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# Adjuvant Chemotherapy for Endometrial Cancer (ACE) trial: A randomized phase II study for advanced endometrial carcinoma

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## Abstract

This study evaluated the feasibility and efficacy of three postoperative adjuvant chemotherapy regimens for endometrial cancer. Endometrioid cancer patients with intermediate-risk stage I and II or high-risk stage III and IV disease were randomly assigned to receive six cycles of either paclitaxel-epirubicin-carboplatin (TEC), paclitaxel-anthracycline (doxorubicin)-carboplatin (TAC), or dose-dense paclitaxel-carboplatin (ddTC). The primary end-point was the completion rate (CRate) of six cycles of treatment. The secondary end-points were progression-free survival (PFS) and overall survival (OS). One hundred and one patients were treated as follows: 33 received TEC, 33 TAC, and 35 ddTC. The CRates for TEC, TAC, and ddTC were 94%,

**Abbreviations:** ACE, Adjuvant Chemotherapy for Endometrial Cancer; AP, doxorubicin plus cisplatin; AUC, area under the curve; CRate, completion rate; ddTC, dose-dense paclitaxel plus carboplatin; DP, docetaxel and cisplatin; EGOG, Echigo Gynecologic Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; G-CSF, granulocyte-colony stimulating factor; GOG, Gynecologic Oncology Group; GOGO, Gynecologic Oncology Group of Osaka; JGOG, Japanese Gynecologic Oncology Group; KCOG, Kansai Clinical Oncology Group; OS, overall survival; PFS, progression-free survival; PORTEC, Post Operative Radiation Therapy for Endometrial Carcinoma; TAC, paclitaxel plus doxorubicin plus carboplatin; TAP, doxorubicin plus cisplatin plus paclitaxel; TC, paclitaxel plus carboplatin; TEC, paclitaxel plus carboplatin plus epirubicin; TGCU, Tohoku Gynecologic Cancer Unit.

64%, and 69%, respectively ($P = .005$). The TEC CRate was significantly higher than for the other two groups. However, the PFS and OS outcomes were not statistically different between the three groups. The 2-year survival rates were 94%, 97%, and 97% for TEC, TAC, and ddTC, respectively. When compared to the current standard treatments for endometrial cancer, TEC is a promising candidate for a phase III trial based on its significantly superior CRate and equivalent PFS and OS. This study is registered with UMIN Clinical Trials Registry (UMIN000008911).

**KEYWORDS**
carboplatin, doxorubicin, endometrial cancer, epirubicin, paclitaxel

## 1 | INTRODUCTION

The per capita incidence of endometrial cancer, already the most common gynecologic cancer worldwide, is steadily increasing in developed countries.[1] The early-stage forms of endometrial cancer are usually highly curable by surgical treatment alone, whereas advanced stages require adjuvant interdictions such as radiotherapy and chemotherapy. Platinum and anthracycline drugs have long been used as standard adjuvant chemotherapy drugs for advanced and recurrent endometrial carcinomas.[2,3] In one study, the standard combination adjuvant treatment with AP was found to be more effective as an adjuvant therapy than whole abdominal irradiation (GOG122),[4] whereas no differences in outcomes between AP and radiotherapy were found in two other trials, one Italian, one Japanese.[5,6] Still, in the NSGO/EORTC trial (Nordic Society of Gynecologic Oncology/European Organization for the Research and Treatment of Cancer) and in the pooled results from two other studies, chemotherapy was found to be superior to radiation therapy.[7]

Before the introduction of paclitaxel into the GOG177 study, OS was not consistently improved in most drug comparison trials. The combination of paclitaxel, doxorubicin, and cisplatin (160, 45, and 50 mg/m$^2$, respectively) was found to be superior to AP (GOG 177). The response rates were 57% in the TAP arm of the study and 34% in the AP arm ($P < .001$); however, despite its better response rate, severe adverse events occurred more frequently with TAP, and it often requires G-CSF support. In one study's TAP arm, there were five treatment-related deaths (3.8%), but none in the AP arm.[8] Thus, considering the severe adverse events associated with TAP, it has not been widely used.

To search for an effective yet tolerable drug to be combined with a paclitaxel regimen for endometrial cancer, various other drug types have been studied. A combination of paclitaxel (175 mg/m$^2$) and carboplatin, with an AUC of 5-6 for six cycles, has been the gold standard regimen for another gynecologic tumor, ovarian cancer. The TC regimen is now also widely used for endometrial cancer.[2] In one study, the response rate to TC for chemonaïve advanced endometrial cancer was 47%.[9] With the addition of epirubicin to TC, TEC therapy has also been reported to be effective for the treatment of advanced and recurrent endometrial cancers.[10,11] Our own retrospective study showed that the TEC response rates for advanced or recurrent endometrial cancer were superior to TC alone (68% response in the TEC group vs 52% in the TC group).[3]

In one study,[12] a TC regimen using ddTC was found to be more effective for ovarian cancer than a triweekly regimen of TC, whereas, in the Mito-7 study, ddTC was not superior to triweekly TC.[13] However, the dose of TC used in the Mito-7 study was not the same as in the other trials mentioned. It is thought that the ddTC regimen is more effective than the triweekly regimen because the dose-interval of ddTC is shorter, which may suppress tumor growth, and the total volume of the ddTC regimen is more than the triweekly regimen. The ddTC regimen has recently been reported to be effective for endometrial cancer as well.[14-16]

As yet another combination therapy based on TC, TAC is a regimen of paclitaxel, doxorubicin, and carboplatin used for ovarian cancer that can also be effective against endometrial cancer. Recently, the endometrial cancer response rate to TAC was reported to be 67%.[17] To evaluate the feasibility of using one or more of these three combination adjuvant regimens for the routine treatment of advanced stage endometrial cancers, we undertook a randomized study comparing the safety and efficacy of TEC, ddTC, and TAC. This three-armed GOGO EM-3 randomized drug study was designed to find the best candidate for a future phase III trial for treatments of advanced or recurrent endometrial cancer. We have called this the ACE trial.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

Our study was undertaken as an intergroup cooperative carried out between GOGO, KCOG, TGCU, and EGOG. Patient participation eligibility required that the case be histologically diagnosed with primary endometrial carcinoma. The patient should have received at least a hysterectomy, salpingo-oophorectomy, and pelvic lymphadenectomy and there should be no residual tumor, or the residual tumor should be less than 2 cm in size.

Those patients at high risk of progression were defined as being in stage III or IV (FIGO 2008). The intermediate risk was defined as being in stage I and II, with one or more of the following factors: (a) histologic grade 3 endometrioid carcinoma with myometrial invasion still within half of the myometrium; (b) histological grade 1, 2 endometrioid carcinomas with an invasion of over half of the myometrium; (c) cervical stromal invasion; (d) vascular invasion; or (e) serous carcinoma, clear cell carcinoma, or undifferentiated carcinoma.

At admission to the study, the patients should not have received prior radiation or chemotherapy and should have had an ECOG performance status of 0-2. The patient's age should have been from 20 to 75 years, with adequate function of all major organs. Patients with a sarcomatous component, a serious complication, or a concurrent infection were not accepted. Written informed consent was obtained from all patients.

## 2.2 | Study design

Patients were registered into the study by an investigator, whereupon the patient was randomly allocated by the data center at a 1:1:1 ratio into one of the three study arms. The minimization method, with surgical stage (I or II vs III or IV) as the adjustment factor, was used for randomization assignment.

For the TEC regimen, epirubicin (50 mg/m$^2$) was infused for 30 minutes, paclitaxel (150 mg/m$^2$) for 3 hours, and carboplatin (AUC 4 mg/mL·min) for 1 hour on day 1. For the TAC regimen, on day 1, doxorubicin (45 mg/m$^2$) was administered for 30 minutes, paclitaxel (150 mg/m$^2$) for 3 hours, and carboplatin was infused at AUC = 5 for 1-2 hours. For the ddTC regimen, on day 1, carboplatin was infused to AUC = 5. On days 1, 8, and 15, paclitaxel (80 mg/m$^2$) was infused. All three regimens were repeated at 3-week intervals. The chemotherapy was to be started within 8 weeks from the time of surgical treatment. Completion of six cycles of the regimen was defined as completed.

The 3-week interval treatments were delayed when any of the following adverse events were observed: number of neutrophils fell below 1500/mm$^3$; number of platelets fell below 75,000/mm$^3$; levels for both aspartate aminotransferase and alanine aminotransferase rose above 100 U/L; serum creatinine levels rose above 1.5 mg/dl; the patient's temperature rose above 38°C; or the patient's performance status fell below 3. Treatments were also interrupted or altered for other adverse events, such as a hematology event greater than grade 3 (Common Terminology Criteria for Adverse Events, version 4.0), an allergic reaction greater than grade 1, or if a physician judged it was appropriate to postpone or skip the treatment, in which case the next treatment course was started within 6 weeks of the previous treatment.

The hematologic criteria used for deciding suspension of the ddTC treatments on days 8 and 15 were if numbers of neutrophils fell below 500/mm$^3$ or platelets fell below 50,000/mm$^3$. If hematologic criteria were not adequate, treatment was delayed for 7 days, and the dose of carboplatin was decreased in the next course. If the hematologic criteria did not return to an adequate status during the next 2 weeks of delay, the ddTC treatment was permanently terminated.

The dose of each chemotherapy was decreased in certain cases, as follows: (a) febrile neutropenia occurred, with neutropenia grade 3 or 4 and fever higher than 38.5°C; (b) neutropenia grade 4 for more than 5 days in a row; (c) grade 4 thrombocytopenia, or grade 3 thrombocytopenia with a bleeding tendency, requiring platelet transfusion; (d) grade 2 or higher peripheral neuropathy; and (e) grade 3 or higher nonhematologic adverse events, except for nausea, diarrhea, and alopecia. The details of the dose reduction scheme are described in Table S1. Following the full completion of the treatment arm, the patient was monitored monthly.

## 2.3 | Statistical analysis

The primary end-point of the study was the CRate of six cycles of each assigned treatment arm. As the purpose of this study was to select a treatment to proceed to the next trial phase, the selection design proposed by Sargent and Goldberg[18] was applied. The CRate for the three regimens was expected to range from 70% to 77%, based on prior studies.[11,14,17] A clinically significant difference in CRate was considered to be 15%, so the difference in true CRate was assumed to be 15%. If the result of this study shows that the highest CRate is 1% or more different from the other two groups, we intended to select that treatment group for the next trial phase. Under these conditions, for correctly selecting the treatment group with the highest Crate, 35 cases per group were required to make the probability 80% or more.

The secondary end-points of this study were PFS and OS curves, which were estimated by the Kaplan-Meier method and compared by the log-rank test. Progression-free survival and OS were defined as the periods from the day of the beginning of chemotherapy to the day of progression of the disease or the death of the patient from the disease was admitted.

Other data were analyzed using the $\chi^2$ test. If there was a significant difference among the three groups, the multiple comparison test was applied, with Bonferroni's correction. The indicated *P* values in the tables are unadjusted. The adverse event data were divided into grades 0, 1, 2 and grades 3, 4, 5, and then compared.

# 3 | RESULTS

## 3.1 | Enrolment and randomization

Between 2013 and 2016, a total of 105 patients were enrolled in the ACE study. The patients were treated at 10 different hospitals: Osaka University Hospital, Kurume University Hospital, Niigata University Medical and Dental Hospital, Kansai Rosai Hospital, Niigata Cancer Center, Iwate Medical University Hospital, Tottori University Hospital, Jichi Medical University Hospital, The Jikei University Hospital, and Osaka Police Hospital. Four of the 105

patients were not randomized; the specific reasons for their nonrandomization are listed in Figure 1. The remaining 101 patients were randomly allocated to treatment arms as follows: 33 patients were assigned to the TEC group, 33 to the TAC group, and 35 to the ddTC group. We found no differences between the three groups for the patients' individual characteristics, listed in Table 1.

### 3.2 | Six-cycle CRate

The CRates of the TEC, TAC, and ddTC groups were 94% (31/33), 61% (20/33), and 69% (24/35), respectively. The CRate for TEC was the highest of the three groups (Table 2).

Table 3 lists the reasons for suspending individual treatments during the study. One TAC case had a progression of the disease; this also occurred for two ddTC cases but none of the TEC group. Three TAC cases and two ddTC cases could not start a scheduled treatment course because of hematologic toxicity. Four TAC patients and two ddTC patients requested discontinuation of their treatment (reason unspecified). Treatment was discontinued because of grade 3 and grade 4 adverse events in one TEC case, five TAC cases, and two ddTC cases.

For three ddTC cases, treatment was discontinued by the patient's doctor. In one case, the patient had a grade1 allergy to the paclitaxel, in another, the patient had interstitial pneumonia, and in the third case, the patient had grade 2 neuropathy.

### 3.3 | Survival analysis

The median follow-up time for TEC was 45.4 months (range, 10.1–62.8 months), 45.5 month (23.3–65.9 months) for TAC, and 47.5 months (21.7–62.6 months) for ddTC. The 2-year PFS rate was 88%, 82%, and 89% in the TEC, TAC, and ddTC groups, respectively. The 2-year survival rate was 94%, 97%, and 97% in the TEC, TAC, and ddTC groups, respectively (Figure 2). According to Kaplan-Meier analysis, the PFS and OS resulting from the three treatments, TEC, TAC, and ddTC, were not statistically different, and this was true regardless of whether they were treated for intermediate-risk (stage I and II) or high-risk (stage III and IV) tumors (Figure S1).

### 3.4 | Adverse events

Grade 3 and 4 neutropenia were observed more frequently in the TEC and TAC groups than in the ddTC group (67%, 73%, and 14%, TEC vs ddTC, $P = .000015$; TAC vs ddTC, $P < .000001$, respectively). Grades 3 and 4 fever were significantly more frequent in the TAC group than in the ddTC group (21% and 0%, respectively, $P = .0044$). The frequency of using G-CSF was significantly higher in the TAC group than in the ddTC group (36% vs 3%, $P = .00046$). The frequency of using G-CSF in the TEC group was 21%, which was not significantly higher than for the ddTC group ($P = .025$; Table S2). The frequency of other adverse events was

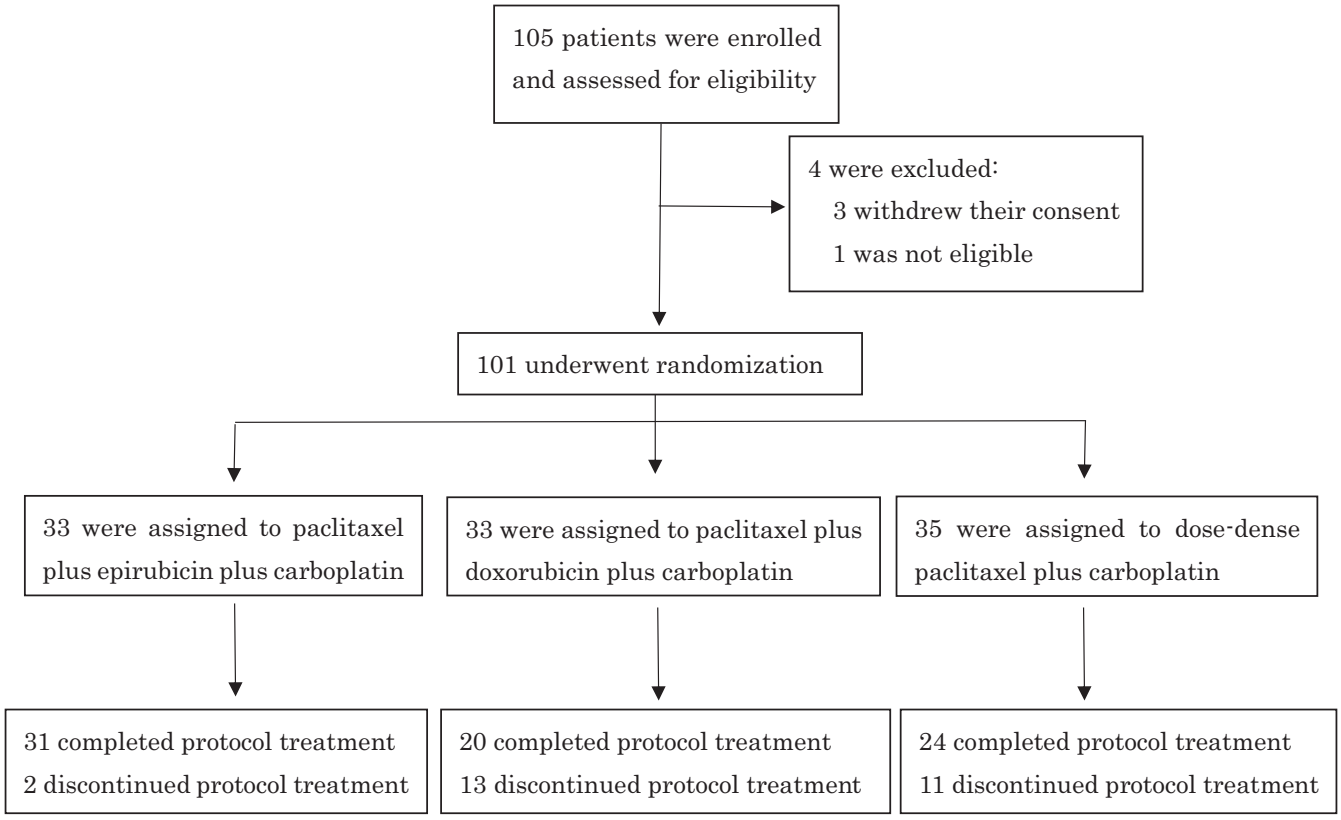



**FIGURE 1** Randomization and follow-up of patients with advanced endometrial carcinoma treated with dose-dense paclitaxel plus carboplatin, paclitaxel plus doxorubicin plus carboplatin, or paclitaxel plus carboplatin plus epirubicin

**TABLE 1** Characteristics of each treatment group of patients with advanced endometrial carcinoma

| | TEC | TAC | ddTC |
|---|---|---|---|
| Mean age (y) | 61 (29–74) | 59 (38–73) | 60 (31–75) |
| Mean height (cm) | 155.3 (143.2–167.9) | 155.2 (142.3–173.4) | 152.2 (142.0–167.0) |
| Mean weight (kg) | 54 (43.0–75.6) | 55 (41.0–77.0) | 53.7 (38.1–86) |
| Performance status | | | |
| 0 | 33 (100) | 32 (97) | 33 (94) |
| 1 | 0 (0) | 1 (3) | 2 (6) |
| Histology | | | |
| Endometrioid carcinoma | 23 (70) | 27 (82) | 22 (63) |
| Mixed carcinoma | 6 (18) | 3 (9) | 3 (9) |
| Serous carcinoma | 1 (3) | 2 (6) | 6 (17) |
| Clear cell carcinoma | 2 (6) | 1 (3) | 3 (9) |
| Squamous cell carcinoma | 0 (0) | 0 (0) | 1 (3) |
| Undifferentiated carcinoma | 1 (3) | 0 (0) | 0 (0) |
| Stage | | | |
| I | 15 (45) | 13 (39) | 16 (34) |
| II | 1 (3) | 3 (9) | 4 (11) |
| III | 15 (45) | 16 (48) | 16 (45) |
| IV | 2 (6) | 1 (3) | 3 (9) |
| Medical history | | | |
| No | 22 (67) | 22 (67) | 26 (74) |
| Yes | 11 (33) | 11 (33) | 9 (26) |
| Comorbidity | | | |
| No | 24 (73) | 23 (70) | 23 (66) |
| Yes | 9 (27) | 10 (30) | 12 (34) |
| Risk of recurrence | | | |
| Intermediate | 15 (45) | 15 (45) | 14 (40) |
| High | 18 (55) | 18 (55) | 21 (60) |

*Note:* Data are shown as median (range) or n (%).

Abbreviations: ddTC, dose-dense paclitaxel plus carboplatin; TAC, paclitaxel plus doxorubicin plus carboplatin; TEC, paclitaxel plus carboplatin plus epirubicin.

**TABLE 2** Completion rate of each treatment group of patients with advanced endometrial carcinoma

| | Six-cycle regimen, n (%) | | |
|---|---|---|---|
| | Completed | Not completed | Average number of cycles completed |
| TEC | 31 (94) | 2 (6) | 5.7 |
| TAC | 20 (61) | 13 (39) | 4.5 |
| ddTC | 24 (69) | 11 (31) | 4.7 |

Abbreviations: ddTC, dose-dense paclitaxel plus carboplatin; TAC, paclitaxel plus doxorubicin plus carboplatin; TEC, paclitaxel plus carboplatin plus epirubicin.

not statistically different in the three groups (Table 4). The frequency of needing to reduce the drug dose was not different in the three groups. The frequency of treatment delay was significantly more frequent in the ddTC group than in the TEC group (36% and 77%, respectively; $P = .0012$; Table S3).

## 4 | DISCUSSION

The primary end-point of this comparative study of combination adjuvant chemotherapies was the successful CRate of six cycles of treatment. Under our rigid criteria, the TEC group had the highest CRate, i.e., TEC exhibited the least, or the most tolerable, toxicities. The results of the 2-year follow-up for the two secondary endpoints, OS and PFS, on the other hand, were not considered to be statistically different among the three groups.

The AUC for carboplatin in each regimen was 4 mg/mL·min in TEC and 5 mg·mL/min in TAC and ddTC. This may be one reason why TEC had the highest CRate. The higher dose of carboplatin

might result in more adverse events such as hematologic toxicity. The AUC = 4 in TEC was determined in the phase I study as the tolerable dose.[11]

Anthracyclines such as doxorubicin have a long history as key drugs in the battle against endometrial cancer. A combination of doxorubicin and cisplatin (AP) is the widely used gold standard regimen. However, because of anthracycline's known serious adverse side effects, such as cardiac toxicity, several different anthracycline-free regimens have been investigated to circumvent them. In one randomized phase III study of adjuvant chemotherapy treatments for endometrial cancer patients (JGOG2043), AP competed against TC and DP. Their findings were identical to those of our current study, in that the OS and PFS were not different between the three groups.[19]

Recently, randomized TAP and TC regimens for advanced or recurrent endometrial cancer were compared (GOG0209). The PFS and OS of the anthracycline-free TC regimen were comparable to those of the anthracycline-containing TAP regimen. However, as expected, adverse events were more frequent for the anthracycline-containing TAP regimen. Consequently, a TC regimen is now recommended over TAP for advanced and recurrent endometrial cancer.[20]

In the current study, two regimens containing the anthracycline doxorubicin, TEC and TAC, were included. The resulting PFS and OS were completely compatible with other recent studies, as there was no statistical difference among the three arms. For instance, the CRate for seven cycles of TAP and TC in the GOG0209 study was 63% and 69%, respectively. In the JGOG2043 study, the CRate for six cycles of chemotherapy was 80% (210/261) for AP, 82% for DP (218/263), and 75% (199/262) for TC.[19]

The CRate for TEC in the current study was 94%, making it appear superior to the CRates of TAC and ddTC (61% and 69%). The CRate for TEC in the current study was superior to the CRate for TC in the JGOG2043 study, and better than the CRate for seven cycles of TC in the GOG0209 study.[19,20] There were no cardiac failures nor treatment-related deaths for the TEC regimen, despite it including the anthracycline drug epirubicin.

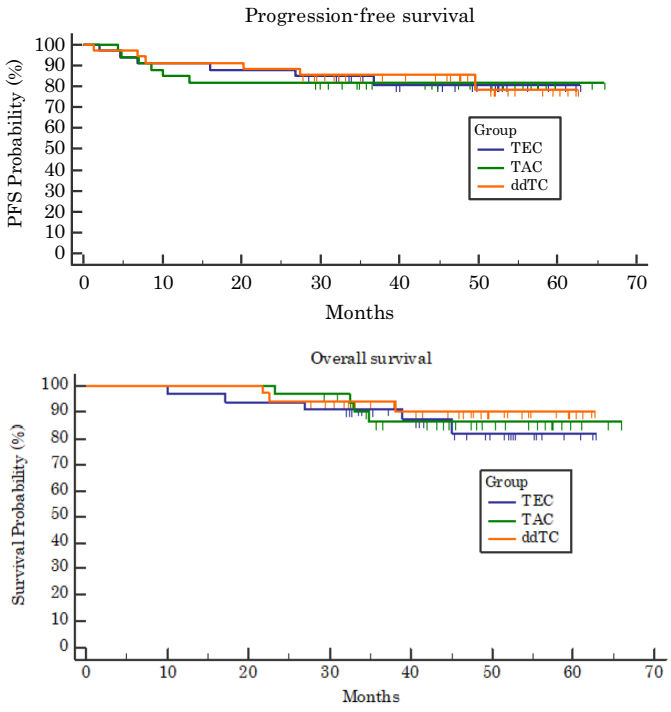
The TC regimen is highly familiar to gynecologic oncologists as a treatment for ovarian cancer, so it is easily used in most hospitals.

**TABLE 3** Reasons for treatment cessation in patients with advanced endometrial carcinoma

| Reason for cessation or alteration of treatment | TEC ($n = 33$) | TAC ($n = 33$) | ddTC ($n = 35$) |
|---|---|---|---|
| Progression of disease | 0 | 1 | 2 |
| Delay or dose reduction for hematologic toxicity | 0 | 4 | 2 |
| Patient withdrew | 1 | 5 | 2 |
| Grade 3 or 4 adverse events | 1 | 5 | 2 |
| Doctor's judgement to withdraw patient | 0 | 0 | 3 |
| Total | 2/33 | 15/33 | 11/35 |

*Note:* Multiple answers were allowed. Two doctors in the TAC group selected two answers, one selected "progressive disease and a grade 3 adverse event", the other responded "patient withdrawal and a grade 3 adverse event."

Abbreviations: ddTC, dose-dense paclitaxel plus carboplatin; TAC, paclitaxel plus doxorubicin plus carboplatin; TEC, paclitaxel plus carboplatin plus epirubicin.




| | 6 months | 12 months | 18 months | 24 months |
|---|---|---|---|---|
| TEC | 94% | 91% | 88% | 88% |
| TAC | 94% | 85% | 82% | 82% |
| ddTC | 97% | 91% | 91% | 89% |

| | 6 months | 12 months | 18 months | 24 months |
|---|---|---|---|---|
| TEC | 100% | 94% | 94% | 94% |
| TAC | 100% | 100% | 100% | 97% |
| ddTC | 100% | 100% | 100% | 94% |

**FIGURE 2** Progression-free survival and overall survival of patients with advanced endometrial carcinoma treated with dose-dense paclitaxel plus carboplatin (ddTC), paclitaxel plus doxorubicin plus carboplatin (TAC), or paclitaxel plus carboplatin plus epirubicin (TEC)

**TABLE 4** Number and percentage of patients with advanced endometrial carcinoma adversely affected by treatment

| | TEC ($n = 33$), n (%) | | TAC ($n = 33$), n (%) | | ddTC ($n = 35$), n (%) | | *P* value | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Toxicity | Grade 1, 2 | Grade 3, 4 | Grade 1, 2 | Grade 3, 4 | Grade 1, 2 | Grade 3, 4 | | TEC vs TAC | TEC vs ddTC | TAC vs ddTC |
| Neutropenia | 6 (18) | 22 (67) | 4 (12) | 24 (73) | 16 (46) | 5 (14) | <.0001 | .789 | .000015* | <.000001* |
| Thrombocytopenia | 8 (24) | 0 (0) | 9 (27) | 2 (6) | 6 (17) | 0 (0) | .1220 | | | |
| Anemia | 17 (52) | 0 (0) | 15 (45) | 1 (3) | 16 (46) | 0 (0) | .3550 | | | |
| Nausea | 18 (55) | 0 (0) | 18 (55) | 1 (3) | 10 (29) | 0 (0) | .3550 | | | |
| Vomiting | 6 (18) | 0 (0) | 5 (15) | 0 (0) | 1 (3) | 0 (0) | .9610 | | | |
| Diarrhea | 0 (0) | 0 (0) | 4 (12) | 1 (3) | 4 (11) | 0 (0) | .3530 | | | |
| Peripheral neuropathy | 12 (36) | 1 (3) | 10 (30) | 1 (3) | 17 (48.5) | 0 (0) | .5820 | | | |
| Fever | 0 (0) | 1 (3) | 0 (0) | 7 (21) | 0 (0) | 0 (0) | .0024 | .053 | .485000 | .004400* |
| Myalgia | 6 (18) | 0 (0) | 2 (6) | 0 (0) | 0 (0) | 0 (0) | .9610 | | | |
| Arthralgia | 10 (30) | 0 (0) | 4 (12) | 0 (0) | 3 (8.5) | 0 (0) | .9610 | | | |
| Cutaneous | 1 (3) | 0 (0) | 1 (3) | 0 (0) | 1 (3) | 0 (0) | .9610 | | | |
| Cardiac function | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | .9610 | | | |
| Renal (Cre) | 3 (9) | 0 (0) | 1 (3) | 0 (0) | 3 (8.5) | 0 (0) | .9610 | | | |
| Hepatic (AST/ALT) | 5 (15) | 0 (0) | 4 (12) | 0 (0) | 5 (14) | 0 (0) | .9610 | | | |
| Pulmonary | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | .9610 | | | |

*Note:* The number of patients with grade 3 or 4 adverse events was compared.

The lack of data in some cells indicates data were analyzed using the chi-square test. If there was a significant difference among the three groups, the multiple comparison test was performed, with Bonferroni's correction.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cre, creatinine; ddTC, dose-dense paclitaxel plus carboplatin; TAC, paclitaxel plus doxorubicin plus carboplatin; TEC, paclitaxel plus carboplatin plus epirubicin.

*Significantly different.

From the results of the GOG0209 study, the TC regimen would be presumed to be the first choice for endometrial cancer as well. Meanwhile, in the GOG0209 study, the OS for women of Japanese descent tended to be better with the TAP regimen than the TC regimen, although the difference was not statistically significant.

There has been one phase II study that found that the ddTC regimen is superior to the TC regimen for advanced endometrial cancer.[15] However, the CRate for ddTC, at 69%, was relatively low. A careful comparison of the ddTC and TC regimens in a large phase III study is now needed.

The PORTEC-3 trial recently found that a combination of adjuvant chemotherapy and radiotherapy was superior to pelvic radiation therapy alone.[21] The regimen used in that study was two cycles of cisplatin (50 mg/m$^2$) given intravenously concurrently with radiotherapy, followed by four cycles of carboplatin (AUC5) and paclitaxel (175 mg/m$^2$). However, six cycles of TC chemotherapy were not inferior to combined adjuvant chemotherapy and radiotherapy (cisplatin [50 mg/m$^2$ on days 1 and 29], together with volume-directed external-beam radiation therapy, followed by four cycles of TC).[22]

There are limitations to our current study. It was mainly designed to compare only the CRate for each arm. The number of patients per arm (33–35) was relatively small and the period of observation (2 years) is so far very short. This is one reason that PFS and OS were not statistically different in these three groups. Many more cases and a much longer observation period will be needed to determine the best regimen for adjuvant chemotherapy for advanced endometrial cancer.

Another reason is that there may be a group of cases that were cured by surgery alone and therefore did not need adjuvant therapy. We included the intermediate-risk group for this study because their treatment was not clear. Additionally, the definition of "intermediate risk for recurrence" was different in each previously published study, differing by study group and country.[23-25] According to Japanese guidelines, adjuvant treatment should be considered for patients with intermediate risk, and in fact is being used by many Japanese affiliations.[25] In the ongoing randomized PORTEC-4a trial, stage I high-intermediate risk endometrial cancer cases are being randomized to adjuvant therapy or observation according to their molecular profile, which was reported in The Cancer Genome Atlas. It is expected that the PORTEC-4a trial will better elucidate the subgroup within the larger intermediate-risk group that would best benefit from specifically molecularly targeted adjuvant therapies.[24] Molecularly targeted "precision medicines" such as checkpoint inhibitors have only recently become important for the treatment of endometrial cancer.[24] When we planned the current study in 2012, molecularly targeted therapy for endometrioid cancer was not yet widely recognized and thus was not included in this study. The use of molecularly targeted therapy is often limited to specific molecular signature subtypes of cancer and often is attempted only after the failure of conventional

chemotherapy. Another consideration is the cost of molecularly targeted therapy, which is much higher than traditional chemotherapies, meaning the latter are still much needed for the routine treatment of endometrial cancer. Thus, their optimal regimens must be elucidated, as we have attempted to do with this study.

In conclusion, the six-cycle CRate for advanced endometrial cancer treatment was highest in the TEC group, compared to TAC and ddTC; however, the PFS and OS of each group were the same. Based on its superior CRate, the TEC regimen is the most feasible of the three regimens for promotion forward for a phase III trial for endometrial cancer.

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## DISCLOSURE

The authors have no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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