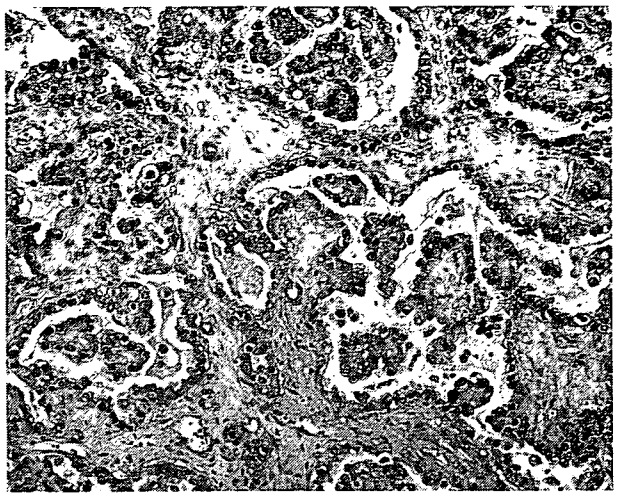

Figure 3 Clear cytoplasm and hobnail pattern at right ovary (HE ×200).

carcinoid and thyroid component admixed. In some foci, a transition from carcinoid structures to thyroid follicles was observed. A teratoid component was not observed, as has been present in most strumal carcinoid cases.

Immunohistologic staining was positive for thyroglobulin and thyroid transcription factor-1 (TTF-1), and focally positive for chromogranin. HE-stained mucinous cystadenoma revealed mucin pools without cellular atypia. In other fields, the strumal carcinoid components were closely admixed with glands lined by mucin-producing cells (Fig. 4b). Goblet cells were found forming small cellular clusters or even acini. Immunohistologic staining was positive for periodic acid Schiff (PAS), alcian blue, and mucicarmine. Immunohistologic staining revealed the existence of PYY in the carcinoid cells (Fig. 5), but not in the clear cell adenocarcinoma cells or the mucinous cystadenoma cells (data not shown).

Adenomyosis and endometriosis were revealed by the existence of endometrium in the myometrium and right tube, respectively. The clinical stage of this tumor was stage Ia for right ovarian cancer and Ic(b) for the left borderline ovarian tumor. The constipation improved after surgery, and the patient was able to defecate daily without laxatives. Three cycles of a combination of paclitaxel (175 mg/m^2) and carboplatin (AUC-5) were administered as postoperative chemotherapy. The levels of serum CA-19-9 and CA-125 decreased to normal ranges. The patient showed no evidence of disease 18 months after the operation.

Discussion

Strumal carcinoid tumors are composed of thyroid tissue intimately admixed with carcinoid tumor, which in the great majority of cases exhibits a trabecular pattern. Usually, strumal carcinoid is not associated with carcinoid syndrome.[5] However, the symptoms, which are closely related to endocrine changes such as virilization, hirsutism, and endometrial hyperplasia, have been reported in a few cases.[5]

A number of ovarian carcinoid patients have been described as having severe constipation.[2-4] In such cases, the expression of PYY has been observed. PYY is a gastrointestinal hormone consisting of 36 amino acids and is distributed in the distal small intestine and colon.[6] PYY participates in regulating a number of physiological actions of the digestive organs, such as pancreatic exocrine secretion, gastric acid secretion, gastrointestinal motility, contraction of the gallbladder, and colonic absorption of water and electrolytes.[7] PYY has been reported to be a possible cause of severe constipation in patients with primary ovarian carcinoid tumor.[2,3] This may be due to inhibition of intestinal motility by the tumor-producing gut hormone, PYY. In the present case, the expression of PYY of this tumor would be the cause of severe constipation. This assumption was supported by the prompt recovery from constipation after removal of the tumor.

The left ovarian tumor comprised a mucinous cystadenoma and strumal carcinoid. Robboy and Scully reported that glands or cysts lined by a mucinous columnar epithelium containing goblet cells were detected within or contiguous to the strumal carcinoid component of the tumor in 46% of their 50 cases.[5] In five of their specimens, the mucinous components were large enough to be considered mucinous cystadenoma.

Clear cell adenocarcinoma was identified at the contralateral ovary in the present case. It appeared to arise from an endometriotic cyst, as a correlation between endometriosis and ovarian cancer, particularly clear cell adenocarcinoma, has been reported. Because a correlation between ovarian carcinoid and endometriosis or clear cell adenocarcinoma of the ovary has not been reported, strumal carcinoid would be coincident with clear cell adenocarcinoma. The prognosis of patients with ovarian carcinoid is favorable when excision of the tumor is feasible. The prognosis for the advanced stage of ovarian carcinoid would be poor, although it is rare.[8,9] There are no data

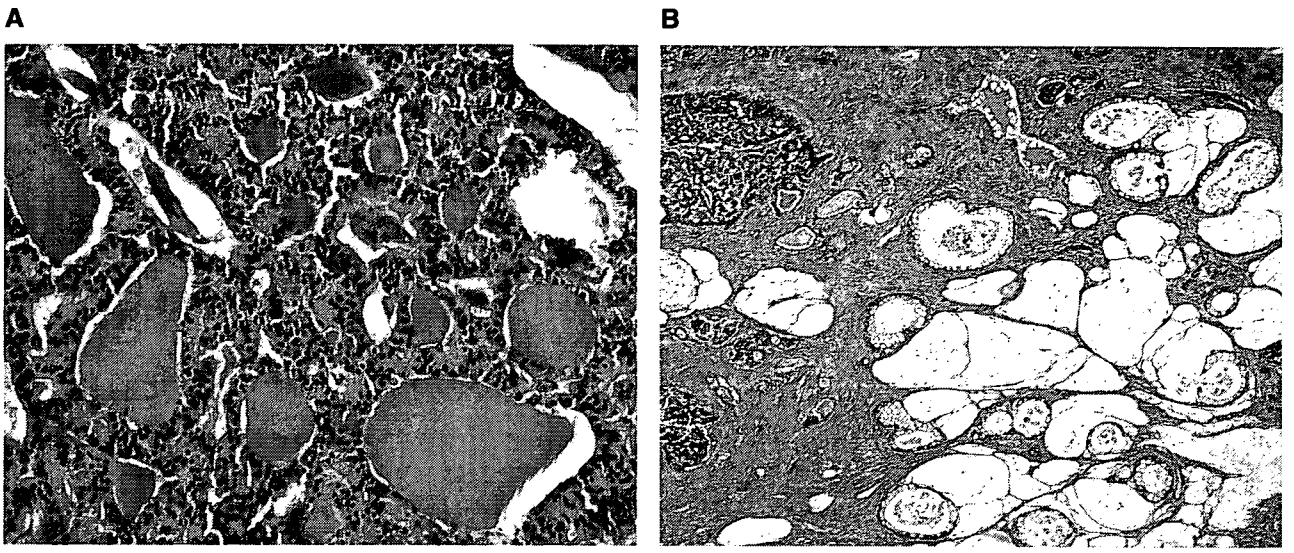

Figure 4 (a) Ribbons of trabecular carcinoid are combined with thyroid follicles (HE ×200). (b) The strumal carcinoid components were closely admixed with goblet cells (HE ×40).

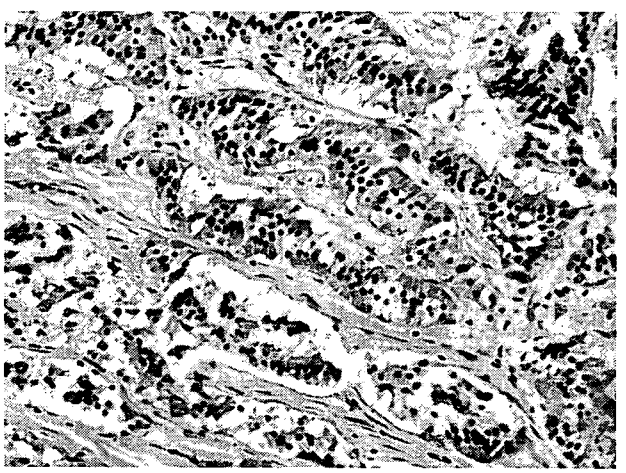

Figure 5 Immunohistochemical staining of strumal carcinoid with anti-peptide YY (PYY) antibody. Most of the cytoplasm of the carcinoid cells was stained with the anti-PYY antibody (×200).

in the literature to support adjuvant chemotherapy or radiation therapy for carcinoid tumors. Moertel *et al.* reported a large phase II trial of combination chemotherapy, cisplatin and etoposide, in which only a 7% response rate was seen.[10] In the case presented here, the combination of paclitaxel and carboplatin was chosen because clear cell adenocarcinoma of the right ovary would contribute to the prognosis of this case.

In conclusion, the authors present a woman with severe constipation probably due to a strumal carcinoid. Interestingly, her constipation helped lead to early detection of clear cell adenocarcinoma.

Acknowledgments

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Shin Nishio, Toru Sugiyama, Tadahiro Shouji, Akira Yoshizaki, Ryo Kitagawa, Kimio Ushijima, Toshiharu Kamura

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84 Theobald's Road
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UK WC1X 8RR
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Pilot study evaluating the efficacy and toxicity of irinotecan plus oral etoposide for platinum- and taxane-resistant epithelial ovarian cancer

Shin Nishio [a], Toru Sugiyama [b,*], Tadahiro Shouji [b], Akira Yoshizaki [b], Ryo Kitagawa [a], Kimio Ushijima [a], Toshiharu Kamura [a]

[a] *Department of Obstetrics and Gynecology, Kurume University School of Medicine, 67 Asahimachi, Kurume, Fukuoka Pretecture, 830-0011, Japan*
[b] *Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, 19-1 Uchimaru, Morioka, Iwate Prefecture, 020-8505, Japan*

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Abstract

Objectives. To evaluate the efficacy and toxicity of combination chemotherapy with intravenous irinotecan and oral etoposide in women with platinum- and taxane-resistant epithelial ovarian cancer.

Methods. Between October 2002 and September 2005, we studied 27 women with platinum- and taxane-resistant epithelial ovarian cancer. Irinotecan was administered in an intravenous dose of 70 mg/m^2 as a 90-min infusion on days 1 and 15 of a 28-day cycle, and etoposide was administered in an oral dose of 50 mg/day on days 1 to 21. For heavily pretreated patients, the initial dose of irinotecan was lowered to 60 mg/m^2. Treatment cycles were repeated until disease progression or unacceptable toxicity.

Results. All 27 patients were eligible and assessable. There were 11 partial responses and 1 complete response for an overall response rate of 44.4%. The median durations of overall response and of stable disease were 11 months and 8 months, respectively. The major toxicity was neutropenia (grade 3, 22.2%; grade 4, 37.1%). Diarrhea was infrequent and mild, and gastrointestinal toxicity was moderate and manageable. Acute myeloid leukemia (M5) developed as a secondary malignancy in 1 patient.

Conclusions. The results of our pilot study suggest that a combination of irinotecan and oral etoposide is effective and tolerable in women with platinum- and taxane-resistant epithelial ovarian cancer.

Keywords: Irinotecan; Oral etoposide; Platinum/taxane-resistant ovarian cancer

Introduction

Various agents and treatment regimens have been introduced to treat recurrent ovarian cancer resistant to platinum/taxane (PT), currently the standard first-line chemotherapy. Generally, relapse within 3 months after first-line platinum containing therapy is defined as platinum-refractory disease, relapse between 3 and 6 months after therapy is defined as platinum-resistant disease and relapse more than 6 months after therapy is defined as platinum-sensitive disease. Topotecan, gemcitabine, etoposide and liposomal doxorubicin produce response rates of 20% to 30%, but the time to progression is usually short, particularly in PT-resistant or -refractory disease [1–3]. Irinotecan is a topoisomerase-I inhibitor similar to topotecan, a drug approved by the Food and Drug Administration (FDA) for the second-line treatment of ovarian cancer [4,5]. Irinotecan has been studied in Japan for the management of ovarian cancer. In a phase II study, 55 patients received irinotecan in a dosage of 100 mg/m^2 once weekly and 150 mg/m^2 once every 2 weeks. The response rate was 23.6%. Major adverse effects were leukopenia, nausea and vomiting, diarrhea and anorexia, with incidences (grade 3 or 4 hematological toxicity and grade 2 or higher nonhematological toxicity) of 57.1%, 60.3%, 44.0% and 67.2%, respectively [6]. This compares favorably with the response to topotecan. Etoposide, a topoisomerase-II inhibitor, has high antitumor activity against various animal and human malignancies [7]. The efficacy of etoposide may be regimen-dependent, since prolonged oral administration has yielded better results than intravenous administration [8,9]. The largest

* Corresponding author. Fax: +81 19 6221900.
E-mail address: sugiyama@iwate-med.ac.jp (T. Sugiyama).

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study to date, performed by the Gynecologic Oncology Group (GOG), reported a response rate of 8.3% [10]. Long-term treatment with oral etoposide has produced better results in women with platinum-resistant ovarian carcinoma [1,11–14]. In a study by de Wit et al. [12], 50 mg/m^2 of oral etoposide was administered for 21 days every 4 weeks to 28 patients with platinum-resistant ovarian cancer, resulting in a response rate of 16.0%. Rose et al. [1] gave oral etoposide to 41 patients with platinum-sensitive or -resistant recurrent ovarian cancer and obtained response rates of 34.6% and 26.8%, respectively.

DNA topoisomerases-I and -II are nuclear enzymes that participate in various genetic processes, including transcription, replication, recombination and chromosome segregation at mitosis [4]. These two DNA topoisomerases are functionally related and act in concert. Both seem to be essential for maintaining cell viability throughout the cell cycle. Topoisomerase-I treatment induces an increase in the S-phase cell population with an increase in topoisomerase-II mRNA expression. Thus, topoisomerase-I can modulate topoisomerase-II levels to enhance the effect of topoisomerase-II inhibitors [15,16]. Therefore, combined use of topoisomerase-I- and topoisomerase-II-targeting agents could theoretically inhibit both DNA and RNA synthesis completely, resulting in synergistic cytotoxicity.

This pilot study was undertaken to evaluate the antitumor efficacy and toxicity of a combination of irinotecan, a DNA topoisomerase-I inhibitor, and oral etoposide, a DNA topoisomerase-II inhibitor, in women with platinum- and taxane-resistant epithelial ovarian cancer.

Patients and methods

Eligibility

Patients were eligible for this study if they satisfied the following criteria: (1) histologically confirmed epithelial ovarian cancer; (2) recurrent disease after previous treatment with platinum and taxanes; (3) an Eastern Cooperative Oncology Group performance (ECOG) status of <2; (4) measurable or assessable disease. Assessable disease was defined according to the following CA-125 criteria: a CA-125 level of greater than 70 U/mL at study entry; this CA-125 level must have at least doubled from the baseline level, providing evidence of disease progression while receiving a previous treatment regimen (as confirmed by at least two separate blood samples obtained >4 weeks apart) (GCIG guidelines) [17]. (5) Age <75 years; (6) adequate laboratory values (leukocyte count >4000/μL, absolute neutrophil count >1500/μL, platelet count >100,000/μL, hemoglobin level >9.5 g/dL, total bilirubin <2.0 mg/dL and serum aspartate aminotransferase or alanine aminotransferase <2 times the upper limit of normal at the center performing the test); and (7) a signed informed consent statement confirming that the subject understood the experimental nature of the study treatment.

Patients were excluded from the study if any of the following applied: (1) Previous treatment with irinotecan or topotecan; (2) concurrent active or uncontrolled infection; (3) any psychiatric disorders potentially interfering with consent or follow-up; (4) pregnant women or nursing mothers; (5) other active malignancies; (6) clinically significant comorbidity (e.g., a history of previous myocardial infarction within the past 6 months, congestive heart failure requiring therapy, a history of seizures or uncontrolled diabetes, clinically apparent metastases to the central nervous system); (7) poor oral intake due to intestinal obstruction; (8) large amounts of pleural effusion, pericardial fluid or ascitic fluid, requiring repeated drainage; (9) previous abdominal radiation therapy; (10) Apparent pulmonary fibrosis or interstitial pneumonia; and (11) watery diarrhea or other health problems that the attending physician felt would interfere with treatment. The study protocol was approved by institutional review board of each participating center.

Platinum/taxane-refractory disease was defined as tumor progression during treatment or within 3 months after the completion of therapy. Platinum/taxane-resistant disease was defined as tumor progression between 3 and 6 months after the completion of the most recent course of therapy. Any regimen that contained a platinum/taxane drug was counted as one regimen for the purpose of this study. For example, if a patient received cisplatin with paclitaxel as first-line therapy and then received weekly carboplatin and paclitaxel after recurrence, the number of regimens was considered to be two ("cisplatin with paclitaxel" and "weekly carboplatin with paclitaxel"). If the patient then received carboplatin monotherapy after progression, the number of regimens was considered to be three ("cisplatin with paclitaxel," "weekly carboplatin with paclitaxel" and "carboplatin").

Treatment schedule

Irinotecan 70 mg/m^2 was administered as a 90-min intravenous infusion on days 1 and 15 of a 28-day cycle. Etoposide 50 mg/day was given orally on an empty stomach at bedtime with metoclopramide or domperidone for 21 days starting on day 1. These starting doses were based on the results of a phase I study [18]. For patients who were heavily pretreated and received the study treatment as third- or fourth-line therapy, the starting dose of irinotecan was reduced to 60 mg/m^2. Treatment cycles were repeated until evidence of disease progression or unacceptable toxicity. A $5HT_3$-antagonist was given before the administration of irinotecan. For etoposide, premedication was left to the discretion of the attending physicians. Routine prophylactic treatment with granulocyte colony-stimulating factor (G-CSF) was not recommended. During the first course of chemotherapy, G-CSF was used to treat grade 4 neutropenia. During subsequent courses, G-CSF could be used to treat grade 3 or 4 neutropenia in accordance with published guidelines [19]. However, etoposide was withheld on days when G-CSF was administered.

Treatment with irinotecan was withheld if the patient had a leukocyte count of less than 2000/μL, a platelet count of less than 100,000/μL, or >grade 2 diarrhea, fever, or both on the day scheduled for treatment. Before the next course was started, the leukocyte count had to be at least 3000/μL, the platelet count at least 100,000/μL and the diarrhea or fever had to have completely resolved. Subsequent doses were decided on the basis of hematologic and nonhematologic toxicity. If the criteria for resuming treatment were not met for more than 6 weeks since the last dose, the patient was withdrawn from the study. The dose of irinotecan for subsequent cycles of treatment was reduced by 10 mg/m^2 if grade 4 neutropenia persisted for more than 7 days, the platelet nadir was less than 50,000/μL or >grade 3 diarrhea occurred in the preceding cycle. The minimum dose of irinotecan was set at 40 mg/m^2. Patients who had evidence of disease progression or intolerable toxicity (grade 4 diarrhea, neutropenic fever, or both for more than 7 days, or grade 2 or higher pneumonitis) were withdrawn from the study. The dose of etoposide was reduced to 25 mg/day if grade 3 or 4 (according to The National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [Version 2]; NCI-CTC ver.2) emesis occurred despite treatment with antiemetic agents.

Study evaluations

All patients underwent a complete blood count, platelet count, serum chemical analyses to measure renal and hepatic functions, electrolyte analysis, urinalysis and toxicity assessments weekly. At the end of each 4-week cycle, the CA-125 level was determined. Antitumor effects were evaluated according to the RECIST criteria [20] on the basis of computed tomographic or magnetic resonance imaging scans in patients with measurable lesions. The GCIG CA-125 response criteria proposed by Rustin et al. [17] were used to evaluate antitumor response in patients without measurable lesions. These evaluations were performed after the completion of each cycle of treatment (4 – 6 weeks). Response in patients with measurable lesions was evaluated on the basis of symptoms or imaging findings. Response in patients with non-measurable lesions was evaluated based on elevation of CA 125.

NCI-CTC Ver. 2 was used to grade organ damage [21]. Survival was calculated from the date of starting the study treatment to the date of death, or data were censored at the time of last contact.

Table 1
Patient characteristics

Characteristic	No. of patients (%)
Age, years	
Median	58
Range	34–71
No. of previous regimens	
1	5 (18.6)
2	12 (44.4)
3	9 (33.3)
≥4	1 (3.7)
Treatment-free interval, months	
<3	19 (70.3)
3–6	8 (29.7)
Performance status (PS)	
0	13 (48.2)
1	7 (25.9)
2	7 (25.9)
Measurable sites or assessable CA-125 (=70 U/mL)	
Visceral	9 (33.3)
Soft tissue	6 (22.2)
Lymph node	2 (7.4)
CA-125	10 (37.1)
Histology	
Serous	19 (70.4)
Mucinous	3 (11.1)
Endometrioid	3 (11.1)
Clear cell	2 (7.4)
No. of cycles: median	5 (range, 1–25)
CR+PR	6 (range, 1–16)
SD	5 (range, 1–25)
PD	2 (range, 2–3)

CR, complete response; PR, partial response; SD, stable Disease; PD, progressive disease.

Statistical analysis

To evaluate toxicity, time-to-event data were analyzed with the use of Kaplan–Meier survival curves. Duration of response was measured from the date an initial response was documented to the date of disease progression, relapse or death. Time to progression was calculated from the date of starting treatment with irinotecan and etoposide to the date of first documentation of tumor progression. Survival time was calculated from the date of diagnosis to the date of death or the date of the last known contact.

This study was designed to test the hypothesis that the true response rate was <0.10 versus the alternative hypothesis that it was >0.25. A two-stage sampling plan was employed, which featured accrual of 27 patients in the first stage and additional accrual of 13 patients in the second phase if at least three responses were observed in the first stage. At least 10 responses among these 40 patients were necessary to reject the null hypothesis. This design featured a size of 0.05 and a power of 0.8.

Results

Between October 2002 and September 2005 at Kurume University Hospital and Iwate Medical University Hospital, we enrolled 27 women with platinum- and taxane-resistant epithelial ovarian cancer. All were eligible for analysis. The characteristics of the subjects are shown in Table 1. The median age was 58 years (range, 34–71 years). The treatment-free interval was less than 3 months in 19 patients and 3 to 6 months in 8. Seventeen patients had measurable lesions. The most common sites of recurrent lesions were the viscera, soft tissue and lymph nodes. Ten patients lacked measurable lesions but had high CA-125 levels (>70 U/mL), with a median value of 100 U/mL (range, 75–350 U/mL) at enrollment. Five patients received the study therapy as second line, 12 as third line, 9 as fourth line and 1 as fifth line.

Response

Of the 17 patients with measurable disease, 10 (47.6%) had objective responses (1 complete response [CR] and 9 partial responses [PR]). Of the 10 patients in whom response was evaluated according to the CA-125 criteria, 6 (42.9%) had at least a 50% decrease in the level of this tumor marker. Two of these patients met the criteria for PR. Thus, the overall rate of objective response (CR+PR according to the RECIST and CA-125 criteria) in this pilot study was 44.4% (12/27) (95% confidence interval, 30.5% to 61.8%). Eleven patients (42.8%) had stable disease (SD), and the other 4 (11.4%) had progressive disease (PD). The progression-free (CR+PR+SD) rate was 85.1%.

The median duration of response in the 12 patients who had objective responses was 11 months (range, 4–18 months). The median duration of SD in the 11 patients who had SD was 8 months (range, 4–22 months). The median time to progression (TTP) in the study group as a whole was 9 months (range, 1–28 months). The median survival was 17 months (range, 3–31 months).

Toxicity and treatment received

The 27 patients received a total of 186 cycles of therapy. The initial dose of irinotecan was 70 mg/m^2 in 19 patients. The dose was subsequently reduced to 60 mg/m^2 in 4 of these patients. Among the 8 patients who initially received irinotecan 60 mg/m^2, the dose was reduced to 50 mg/m^2 in 1. There was no difference in response between 70 mg/m^2 and 60 mg/m^2. In 179 cycles, irinotecan was administered on days 1 and 15 as scheduled. In 3 cycles the dose of irinotecan scheduled for day 1 was delayed. In 4 cycles the dose of irinotecan scheduled for day 15 was skipped.

Table 2
Adverse effects (n=27)

	Grade (%)				
Adverse effect	1	2	3	4	≥3
Leukopenia	2	10	10	4	14 (51.9)
Neutropenia	4	7	6	10	16 (59.3)
Thrombocytopenia	0	1	2	0	2 (7.4)
Anemia	1	3	10	0	10 (37.1)
Nausea	13	7	3	1	4 (14.8)
Vomiting	13	2	3	1	4 (14.8)
Diarrhea	6	1	2	0	2 (7.4)
Renal	0	0	0	0	0
Neurotoxicity	0	0	0	0	0
Infection	1	0	2	1	3 (11.1)
Febrile neutropenia	0	0	2	1	3 (11.1)
Secondary malignancy	–	–	0	1[a]	1 (3.7)

[a] Acute myeloid leukemia (AML).

The dose of oral etoposide was reduced in 8 (29.6%) of the 27 patients. All patients were in-patients during first cycle of treatment; after the first cycle 24 patients (88%) were out-patients.

Table 2 lists adverse effects according to the highest grade during treatment. The nadir of the neutrophil count was usually reached around day 15, with recovery in most patients by day 18. During the first course of treatment, G-CSF was administered to 6 patients (22.2%) who had grade 4 neutropenia, and in subsequent courses a total of 7 patients (25.9%) received G-CSF. The median duration of treatment with G-CSF was 5 days (range, 2–11 days).

One 64-year-old woman had grade 4 acute myeloid leukemia (AML; karyotype of M5) as a secondary malignancy after 10 treatment cycles. The white cell count rose to $277 \times 10^2/\mu L$ after 10 cycles, and bone marrow examination confirmed AML. Despite 2 cycles of cytarabine and idarubicin, complete remission was not achieved. The patient did not respond to subsequent treatment, including 1 cycle of mitoxantrone, etoposide and cytarabine (MEC), 2 cycles of cytarabine and aclarubicin and 1 cycle of aclarubicin, vincristine and daunorubicin, She died from acute respiratory failure of unknown cause 13 months after initial treatment.

Discussion

Despite therapeutic advances during the past 5 decades, culminating in the development of cytoreductive surgery followed by PT chemotherapy, more than 60% of patients with ovarian cancer die of recurrent disease. In patients with PT-refractory or resistant disease, the response rate remains between 15% and 20%, with median survival of only 8 months [22]. In this study, all patients received the first cycle of therapy on an in-patient basis, whereas 24 (88%) received subsequent cycles as out-patients. Thus, irinotecan plus oral etoposide maintained the patients' quality of life (QOL). Such treatments must achieve a balance between antitumor effectiveness and toxicity. The results of our pilot study, performed at 2 centers, suggest that combination therapy with irinotecan and oral etoposide produces high rates of objective responses in women with recurrent ovarian cancers, especially PT-resistant disease. Our results also demonstrated that this regimen is relatively well tolerated even in heavily pretreated patients who have received multiple chemotherapeutic agents, including platinum compounds and taxanes.

In this study, the RECIST criteria [20] were used to assess response in patients with measurable disease, and the GCIG CA-125 response criteria [17] were used in patients without measurable disease. Our overall objective response rate (44.4%) was high, given that disease resistance to prior chemotherapy was higher than that in most previous trials of second-line therapy for ovarian cancer. Of note, the non-progression (CP + PR + SD) rate was 85.1%. However, this study included seven patients who were sensitive relapse in the first-line and might produce higher response rate. Actually, the response rate might be lower in general population of platinum/taxanes resistance. A study by van der Burg et al. [23] reported response rates of 46%, 91% and 92% in patients who had progression at 0–4, 4–12 and >12 months, respectively, while receiving a combination of weekly cisplatin and oral etoposide. Meyer et al. [24] reported a response rate of 46% in patients who had progression within 6 months while receiving the same regimen.

The responses to irinotecan plus oral etoposide were durable, with a median TTP of 9 months, as compared with 2.8 to 4 months in studies of single-agent irinotecan [6,25,26]. Our results suggest that irinotecan and oral etoposide may have "supra-additive" or synergistic effects against ovarian cancer, consistent with the findings of *in vitro* studies [27].

The frequency of grades 3 and 4 neutropenia with our regimen of irinotecan plus oral etoposide was slightly higher than that of hematological toxicity reported for irinotecan alone, but all reactions could be managed successfully. The frequency of severe diarrhea, a toxic effect specific to irinotecan, was less than expected. In patients with metastatic platinum-resistant or-refractory ovarian cancer, Bodurka et al. [25] found that single-agent irinotecan at a dose of 300 mg/m^2 given every 3 weeks had an overall response rate of 17.2% and caused reversible >grade 3 neutropenia and diarrhea in 36% and 33% of patients, respectively. Matsumoto et al. [26] reported a response rate of 29% and reversible >grade 3 neutropenia and diarrhea in 17.8% and 10.7% of patients, respectively, during treatment with irinotecan 100 mg/m^2 on days 1, 8 and 15 of a 28-day cycle. The frequency of severe diarrhea caused by irinotecan can thus be reduced by modifying the treatment schedule. However, 17 patients were under 60 years old. Previous studies have found that older patients with ovarian cancer are less likely to receive intensive chemotherapy regimens [28–30], and in clinical practice there is often concern about the tolerability of cytotoxic agents in older patients. Thus, our regimen might be more toxic in the general population of women with ovarian cancer.

In 1 patient AML (M5) developed as a secondary malignancy after 10 cycles of treatment. Topoisomerase-II-related AML, initially noted as a therapy-related complication of childhood leukemia [31], is characterized by lack of a myelodysplastic phase, no dysplastic changes in diagnostic bone marrow specimens, a short latency period (usually less than 3 years), balanced chromosomal translocations involving 11q23 and variable chemosensitivity [32]. Rose et al. [1] reported that AML developed in 3 of 52 patients with ovarian cancer 16, 27 and 35 months after receiving a cumulative dose of 200 mg/m^2, 1200 mg/m^2 and 2400 mg/m^2, respectively. Rose et al. [33,34] also reported that AML developed in 1 patient with ovarian cancer after 10 courses of chemotherapy with oral etoposide (total dose, 16,550 mg) and 1 patient with uterine leiomyosarcoma after 7 courses of chemotherapy with oral etoposide (total dose, 7350 mg/m^2). These leukemias are characteristically related to the cumulative dose of etoposide and have a shorter latency period (median, 24 to 30 months) than the AMLs associated with alkylating agent therapy. Le Deley et al. [35] reported that the risk of AML was related to the cumulative dose of etoposide, with a particularly high risk at dose levels exceeding 6 g/m^2. The total dose of etoposide received by our patient who had AML was 10.5 g. Because the efficacy of continuous palliative treatment with etoposide is offset by its strong leukemogenicity when the total dose exceeds

6 g/m^2, we recommend that our regimen is not given for more than 6 cycles, even if the response is sustained.

Recurrent ovarian cancer, especially PT-resistant disease, is incurable. Single-agent therapy is therefore frequently used for disease management, attempting to maximize therapeutic response while minimizing toxicity. In patients with platinum-sensitive recurrent ovarian cancer, randomized studies have shown that carboplatin-based combination therapies are more effective than carboplatin alone [36]. In contrast, survival with combination chemotherapy has not been found to be superior to that with single-agent therapy in platinum-resistant ovarian cancer. The results of our study suggest that a combination of irinotecan and oral etoposide might extend survival and maintain the QOL of patients with chemoresistant ovarian cancer. Given that our subjects had PT-resistant recurrent ovarian cancers, the median survival time of 17 months appears very promising. However, we had initially planned to enroll 43 patients, but could not because of poor accrual. Moreover, the study was done at only two centers, and secondary leukemia developed in 1 patient after ten cycles. The small size of our study and the lack of a control group preclude us from concluding that irinotecan plus oral etoposide should be the treatment of choice for PT-resistant ovarian cancer. Well-designed phase II trials are needed to confirm the efficacy and toxicity of up to 6 cycles of irinotecan plus oral etoposide or to refute our findings. A nationwide multicenter phase II study is now being considered by the Japan Clinical Oncology Group (JCOG), a large cooperative group.

In conclusion, we believe our results, although preliminary, justify further studies of irinotecan plus oral etoposide in patients with PT-resistant ovarian cancer.

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ORIGINAL REPORT

Multicenter Phase II Study of Fertility-Sparing Treatment With Medroxyprogesterone Acetate for Endometrial Carcinoma and Atypical Hyperplasia in Young Women

Kimio Ushijima, Hideaki Yahata, Hiroyuki Yoshikawa, Ikuo Konishi, Toshiharu Yasugi, Toshiaki Saito, Toru Nakanishi, Hiroshi Sasaki, Fumitaka Saji, Tsuyoshi Iwasaka, Masayuki Hatae, Shoji Kodama, Tsuyoshi Saito, Naoki Terakawa, Nobuo Yaegashi, Masamichi Hiura, Atsuhiko Sakamoto, Hitoshi Tsuda, Masaharu Fukunaga, and Toshiharu Kamura

From the Japan Gynecologic Cancer Study Group, Tokyo; Department of Obstetrics and Gynecology, Kurume University, Kurume; Department of Obstetrics and Gynecology, Kyushu University; Department of Gynecology, National Kyushu Cancer Center, Fukuoka; Department of Obstetrics and Gynecology, University of Tsukuba, Tsukuba; Department of Obstetrics and Gynecology, Shinshu University, Matsumoto; Department of Obstetrics and Gynecology, University of Tokyo, Tokyo; Department of Gynecology, Aichi Cancer Center Hospital, Nagoya; Department of Obstetrics and Gynecology, Kashiwa Hospital, Jikei University, Kashiwa; Department of Obstetrics and Gynecology, National Kure Medical Center, Kure; Department of Obstetrics and Gynecology, Saga University, Saga; Department of Obstetrics and Gynecology Kagoshima City Hospital, Kagoshima; Department of Gynecology, Niigata Cancer Center, Niigata; Department of Obstetrics and Gynecology, Sapporo Medical University, Sapporo; Department of Obstetrics and Gynecology, Tottori University, Yonago; Department of Obstetrics and Gynecology, Tohoku University, Sendai; Department of Gynecology, National Shikoku Cancer Center, Matsuyama; Department of Pathology, Kyorin University, Mitaka; Department of Pathology, National Defense Medical College, Tokorozawa; and the Department of Pathology, Third Hospital, Jikei Medical University, Komae, Japan.

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Address reprint requests to Kimio Ushijima, MD, PhD, Department of Obstetrics and Gynecology, Kurume University School of Medicine, 67 Asahi-Machi, Kurume 830-0011, Japan; e-mail: kimi@med.kurume-u.ac.jp.

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ABSTRACT

Purpose
To assess the efficacy of fertility-sparing treatment using medroxyprogesterone acetate (MPA) for endometrial carcinoma (EC) and atypical endometrial hyperplasia (AH) in young women.

Patients and Methods
This multicenter prospective study was carried out at 16 institutions in Japan. Twenty-eight patients having EC at presumed stage IA and 17 patients with AH at younger than 40 years of age were enrolled. All patients were given a daily oral dose of 600 mg of MPA with low-dose aspirin. This treatment continued for 26 weeks, as long as the patients responded. Histologic change of endometrial tissue was assessed at 8 and 16 weeks of treatment. Either estrogen-progestin therapy or fertility treatment was provided for the responders after MPA therapy. The primary end point was a pathologic complete response (CR) rate. Toxicity, pregnancy rate, and progression-free interval were secondary end points.

Results
CR was found in 55% of EC cases and 82% of AH cases. The overall CR rate was 67%. Neither therapeutic death nor irreversible toxicities were observed; however, two patients had grade 3 body weight gain, and one patient had grade 3 liver dysfunction. During the 3-year follow-up period, 12 pregnancies and seven normal deliveries were achieved after MPA therapy. Fourteen recurrences were found in 30 patients (47%) between 7 and 36 months.

Conclusion
The efficacy of fertility-sparing treatment with a high-dose of MPA for EC and AH was proven by this prospective trial. Even in responders, however, close follow-up is required because of the substantial rate of recurrence.

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INTRODUCTION

Endometrial carcinoma (EC) in women younger than 40 years of age represents 2% to 14% of all cases. Obesity, ovarian dysfunction such as polycystic ovary (PCO) syndrome, and nulliparity are risk factors. Histologically, 90% of cases are well differentiated (grade 1 [G1]) endometrioid adenocarcinoma, frequently accompanied by endometrial hyperplasia.[1-4] The incidence of myometrial invasion and lymph node metastasis are rare.[5,6] Atypical endometrial hyperplasia (AH) is a precancerous lesion, and approximately 30% of the cases will progress to EC within several years.[7] The standard treatment for EC is staging laparotomy, including hysterectomy and bilateral salpingo-oophorectomy. The 5-year survival rate exceeds 93% in stage IA disease.[8] Thus, young patients with EC at stage IA are cured by the standard treatment in exchange for losing their fertility.

The conservative treatment for young women with EC and AH who desire to conceive has been a challenging issue. Some case reports have revealed that synthesized progestins such as medroxyprogesterone acetate (MPA) are effective as a conservative treatment of AH and G1 EC.[9-13] In our retrospective study, 15 of 18 women with AH and 9 of 12 women with G1 EC at presumed IA stage showed CR with MPA treatment.[9] Nevertheless, there have been no prospective trials to investigate the optimal dosage, duration of treatment, curative rate of MPA treatment, or pregnancy rate after this therapy in young

women with EC and AH. Therefore, we conducted a multicenter, prospective phase II study on MPA treatment.

PATIENTS AND METHODS

Sixteen institutions belonging to the Japan Gynecologic Cancer Study Group were registered. Eligible patients were between 20 and 39 years, had histologically confirmed AH or G1 EC at presumed stage IA, and desired to preserve fertility. Endometrial tissue sampling for diagnosis should be carried out by dilation and curettage (D&C). Other inclusion criteria were Eastern Cooperative Group performance status of 0 to 1, no prior treatment for endometrial lesion, body mass index (BMI) of less than 35, adequate hepatic and renal function, no abnormality in blood coagulation tests nor history of thromboembolism. All patients received pelvic magnetic resonance imaging before registration, and myometrial invasion or any extra uterine lesion was ruled out by institutional radiologist. The protocol was reviewed and approved by the institutional review board of each participating center, and all patients gave written informed consent before participation.

Treatment

Patients were scheduled to receive 600 mg of MPA with 81 mg of aspirin, orally on a daily basis for 26 weeks, followed by cyclic estrogen-progestin therapy for 6 months. If patients desired to conceive, fertility treatment was initiated immediately. If patients did not desire to conceive at that time, cyclic estrogen-progestin therapy was recommended to be continued until the patient desired to conceive.

Evaluation of Response and Follow-Up

The treatment schedule was summarized in Figure 1. Response was assessed histologically at 8 and 16 weeks of MPA treatment. Thickness of the endometrium was measured by transvaginal ultrasonography (TVUS) at 8 and 16 weeks. At 26 weeks of MPA treatment, hysteroscopy and endometrial curettage was performed for the final evaluation. The histologic diagnosis of all specimens obtained by D&C was made by central pathologic review (CPR), which consisted of three certified pathologists. Pathologic response to MPA treatment was categorized as complete response (CR), partial response (PR), no change (NC), and progressive disease (PD). CR was defined as the absence of any hyperplastic or cancerous lesion. PR was defined as residual lesion with degeneration and atrophy of endometrial glands. NC was defined as residual lesion without degeneration or atrophy of endometrial glands. PD was defined as the appearance of grade 2 (G2) or 3 EC. PD also was clinically defined when the endometrium showed larger than 20 mm of thickness measured by TVUS, or when myometrial invasion or extrauterine lesion were recognized. The protocol treatment was stopped and hysterectomy was recommended in the following situations: PD or NC at 8 weeks and PR or NC at 16 weeks in EC patients; PD at 8 weeks and NC or PD at 16 weeks in AH patients (Fig 1). Adverse effects were evaluated according to National Cancer Institute Common Toxicity Criteria version 2. The clinical course was followed-up for 3 years from the final patient enrollment in the study. Subsequent treatment after recurrence was not regulated. The Pearson χ^2 test and two sample t-test were employed for statistical analysis. Significance was held at the standard value of $P < .05$. The primary end point was the pathologic CR rate. Adverse effect, overall survival, progression-free interval (PFI), pregnancy rate, and recurrence rate were secondary end points. Hormone receptors were not examined in this study.

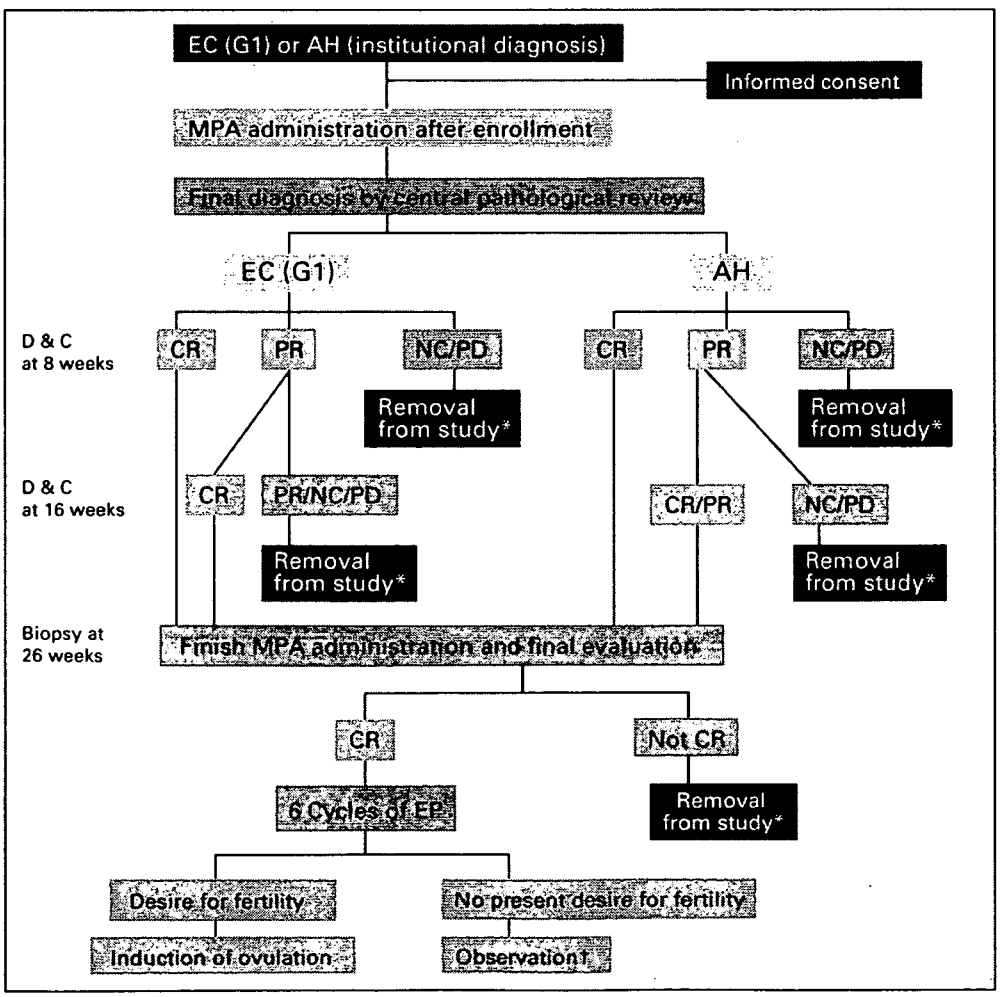

Fig 1. Study design. EC, endometrial carcinoma; G1, grade 1; AH, atypical endometrial hyperplasia; MPA, medroxyprogesterone acetate; D&C, dilation and curettage; CR, complete response; NC, no change; PD, progressive disease; EP, estrogen and progestin. (*) Hysterectomy is recommended in cases of removal from study. (†) Continuous Estrogen Progestin therapy is recommended in observation

RESULTS

Patient Characteristics

Although 47 patients were enrolled onto this study, two patients were excluded due to G2 EC by CPR diagnosis. The 45 eligible patients receiving MPA treatment consisted of 28 with EC and 17 with AH. All patients were nulligravida. The age of the patients ranged from 22 to 39 (mean 31.7 ± 2.8). BMI ranged from 16.0 to 32.7 (mean 22.8 ± 3.9). Twenty-seven of the 45 (60%) patients had a history of irregular menstrual period, and 7 of the 45 (16%) satisfied criteria for PCO syndrome (Table 1).

Histopathologic Diagnosis by CPR

Among the 47 patients, discrepancies in the histologic diagnosis between CPR and each institution before treatment were found in nine patients (Table 2). Seven patients were between the diagnosis of G1 EC and AH. Two cases were excluded from the study because CPR changed the diagnosis of G1 to G2. Thus, the rate of agreement between institutional and CPR diagnoses was 81%.

Response to MPA Treatment

Clinical response was summarized in Table 3. Among the 28 patients with EC, six voluntarily withdrew from this study and underwent hysterectomy before completion of the protocol treatment, even though they showed PR at 8 weeks. Among the 22 patients who completed the protocol treatment, 12 patients showed CR. Thus, the CR rate per protocol was 55% (12 of 22 patients). Three patients with EC who showed NC at 16 weeks underwent hysterectomy. Regarding the 17 AH patients, no one withdrew from the protocol. Fourteen of the 17 patients showed CR at 26 weeks. The CR rate for AH was 82% (14 of 17 patients). Accordingly, a total of 26 patients showed CR, and the CR rate per protocol was 67% (26 of 39 patients). Among the 26 patients with CR, six of 12 EC patients (50%), and nine of 14 AH patients (64%) showed CR at 8 weeks. Eleven of 12 EC patients (92%) and 12 of 14 AH patients (86%) showed CR at 16 weeks (Table 4). No patients with PD were recorded during the MPA treatment. There were no correlations between treatment response and clinical characteristics such as PCO and BMI.

Endometrial Thickness

Measurement of endometrial thickness using TVUS was available in 41 patients. Data were analyzed according to the final response to MPA treatment. Among the 27 EC patients, the endometrium during the treatment of 12 CR patients was significantly thinner than that of 15 PR or NC patients (ie, the endometrial thickness was 6.5 ± 3.5 mm at 8 weeks and 4.2 ± 1.4 mm at 16 weeks in CR patients). In PR and NC patients, it was 14.7 ± 9.3 mm at 8 weeks and 10.3 ± 6.8 mm at 16 weeks. Among the 14 AH patients, however, there was no remarkable difference in endometrial thickness between CR and non-CR patients. Among the 27 EC patients, 11 patients with an 8-week endometrial thickness thinner than pretreatment had a CR rate of 73% at 26 weeks. In contrast, 16 patients with an 8-week endometrial thickness thicker than pretreatment had a CR rate of only 25%.

Table 1. Patient Characteristics (N = 45)

Characteristic	Patients No.	%
Histology		
EC G1	28	62.2
AH	17	37.8
Age, years		
Mean	31.7 ± 2.8	
Range	22-39	
BMI		
Mean	22.8 ± 3.9	
Range	16.0-32.7	
Irregularity of period	27	60.0
PCO syndrome	7	15.6
Nulligravida	45	100

Abbreviations: G1, grade 1; EC, endometrial carcinoma; AH, atypical endometrial hyperplasia; BMI, body mass index; PCO, polycystic ovary.

Table 2. Comparison Between Institutional Diagnosis and CPR Diagnosis

Institutional Diagnosis	CPR Diagnosis	No. of Patients
AH	AH	12
	G1 EC	2
G1 EC	G1 EC	26
	AH	5
	G2 EC	2*

Abbreviations: CPR, central pathologic review; AH, atypical endometrial hyperplasia; G1, grade 1; EC, endometrial carcinoma; G2, grade 2.
*These cases were omitted from this study.

Adverse Effect

Body weight gain was the most remarkable toxicity; grade 3 in two patients and grade 2 in two patients. Liver dysfunction was found in five patients, including one patient with grade 3 and three patients with grade 2. Abnormality in blood coagulation tests was found in one patient (grade 1 for antithrombin III and fibrinogen). Neither thromboembolism nor treatment-related death was noted.

Pregnancy Outcome

Five patients (three EC and two AH) desired to continue further MPA treatment despite PR after 26 weeks of protocol treatment, and four of them (two EC and two AH) achieved CR by 3 to 6 months of additional treatment. Thus, the total number of CR patients was 30. Among them, 20 patients desired to conceive immediately, and 11 patients had 12 conceptions during the 3-year follow-up period, including one patient with additional MPA. There were seven normal, full-term deliveries, including two twin pregnancies and five spontaneous abortions. All 12 pregnancies, except one normal pregnancy and one abortion, were brought about by fertility treatment, and five of them were achieved by in vitro fertilization and embryo transfer

Table 3. Response to MPA

Response	EC (n = 22)* No.	%	AH (n = 17) No.	%
CR	12	55	14	82
PR	7	32	3	18
NC	3	14	0	0

NOTE. Overall CR rate is 67% (26 of 39 patients).
Abbreviations: MPA, medroxyprogesterone acetate; EC, endometrial carcinoma; AH, atypical endometrial hyperplasia; CR, complete response; PR, partial response; NC, no change.
*Six patients elected to drop out of the study.

Table 4. Treatment Period and CR Rate

	Weeks					
	8		16		26	
Histology	No.	%	No.	%	No.	%
EC, CR = 12	6	50	11	92	12	100
AH, CR = 14	9	64	12	86	14	100

Abbreviations: CR, complete response; EC, endometrial carcinoma; AH, atypical endometrial hyperplasia.

(IVF-ET) program. No remarkable maternal-fetal complications related to MPA treatment were found (Table 5).

PFI and Recurrence

During the follow-up period (25 to 73 months; median, 47.9 months), a recurrent lesion in the endometrium was found in 14 (47%) of the 30 patients, including eight (57%) of 14 EC and six (38%) of 16 AH. Median PFI was 34.6 months in EC and 44.2 months in AH. There was no statistical difference in either the recurrence rate or PFI between EC and AH. However, recurrence was seen in eight (73%) of 11 patients having anovulatory cycles during the observation period, whereas in only six (32%) of 19 patients having ovulatory cycles. In addition, recurrence was found in 11 (69%) of 16 patients who had an observation period without use of estrogen-progestin therapy or fertility treatment (2 to 52 months). Thus, patients who had anovulatory cycles or treatment-free periods had significantly higher rates of recurrence. After the diagnosis of recurrence, eight of 14 patients who still desired fertility were treated by MPA treatment again. Six of them showed an initial disappearance of lesion, but lesion recurred in five patients. Throughout the observation period, one patient developed an extrauterine lesion. She had achieved CR at 26 weeks of the protocol treatment, and then received MPA therapy three more times for repeated recurrences. Exploratory laparotomy at 2 years after the initial MPA treatment revealed peritoneal carcinomatosis. Pathologic study of the samples from the peritoneum and surface of the resected ovary revealed G2 endometrioid adenocarcinoma without papillary serous carcinoma element. The patient died of disease 4 months after surgery. The disease was speculated as synchronous malignancies of both endometrial and peritoneal carcinomas because there was no endometrial malignancy 3 months before the development of the peritoneal lesions.

Pathology of Surgical Specimens

Total abdominal hysterectomy was performed on 19 patients, including 14 patients who failed to reach CR by the protocol MPA treatment and five patients who achieved CR but subsequently developed recurrence. The ovary was preserved in nine patients (six bilateral and three unilateral). Sampling from pelvic and/or para-aortic lymph nodes was performed in 11 patients. Among them, three AH patients were included, and G1 EC was found in two of their hysterectomy specimens. Minimal myometrial invasion of smaller than 5 mm was identified in seven patients. Small malignant lesions in the ovary were identified in two patients (G1 endometrioid adenocarcinoma). Lymph node metastases were not recognized in any patients.

DISCUSSION

As the number of younger women with EC has increased, fertility-sparing treatment has received much attention. Since the early 1980s, there have been several reports on conservative treatment with progestins for early-stage endometrial cancer in young women. Most of them were small series and retrospective studies from single institutions. Response rates and recurrence rates varied[9-13] (ie, the response rate for EC and AH ranged from 57% to 76% and 83% to 92%, respectively, and the recurrence rate ranged from 11% to 50%). Such variations were probably due to the differences in drugs used, dosage, and duration of treatment. Daily doses of megestrol acetate ranged between 10 and 400 mg, and that of MPA ranged between 200 and 800 mg. In our previous multicenter retrospective study, 600 mg of MPA revealed a higher response rate than those of 400 and 200 mg.[9] Therefore, our prospective study was conducted to clarify the accurate CR rate of treatment with MPA at a fixed dose of 600 mg/d for 26 weeks, and has demonstrated that the CR rate for EC and AH was 55% and 82% respectively, and the recurrence rate was 57% and 38%, respectively. Among the patients who achieved CR, approximately half of

Table 5. Pregnancy Outcome

Patient No.	Age (years)	Histology	PCO Syndrome (Y/N)	Ovulation Induction	Outcome	Complication
1	31	AH	N	CLM	NTVD, spontaneous abortion	Free
2	28	AH	N	CLM/hMG/hCG	NTVD	Free
3	33	AH	Y	hMG/hCG IVF-ET	C/S	Twin pregnancy
4	29	AH	N	hMG/hCG	NTVD	Free
5	35	EC	N	hMG/hCG IVF-ET	C/S	Twin pregnancy, PIH
6	33	EC	N	hMG/hCG IVF-ET	NTVD	Free
7	32	EC	N	Free	NTVD	Free
8	35	AH	N	CLM IVF	Spontaneous abortion	
9	31	AH	N	hMG/hCG IVF-ET	Spontaneous abortion	
10	28	AH	N	CLM	Spontaneous abortion	
11	37	EC	N	hMG/hCG IVF-ET	Spontaneous abortion	

Abbreviations: PCO, polycystic ovary; Y, yes; N, no; AH, atypical endometrial hyperplasia; CLM, clomifene citrate; NTVD, normal transvaginal delivery; hMG, human menopausal gonadotrophin; hCG, human chorionic gonadotropin; IVF-ET, in vitro fertilization and embryo transfer; C/S, cesarian section; EC, endometrial carcinoma; PIH, pregnancy-induced hypertension.

them were diagnosed as CR at 8 weeks, and 92% of them were CR at 16 weeks of treatment. There were eight patients who were considered as CR for the first time at 16 weeks. Some histologic change corresponding to PR was recognized from all of their 8-week D&C specimens. These results must be distinguished from nonresponders. Meanwhile, nonresponders at 8 weeks can hardly have a chance to achieve CR.

The most serious toxicity of MPA was thought to be thromboembolism. In this study, however, no patients suffered from thromboembolism, including six obese patients with a BMI of more than 30. Cotreatment of 600 mg of MPA with 81 mg of aspirin was considered safe up to 26 weeks.

Another important problem in conservative therapy was the lack of confidence in the pathologic diagnosis on endometrial tissue. A Gynecologic Oncology Group study revealed concurrent EC was found in 42.6% of the hysterectomy specimens of the patients diagnosed as AH by endometrial biopsy in the community hospital.[14] Kaku et al[9] reported 10 pathologic discrepancies among 39 patients with G1 EC and AH. Thus, substantial numbers of AH cases might be included in the previous studies of conservative treatment for EC. However, in this study, all the specimens for initial diagnosis were obtained by D&C. CPR was conducted by the same pathologists as in the previous retrospective study.[9] These factors brought accurate diagnoses and contributed to the difference in the CR rate between EC and AH. Among three AH patients who received hysterectomy, EC was found in the hysterectomy specimens of the two patients. Nevertheless, one patient was refractory to MPA and hysterectomy was carried out at 7 months after the initial diagnosis, and the other patient underwent hysterectomy at recurrence after 9 months of remission. Most researchers will agree that the indication for fertility-sparing treatment is restricted to presumed IA stage. Nevertheless, the diagnostic accuracy of myometrial invasion by imaging studies is limited. In detecting myometrial invasion by magnetic resonance imaging, the rate of accuracy varied between 68% and 82%.[15] CT scan failed to identify myometrial invasion in 39% of patients.[16] This study also showed that seven of 19 patients who underwent hysterectomy had minimal myometrial invasion. Therefore, we should recognize that a small number of patients with EC having myometrial invasion will be included in the fertility-sparing treatment protocol. We had four more patients who achieved CR after an additional 3 to 6 months of MPA treatment following 26 weeks of treatment. It might be acceptable if only for the PR patients to continue MPA treatment for an additional 6 months. Nevertheless, longer-term hormonal treatment cannot be warranted for poor responders.

The present study has shown the usefulness of TVUS for assessment of the response to MPA treatment. TVUS studies demonstrated that good responders of EC had an endometrium statistically thinner than that of poor responders at both 8 and 16 weeks. In addition, thinner endometrium at 8 weeks than at pretreatment predicted CR at 26 weeks with 73% possibility, whereas CR will be obtained in only 25% of cases with thicker endometrium at 8 weeks than at pretreatment. Therefore, observation of endometrial thickness by TVUS during MPA treatment had a predictive value for responders. On the other hand, there were no correlations between the response to MPA and the endometrial thickness at pretreatment, or other clinicopathologic characteristics such as PCO or BMI, indicating the difficulty in the selection of ideal patients suitable for this treatment.

Conception is the ultimate goal of fertility-sparing treatment. Nevertheless, young patients with EC tended to have fertility problems. Case reports showed that most EC patients who successfully conceived after conservative treatment underwent infertility therapy, including assisted reproductive technologies.[17,18] Jadoul and Donnez reported[19] that 55% of 17 pregnancies after progestin treatment were brought on by IVF. In this series, 11 of 12 pregnancies were brought about using infertility therapy, including five cases by IVF-ET, suggesting that immediate infertility treatment is recommended for patients in this setting.

Even in responders, EC subsequently developed recurrence with a considerably high incidence.[9,11,12] Patients who desire to conceive should have ovulatory induction, and those who do not wish to conceive should be treated by cyclic estrogen-progestin therapy. Recent reports have revealed that levonorgestrel IUD well suppressed a hyperplastic endometrium.[20] Although, the efficacy of progestin IUD for EC remains unclear, it may be an alternative to estrogen-progestin therapy during the observation period for patients who do not desire to conceive at that moment. On the other hand, longer-term or repeated hormonal treatment should be avoided, as patients with EC younger than 40 years were reported to have a two to seven times higher risk for ovarian carcinoma or peritoneal carcinomatosis than those at older ages.[21,22] In fact, we encountered two patients with ovarian lesion considered as synchronous malignancy, and another patient who developed peritoneal carcinomatosis 2 years after initial MPA treatment.

Our multicenter prospective study showed fertility-sparing treatment with MPA to be an effective therapy with the least toxicities for young patients with AH and those with G1 EC at presumed IA stage. Nevertheless, EC lesions may recur at a considerably high frequency, and patients may develop synchronous malignancy in the ovary or peritoneum, which clearly indicates that a patient's excessive anticipation of fertility preservation may threaten her life. Patients should be informed of the risks and limitations of this conservative treatment. The validity of prophylactic hysterectomy and bilateral adnexectomy for those patients who have elected to stop bearing children is still uncertain. Further investigation is needed for the application of this procedure.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Hiroyuki Yoshikawa
Administrative support: Kimio Ushijima
Provision of study materials or patients: Kimio Ushijima, Hideaki Yahata, Hiroyuki Yoshikawa, Ikuo Konishi, Toshiharu Yasugi, Toshiaki Saito, Toru Nakanishi, Hiroshi Sasaki, Fumitaka Saji, Tsuyoshi Iwasaka, Masayuki Hatae, Shoji Kodama, Tsuyoshi Saito, Naoki Terakawa, Nobuo Yaegashi, Masamichi Hiura
Collection and assembly of data: Kimio Ushijima, Hideaki Yahata, Toshiharu Yasugi, Toshiaki Saito, Toru Nakanishi, Hiroshi Sasaki, Fumitaka Saji, Tsuyoshi Iwasaka, Masayuki Hatae, Shoji Kodama, Tsuyoshi Saito, Naoki Terakawa, Nobuo Yaegashi, Masamichi Hiura
Data analysis and interpretation: Kimio Ushijima, Hideaki Yahata, Hiroyuki Yoshikawa, Ikuo Konishi, Atsuhiko Sakamoto, Hitoshi Tsuda, Masaharu Fukunaga, Toshiharu Kamura
Manuscript writing: Kimio Ushijima, Toshiharu Kamura
Final approval of manuscript: Hideaki Yahata, Hiroyuki Yoshikawa, Ikuo Konishi, Toshiharu Kamura

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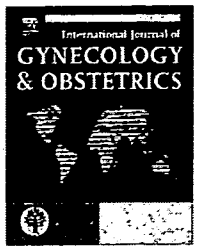

CLINICAL ARTICLE

Surgical treatment for neuroendocrine carcinoma of the uterine cervix

T. Kasamatsu [a,*], Y. Sasajima [b], T. Onda [a], M. Sawada [a], T. Kato [a], M. Tanikawa [a]

[a] *Division of Gynecology, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan*
[b] *Division of Diagnostic Pathology, National Cancer Center Hospital, Tokyo, Japan*

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Abstract

Objective: To identify the best operative approach for neuroendocrine cervical carcinoma (NECC). *Methods:* The records of surgically treated patients with stages IB to IIB NECC were reviewed. *Results:* Of 10 patients who met the study criteria for NECC and underwent radical hysterectomy, 4 had pT1bN0, 4 had pT1bN1, 1 had pT2aN0, and 1 had pT2bN1 disease. Those with pT1bN1 or pT2bN1 disease received postoperative adjuvant radiotherapy and/or chemotherapy, and recurrence occurred in 7 patients (70%). Among these 7 patients, 5 (71%) had a primary NECC tumor with deep stromal invasion and 5 (71%) had extrauterine disease (parametrium and/or lymph node). The recurrences in 6 patients (86%) were located outside the pelvis (lung, liver, or brain). Stromal invasion was 6 mm or less in the 3 patients who did not experience disease recurrence. *Conclusions:* Pelvic control by radical hysterectomy may not be beneficial for patients with NECC except for those with an early invasive lesion.

1. Introduction

Neuroendocrine carcinoma arising from the uterine cervix is an uncommon malignancy comprising less than 5% of all cervical malignancies [1]. Histopathologically, neuroendocrine cervical carcinoma (NECC) resembles small cell carcinoma of the lung and is classified as small cell carcinoma of the cervix in the World Health Organization International Histologic Classification of Tumors. It is noted for its very aggressive behavior and has the poorest prognosis of the various cervical carcinomas, even after multimodal therapy. In a recent study, the 5-year survival rate of patients with International Federation of Gynecologists and Obstetricians (FIGO) stage IB1 disease was between 50% and 60%, which was significantly poorer than the 90% rate for patients with stage IB1 squamous cell carcinoma [2]. In that study, none of the patients whose disease was more extensive than stage IB1 or who had clinical evidence of lymph node metastasis survived

* Corresponding author. Tel.: +81 3 3542 2511; fax: +81 3 3542 3815.
E-mail address: Takasama@ncc.go.jp (T. Kasamatsu).

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their disease. It has been suggested that the poor outcome in patients with NECC is due to early and frequent metastasis.

Owing to the rarity of NECC, no multicenter study has been conducted on the disease and the optimal initial therapeutic approach has not been clarified. On the other hand, in patients with stages IB to II cervical carcinoma of the ordinary histologic type, radical hysterectomy followed by adjuvant pelvic radiation is the standard surgical approach. Radical hysterectomy has also been employed for the treatment of NECC. The present retrospective study was carried out to assess the efficacy of surgical treatment for NECC; establish a framework for designing new therapeutic strategies; and improve prognosis.

2. Patients and methods

The medical records and pathologic materials of 2096 patients with cervical carcinoma who were treated at the Gynecology Division and Diagnostic Pathology Division of the National Cancer Center Hospital in Tokyo, Japan, between 1980 and 2004 were reviewed. The study criteria were the following: having a lesion that fulfilled the histologic criteria for neuroendocrine carcinoma according to the WHO International Histologic Classification of Tumors and the Armed Forces Institute of Pathology; having stage IB to IIB disease; and having undergone primary radical hysterectomy. Patients in whom only a portion of the tumor showed neuroendocrine features were excluded. The biopsy materials were immunohistochemically stained for keratin, carcinoembryonic antigen, chromogranin, synaptophysin, and neuron-specific enolase (NSE). For this study, a gynecologic pathologist re-examined all hysterectomy materials. All patients were staged according to the 1994 FIGO staging system. Those treated before 1994 were retrospectively restaged based on their clinical records and pathologic findings.

Every 2 to 6 months, the patients found to be asymptomatic after the primary radical hysterectomy underwent a pelvic examination and a chest radiograph, and had a cervical smear taken and tumor markers measured (chiefly, NSE). Symptomatic patients then underwent appropriate examinations by ultrasound, computed tomography, and/or magnetic resonance imaging. Follow-up continued through March 2006. Survival curves were obtained by the Kaplan–Meier method.

3. Results

Among the 2096 patients with cervical carcinoma, 10 met the study criteria and were diagnosed as having pure NECC. Their median age was 41 years (range, 28–61 years) and median follow-up time (or time to death) was 25 months (range, 8–204 months). No patient was lost to follow-up. Eight patients had FIGO stage IB1 disease, one had stage IB2, and one had stage IIB. Table 1 shows the clinical characteristics of the 10 patients. All underwent radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. All tumors were completely removed. Adjuvant radiotherapy or chemotherapy was administered to the 5 patients in whom lymph node metastasis or parametrial invasion was diagnosed from the surgically resected materials. Two of these 5 patients received radiotherapy to the whole pelvis and the para-aortic field, for a total dose of 45 to 50 Gy; 1 received radiotherapy to the whole pelvis alone; and the remaining 2 were treated with a chemotherapy regimen (one was treated with a combination of cisplatin, doxorubicin, and cyclophosphamide and the other with cisplatin and etoposide).

Eight patients had stage pT1b disease and 2 patients had stage pT2 disease. Lymph node metastasis was found in 4 (50%) and lymph-vascular space invasion was found in 7 (88%) of the 8 patients found from the surgically resected materials to have stage pT1b disease. The primary lesions of the 2 patients with stage pT2 disease showed lymphovascular invasion.

Disease recurred in 7 patients (70%) at a median interval of 8 months following initial surgery (range, 4–26 months). Of these 7 patients, 6 (86%) died at a median interval of 16 months after the onset of recurrence despite aggressive multimodal therapy (systemic chemotherapy, radiation, and surgery). For the 10 patients, the cumulative 5-year survival rate was 43% and the median survival time was 29 months. The disease-free survival rate was 50% at 24 months and 30% at 36 months.

In the 3 patients in whom disease did not recur, the primary tumor was an early invasive lesion of 6 mm or less (3, 5, and 6 mm, respectively). In the 7 patients in whom disease recurred, it was a deeply invasive lesion (median, 19 mm [range, 6–40 mm]). Pelvic lymph node metastasis was found in the surgically resected materials of 1 (33%) of the 3 patients with no recurrence and in 4 (57%) of the 7 patients with recurrence.

Table 1 Clinical characteristics of the patients with NECC and their status

Patient no.	Postsurgical stage	Tumor size, mm		Adjuvant therapy	Initial failure sites	Status (no. of months)
		Depth	Length			
1	pT1b1N0	3	14	None	NA	NED (29)
2	pT1b1N0	5	40	None	NA	NED (122)
3	pT1b1N0	15	28	None	Liver, lung	DOD (65)
4	pT1b1N0	18	29	None	Pelvic wall	DOD (18)
5	pT1b1N1	6	20	Radiotherapy	Liver, lung	DOD (29)
6	pT1b1N1	6	38	Chemotherapy	NA	NED (204)
7	pT1b1N1	20	24	Radiotherapy	Liver	DOD (8)
8	pT1b2N1	40	80	Radiotherapy	Liver, lung	DOD (22)
9	pT2aN0	10	20	None	Pelvic wall, PALN	DOD (22)
10	pT2bN1	25	50	Chemotherapy	Pelvic wall, Brain	AWD (21)

Abbreviations: AWD, alive with disease; DOD, dead of disease; NA, not applicable; NED, no evidence of disease; PALN, para-aortic lymph node.

The initial recurrence sites were located outside the pelvis in 6 (86%) of these 7 patients and in the pelvic sidewall of the remaining patient. In the 9 patients with distant metastasis the most frequent site was the liver (in 4 patients [44%]), followed by the lung (in 3 [33%]), the brain (in 1 [11%]), and para-aortic lymph nodes (in 1 [11%]).

4. Discussion

NECC has the poorest prognosis of the various cervical carcinomas owing to early and frequent metastasis. Because of the rarity of the disease, no large-scale multicenter study has been performed and the optimal initial therapeutic approach to NECC has not been determined. Radical hysterectomy, which is the standard surgical procedure for stages IB to II cervical carcinoma of the ordinary type, has been adopted for the treatment of NECC. Sevin et al. [3] reported a 5-year survival rate of 36.5% for patients with stages IB to IIA NECC who underwent radical hysterectomy followed by adjuvant chemotherapy, compared with 71.6% for patients with cervical carcinoma of other histologic subtypes. At our institute, the cumulative 5-year survival rate was 43% for patients with stages IB to IIB NECC, whereas it was 84%, 78%, and 65%, respectively, for stages IB, IIA, and IIB cervical carcinoma of the ordinary type [4]. The traditional surgical approach therefore does not appear to be effective in patients with NECC.

Using as search words *small cell carcinoma* and *uterine cervix* as well as *neuroendocrine carcinoma*, we conducted a Medline search of the articles on NECC published in English from January 1976 to July 2006, selecting those reporting on more than 5 patients and specifying both sites of recurrence and outcomes. This literature provided information on a total of 49 patients, including our own, who underwent radical hysterectomy for stages IB to IIB disease. The clinical

Table 2 Outcome and patterns of recurrence in patients with neuroendocrine cervical carcinoma who underwent radical hysterectomy

Author	No. of patients	Adjuvant therapy (no. of patients)	No. of recurrent sites	Status (no. of patients)
Perrin and Ward [12]				
IB	4	Chemoradiotherapy (n=4)	Locoregional (n=2)	NED (n=1)
IIA	1	None (n=1)	Lung (n=2)	DOD within 12 months (n=4)
			Liver (n=1)	
			Brain (n=1)	
			Thoracic spine (n=1)	
Chang et al. [13]				
IB	19	Chemotherapy (n=23)	Locoregional (n=5)	NED (n=13)
			Lung (n=5)	DOD within 10 months of recurrence
II	4		Liver (n=5)	(n=10)
			Brain (n=3)	
			Distant node (n=3)	
			Bone (n=2)	
			Kidney (n=2)	
			Breast (n=1)	
			Spleen (n=1)	
			Adrenal gland (n=1)	
Viswanathan et al. [2]				
IB	6	Chemotherapy (n=4)	Locoregional (n=2)	NED (4)
		None (n=2)	Distant node (n=1)	DOD (2)
			Liver (n=1)	
			Bone (n=1)	
			Breast (n=1)	
Tsunoda et al. [14]				
IB	3	Chemotherapy (n=2)	Locoregional (n=1)	NED (n=2)
IIB	2	Radiotherapy (n=2)	Lung (n=1)	DOD within 16 months (n=3)
		None (n=1)	Liver (n=1)	
			Brain (n=1)	
			Kidney (n=1)	
Present study				
pT1b	8	Chemotherapy (n=2)	Locoregional (n=3)	NED (n=3)
pT2	2	Radiotherapy (n=3)	Liver (n=4)	AWD (n=1)
		None (n=5)	Lung (n=3)	DOD within 65 months (n=6)
			Distant node (n=1)	
			Brain (n=1)	

Abbreviations: AWD, alive with disease; DOD, dead of disease; NED, no evidence of disease.

characteristics of these 49 patients are summarized in Table 2. Forty patients (82%) had stage IB or pT1b disease; 31 (63%) received adjuvant chemotherapy; 9 (18%) received radiotherapy or chemoradiotherapy; and the remaining 10 (20%) did not receive adjuvant therapy. Fourteen patients were treated with combination chemotherapy using vincristin, doxorubicin, and cyclophosphamide alternating with cisplatin and etoposide; 8 were treated with cisplatin, vinblastin, and bleomycin; 3 were treated with cisplatin and etoposide; and 3 were treated with cisplatin, doxorubicin, and etopocide. Recurrence occurred in 26 patients (53%) and 25 patients (51%) died of the disease. Among those in whom disease recurred, 23 (88%) had extrapelvic metastasis. Of the 45 distant sites of recurrence, the most frequently reported were the lung (27%) and liver (27%), followed by a distant node (11%), and the brain (13%). Based on these findings, the development of widespread hematogenous metastasis is the most important pattern in NECC, and controlling hematogenous spreading should be a top priority in the attempt to improve the survival of patients with this type of cervical carcinoma.

In comparison, the prognosis for patients with cervical squamous cell carcinoma who are treated with radical hysterectomy is good. Recurrence develops in 10% to 15% of patients with stages IB or IIA disease who undergo radical hysterectomy, with or without postoperative radiation of the whole pelvis [5]. Following radical hysterectomy, the difference in outcome among patients with squamous cell carcinoma and those with NECC may be due to differences in the biologic behavior of the carcinomas. In patients with NECC, pelvic control alone usually does not lead to a good outcome because of the high incidence of distant metastasis in the early stage.

Lymphedema and bladder dysfunction develop in almost all patients who undergo radical hysterectomy [6]. Morbidities associated with radical hysterectomy include chronic bladder dysfunction (in 3% of patients), ureterovaginal or vesicovaginal fistula (in 1%–2%), lymphocele formation (in 5%), small bowel obstruction (in 1%), pulmonary embolism (in 1%–2%), injury to the obturator or genitofemoral nerve, and blood loss requiring transfusion [7]. These complications may interfere with systemic postoperative adjuvant therapy for the control of distant metastasis. Thus, radical hysterectomy does not appear to be beneficial in patients with NECC, and indications for this treatment should be limited.

In the present study, the stromal invasion of the primary tumor was 6 mm or less in patients who did not experience recurrence and a median of 19 mm in those who experienced recurrence. The incidence of pelvic lymph node metastasis was higher among patients who experienced recurrence than in those who did not. And 2 series of meta-analyses demonstrated that the presence of lymph node metastasis was the most important factor for a poor prognosis [8,9]. Viswanathan et al. [2] reported that none of their patients with clinical evidence of lymph node metastasis survived their disease. In patients with NECC, radical hysterectomy may be indicated only in cases of early invasive lesion with no lymph node metastasis.

Theoretically, to reduce the incidence of widespread distant metastasis after hysterectomy, adjuvant systemic chemotherapy is indicated. As no large-scale, multicenter study has been conducted with patients diagnosed as having NECC, no optimal regimen has been established for treating the disease. A regimen originally developed for the treatment of small cell carcinoma of the lung, which includes cisplatin and etoposide, has been tried. Although several studies have suggested the combination of cisplatin and etoposide to be beneficial, they reported on small numbers of patients [8,10,11]. Multicenter randomized controlled trials are needed.

In conclusion, pelvic control by radical hysterectomy does not appear to be generally beneficial for patients with NECC, and it should be limited to those with an early invasive lesion without obvious lymph node metastasis. Rather, nonradical hysterectomy followed by new, aggressive adjuvant chemotherapy may be considered following surgery.

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