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ORIGINAL ARTICLE

Chemotherapy for endometrial carcinoma (GOGO-EM1 study): TEC (paclitaxel, epirubicin, and carboplatin) is an effective remission-induction and adjuvant therapy

Tomomi Egawa-Takata · Yutaka Ueda · Chie Kuragaki · Takahito Miyake · Takashi Miyatake · Masami Fujita · Kiyoshi Yoshino · Ryuichi Nakashima · Mika Okazawa · Tateki Tsutsui · Ken-Ichirou Morishige · Tadashi Kimura · Masato Yamasaki · Takamichi Nishizaki · Masaaki Nagamatsu · Kimihiko Ito · Masahiro Asada · Kazuhide Ogita · Akinori Wakimoto · Toshiya Yamamoto · Yukihiro Nishio · Takayuki Enomoto

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Abstract
Background TAP chemotherapy (paclitaxel, doxorubicin, and cisplatin) is effective for advanced and recurrent endometrial carcinoma, but has occasional severe toxicity. TEC chemotherapy (paclitaxel, epirubicin, and carboplatin) has been suggested to have less toxicity; however, the optimal dosage has yet to be determined.
Patients and methods Phase I/II prospective study for TEC therapy was performed. A retrospective comparison of the prognosis between adjuvant TEC therapy and radiation for completely resected cases with risk factors was also performed.
Results The recommended dose of TEC therapy was determined to be paclitaxel 150 mg/m^2, epirubicin 50 mg/m^2, and carboplatin AUC 4. A TEC regimen at this dose level was shown to be tolerable. The response rate and median overall survival were 74% and 37 months for those with advanced primary disease (Group B) and 50% and 26 months for recurrent tumors (Group C), respectively. A retrospective comparison showed that adjuvant TEC therapy for completely resected stage III cases improved their prognosis when compared to an adjuvant radiation therapy.
Conclusion TEC therapy was demonstrated to be a tolerable and effective treatment, not only as a remission-induction

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T. Egawa-Takata · Y. Ueda · C. Kuragaki · T. Miyake · T. Miyatake · M. Fujita · K. Yoshino · R. Nakashima · M. Okazawa · T. Tsutsui · K.-I. Morishige · T. Kimura · T. Enomoto (✉)
Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan
e-mail: enomoto@gyne.med.osaka-u.ac.jp

T. Miyake · M. Yamasaki
Osaka Rosai Hospital, 1179-3 Kita-ku Nagasone-cho, Sakai, Osaka 591-8025, Japan

M. Okazawa · M. Nagamatsu
Kaizuka City Hospital, 3-10-20 Hori, Kaizuka, Osaka 597-0015, Japan

T. Nishizaki
Suita Municipal Hospital, 2-13-20 Katayama-cho, Suita, Osaka 564-0082, Japan

K. Ito
Kansai Rosai Hospital, 3-1-69 Inabaso, Amagasaki, Hyogo 660-8511, Japan

M. Asada
Itami City Hospital, 1-100 Koyaike, Itami, Hyogo 664-8540, Japan

K. Ogita
Rinku General Medical Center, 2-23 Rinku Orai-kita, Izumisano, Osaka 598-8577, Japan

A. Wakimoto
Osaka Koseinenkin Hospital, 4-2-78 Fukushima, Fukushima-ku, Osaka 553-0003, Japan

T. Yamamoto
Sakai Municipal Hospital, 1-1-1 Sakai-ku Minami Yasui-cho, Osaka 590-0064, Japan

Y. Nishio
Osaka Police Hospital, 10-31 Kitayama-cho, Tennoji-ku, Osaka 543-0035, Japan

therapy for advanced and recurrent endometrial carcinomas but also as the adjuvant therapy.

Keywords Endometrial cancer · Combination chemotherapy · TEC · Paclitaxel · Epirubicin · Carboplatin

Abbreviations

CAP	Cisplatin, adriamycin, and cyclophosphamide
TAP or AP	Doxorubicin and cisplatin (with or without paclitaxel)
TC or TEC	Paclitaxel and carboplatin (without or with epirubicin)
TEP	Paclitaxel, epirubicin, and cisplatin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration versus time curve
CR	Complete response
DLT	Dose limiting toxicity
FIGO	International Federation of Gynecology and Obstetrics
G-CSF	Granulocyte-colony stimulating factor
GOG	The gynecologic oncology group
GOGO	The gynecologic oncology group of Osaka
Gy	Gray, unit of absorbed radiation
MTD	Maximum tolerated dose
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RR	Responsive rate
RT	Radiation therapy
SD	Stable disease
WAI	Whole-abdominal radiation therapy
WBC	White blood cells
5-HT_3	5-hydroxytriptamine-3

Introduction

Endometrial cancer is the most common gynecological cancer in the Western world. Although its incidence has increased during the last three decades, its treatment has also evolved considerably during the same period. Surgical therapy currently consists of hysterectomy, bilateral salpingo-oophorectomy, and retroperitoneal lymph node dissection. Prognostic factors for the disease include histological type and differentiation, stage, level of myometrial invasion, peritoneal cytology, lymph node metastasis, and adnexal metastasis [1, 2].

In the past, patients with poor prognostic factors usually underwent adjuvant post-operative irradiation. Recently, a randomized study by the Gynecologic Oncology Group (GOG #122) revealed that a combined chemotherapy of AP (doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2) was superior to whole abdominal irradiation (45 Gy WAI) as the adjuvant therapy. However, significant hematologic and cardiac toxicity and treatment-related death were detected in the chemotherapy arm of the AP study [3].

Recently, a randomized study showed a better response rate and longer progression-free and overall survival rates (PFS and OS) using TAP (a combination of paclitaxel (160 mg/m^2), doxorubicin (45 mg/m^2), and cisplatin (50 mg/m^2)) than with AP (GOG #177) [4]. However, the neurologic toxicity was even worse for the patients receiving TAP, with 39% suffering grade 2–3 peripheral neuropathy, compared with 5% of those in the group receiving AP. Three patients (2%) on the TAP arm, versus none on AP arm, developed grade 3 heart failure, and treatment-related death occurred in five patients (4%) on the TAP arm, versus none with AP. Thus, the TAP regimen is often avoided because of its toxicity, despite its proven better effectiveness for advanced and recurrent endometrial cancer. GOG is currently running a study to compare the combination of paclitaxel and carboplatin (TC) with TAP.

Lissoni et al. reported that TEP (a combination of paclitaxel 175 mg/m^2, epirubicin 70 mg/m^2, and cisplatin 50 mg/m^2) exhibited high anti-tumor activity against advanced endometrial carcinoma and good tolerability [5]. The TEP response rate for advanced endometrial carcinoma was 73%; however, grade 3–4 neutropenia occurred in 61% of the recipients, with possibly one related death.

More recently, TEC, a combination of paclitaxel (150 mg/m^2), epirubicin (50 mg/m^2), and carboplatin (AUC 5), when combined with G-CSF support, was shown to be potently active against metastatic and recurrent endometrial carcinomas. This TEC treatment was accompanied by grade 3–4 neutropenia in 15.5% and grade 2–3 neurotoxicity in 19% of patients [6]. However, a determination of the proper dosage for the TEC regimen was not performed, and its effectiveness as an adjuvant therapy remains to be clarified.

In our phase I/II prospective study being described here, we first determined the optimal dose for TEC therapy; subsequently, we analyzed the safety and responsiveness to the regimen for advanced or recurrent endometrial carcinomas. Moreover, we studied the effectiveness of our TEC regimen as an adjuvant therapy for optimally resected endometrial cancer with risk factors of recurrence.

Materials and methods

This study was conducted during the period of 1999–2007 by the Gynecologic Oncology Group of Osaka (GOGO)

that included Osaka University Hospital, Osaka Rosai Hospital, Kaizuka City Hospital, Suita Municipal Hospital, Kansai Rosai Hospital, Itami City Hospital, Osaka Kouseinenkin Hospital, Rinku General Medical Center, Sakai Municipal Hospital, and Osaka Police Hospital.

Eligibility

Participation eligibility required that the patient have adequate hematologic findings (WBC $\geq$ 3,000/μl, platelets $\geq$ 100,000/μl, granulocytes $\geq$ 1,500/μl, and hemoglobin $\geq$ 10 g/dl), and renal (creatinine $\leq$ 2 mg/dl) and hepatic (bilirubin $\leq$ 3 mg/dl, AST and ALT $\leq 2\times$ the institutional normal value) functions. A relative performance status of 0–2 was needed. The tumors needed to be histologically diagnosed as being a primary or recurrent endometrial carcinoma. The age of the patients needed to be 70 years of age or less, and the patient needed to have an estimated remaining survival time of greater than 3 months. Those with synchronous cancers or with serious concomitant medical illnesses were deemed ineligible. All patients provided voluntary written informed consent before the treatment commenced.

Phase I component

Adverse treatment effects were graded based on WHO criteria for toxicity. For our phase I study of TEC therapy, the maximum tolerated dose (MTD) levels of paclitaxel, epirubicin, and carboplatin were evaluated. The drugs were administered every 3–4 weeks for 3–6 cycles. The starting dose was set at 150 mg/m^2 for paclitaxel, 50 mg/m^2 for epirubicin, and AUC 4 for carboplatin. G-CSF (granulocyte colony-stimulating factor) was used to support hematopoiesis when grade 4 neutropenia, or grade 3 neutropenia with fever, was observed.

A 3 + 3 study design was used for dose escalation. The first and second dose escalation indicated an AUC of 4.5 to 5 for carboplatin, the third escalation found 175 mg/m^2 for paclitaxel, and the fourth escalation was 70 mg/m^2 for epirubicin. The first reduction indicated 30 mg/m^2 for epirubicin, the second indicated 135 mg/m^2 for paclitaxel, and the third indicated AUC 3.5 for carboplatin. Dose limiting toxicity (DLT) was defined as when grade-4 hematologic toxicity and grade-3 non-hematologic toxicity occurred. MTD indicated the highest dose level at which $\leq$33% of patients ($\leq$2 of 6 patients) experienced a DLT, and the recommended phase II dose was the MTD, as previously described [7].

Phase II component

For our phase II study, the patients were divided into three groups. The patients with no residual tumor larger than 1 cm after surgery, but who still had a significant risk for a recurrence, were placed in Group A. Surgery typically consisted of a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and a lymphadenectomy for staging. Lymphadenectomy was omitted when the histology was diagnosed as grade-1 endometrioid adenocarcinoma without invasion of the myometrium. Cytoreductive surgery was added as needed. The considerations for assigning a high risk for a recurrence included being FIGO (International Federation of Gynecology and Obstetrics) stage III or IV, a myometrium invasion of >1/2, or a special type of histology, such as endometrioid adenocarcinoma grade 3, clear cell carcinoma, uterine serous papillary carcinoma, or carcinosarcoma.

The stage IIIa patients who had only a positive peritoneal cytology and none of the other risk factors described above were not included. Treatment was repeated every 3–4 weeks and continued for 3 or 6 cycles until disease progression or unacceptable toxicity. Stage III or IV patients or recurrent disease was planned to receive 6 cycles of TEC therapy. Patients with other risks were planned to receive 3 cycles of the therapy.

Patients who had a measurable tumor with CT larger than 1 cm remaining after cytoreductive surgery were combined with patients who received primary TEC therapy for an inoperable tumor as Group B. Patients suffering from a recurrent disease were defined as Group C. In Group C, 9 patients received surgery and adjuvant radiation, and one patient underwent surgery alone, with no follow-up adjuvant. Our study patients' characteristics are listed in Table 1. Patients in Group A were treated with TEC at the phase II dose determined in our phase I study. Any and all patients who received TEC therapy at the same dose as the recommended phase II dose were included in our study.

The primary endpoints of the phase II trial were the toxicity of TEC regimen and the clinical response for the patients with advanced (Group B) and recurrent (Group C) endometrial cancer.

The secondary endpoints of our phase II study were the progression-free survival and overall survival. We used RECIST (version 1.0, response evaluation criteria in solid tumors) for evaluating the therapy response. A complete response (CR) required regression of all tumors. A partial response (PR) required >30% reduction in the sum of the largest diameter of the target legions. A progressive disease (PD) means that new lesions appeared, or the sum of the largest diameter of the target lesions enlarged >20%. All other diseases were considered to be a stable disease (SD).

Progression-free survival (PFS) and overall survival (OS) of the three groups were evaluated over a median follow-up period of 36 and 37 months for Group A, 12 and 26 months for Group B, and 6 and 18 months for Group C, respectively.

Table 1 Clinical characteristics of the patients enrolled in the phase II study

	Group A $n = 99$	Group B $n = 20$	Group C $n = 10$
Age			
Median	56 (34–69)	57 (47–68)	57 (34–69)
Histology			
Endometrioid	70 (70%)	14 (70%)	6 (60%)
UPSC	6 (6%)	4 (20%)	0 (0%)
Clear cell	5 (5%)	0 (0%)	2 (20%)
Others	18 (18%)	2 (10%)	2 (20%)
Stage			
I	36 (36%)	0 (0%)	2 (20%)
II	15 (15%)	0 (0%)	1 (1.0%)
III	44 (44%)	7 (35%)	7 (70%)
IV	4 (4%)	13 (65%)	0 (0%)

Group A: Patients with no residual tumor larger than 1 cm

Group B: Patients who had measurable disease bigger than 1 cm after a surgery, and those who received TEC therapy as the first treatment because their tumors were inoperable

Group C: Patients with recurrent disease

UPSC Uterine papillary serous carcinoma

All patients received intensive follow-up by gynecologists. The number of follow-up visits per year in the first year, the second and third years, the fourth and fifth years, and the sixth year was 12, 4–6, 2 and 1 visit, respectively. Routine physical examinations, including a pelvic-rectal examination, vaginal-vault cytology, and transvaginal ultrasonography (TV-USG), were performed every visit. A CT scan and chest X-ray was performed semi-annually in the first year and annually thereafter. We tested for tumor markers, including CA125, one to four times annually in a subset of the cases. Roughly, 90% of the patients in this retrospective study were treated by these follow-up strategies.

Analysis of efficacy of adjuvant TEC therapy (Group A) compared to radiation therapy

We evaluated the efficacy of the TEC regimen as an adjuvant therapy in Group A patients for both completely resected and optimally resected endometrial cancer cases having residual diseases equal to or less than 1 cm, with risk factors of recurrence. The prognosis of these patients was compared to that of the patients who did not agree to participate in the TEC trial, and so received radiation as an adjuvant therapy during the same study period. These patients agreed to a retrospective analysis to compare the efficacy of TEC chemotherapy and radiation therapy. The costs of chemotherapy and radiation therapy were not compared in the present study.

Statistical analysis

MedCalc (MedCalc Software, Mariakerke, Belgium) was used for statistical analysis. The frequency of adverse effects in the two groups was compared by Fisher's exact test. Distribution of patients' age, histology, and stage were analyzed by the Mann–Whitney U-test or the chi-square test. PFS and OS curves were constructed using the Kaplan–Meier method and evaluated for statistical significance by the log-rank test. Results were considered to be significant when the P value was less than 0.05.

Statements of ethics

This study was approved by the Institutional Review Board and Ethics Committee at each participating institution and all patients provided written informed consent.

Results

Phase I

During the phase I component of this study, assessable patients were enrolled to receive each dose level. Initially, three patients were tested at the starting doses of 150 mg/m^2 for paclitaxel, 50 mg/m^2 for epirubicin, and AUC 4 for carboplatin. One patient encountered a DLT at this dose level; therefore, an additional three patients were tested at the same dosage. One of these patients also encountered a DLT. Thus, 2 of the 6 patients (33%) encountered DLT at this starting dose level, and this dose level was deemed to be the MTD. We proceeded with this as the recommended phase II dosage.

Phase II

Safety

In total, 172 patients were pre-eligible for the phase II study; however, 43 of the resection patients determined to have risk factors for recurrence declined to participate in our experimental drug study and were thus excluded from our phase II analysis.

The 129 patients who did enroll in our phase II drug study were treated with the TEC MTD (150 mg/m^2 for paclitaxel, 50 mg/m^2 for epirubicin, and AUC 4 for carboplatin) and were evaluated for the safety of the TEC regimen. Four patients could not continue the TEC therapy more than 3 courses: one patient suffered anaphylactic shock in reaction to the paclitaxel during her first cycle of treatment, two others acquired grade 4 neutropenia accompanied by severe infection, and the fourth patient

refused to continue the treatment due to grade 3 nausea and emesis. In addition, the records concerning the side-effects for 2 other patients were inaccessible.

The potential adverse effects linked to the MTD of TEC therapy in our phase II study are listed in Table 2. Cardiac failure and treatment-related death did not occur. Grade 3–4 non-hematologic toxicity was infrequent, except that grade 3–4 alopecia was observed in most patients but was reversible following therapy cessation. Grade 3 nausea and vomiting occurred in 2 patients (2%). Grade 3 neutropenia was detected in 35 patients (27%) and grade 4 in 87 patients (67%); febrile neutropenia was observed in 17 patients (13%). G-CSF was used to support the immune and hematopoietic systems in 113 patients (88%). Grade 3 anemia was detected in 14 patients (11%) and grade 4 in four patients (3%). Of those with anemia, three of the patients with grade 3 and two of the patients with grade 4 endured continuous genital bleeding.

Anti-tumor effect (response), PFS, and OS

The 129 patients who received TEC therapy were divided into three risk groups: 99 in Group A, 20 in Group B, and 10 in Group C. The response rate of one Group B patient was undetermined because she refused to be examined by CT after the therapy. The anti-tumor effect was evaluated in Group B and Group C, and the response rates were 74% in Group B (CR in 3, PR in 11, SD in 1, and PD in 4 patients) and 50% in Group C (CR in 0, PR in 5, SD in 0, and PD in 5 patients) (Table 3). This difference was not statistically significant. Endometrioid tumors exhibited a 75% (15 of 20 cases) response rate and non-endometrioid tumors exhibited a 44% (4 of 9 cases) response rate. However, this difference was not statistically significant ($P = 0.39$, by Fisher's exact test).

The PFS and OS of the three groups are shown in Table 4. We obtained by TEC therapy a median OS of 37 months in resected cases with risk factors of recurrence (Group A), 26 months in advanced cases (Group B), and 19 months in recurrent cases (Group C).

Efficacy of TEC as an adjuvant therapy

While our phase II TEC study was being conducted, there were 43 eligible patients with risk factors of recurrence who had declined direct participation in our drug study. These patients opted for radiation adjuvant therapy (Group RT). The distribution of age and histology and the proportion of stage I and II disease of these cases were not different from those in Group A (supplementary Table 1). The PFS and OS of these stages were not different when compared with the RT group (supplementary Figure 1).

We next conducted subgroup analysis by stages. Only four stage IV cases received TEC; thus, a comparison between Group A and Group RT for stage IV tumors was impossible. In stages I and II, PFS and OS of all stages in Group A were not different from those in Group RT (data not shown). In stage III, the prognosis was compared between Group A and Group RT. Patients' characteristics are listed in Table 5. Distribution of age, histology, stage subclass, and sites of recurrence were not significantly different between the two groups. Both PFS and OS were demonstrated to be significantly better in Group A than Group RT (Fig. 1, $P = 0.034$ and $P = 0.040$ by the log-rank test, respectively).

Table 2 Number of patients affected (%) Grade of adverse effects were based on WHO criteria for toxicity

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	3 (2%)	1 (0.8%)	3 (2%)	35 (27%)	87 (67%)
Thrombocytopenia	88 (68%)	22 (17%)	16 (12%)	2 (2%)	1 (0.8%)
Anemia	27 (21%)	58 (45%)	25 (19%)	14 (11%)	4 (3%)
Nausea/vomiting	24 (18%)	83 (64%)	19 (15%)	2 (2%)	0 (0%)
Diarrhea	124 (96%)	3 (2%)	2 (2%)	0 (0%)	0 (0%)
Peripheral neuropathy	40 (31%)	86 (67%)	3 (2%)	0 (0%)	0 (0%)
Fever	105 (81%)	7 (5%)	17 (13%)	0 (0%)	0 (0%)
Myalgia arthralgia	30 (23%)	92 (71%)	7 (5%)	0 (0%)	0 (0%)
Cutaneous	121 (94%)	6 (5%)	1 (0.8%)	1 (0.8%)	0 (0%)
Cardiac function	129 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cardiac rhytm	125 (97%)	4 (3%)	0 (0%)	0 (0%)	0 (0%)
Renal (Cre)	128 (99%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)
Hepatic (AST/ALT)	124 (96%)	4 (3%)	1 (0.8%)	0 (0%)	0 (0%)
Pulmoualy	129 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Allergy	128 (99%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)

Table 3 Anti-tumor effect (response rate) of TEC therapy

Histology	No. of patients				Response rate (%)
	CR	PR	SD	PD	
Group B					
Endometrioid	2	9	1	1	85
Non-endometrioid	1	2	0	3	75
Group C					
Endometrioid	0	4	0	3	57
Non-endometrioid	0	1	0	2	33

The anti-tumor effect of TEC was evaluated in Group B and Group C. Response rates were 74% in Group B and 50% in Group C. This difference was not statistically significant. Endometrioid tumors exhibited a 75% response rate in total; however, non-endometrioid tumors responded in 44% of cases, showing no significant difference

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 4 PFS and OS of Groups A, B and C

	OS	PFS
Group A	37 (2–108)	36 (1–108)
Group B	26 (5–57)	12 (3–53)
Group C	19 (4–53)	6 (2–16)

Group A: Patients with no residual tumors larger than 1 cm

Group B: Patients who had measurable disease bigger than 1 cm after a surgery and those who received TEC therapy as the first treatment because their tumor was inoperable

Group C: Patients with recurrent disease

PFS progression-free survival (months)

OS overall survival (months)

Discussion

Systemic chemotherapy is now a standard treatment for advanced and recurrent endometrial carcinomas. The key drugs for this treatment have been the anthracycline and platinum derivatives. A previous study revealed that AP was superior to radiation as an adjuvant therapy; however, severe toxicity and treatment-related deaths were detected in the AP arm [3]. A retrospective study demonstrated that TC was a well tolerated and active regimen for the treatment of resected stages III and IV cases [8]. However, a role of a combination chemotherapy using anthracycline and platinum has been only minimally evaluated [9–11], One such study demonstrated that CAP (cyclophosphamide, doxorubicin and cisplatin) provided a higher PFS and OS rates than radiation in the subgroups of stage Ic in patients over 70 years old or with grade 3 endometrioid adenocarcinoma and stage II/IIIa [9]. In another study, TAP was shown to be superior to the previously regarded standard regimen of AP [12]. However, use of the TAP regimen is often avoided because of its potential for severe toxicity, despite its proven effectiveness for advanced and recurrent endometrial cancer. More recently, the regimen termed TEC was shown to be active in metastatic and recurrent endometrial carcinoma, with tolerable toxicity when accompanied by G-CSF support [6]. However, prior to this current study, the proper TEC dose regimen was undetermined.

Table 5 Patients' characteristics of Group A and Group RT of adjuvant therapy (Stage III)

	Group RT $n = 13$	Group A $n = 44$	*P* value
Age			
Median	53 (44–65)	57 (34–69)	0.13
Histology			
Endometrioid	9 (69%)	32 (73%)	0.82
UPSC	1 (8%)	3 (7%)	
Clear cell	1 (8%)	1 (2%)	
Others	2 (15%)	8 (18%)	
Stage			
III a	3 (23%)	16 (36%)	0.54
III b	0 (0%)	1 (2%)	
III c	10 (77%)	27 (61%)	
Site of recurrence			
Local alone	2 (33%)	2 (25%)	1.00
Distant	4 (67%)	6 (75%)	

Patients of stage III who received TEC therapy as an adjuvant (Group A) and those of stage III who received traditional radiation as an adjuvant therapy (Group RT). Distribution of age and histology was not different between the two groups

UPSC Uterine papillary serous carcinoma

Local alone: recurrence inside of the pelvis

Distant: recurrence out of the pelvis, with or without local recurrence

In our phase I prospective study of TEC therapy, a dose level of 150 mg/m^2 for paclitaxel, 50 mg/m^2 for epirubicin, and AUC 4 for carboplatin was determined to be the optimal dose to use for phase II. Our phase II study demonstrated good tolerance for TEC therapy. In a previous study that showed the safety and effectiveness of a TEC regimen for advanced or recurrent endometrial cancer, paclitaxel and epirubicin were used at the same dose level as in our present study [6]; however, their dose of carboplatin was set at AUC 5, one AUC higher than the AUC 4 used in our study. In their study, grade 3–4 neutropenia, thrombocytopenia, anemia, neuropathy, and grade 2–4 neutropenic fever occurred in 15.5, 2.0, 5.5, 5.0, and 2% of their patients, respectively, and in our study, these same side-effects occurred in 94, 2.8, 0, and 13% of our patients, respectively.

G-CSF was routinely administered from day 5 onward until the total WBC count recovered to an excess of

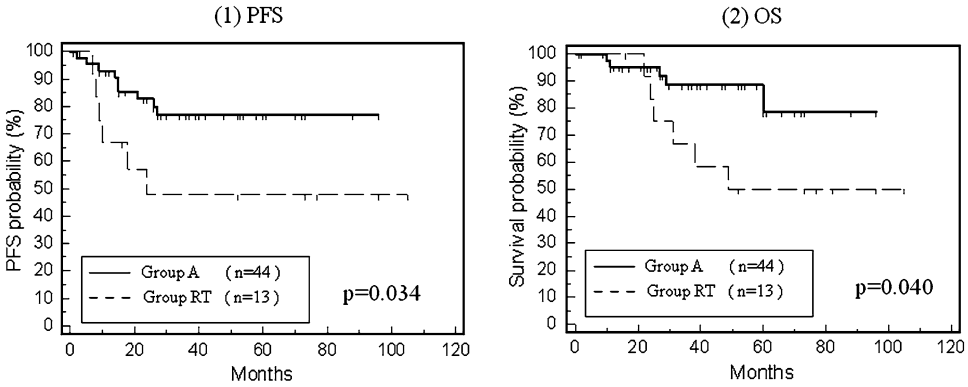

Fig. 1 PFS and OS of TEC and RT groups for adjuvant therapy (Stage III). Both PFS and OS were demonstrated to be significantly better in the TEC group than RT group ($P = 0.034$ and $P = 0.040$ by log-rank test, respectively). *Solid line*: Group A, *Broken line*: Group RT

10,000/μl in the Papadimitriou study. On the other hand, in our study, the G-CSF was administered only when total the WBC/neutrophil count decreased to under 1,000/500 per μl. We feel that this is the reason why severe neutropenia was more frequently observed in our study, despite the lower dose of carboplatin used. We compared our results to the toxicity data acquired from 126 ovarian cancer patients who received a combination of paclitaxel (175 mg/m^2) and carboplatin (AUC 5) (TC) therapy in a similar study conducted in our institute as a multi-center phase I/II study. We found no significant difference in the frequency of grade 3–4 hematologic and non-hematologic toxicities (our unpublished data). These results imply that TEC is an acceptably tolerable chemotherapeutic regimen for endometrial cancer.

The TEC response rate of 66% for advanced and recurrent endometrial carcinoma (CR in 3, PR in 11, SD in 1, and PD in 4 in the advanced group, and CR in 0, PR in 5, SD in 0, and PD in 5 in the recurrent group) was almost equal to that of Papadimitriou's study [6], and similar to the 57% reported for TAP therapy in the GOG #177 study [4]. The median PFS and OS in our study were, respectively, 12 and 26 months in advanced cases, and 6 and 18 months in recurrent cases, which was relatively longer than those in Papadimitriou's study [6]. These results indicate that TEC is an active regimen for the treatment of advanced and recurrent endometrial cancer. Pegylated liposomal doxorubicin has the potential advantage of allowing repeated administration with a lesser likelihood of cumulative cardiotoxicity and was shown to have antitumor activity against ovarian cancer [13]. However, it has only limited activity in endometrial cancer [14, 15].

A retrospective comparison of the survival rates between TEC (Group A) and radiation (Group RT) in resected cases with risk factors of recurrence demonstrated no significant difference. In particular, a subgroup analysis by tumor stages exhibited both PFS and OS of stage III was significantly better in Group A than in Group RT ($P = 0.034$ and $P = 0.040$ by the log-rank test, respectively), indicating a possible role of TEC as an adjuvant. Because less than half of the patients with stage III tumors relapsed or died in our study, the median PFS and OS were not evaluated accurately; however, the durations were estimated to be longer than 96 months at the time of evaluation. These results appeared to be better than the 13 months of PFS and 47 months of OS of the patients who received adjuvant TC therapy in a previous study [8]; however, their study included 50% stage IV cases.

In the present study, the recommended dose of TEC therapy was determined to be paclitaxel 150 mg/m^2, epirubicin 50 mg/m^2, and carboplatin AUC 4. A TEC regimen at this dose level was shown to be tolerable and effective as a remission-induction therapy for advanced and recurrent endometrial cancer. It was also demonstrated, for the first time, that adjuvant TEC therapy for optimally resected stage III cases improved their prognosis when compared to a traditional adjuvant radiation therapy. However, in this study, the effectiveness of TEC was not compared to TC in both advanced and recurrent and adjuvant cases. A further prospective randomized study is still necessary to establish a standard regimen of chemotherapy for the advanced and recurrent cases and the optimally resected cases with risk factors of recurrence.

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Conflict of interest There are no conflicts of interest.

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