Adjuvant chemotherapy with paclitaxel and carboplatin in non-endometrioid carcinoma of the uterus

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Summary

Purpose of investigation: Uterine papillary serous carcinoma (UPSC) and uterine clear cell carcinoma (UCCC) represent more aggressive tumors than the more common endometroid cancers, exhibiting a propensity for distant metastasis. The aim of this study was to investigate the activity and safety of paclitaxel/carboplatin chemotherapy as the only adjuvant treatment in patients with surgically resected UPSC and UCCC.

Methods: Fifteen patients with Stage IB-IV UPSC or UCCC were treated with a mean of six courses of paclitaxel 175 mg/m^3 plus carboplatin AUC 5 at three-week intervals, three to six weeks after undergoing surgery with curative intent. No patient had residual disease after surgery and none underwent pre- or post-chemotherapy irradiation.

Results: With a median follow-up of 29.4 months, six patients (40%) relapsed and two (13%) died of disease. Mean time to recurrence was 16.9 months. Recurrence rate per Stage was 17% for Stage IB/C, 57% for Stage IIIA/C and 50% for Stage IV. Projected 5-year overall survival and progression-free survival was 79.7% and 55.7%, respectively. All relapses were abdominopelvic whereas in one case pelvic recurrence was accompanied by lung metastasis. The most frequent grade 3-4 toxicity was neutropenia.

Conclusion: Chemotherapy with paclitaxel plus carboplatin is feasible and possibly prevents distant metastasis when used as adjuvant in UPSC and UCCC.

Key words: Endometrial cancer; Uterine papillary serous carcinoma; Uterine clear cell carcinoma; Adjuvant chemotherapy; Paclitaxel.

Introduction

Cancer of the uterine corpus is the most common gynecologic malignancy and the fourth most frequent cancer in women. In the United States, an estimated number of over 40,000 new cases per year result in more than 6,000 deaths annually. On the other hand, endometrial cancer is the most curable among the ten most frequent cancers in women as well as the most curable among gynecologic malignancies [1, 2]. Uterine papillary serous carcinoma (UPSC) and uterine clear cell carcinoma (UCCC) account for about 10% of endometrial cancers, yet, they are responsible for almost 50% percent of treatment failures [3]. Their natural history differs from that of the more common endometrioid cancers, since they exhibit a propensity for early metastasis as well as an increased recurrence potential, usually invading the upper abdomen or producing hematogenous metastasis [4-13].

The mainstay of uterine corpus cancer treatment is surgery followed by adjuvant radiation therapy (external beam irradiation and brachytherapy) for stages greater than IB or tumors of poor differantiation. Chemotherapy with platinum analogues, anthracyclines, cyclophosphamide and paclitaxel, alone or in combination, is usually reserved for advanced, inoperable or recurrent disease [1]. In the case of UPSC as well as UCCC, the high rate of treatment failures in comparison to endometrioid adenocarcinomas [3, 4, 7] has led to the exploration of more specialized approaches. Extensive surgical staging, more aggressive adjuvant irradiation regimens and adjuvant chemotherapy have been used with promising results but the optimal approach has not been clearly established.

Until recently, the chemotherapeutic regimen with the widest application in UPSC/UCCC has been the combination of cisplatin, doxorubicin and cyclophosphamide (PAC). Nevertheless, the administration of this regimen to patients with advanced or recurrent endometrial cancer has been associated with modest activity (20-27% objective response rates) and with significant toxicity [14-18]. Paclitaxel, a novel agent with efficacy in the treatment of many neoplasms [19-22] is an active agent against endometrial cancer. Paclitaxel monotherapy has achieved objective response rates of 27-37% [20, 21, 23], whereas its combination with platinum analogues has demonstrated response rates up to 78% in previously untreated patients [24].

In the present study the potential and effectiveness of the combination of carboplatin with paclitaxel is explored as the only adjuvant treatment for patients with endometrial cancer of aggressive histologic type (UPSC and UCCC) after radical surgery.

Patients and Methods

Between 1998 and 2003, 15 UPSC and UCCC patients were referred to the Oncology and Hematology Unit of the Department of Clinical Therapeutics of the University of Athens for

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adjuvant treatment after undergoing surgery with curative intent. All patients had had a total hysterectomy with bilateral oophorectomy and peritoneal fluid sampling or washings. Regional lymph-node sampling and omentectomy were performed in selected cases. No patient underwent radiation therapy before or after the operation.

Patients were staged according to the FIGO staging system for endometrial cancer. Patients with hematogenous metastasies were excluded form the study. Patients with positive peritoneal cytology or omental involvement were included, provided they had no residual disease after surgery as determined intraoperatively by the surgeon and no measurable or evaluable disease in postoperative imaging. Histology samples were reviewed and the histological diagnosis was confirmed by a single expert pathologist.

Baseline evaluation included complete blood counts, renal and hepatic function assessment, CT scans of the thorax and abdomen, as well as serum CA125 quantification.

Complete restaging was performed after the completion of six courses of chemotherapy. Patients were thereon followed up every six months with complete physical examination, CT scans of the abdomen and pelvis, chest X-ray, and CA125 measurement. Additional investigations were performed if clinically indicated. Sites of disease relapse were recorded and recurrence was distinguished as local (pelvic), abdominal or distant.

Chemotherapy

The patients were scheduled to receive six courses of chemotherapy, on an outpatient basis, beginning three to six weeks after surgery. The regimen included paclitaxel, 175 mg/m^2 over three hours, immediately followed by carboplatin over one hour. Carboplatin doses were calculated according to the Calvert Formula [25] to predict an area under the curve of 5. Chemotherapy was administered every three weeks. Complete blood counts, serum CA125 and creatinine levels were obtained before the administration of each course.

Pretreatment included ondasetron, dexamethasone, ranitidine and dimetindene administered intravenously one hour before chemotherapy. The regimen was administered on schedule if absolute neutrofil count (ANC) was above 1.5 x 10^9/l (normal range s2 to 7.5 x 10^9/l) and the platelet count above 100 x 10^9/l (normal range 140 to 450 x 10^9/l). If ANC was lower, G-CSF was administered until ANC recovery, the course was delayed for one week and prophylactic administration of G-CSF was initiated between courses.

Twenty percent dose reductions of both agents were applied in cases of prolonged (more than five days) grade 4 neutropenia, febrile neutropenia in G-CSF supported patients or grade 4 thrombocytopenia. Furthermore, paclitaxel doses were reduced by 20% in patients experiencing intolerable neurosensory symptoms or intolerable myalgias.

Statistical analysis

Survival was calculated from the day of the initiation of chemotherapy. Survival curves for disease-free survival and overall survival were produced with the Kaplan and Meier method. All analyses were performed using the SPSS version 11.0 software (SPSS Inc, Chicago, IL).

Results

Patient characteristics are summarized in Table 1. Six patients had Stage I disease and seven patients had Stage III disease. Two additional patients that were included in the study had Stage IVB disease because of omental involvement and/or peritoneal seedings. Both had undergone a total omentectomy and all macroscopical or palpable lesions were excised. Most patients (n = 11) had papillary serous cancers and all tumors were grade 2 or 3.

All patients received six courses of chemotherapy except one who refused to continue after the third course. Nine patients (60%) received full dosages of both agents without delays. Three patients (20%) received carboplatin in full doses but paclitaxel doses were modified due to neurotoxicity (n = 2) or intolerable myalgias (n = 1). In two patients (13.3%) the doses of both agents were modified because of serious hematologic toxicity.

Grade 3/4 neutropenia occurred in eight cases (53.4%). There was only one case of febrile neutropenia (6.7 %) which was treated on an outpatient basis with oral antibiotics and G-CSF and resolved with no further complications. Also, there was only one case of grade 3 thrombocytopenia. The most frequent non-hematological toxicities were neurosensory toxicity (n = 14, 93.4%) and nausea and vomiting (n = 8, 53%). Alopecia and transient myalgia were observed in all cases. There were no grade 4 non-hematological toxicities, while grade 3 toxicities were infrequent: neurosensory (n = 2, 13.3%), nausea and vomiting (n = 1, 6.7%), myalgia 6.7% (n = 1, 6.7%).

Table 1. — *Patient characteristics.*

Patients		No. = 15
Age		70.42 (51.08-76.85)
Stage	IB	n = 5 (33%)
	IC	n = 1 (7%)
	IIIA	n = 2 (13%)
	IIIC	n = 5 (33%)
	IVB	n = 2 (13%)
Histology	UPSC	n = 11 (73%)
	UCCC	n = 3 (20%)
	Mixed (UPSC+UCCC)	n = 1 (7%)
Grade	grade 2	n = 6 (40%)
	grade 3	n = 9 (60%)
Type of Surgery	TAH+BSO	n = 3 (20%)
	TAH+BSO+oment.	n = 3 (20%)
	TAH+BSO+oment.+ LND	n = 3 (20%)
	TAH+BSO+LND	n = 6 (40%)

UPSC: uterine papillary serous carcinoma, UCCC: uterine clear cell carcinoma; TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; LND: pelvic lymph-node sampling/dissection; oment.: omentectomy.

Table 2. — *Patient outcomes per stage and histology.*

Stage	Histology	Outcome
IB (n = 5)	UPSC n = 5	1AWD, 4DF
IC (n = 1)	UPSC n = 1	1DF
IIIA (n = 2)	UPSC n = 1	1DOD
	UCCC n = 1	1DOD
IIIC (n = 5)	UPSC n = 2	1AWD, 1DF
	UCCC n = 2	2DF
	UPSC+UCCC n = 1	1AWD
IVB (n = 2)	UPSC n=2	1DF, 1AWD
Total (n = 15)	UPSC n = 11	1DOD, 3AWD, 7DF
	UCCC n = 3	1DOD, 2DF
	UPSC+UCCC n = 1	1AWD

UPSC: uterine papillary serous carcinoma; UCCC: uterine clear cell carcinoma; DOD: dead of disease; AWD: alive with disease; DF: disease free.

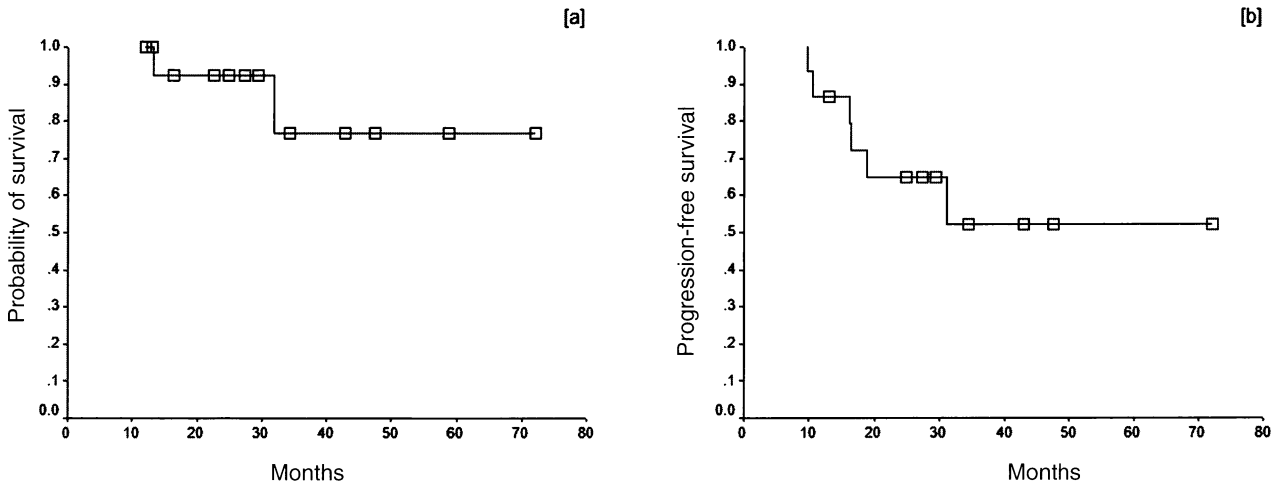

Figure 1. — Overall survival (a) and progression-free survival (b) of 15 patients with non-endometrioid uterine cancer treated with paxlitaxel and carboplatin.

Survival

Table 2 summarizes the outcomes of the patients per stage and histology. With a median follow-up of 29.4 months (range: 12-72) six patients (40%) relapsed and two of them (13.3%) died (13 and 32 months after the initiation of treatment, respectively), whereas 60% (n = 9) of the patients remained free of disease, and 26.7% (n = 4) were alive with disease.

For patients who relapsed, time to disease recurrence ranged from 9.8 to 31 months from the initiation of chemotherapy (median: 16.2 months). One patient suffered a late relapse, 31 months after the initiation of chemotherapy, while five out of six relapses occured within two years (9.8-18.9 months). In five of the six recurrences, the abdomen (n = 3) or pelvis and abdomen (n = 2) was the site of relapse, whereas only one patient relapsed with distant metastasis (lung) and pelvic disease.

Kaplan-Meier curves for overall survival and disease-free survival are illustrated in Figure 1. The projected 5-year survival was 79.7% (95% confidence interval [CI]: 53.3-100), while the projected 5-year progression-free survival was 55.7% (95% CI : 26.9-83.8).

Both Stage IV patients that are included in the study are still alive. One relapsed ten months after the initiation of chemotherapy with ascites and is currently under treatment, while the other remains free of disease 47 months after the initiation of adjuvant chemotherapy. In patients with Stage I, disease recurrence occurred in one (17%), while the respective rate for Stage III patients was 57% (n = 4/7).

Discussion

Endometrial cancer is considered a highly curable disease. Nevertheless, the subgroup of UPSC and UCCC comprises tumors which exhibit an aggressive behavior. These neoplasms have a propensity to metastasize outside the uterus and pelvis early in their natural history, even when the primary tumor is confined to the uterus and myometrial invasion is minimal or absent [2-4, 8, 9, 13]. They are also usually diagnosed in more advanced stages, with extrauterine disease present in 38%-74% [13, 26, 27] of newly diagnosed UPSC/UCCC patients, whereas endometrioid uterine cancer is diagnosed as Stage I disease in 75%-81% [1, 3, 26] of the cases. Moreover, UPSC and UCCC relapses occur more frequently in extrapelvic sites and especially the upper abdomen [3, 12, 13]. Five-year survival (all stages) is reported around 18-46% for UPSC and 25-58% for UCCC, compared to 69%-79% for endometrioid carcinomas [2, 3, 12, 13, 26]. UPSC carries the worst prognosis among endometrial cancer variants with 5-year survival ranging from 54%-72% for surgical Stage I to 0-20% for Stage IV [1-3, 10, 13, 26, 27].

Both radiotherapy and chemotherapy have been used as adjunctive therapy of UPSC and UCCC but the optimal approach has not been defined in this setting. Most reports on the use of chemotherapy in UPSC and UCCC [1-3, 12, 14-18, 27-32] refer to platinum-doxorubicin regimens that have long been considered the most efficacious among available chemotherapeutic options for high-risk endometrial cancer. In most cases, results in UPSC and UCCC have been modest, calling for the development of better chemotherapy for these aggressive neoplasms.

In recent years, there have been increasing reports for the considerable activity of paclitaxel-containing regimens against UPSC [24, 33-36]. Zanotti *et al.* [34] observed 89% serological responses in patients treated with carboplatin plus paclitaxel for persistent disease and 63% objective responses in patients treated for recurrent disease. Hoskins *et al.* [24] investigated the use of the same combination with and without irradiation in primarily advanced (Stage III/IVB) or recurrent UPSC reporting 60% responses in the primary treatment setting, and 50% in the second-line treatment setting.

In the present series we analyzed UPSC and UCCC patients with no residual disease after surgery who were treated postoperatively with carboplatin and paclitaxel chemotherapy and were not subjected to any form of adjuvant radiation therapy. We believe that the homogeneous treatment represents an advantage of our study over previous reports which involved mixed populations in terms of postoperative management.

The carboplatin/paclitaxel regimen was, overall, well tolerated. Toxicity was mainly hematological, easily reversible and did not result in life-threatening events. Myalgia and neurotixicity were frequent but there were no persistent symptoms after the completion of treatment. Moderate or severe neutropenia was also frequent (53%) and in the same range with adjuvant PAC in similar populations (32-50%) [14-18]. Febrile neutropenia occurred in only one case (6.7%) while relevant rates for PAC are reported up to 15% [14, 18, 37]. PAC is also associated with cardiotoxicity in up to 15% of treated patients, as well as with an up to 9% incidence of treatment-related deaths [15, 17, 18]. The absence of cardiotoxicity, persistent toxic effects and treatment-related deaths probably indicate a favorable toxicity profile for the combination of carboplatin with paclitaxel among available options in this setting.

The recurrence rate in our series of 15 UPSC/UCCC patients was 40% during a median follow-up period of more than 29 months. Relapses occurred in five of the 12 UPSC or mixed-histology patients (41%) and in one of the three UCCC patients (33%). These figures are at least comparable with the results of radiation or multimodality adjuvant treatments in similar populations where recurrences have been reported to reach 44-69% [2, 12, 27, 38]. Price *et al.* [15] has reported 42% recurrences in UPSC patients with no measurable disease after surgery who were treated postoperatively with PAC. These results are similar to ours, yet, we believe that the superior toxicity profile of carboplatin/paclitaxel should be taken into account in this comparison. In addition, our results are comparable with those of adjuvant whole abdominopelvic irradiation which has achieved recurrence rates ranging from 39% to 51% in UPSC/UCCC [38, 39] but also resulted in chronic grade 3 and 4 toxicity in up to 19% of the patients [39].

In our study there was only one case of relapse among Stage I patients (17%). This is consistent with other reports showing high cure rates in these stages with either radiotherapy [12, 27, 29, 38] or chemotherapy [15, 29]. Taking into consideration the favorable toxicity profile of paclitaxel/carboplatin, this regimen represents an effective and well tolerated treatment in low stage UPSC/UCCC. Relapse rates in Stage III-IV disease (54%) remained high but still compare favorably with the respective figures in existing reports [2, 12, 15, 27]. However, the results in these reports as well as ours underline the need for developing more effective adjuvant treatments for this group of patients.

Relapses in most cases (n = 5/6, 83%) were confined in the pelvis and abdomen. The fact that the pelvic element was present in 50% of the relapses (n = 3/6) may lead to the conclusion that pelvic irradiation should be added in an adjuvant approach since it definitely decreases the occurrence of pelvic relapse [12, 27, 40]. Nevertheless, it should be taken into consideration that in all cases of pelvic recurrence, local disease was accompanied by abdominal or hematogenous metastasis. Abdominopelvic recurrence remains a major problem in UPSC and UCCC and many approaches have been evaluated against it, including aggressive irradiation regimens and intraabdominal chemotherapy. Extended field irradiation and whole abdominal or abdominopelvic radiotherapy have produced some encouraging results [38-41], but the added short- and long-term toxicity of abdominal irradiation is considerable. Regarding the intraperitoneal administration of cytotoxic agents, there have been only isolated studies in UPSC reporting no advantages over intravenous chemotherapy as well as technical difficulties that may render the method inapplicable in many cases [18].

In our group of 15 patients, hematogenous metastasis after treatment occurred in only one case (6.7%), while UPSC relapses with hematogenous elements are frequently reported in 26%-34% of cases [4, 12, 40]. Although the number of our patients is small, this result suggests a protective effect of paclitaxel/carboplatin against hematogenous dissemination of non-endometrioid uterine cancer.

Conclusion

In conclusion we could summarize that paclitaxel/carboplatin is a well tolerated regimen, with probable efficacy as adjuvant therapy in Stage I-IV UPSC and UCCC patients with no residual disease after surgery and appears to reduce the occurrence of distant metastasis. Definite conclusions cannot be drawn from our study due to the small number of patients included but there is clear indication that this regimen is feasible in this setting and deserves further evaluation.

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