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Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅳ. 研究成果の刊行物・別刷

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Clinicopathologic manifestations of early-onset endometrial cancer in Japanese women with a familial predisposition to cancer

Wataru Yamagami†, Nobuyuki Susumu†, Kouji Banno, Takeshi Hirao, Fumio Kataoka, Akira Hirasawa, Nao Suzuki, Daisuke Aoki and Shiro Nozawa

Department of Obstetrics and Gynecology, Keio University School of Medicine, Tokyo, Japan

Abstract

Aim: The number of patients under 40 years of age with early-onset endometrial cancer is on the rise in Japan. Preservation of fertility in younger patients is a critical issue. In order to examine the clinical and pathological characteristics of these patients, cases of early-onset endometrial cancer at a single hospital were analyzed.

Methods: Seventy-four patients were diagnosed with endometrial cancer before age 40 and included in this study after obtaining informed consent.

Results: The clinical characteristics included a significantly higher prevalence of complications such as nulligravidity and nulliparity ($P < 0.001$). Pathologically, well-differentiated endometrial carcinoma was significantly more frequent ($P = 0.011$). The 5-year survival rate was high (98.7%). In regards to the relationship between clinicopathological features and grade of differentiation, the prevalence of G2 and G3 carcinoma was not significantly lower ($P = 0.24$) in patients with obesity. Although the frequency of G2 and G3 carcinoma was significantly higher in patients with a family history of cancer ($P = 0.02$), their 5-year survival rate was not significantly lower (100%).

Conclusion: This study found that these two types of early-onset endometrial cancer are clinicopathologically different. In patients with a family history of cancer, their body mass index was lower, and the frequency of G2 and G3 carcinoma was significantly higher, but their 5-year disease-free survival rate was not significantly lower.

Key words: endometrial cancer, family history of cancer, HNPCC, obesity.

Introduction

Recently, the number of patients with endometrial cancer has increased in Japan.[1] Dietary changes to the Western lifestyle, resulting in excessive fat intake and leading to obesity, are cited as primary causes of this increase.[2,3] Similarly, the prevalence of premenopausal endometrial cancer has also increased. As endometrial carcinoma occurs at a high frequency in patients with hereditary non-polyposis colorectal cancer (HNPCC), it has been suggested that some endometrial cancers are familial, indicating a predisposition to cancer, attracting significant attention to young patients.[1,4,5] Although different pathways are thought to underlie endometrial carcinogenesis, the detailed mechanisms of carcinogenesis remain poorly understood. The

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Reprint request to: Dr Wataru Yamagami, Department of Obstetrics and Gynecology, Keio University School of Medicine, Shinanomachi 35, Shinjuku-ku, Tokyo 160–8582, Japan. Email: y_gami@msc.biglobe.ne.jp

†These two authors contributed equally to this work.

definition of early-onset endometrial cancer is not consistent in published reports (under ages 40, 45 or 50).[2,6–13] Most reports, however, define early-onset endometrial cancer as occurring before age 40. It has been reported that early-onset endometrial cancer is generally estrogen-dependent, is a well-differentiated endometrioid adenocarcinoma, and, if treated in early stages, has a favorable prognosis.[2,6–8,10–13] Some reports reveal that about half of the patients have never been pregnant, due to infertility from complications of polycystic ovarian syndrome (PCOS) or ovulation disorder.[6,14]

At present, surgical hysterectomy is the primary treatment for endometrial cancer. As the number of patients with endometrial cancer has been traditionally low in Japan and endometrial cancer occurs most frequently after menopause, total hysterectomy is relatively acceptable for those patients. At the present time, however, due to the increase in early-onset endometrial cancer and the etiologic characteristics frequently leading to complications of infertility, the preservation of fertility has to be taken into serious consideration in an increasing number of cases. Therefore, therapeutic methods, such as hormone (progesterone) therapy, that enable preservation of the uterus have been examined. As the efficacy of hormone therapy is not high, 62% of the patients who choose this therapy at our hospital have recurrence.[15] Fertility preservation alone is not a sufficient reason for choosing this method of treatment, therefore necessitating the development of new treatment methods.[6,16,17]

To examine whether early-onset endometrial cancer, which we define as having an onset before 40 years of age, can be further divided clinicopathologically, we analyzed the clinical and pathological manifestations in 74 cases of early-onset endometrial cancer.

Methods

Of 780 endometrial cancer patients who were treated at Keio University Hospital from 1975 to 2001, 74 patients (age 25–39 years, 34.1 ± 3.6 years) were diagnosed before age 40 with early-onset endometrial cancer and were examined after obtaining informed consent.

The diagnosis of endometrial cancer was made by pathological identification of malignant tissue in the endometrium. The surgical stage, histological type and tumor differentiation were classified according to the criteria of the 1988 International Federation of Gynecology and Obstetrics (FIGO). For some cases in which surgery was not performed, clinical staging was also performed by transvaginal ultrasound, magnetic resonance imaging (MRI) and computed tomography (CT). Clinical characteristics were determined on initial physical examination and history at the time of hospitalization. Obesity was defined as a body mass index (BMI; weight/height^2) of greater than 25, which is the criterion of the Japanese Society for the Study of Obesity, at the time of the initial physical examination. Polycystic ovary (PCO) was considered present when a large number of ovarian follicles were observed by ultrasound or pathological examination of surgical samples. The patient was considered to have a positive family history of hereditary non-polyposis colon cancer (HNPCC)-associated cancer when more than one member within second relatives had had colorectal, endometrial, small intestinal, ureteral or renal cancer, which are included in the new Amsterdam criteria for HNPCC, along with gastric or breast cancer, which are reported to be associated with HNPCC.[18,19] Breast cancer occurs in some women with a germline mutation of the *hMSH6* gene, one of the genes responsible for HNPCC.[20]

Statistical significance was determined by the chi-squared test. The 5-year survival rate was calculated by the Kaplan–Meier method and significance was determined by the generalized Wilcoxon method.

Results

The total number of endometrial cancer patients appeared to increase at our hospital over the years, as did early-onset endometrial cancer (data not shown). The age distribution of endometrial cancer patients is shown in Figure 1. The mean age of onset for

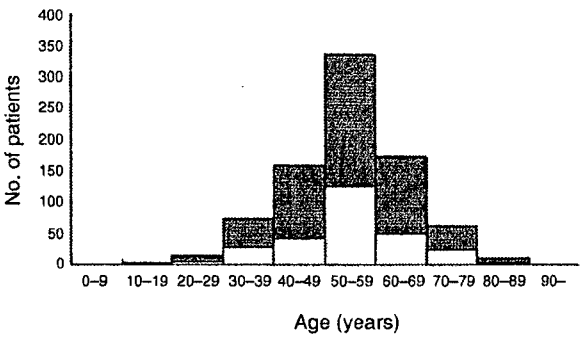

Figure 1 Age at onset of endometrial cancer. The mean age of onset of endometrial cancer was 54 years for both groups with and without a family history of hereditary non-polyposis colorectal cancer-associated cancer.

endometrial cancer was 54.2 ± 10.6 years (range 25–87 years), and was similar for patients with a familial predisposition to cancer (mean 53.8 ± 10.2 years, range 25–80 years). Of these cases, 74 patients were under the age of 40 (22 patients with a familial predisposition to cancer), accounting for 9.5% of the total (9.8% of the patients with a familial predisposition to cancer).

Clinicopathological manifestations of endometrial cancer were compared between patients over age 40 and patients under age 40.

In early-onset endometrial cancer (Figs 2 and 3), the percentage of FIGO stage I cancers was higher (73%). More cases (66%) had a grade 1 (G1) differentiation and fewer cases (3%) had grade 3 (G3) of poor differentiation. Hysterectomy was chosen as a common treatment in many cases of endometrial cancer. However, there was a large number of younger cases, 23%, in which methoxyprogesterone acetate (MPA) treatment was selected to preserve fertility (Fig. 4). The 5-year survival rate in early-onset endometrial cancer was better than in the group of patients 40 years or older (Fig. 5), but the survival rate in FIGO stage I was not significantly different between the two groups (Fig. 6). Most of early-onset endometrial cancer was early cancer, Stage I, therefore the prognosis was good.

Clinical manifestations of early-onset endometrial cancer are shown in Table 1. The prevalence of nulligravidity and nulliparity was significantly higher ($P < 0.001$) in younger patients compared to patients over age 40. The younger patients had a significantly

Table 1 Clinical manifestations of early-onset endometrial cancer in patients aged <40 years and those aged ≥40 years

Clinical items	<40 years (%)	≥40 years (%)	*P*-value
Nulligravidity	71.2 (52/73)	19.2 (131/681)	<0.001*
Nulliparity	83.6 (61/73)	25.6 (172/681)	<0.001*
Spontaneous abortion	6.9 (5/72)	16.8 (114/679)	0.030**
Induced abortion	12.3 (9/73)	28.8 (196/681)	0.003**
Family history of cancer	30.1 (22/73)	29.8 (202/678)	0.951
Double cancer	13.0 (7/54)	15.2 (71/468)	0.667
Obesity	30.0 (21/70)	27.0 (172/638)	0.588

*$P < 0.01$, **$P < 0.05$.

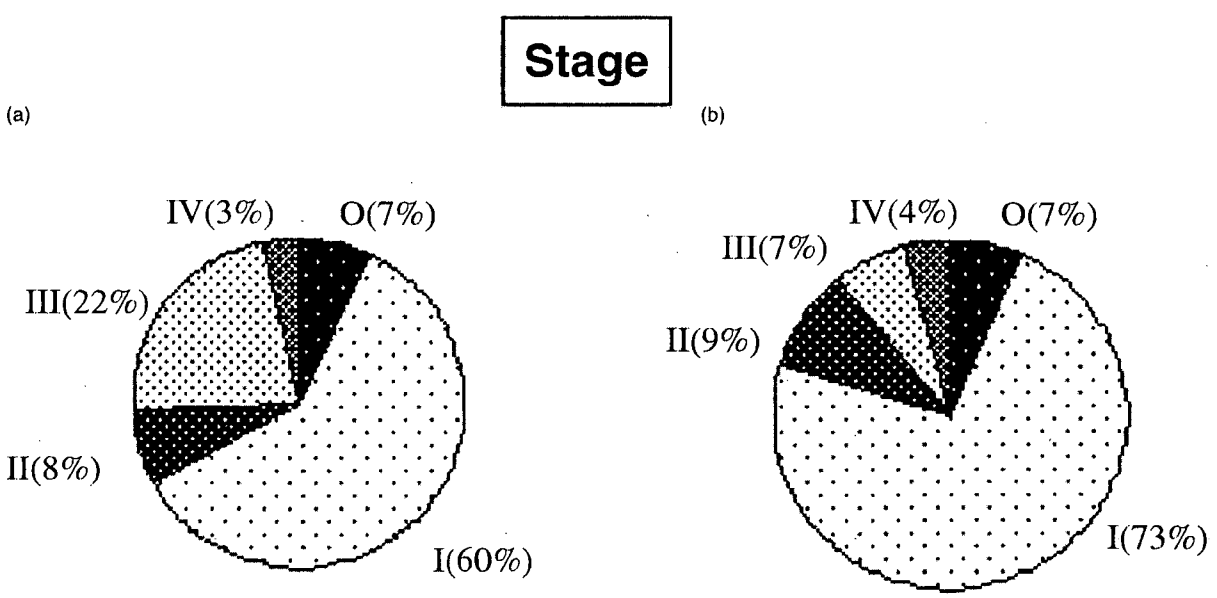

Figure 2 Clinicopathologic characteristics of early-onset endometrial cancer. Clinical stages are shown. (a) Patients ≥40 years old; (b) patients <40 years. There are more early stage tumors of FIGO stage I in early-onset endometrial cancer patients under 40 years.

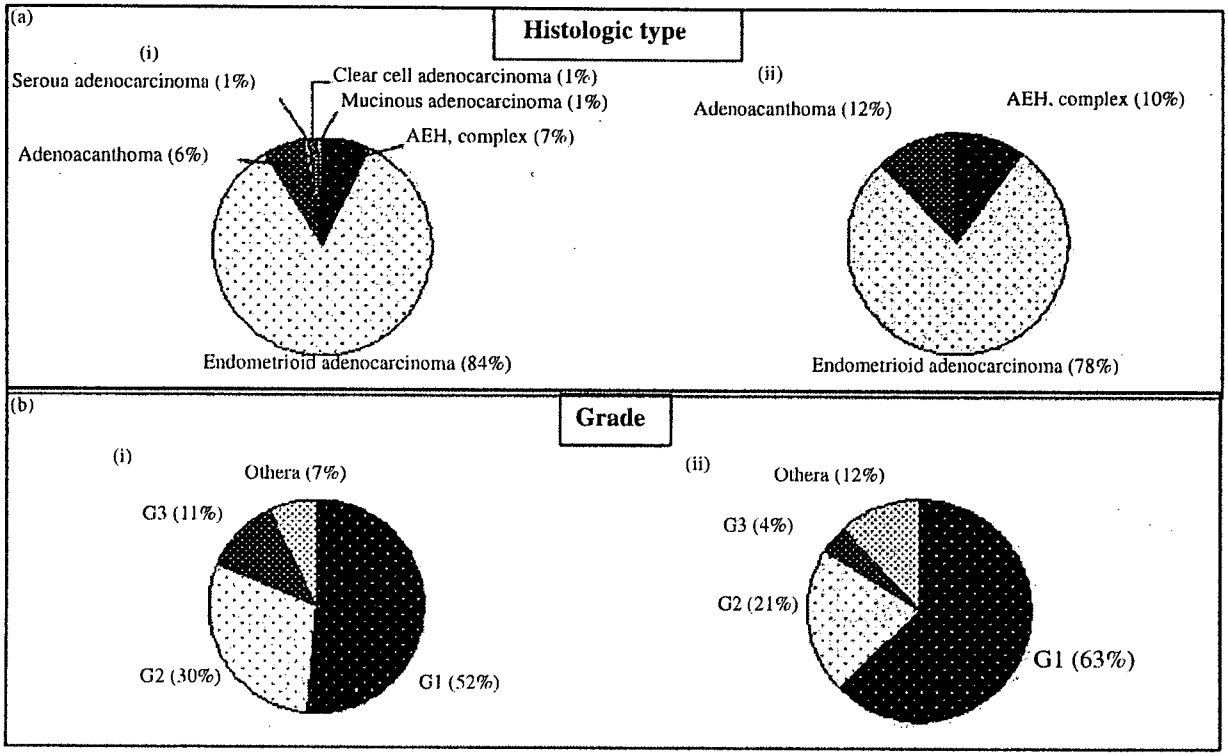

Figure 3 Clinicopathologic characteristics of early-onset endometrial cancer. (a) Histologic type and (b) differentiation grade. (i) Patients aged ≥40 years; (ii) patients aged <40 years. There are more endometrioid adenocarcinomas and well-differentiated tumors in early-onset endometrial cancer patients aged <40 years.

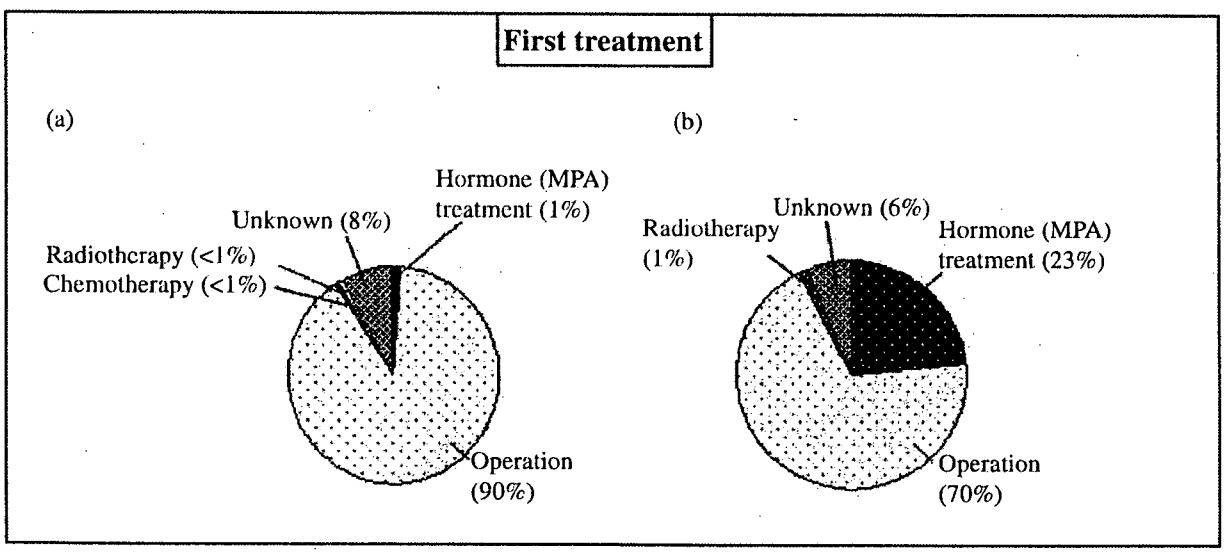

Figure 4 First treatment choice for early-onset endometrial cancer. The first treatment carried out for endometrial cancer in patients (a) ≥40 years and (b) <40 years. Hormone (progesterone) treatment was chosen more frequently for early-onset cancer.

lower prevalence of miscarriage or abortion ($P < 0.05$). Table 2 shows the pathological characteristics of early-onset endometrial cancer. In younger patients, there was a significantly lower prevalence of FIGO stage III and IV ($P = 0.015$), a significantly higher prevalence of well-differentiated endometrial carcinoma ($P = 0.011$), and a significantly lower prevalence of myometrial invasion, vessel permeation and lymph node metastasis ($P < 0.05$). There was no significant difference in adnexal metastasis or cervical invasion ($P = 0.94$ and 0.22).

The relationship of prognostic factors to the FIGO surgical stage and grade of differentiation was analyzed to examine prognostic factors in early-onset endometrial cancer. Although there were no significant relationships among obesity, PCO and surgical stage, grade of differentiation, the prevalence of poorly differentiated carcinoma appeared to be significantly higher ($P = 0.02$) in patients with a familial predisposition to cancer (Table 3). In addition, we analyzed the relationship between the patients with a familial predisposition to cancer and BMI. The prevalence of poorly differentiated carcinoma tended to be higher in patients with a familial predisposition to cancer associated with low BMI ($P = 0.05$) (Table 4).

However, in terms of prognostic factors, we found that the 5-year survival rate was favorable whether or not the patients had a family history of HNPCC-associated cancer (100% vs. 98%) although G2 and G3 carcinomas were more frequent in the patients with a family history of HNPCC-associated cancer. The 5-year survival rate was 100% in G2 and G3 carcinomas with a family history of HNPCC-associated cancer.

Discussion

Endometrial carcinoma has been classified into two types. One is an estrogen-dependent type that becomes cancerous following continuous proliferation of the endometrium induced by chronic exposure to estrogen. The other is an estrogen-independent type that develops into atrophic endometrium. It is known that the estrogen-dependent type occurs in relatively younger patients and is well-differentiated with a

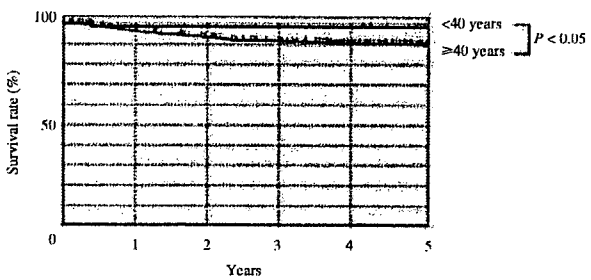

Figure 5 Five-year survival rate for early-onset endometrial cancer. The 5-year survival rate in early-onset endometrial cancer was better for patients aged <40 years than those aged ≥40 years (Kaplan–Meier analysis).

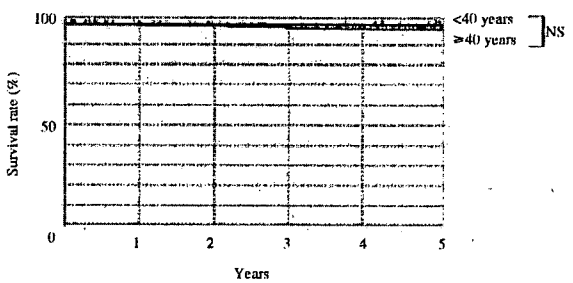

Figure 6 Five-year survival rate for early-onset endometrial cancer in early stage tumors of FIGO stage I. The survival rate in FIGO stage I was not significantly different between patients aged <40 years and those aged ≥40 years (Kaplan–Meier analysis). NS, not significant.

Table 2 Pathologic manifestations of early-onset endometrial cancer in patients aged <40 years and those aged ≥40 years

Pathologic items	<40 years (%)	≥40 years (%)	*P*-value
Stage III–IV	11.0 (8/73)	23.4 (165/705)	0.015*
Differentiation (G2, G3)	25.7 (19/74)	40.9 (282/690)	0.011*
Muscle invasion $>^1/_2$	4.5 (3/66)	28.2 (195/691)	<0.001**
Vessel permeation	3.2 (2/63)	29.0 (196/675)	<0.001**
Lymph node metastasis	1.5 (1/66)	8.7 (61/704)	0.041*
Adnexal metastasis	10.3 (7/68)	10.0 (70/700)	0.938
Cervical invasion	10.6 (7/66)	16.3 (115/704)	0.223
Positive cytodiagnosis	45.1 (32/71)	58.8 (399/678)	0.025*

*$P < 0.05$, **$P < 0.01$.

Table 3 Relationship between the FIGO clinical stage and the cancer differentiation grade in early-onset endometrial cancer in patients with a familial predisposition to cancer

Clinical items	*n*	Stage III and IV		Grade 2 and 3	
		% (*n*)	*P* value	% (*n*)	*P*-value
Obesity					
Positive	21	9.5 (2)	0.61	14.3 (3)	0.24
Negative	49	6.1 (3)		26.5 (13)	
Polycystic ovary					
Positive	36	11.1 (4)	0.21	16.7 (6)	0.26
Negative	32	3.1 (1)		28.1 (9)	
Family history of cancer					
Positive	22	13.6 (3)	0.58	40.9 (9)	0.02*
Negative	51	9.8 (5)		15.7 (8)	

*$P < 0.05$.

Table 4 Body mass index of poorly differentiated tumors in early-onset endometrial cancer in patients with a familial predisposition to cancer

BMI	*n*	Grade 2 and 3 (%)		*P* value
		Positive predisposition	Negative predisposition	
<20	19	62.5 (5/8)	18.2 (2/11)	0.048*
>20	54	28.5 (4/14)	15.0 (6/40)	0.261
>25	21	20.0 (1/5)	12.5 (2/16)	0.676
Total	73	40.9 (9/22)	15.7 (8/51)	0.019*

*$P < 0.05$.

favorable prognosis, and that the estrogen-independent type occurs in older patients.[6,21,22] Recently, endometrial cancer with a genetic background has been reported in cases of HNPCC, and an abnormality of a DNA mismatch repair gene is considered to be a causative factor.[1,23–25] In addition to colorectal cancer, the following are frequently observed within the family of an HNPCC patient: endometrial cancer, ureteral cancer, renal cancer, small intestinal cancer and breast cancer.[6,26]

In the present study, we examined the clinicopathological characteristics of 74 patients with early-onset endometrial cancer. We found that well-differentiated, FIGO stage I carcinoma with a favorable prognosis was more frequently observed in early-onset endometrial cancer compared to that in patients over age 40. These results suggest that most early-onset carcinomas in younger patients are estrogen-dependent. As complications of nulligravidity and nulliparity are often observed clinically in patients with early-onset endometrial cancer, abnormal female hormones appear to be associated with its carcinogenesis. Although hysterectomy was the initial treatment of choice, fertility preservation is a primary concern in many younger patients, and there are many cases in which progesterone therapy is performed in consideration of the early stage of the disease.

Pathological analysis of early-onset endometrial cancers shows that the frequency of myometrial invasion, vessel permeation and lymph node metastasis is low. However, there is no significant difference in cancer progression such as cervical invasion and ovarian metastasis compared to cases over the age of 40. Based on the results of this study, careful consideration toward preservation of the ovaries in surgery for early-onset endometrial cancer is essential, and ovarian biopsy, by unilateral oophorectomy or contralateral wedge resection, may be desirable.

Pathological characteristics were compared in separate groups based on the clinical background of early-onset endometrial cancer: one group with obesity and one with a familial predisposition to cancer. Well-differentiated carcinoma tended to be more frequent in the group with obesity. There are reports showing an association of obesity or PCO with endometrial carcinogenesis in a chronic estrogen-stimulated condition.[27–29] In obesity, the aromatase activity in fat tissue converts ovarian- and adrenal gland-derived androgen to estrone, generating a chronic estrogen-stimulated condition. In PCO, estrogen is secreted continuously, without progesterone secretion, due to anovulation. In both cases therefore it has been suggested that carcinogenesis originates from endometrial hyperplasia following hypertrophy of the endometrium, and well-differentiated carcinoma is frequently observed. These are known to be the common mechanisms of carcinogenesis for early-onset endometrial cancer.

In contrast, it has been suggested that early-onset endometrial cancer in patients with a familial predisposition to cancer may be caused by a different

mechanism of carcinogenesis, because poorly differentiated carcinomas tend to be more frequent. As these patients tend to have a low BMI, this type of endometrial cancer cannot be explained by estrogen-dependent carcinogenesis. There were more cases of poorly differentiated early-onset endometrial cancer with lower BMI (thin patients), 5/8 cases (63%) with BMI < 20, so we suggest that early-onset endometrial carcinogenesis is related to genetic factors, except estrogen-dependent factors. However, the prognosis is not so poor in patients with a familial predisposition to cancer. It is interesting that frequent development of poorly differentiated tumors and favorable prognosis are reported in endometrial cancer associated with HNPCC.[25,30] In HNPCC, it is also reported that lymphocyte infiltration is significantly more frequent in the tumor tissue, suggesting that activation of cellular immunity may contribute to a favorable prognosis.[25,31-33] As some cases of early-onset endometrial cancer with familial predisposition to cancer may be caused by DNA mismatch repair gene mutations as in HNPCC, the favorable prognosis could result from a similar mechanism to that in HNPCC. Another report showed that infiltration of CD8+ lymphocytes into tumors was also involved with prognosis in endometrial cancer[34] and lymphocyte infiltration was frequently found in microsatellite instability (MSI)-positive tissues of endometrial cancer from our patients.[15]

Progesterone therapy, which is a potential therapy for fertility preservation in early-onset endometrial cancer, could be effective for estrogen-stimulated tumors, whereas its efficacy could be different for cases with a family history of cancer, because of different mechanisms of carcinogenesis. This could be one factor contributing to the limited efficacy of progesterone therapy against endometrial cancer. Currently, there are many reports concluding that fertility-preserving therapy is not appropriate in poorly differentiated endometrial carcinomas.[3,17] However, our study suggests that some cases of poorly differentiated carcinomas in early-onset endometrial cancer could show a favorable prognosis depending on the clinical background. This study suggested that the clinicopathological manifestations of early-onset endometrial cancer could be useful information in predicting the prognosis. Therefore, early-onset endometrial cancer should be divided into subgroups based on these clinicopathological manifestations, and therapeutic efficacy against early-onset endometrial cancer could be further improved by selecting the treatment according to the clinicopathological manifestations.

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Phase II trial of docetaxel in advanced or metastatic endometrial cancer: a Japanese Cooperative Study

N Katsumata*[,1], K Noda[2], S Nozawa[3], R Kitagawa[1], R Nishimura[4], S Yamaguchi[4], D Aoki[3], N Susumu[3], H Kuramoto[5], T Jobo[5], K Ueki[6], M Ueki[6], I Kohno[7], K Fujiwara[7], Y Sohda[8] and F Eguchi[8]

[1]Department of Medical Oncology, National Cancer Center Hospital, 104-0045 Tokyo, Japan; [2]Kinki University, Osakasayama, Japan; [3]Department of Obstetrics and Gynecology, School of Medicine, Keio University, 160-8582 Tokyo, Japan; [4]Department of Gynecology, Hyogo Medical Center for Adults, 673-8558 Akashi, Japan; [5]Department of Obstetrics and Gynecology, Kitasato University, 228-8555 Sagamihara, Japan; [6]Department of Obstetrics and Gynecology, Osaka Medical College, 569-8686 Takatsuki, Japan; [7]Department of Obstetrics and Gynecology, Kawasaki Medical School, 701-0192 Kurashiki, Japan; [8]Department of Obstetrics and Gynecology, Aso Iizuka Hospital, 820-8505 Iizuka, Japan

The purpose of this study was to determine whether docetaxel has antitumour activity in patients with advanced or recurrent endometrial carcinoma. Chemotherapy-naïve or previously treated patients (one regimen) with histopathologically documented endometrial carcinoma and Eastern Cooperative Oncology Group performance status ⩽2 entered the study. Docetaxel 70 mg m^{-2} was administered intravenously on day 1 of a 3-week cycle up to a maximum of six cycles. If patients responded well to docetaxel, additional cycles were administered until progressive disease or unacceptable toxicity occurred. Of 33 patients with a median age of 59 years (range, 39–74 years) who entered the study, 14 patients (42%) had received one prior chemotherapy regimen. In all, 32 patients were evaluable for efficacy, yielding an overall response rate of 31% (95% confidence interval, 16.1–50.0%); complete response and partial response (PR) were 3 and 28%, respectively. Of 13 pretreated patients, three (23%) had a PR. The median duration of response was 1.8 months. The median time to progression was 3.9 months. The predominant toxicity was grade 3–4 neutropenia, occurring in 94% of the patients, although febrile neutropenia arose in 9% of the patients. Oedema was mild and infrequent. Docetaxel has antitumour activity in patients with advanced or recurrent endometrial carcinoma, including those previously treated with chemotherapy; however, the effect was transient and accompanied by pronounced neutropenia in most patients.

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Most patients with endometrial cancer are diagnosed at an early stage when surgery alone may result in cure. However, the outcome for women with advanced stage or recurrent disease is poor and rarely curable. Both single-agent and combination regimens of chemotherapy have been studied in women with advanced endometrial carcinoma. Currently, no standard chemotherapy regimen for endometrial cancer exists, but single-agent doxorubicin is active, with responses observed in up to one-third of previously untreated patients (Moore *et al*, 1991). Other single agents with modest activity include cisplatin (Thigpen *et al*, 1984a, 1989) and carboplatin (van Wijk *et al*, 2003). Although the response rates with the combination doxorubicin–cisplatin appear to be higher than those achieved with either agent alone, there is no evidence that survival is any longer with combination therapy. In the Gynecologic Oncology Group (GOG) trial comparing doxorubicin alone with doxorubicin–cisplatin, the response rates and progression-free survival were better with the combination regimen (42 *vs* 25%, 5.7 *vs* 3.8 months, respectively), but overall survival (OS) had not significantly improved (Thigpen *et al*, 2004).

*Correspondence: Dr N Katsumata; E-mail: nkatsuma@ncc.go.jp
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The taxanes, paclitaxel and docetaxel, are potent chemotherapeutic agents that block tubulin depolymerisation, leading to the inhibition of microtubule dynamics, and have significant clinical efficacy for various solid tumours. Paclitaxel has been evaluated as an active agent for endometrial cancer (Ball *et al*, 1996; Lissoni *et al*, 1996; Lincoln *et al*, 2003). However, preclinical data show that docetaxel has increased potency and an improved therapeutic index compared with paclitaxel (Bissery *et al*, 1995), and its short 1-h infusion time offers a substantial clinical advantage over the prolonged infusion durations required with paclitaxel. Docetaxel and paclitaxel also have substantially different toxicity profiles. In particular, docetaxel has a significant lower incidence of neurotoxicity in comparison to paclitaxel (Hsu *et al*, 2004).

The present phase II trial was designed to evaluate the clinical efficacy and tolerability of docetaxel 70 mg m^{-2} in patients with advanced or recurrent endometrial cancer.

PATIENTS AND METHODS

Eligibility criteria

Eligible patients aged between 20 and 74 years, with a life expectancy in excess of 3 months, and Eastern Cooperative

Oncology Group (ECOG) Performance Status (PS) of 0–2 had histologically documented primary stage III, IV or recurrent endometrial carcinoma. Tumours were staged according to the International Federation of Gynecology and Obstetrics criteria. All patients had measurable disease according to the response evaluation criteria in solid tumours (RECIST) (Therasse *et al*, 2000). Measurable lesions defined unidimensionally were $\geqslant 20$ mm using conventional imaging, or $\geqslant 10$ mm with spiral computed tomographic scan. Patients were either chemotherapy-naivé or had received one prior chemotherapy regimen for endometrial cancer, with 4 weeks between prior therapy and study treatment. Prior treatment with a taxane was not allowed. Adequate organ function was required for study entry: neutrophil count $\geqslant 2000\,\mu l^{-1}$, platelet count $\geqslant 100\,000\,\mu l^{-1}$, haemoglobin $\geqslant 9.0\,g\,dl^{-1}$, serum bilirubin level $\leqslant 1.5\,mg\,dl^{-1}$, normal hepatic function (asparate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels $\leqslant 2.5$ times upper limit of the institutional normal (ULN)), serum creatinine level $\leqslant 1.5\,mg\,dl^{-1}$, PaO_2 $\geqslant 60$ mmHg and normal electrocardiogram. Patients with any of the following conditions were excluded from the study: sarcoma component, active infection, severe heart disease, interstitial pneumonitis, past history of hypersensitivity, peripheral neuropathy, malignant or benign effusions requiring drainage, active brain metastasis, or active concomitant malignancy. All patients gave informed consent before entering this study, which was approved by the institutional review boards at all participating institutions.

Treatment schedule

Docetaxel $70\,mg\,m^{-2}$ was infused over a 1–2-h period. The treatment was repeated every 3 weeks unless there was documented disease progression or unacceptable toxicity. Prophylactic medications for nausea, vomiting or hypersensitivity reactions were given if these symptoms occurred. No routine premedication was given for hypersensitivity reactions and fluid retention during the first cycle of treatment. The patient's physician identified all hypersensitivity reactions and, if deemed necessary, the investigator administered premedication drugs.

Treatment was delayed for up to 3 weeks in the event of toxicity, but was restarted when the neutrophil count was $\geqslant 1500\,\mu l^{-1}$, platelet count $\geqslant 100\,000\,\mu l^{-1}$, AST/ALT/ALP levels $\leqslant 2.5$ times ULN, and neuropathy or oedema $\leqslant$ grade 1. Docetaxel dosage was reduced by $10\,mg\,m^{-2}$ if febrile neutropenia occurred, if there was bleeding with grade 3–4 thrombocytopenia requiring a platelet transfusion, or if a patient experienced any grade 3–4 nonhaematologic toxicities except nausea, vomiting, anorexia, fatigue, alopecia or hypersensitivity.

Response and toxicity evaluation

The tumour response was assessed according to the standard RECIST criteria (Therasse *et al*, 2000). Target lesions included all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total. Complete response (CR) was defined as the complete disappearance of all target and nontarget lesions, with no development of new disease. Partial response (PR) was defined as a reduction by $\geqslant 30\%$ in the sum of the longest diameter of target lesions. Complete response or PRss were confirmed by repeat assessments performed no less than 4 weeks after the criteria for response were first met. Progressive disease (PD) was defined as an increase by $\geqslant 20\%$ in the sum of the longest diameter of all target lesions, or the appearance of one or more new lesions and/or unequivocal progression of existing, nontarget lesions. Stable disease (SD) was defined as neither sufficient lesion shrinkage to qualify for a PR, nor sufficient increase to qualify for PD. Best response was defined as the most CR achieved by a patient (thus, each patient had a single best response: CR, PR, SD or PD), and the date of best response was the date it was first detected. Time to progression (TTP) was defined as the time from the first medication to the date of a PD event or death (due to endometrial cancer or study drugs). All tumours were radiographically assessed for response every 6 weeks. An independent response review committee (IRRC) evaluated all tumour responses after the investigators had completed their judgement.

Toxicities were evaluated with respect to incidence and severity using National Cancer Institute common toxicity criteria (NCI-CTC, version 2.0) (Trotti *et al*, 2000).

Statistical consideration

Assuming a response rate of 20%, the study was designed with 80% power such that the lower limit of the 95% confidence interval (CI) for the estimate of the response rate was greater than 0.05. A sample size of 32 evaluable patients was required.

The primary end point was overall tumour response (determined by the IRRC) with the corresponding 95% CI using the exact binominal method for the evaluable population. The secondary end point of this study was safety. The Kaplan–Meier (KM) method was used to determine the TTP and median survival time (MST) in the evaluable population.

RESULTS

Patient characteristics

A total of 33 patients were enrolled on the study from April 2001 to October 2003 and one patient was unevaluable as a result of having received prior treatment with paclitaxel and doxorubicin–platinum regimens. The median age of the intent to treat (ITT) population ($n=33$) was 59 years (range 39–74) and 70% patients had ECOG PS 0 (Table 1). Several patients had unfavourable histologic characteristics: adenosquamous features (three) and uterine papillary serous cancers (two). Most patients (88%) had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy, and one-third of patients had prior radiotherapy. Of those patients who had received prior chemotherapy ($n=14$), 10 had received combination doxorubicin–platinum in combination, three had received platinum alone and one had received oral fluorouracil. All 33 patients were evaluated for toxicity and survival, while 32 patients were evaluated for response and TTP.

Treatment delivery

Overall, 32 patients received a total of 133 cycles of docetaxel and the median number of cycles of docetaxel was four (range, 1–13). Five patients (15%) experienced dose reductions for the following reasons: two patients experienced febrile neutropenia (in one patient this occurred twice) and three patients had grade 3 nonhaematologic toxicities: diarrhoea (occurred twice in one patient), hyperglycaemia, hyperkalaemia and supraventricular tachycardia.

Response

Table 2 presents the assessment of response to treatment. Two patients, one who was chemotherapy-naïve and the other who had received prior therapy, were not assessable for response because they had received only one cycle of treatment. Before evaluation by the IRRC, primary physicians had reported two CRs and nine PRs. The IRRC judged one CR as a PR, two PR as SD and one SD as a PR. Therefore, the overall response rate for 10 of 32 patients was 31% (95% CI, 16.1–50.0%). Of 13 patients who had prior chemotherapy, three (23%) achieved a PR: two had received doxorubicin–platinum and one platinum alone. The histologic analysis revealed responses among the following tumour types: