospective study included all patients with UPSC and UCCC variants whose conditions were diagnosed in Meir Medical Center, Kfar-Saba, Israel, from January 1995 through November 2006. Epidemiological data were retrieved from medical records. The chemotherapy regimen included 6 cycles of carboplatin (area under the curve, 6) combined with paclitaxel (175 mg/m²), administered q3 weeks in an outpatient setting after surgery. Patients who completed 4 cycles or more of the regimen were included in the data analysis. The treatment was continued up to a planned 6 cycles in patients with a complete or partial response or with a stable disease unless there was an evidence of disease progression, unacceptable toxicity, or patient refusal of treatment. Safety was assessed using laboratory parameters and continuous monitoring of adverse events. A complete blood cell count was performed before each treatment. Toxicity evaluations and blood chemistry analyses were performed at the end of each 3-week cycle. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (version 3.0). Response was defined using the World Health Organization response criteria and assessed by physical examination and cancer antigen 125 analyses before each treatment cycle. A computed tomography was performed every 3 cycles or, before that, in the presence of clinical evidence of disease progression. Any patient who achieved a complete response underwent computed tomography 4 to 8 weeks later.

RESULTS

A total of 45 women had a diagnosis of UPSC and UCCC during this period, and 21 were eligible for the chemotherapy data analysis. Twenty-four patients were excluded from this analysis: 18 who did not receive adjuvant chemotherapy at all, 4 who received a different chemotherapy regimen, 1 who did not undergo surgery because of poor performance status, and 1 who was lost to follow-up. All 21 patients underwent surgery before the chemotherapy initiation, with optimal debulking achieved in 90%. The median age at diagnosis was 74 years (range, 47–87 years), the median Eastern Cooperative Oncology Group performance status was 1 (range, 0–2), and the median follow-up time was 25 months (range, 8–61 months). Additional characteristics of the study patients are presented in Table 1. Most of the patients (14/21, 66.7%) had stage III or IV disease. Five patients received pelvic radiotherapy after the chemotherapy plan. The median number of administered chemotherapy cycles was 6 (range, 4–8 cycles). The clinical outcome is presented in Table 2. Nineteen patients (90%) have been defined with clinical no evidence of disease (cNED) after completion of the chemotherapy regimen. Despite the high percentage of cNED, 11 patients in this series developed recurrent disease, with a median progression-free interval (PFI) of 13 months (range, 1–59 months). The 2-year survival rate in our study was 64%, with a median survival of 27 months. At the time of reporting, 12 of the 21 patients have already died of disease (Fig. 1).

TABLE 1. Patient's characteristics

	No. Patients (n = 21)	%
Optimal debulking	19	90.5
Stage at diagnosis, World Health Organization criteria		
I-II	7	33.3
III-IV	14	66.7
Radiotherapy	5	23.8

TABLE 2. Response to chemotherapy

	No. Patients (n = 21)	%
cNED	19	90
Persistent disease	2	10
Recurrence (n = 19)	11	58
Mortality	12	57

Hematologic and nonhematologic toxicities were assessed in all patients. Grade 3 toxicity occurred in 7 patients (33%), whereas none encountered grade 4 toxicity. Grade 3 neutropenia and grade 3 anemia occurred in 3 and 1 patients, respectively. Three patients developed grade 3 neuropathy, and 1 patient experienced type 1 hypersensitivity to carboplatin. Dose reductions were required in 6 (29%) of 21 patients, treatment delays in 6 (29%) of 21, and cessation of treatment in 2 (10%) of 21.

DISCUSSION

Different chemotherapy regimens have been evaluated in previous studies as adjuvant and salvage treatments of UPSC and UCCC. The Gynecologic Oncology Group 122 study demonstrated that progression-free and overall survivals of patients with advanced endometrial cancer were significantly improved after doxorubicin and cisplatin treatment compared with whole abdominal irradiation alone.¹⁰ Price et al¹¹ evaluated combined treatment with cisplatin, doxorubicin, and cyclophosphamide (PAC) in a group of 30 patients with UPSC. In the adjuvant setting, 58% were alive with cNED, at median follow-up of 24 months, and 42% recurred, with a median survival of 14 months. Severe toxicity was observed in all patients. Levenback et al¹² evaluated 20 patients with advanced or recurring UPSC, treated with the PAC regimen and demonstrated a median PFI of 9 months with 70% of the patients experiencing moderate-severe toxicity. Hoskins et al¹³ treated advanced or recurrent endometrial cancer with carboplatin and paclitaxel and found a 60% response rate in advanced UPSC and 50% for recurrent UPSC. Toxicity in his report was manageable, reversible, and predominantly hematologic. Kelly et al³ reported improved disease-free and overall survivals in 74 patients with stage I UPSC who received platinum-based chemotherapy. Dietrich et al¹⁴ treated patients with stage I UPSC with carboplatin and paclitaxel chemotherapy. With a median follow-up of 41 months (range, 10–138 months), 20 of 21 patients were alive with no recurrence.

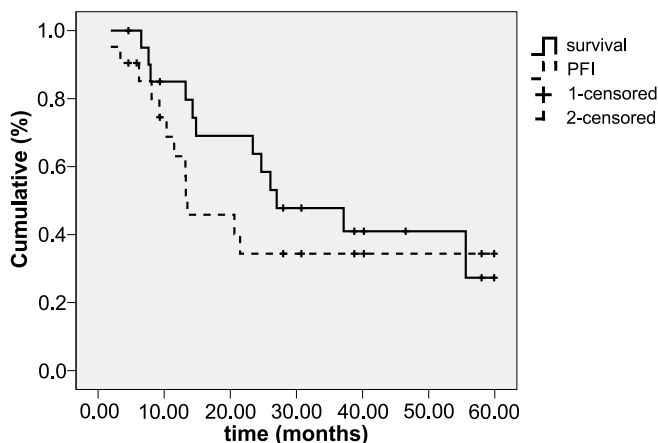


FIGURE 1. Survival and PFI curves.

The median PFI in our study was 13.5 months, with a mean follow-up of 27 months. The results of our study show an acceptable toxicity; we found 14% grade 3 neutropenia, and only 29% of the patients required dose reduction. Only 3 previous studies evaluated the efficacy and toxicity of platinum and paclitaxel as adjuvant chemotherapy in all stages of UPSC. Zanotti et al¹⁵ evaluated the efficacy of paclitaxel alone or combined with cisplatin. Twenty-four patients in their report received the treatment on adjuvant setting or for recurrent disease. With a mean follow-up of 35 months, the median PFI was 30 months when the regimen was administered as an adjuvant treatment. Bozas et al⁸ and Vaidya et al⁹ summarized their experience with a similar combined regimen of PC for advanced UPSC and UCCC. The median follow-ups in these studies were 29.4 and 29.5 months, with median PFIs of 16.2 and 17.5 months, respectively. The regimen of PC has been reported to be well tolerated in the above-mentioned other 2 studies with a mainly hematological toxicity. The major limitation of the current study is its retrospective analysis; however, its importance is because of the large series of patients with UPSC who contributed significant data of response to the PC regimen.

All of the patients in the present study underwent surgery; therefore, we could not compare surgical treatment to other treatment modalities. The groups were too small to analyze the significance of radiotherapy with and without chemotherapy.

Only 1 patient in our study had the subhistological diagnosis of UCCC, and we elected to include her in the analysis, similar to the methods that have been reported in the above-mentioned previous studies.

In conclusion, the updated data presented here and in the other studies demonstrate a favorable activity and acceptable toxicity profile for PC in patients with UPSC and UCCC. Despite the relatively high rate of cNED at completion of the planned chemotherapy, most of these patients experienced disease relapse and eventually succumbed to their disease. Thus, further research for a better treatment of this aggressive disease is needed.

REFERENCES

1. Alobaid A, Bruchim I, Verkooijen H, et al. Adjuvant therapy for patients with stage I papillary serous endometrial cancer. *Eur J Surg Oncol*. 2006;32:358–362.
2. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. *Int J Gynecol Obstet*. 2003;83(suppl 1):79–118.
3. Kelly MG, O'Malley DM, Hui P, et al. Improved survival in surgical stage I patients with uterine papillary serous carcinoma (UPSC) treated with adjuvant platinum-based chemotherapy. *Gynecol Oncol*. 2005;98:353–359.
4. Hendrickson M, Ross J, Eifel P, et al. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. *Am J Surg Pathol*. 1982;6:93–108.
5. Goff BA, Kato D, Schmidt RA, et al. Uterine papillary serous carcinoma: patterns of metastatic spread. *Gynecol Oncol*. 1994;54:264–268.
6. Gehrig PA, Groben PA, Fowler WC Jr, et al. Noninvasive papillary serous carcinoma of the endometrium. *Obstet Gynecol*. 2001;97:153–157.
7. Sovak MA, Hensley ML, Dupont J, et al. Paclitaxel and carboplatin in the adjuvant treatment of patients with high risk stage III and IV endometrial cancer: a retrospective study. *Gynecol Oncol*. 2006;103:451–457.
8. Bozas GT, Bamias A, Kastritis E, et al. Adjuvant chemotherapy with paclitaxel and carboplatin in non-endometrioid carcinoma of the uterus. *Eur J Gynaecol Oncol*. 2005;26:627–631.
9. Vaidya AP, Littell R, Krasner C, et al. Treatment of uterine papillary serous carcinoma with platinum based chemotherapy and paclitaxel. *Int J Gynecol Cancer*. 2006;16(suppl 1):267–272.
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 Gynecology Oncology Group Study. *J Clin Oncol*. 2006;24:36–44.
11. Price FV, Chambers SK, Carcangiu ML, et al. Intravenous cisplatin, doxorubicin, and cyclophosphamide in the treatment of uterine papillary serous carcinoma (UPSC). *Gynecol Oncol*. 1993;51:383–389.
12. Levenback C, Burke TW, Silva E, et al. Uterine papillary serous carcinoma (UPSC) treated with cisplatin, doxorubicin, and cyclophosphamide (PAC). *Gynecol Oncol*. 1992;46:317–321.
13. Hoskins PJ, Swenerton KD, Pike JA, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. *J Clin Oncol*. 2001;19:4048–4053.
14. Dietrich CS 3rd, Modesitt SC, Depriest PD, et al. The efficacy of adjuvant platinum-based chemotherapy in Stage I uterine papillary serous carcinoma (UPSC). *Gynecol Oncol*. 2005;99:557–563.
15. Zanotti KM, Belinson JL, Kennedy AW, et al. The use of paclitaxel and platinum-based chemotherapy in uterine papillary serous carcinoma. *Gynecol Oncol*. 1999;74:272–277.