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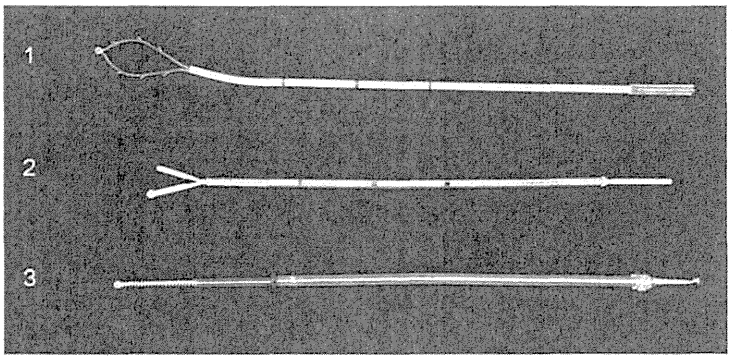

Fig. 6. Three different sampling instruments were used. 1 = Soft Cyto (Soft Medical Co. Ltd.); 2 = Endocyte (Laboratoire CCD); 3 = Honest Uterine Brush (Honest Medical Co. Ltd.).

the number of controls yielded a specificity of 98.5%. Since the median age of the controls was 12 years below that of the cancer patients, we tested for age bias in the controls by splitting them into two groups (<60 and ≥60 years) and calculated the specificity for each of the two groups. Both groups had nearly identical values: 98.5 and 98.8%, respectively. Other splits using different age thresholds yielded similar results, thus ruling out any meaningful age bias in the control group.

Discussion

In this study of histologically confirmed cases, the sensitivity of cytology for detecting endometrial cancer was 88.8%, and the specificity for identifying a normal endometrium was 98.5%. The relationships between the clinical data on endometrial cancer and the cytological results were also examined. To the best of our knowledge, this is the largest study of its kind, and it provides basic data for the evaluation of endometrial cytology.

There have been several reports concerning the accuracy of endometrial cytology for endometrial cancer. Bistoletti et al. [6] reported that 40 cases were diagnosed by endometrial cytology in 42 uterine cancer patients and they showed a sensitivity of 95%. LaPolla et al. [7] reported that the sensitivity of the EndPap sampler was 90% (59 of 66 endometrial cancer cases were accurately diagnosed). Byrne [8] reported that the sensitivity of the Endocyte sampler was 92% (11 of 12 endometrial cancer cases were accurately diagnosed). The sensitivity found in the present study was slightly lower than those found in previous reports, but it may represent a more authentic value because first results were analyzed separately in a much larger number of cases. In a screening setting, first results are important. Early-stage carcinomas tend to be small and localized compared to those in advanced stages, which increases the likelihood that the sampling instrument does not make sufficient contact with the tumor to gather an ample amount of carcinogenic cells from the specimen. Furthermore, the morphology of well-differentiated endometrioid adenocarcinoma cells is roughly comparable to that of normal endometrial cells.

Either of these situations leads to a heightened possibility of a false-negative diagnosis. Our sensitivity findings indicate that 11.2% of endometrial cancer cases would be missed if endometrial cytology were the only test used in the screening setting. We have determined that the possibility of misdiagnosing endometrial cancer by cytology alone exists primarily due to three factors: bleeding where excessive erythrocytes mask cancer cells, infection where excessive leukocytes mask cancer cells, and insufficient cells where there are so few cells in the specimen that cancer cells present in the endometrium are mostly absent in the specimen (data not shown). Without uniform guidelines to the contrary, these cases are often

reported as negative. However, in all such cases, further testing in a timely manner should be considered essential. The present data suggest that endometrial cytology shows a relatively high, but not ideal, sensitivity for endometrial cancer.

Alternatives

The evaluation of endometrial histology by biopsy is still the standard for determining the status of the endometrium [9]. Stovall et al. [10] showed a sensitivity of 97.5% for preoperative histological diagnoses with a Pipelle for 40 patients with uterine cancer. Other reports, which evaluated 176 cases including cancer and noncancer patients, showed a high agreement rate between Pipelle and D&C results, and if endometrial information was obtained by ultrasound, the sensitivity and the specificity was 92 and 96%, respectively [11].

On the other hand, limitations to biopsied endometrial histology have also been reported. Guido et al. [12] reported a relatively low sensitivity (83%) of Pipelle biopsy in 65 endometrial cancer patients. The authors concluded that the tumors localized to a polyp or small area of the endometrium may go undetected by the instrument. Buccoliero et al. [13] found that cytology provided sufficient material more often than biopsy, and showed the benefit of endometrial liquid-based cytology. Furthermore, a low correlation rate between D&C and Pipelle biopsy of 79% for histological diagnosis was reported in 127 cancer and noncancer patients [14]. Kondo et al. [15] noted that the combination of histological diagnosis and cytology showed the highest detection rate. These data suggest that endometrial biopsy has some limitations for clinical usage, and there are negative opinions with respect to the use of these instruments in screening for endometrial cancer [16, 17].

The findings of transvaginal ultrasound, such as endometrial thickness and irregularity, are also important for the detection of endometrial cancer. Vuento et al. [18] reported screening results with transvaginal ultrasound for 1,074 asymptomatic postmenopausal women, using a cutoff value of 4 mm double-layer endometrial thickness. The authors found 3 endometrial cancer patients among 313 cases with values above the cutoff value and reported that the sensitivity and the specificity for endometrial cancer was 100 and 71%, respectively. Another study showed that, in cases of postmenopausal bleeding, an endometrial thickness >5 mm on transvaginal ultrasound displayed a 7.3% risk of endometrial cancer, whereas this risk was only 0.07% if the endometrial thickness was ≤5 mm [19]. However, the usefulness of transvaginal ultrasound for screening remains controversial. The cost to discover one endometrial cancer by transvaginal ultrasound is estimated to be 1.5–2 times that for breast cancer screening [20]. Another report showed that there is no prognostic advantage for asymptomatic endometrial cancer patients screened by transvaginal ultrasound compared with symptomatic patients with bleeding [21]. These data suggest that transvaginal ultrasound, like other methods, has its limitations in screening for endometrial cancer.

Based on these findings, cytological screening for endometrial cancer in Japan is offered to high-risk women and is called 'selective screening'. Cervical cancer screening by cervical cytology is called 'mass screening', because this screening is offered biannually to all women over 20 years of age under the Japanese national health insurance program. At the time of cervical screening, if a participant complains of abnormal genital bleeding, postmenopausal bleeding, or abnormal menstruation, she becomes a candidate for selective screening by endometrial cytology. One report compared the prognosis of endometrial cancer detected by this screening methodology with that of endometrial cancer detected at outpatient clinics, and it showed that the 5-year survival rate was significantly higher in the screening group [22]. However, this is only one report to support the effectiveness of selective screening for endometrial carcinoma with endometrial cytology; its efficacy requires further evaluation.

In this study, the positive rate of endometrial cytology was high in the advanced stage and in nonendometrioid and undifferentiated cases. Thus, it is important to note that early-

stage and well-differentiated endometrioid adenocarcinoma cases have some possibility of being misdiagnosed by endometrial cytology. However, excepting clinical stage III, the positive-plus-suspicious rate (defined as sensitivity) was not significantly different between clinical stages, histological types, differentiation grades, and sampling instruments. The category of suspicious cases includes those suspicious for malignancy and those suspicious for hyperplasia with or without cellular atypia. In the present study, about 25% of the endometrial cancer cases were classified as suspicious. To distinguish this broad spectrum of suspicious cases, a new reporting system has been proposed [23, 24]. If this new reporting system were adopted in this study, the sensitivity and specificity might be changed. Furthermore, liquid-based endometrial cytology is beginning to be utilized, and it seems that a different diagnostic definition is necessary from that of traditional cytology [25, 26]. Further study is needed to evaluate these new concepts.

Limitations

There are two limitations to this study. First, no central pathological review was performed in this retrospective study. The histological and cytological diagnoses were made by experienced pathologists and cytotechnologists at each institution. A central pathological review should be a feature of a future study, but the effect of such a review is expected to be small, since no obvious difference between the institutions was seen in the data, including case proportions according to stage, histological type, differentiation, and cytodiagnosis (data not shown). Second, the size and location of the cancer are among the risk factors that affect the positive rate of endometrial cytology, but they could not be analyzed in the present study. Further study is needed to clarify the risk factor of misdiagnosis by endometrial cytology using tumor size and location data.

Conclusion

Endometrial cytology compares favorably with histology in the detection of uterine cancer. It is most sensitive for clinical stage III cancer. The sensitivity increases with increasing cellular differentiation and when a reexamination is included. The choice of instrument can affect the positive rate, but when suspicious results are included, the sensitivity is indifferent to the instrument type. This study provides new and important data for evaluating the efficacy of endometrial cytology.

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Disclosure Statement

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Radiation Therapy for Chemotherapy-Resistant Recurrent Epithelial Ovarian Cancer

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Key Words
Ovarian cancer · Radiation therapy · Recurrence · Chemoresistance

Abstract
Objectives: While radiation therapy is administered as a palliative treatment for recurrent ovarian cancer, it remains unclear whether it improves the prognosis. ***Methods:*** The effects and adverse events of radiation therapy for patients with recurrent epithelial ovarian cancer were investigated using medical records. ***Results:*** Herein, 46 subjects comprising 33 patients whose recurrent lesions were contained within the irradiation field (therapeutic radiation group; TRG) and 13 patients with some recurrent lesions outside the irradiation field (palliative radiation group; PRG) were included. The TRG achieved a response rate (RR) of 66%, a disease control rate (DCR) of 100%, a progression-free survival (PFS) of 10 months, and an overall survival (OS) of 20 months. The PFS after radiation therapy was significantly longer than that following chemotherapy received just before radiation therapy. The PFS of patients with recurrent intrapelvic lesions was longer than that of patients with some extrapelvic recurrence. There was no significant association between PFS after radiation therapy and the duration from the previous chemotherapy or histological type. The RR, DCR, PFS, and OS of the PRG were 30 and 90% and 2 and 6 months, respectively. Serious adverse events were rare. ***Conclusions:*** Radiation therapy is a potential option for chemotherapy-resistant, localized recurrent ovarian cancer.

Introduction

In the USA, 21,550 people are diagnosed with epithelial ovarian cancer annually, 14,600 of whom die from the disease [1]. Approximately 55% and over 70% of progressive epithelial ovarian cancers recur within 2 and 5 years, respectively [2]. The median survival time after recurrence is approximately 2 years, and it is difficult to achieve a complete cure after recurrence [3]. Chemotherapy is the main treatment for recurrent cancer. However, those patients suffering recurrence less than half a year from the termination of chemotherapy are considered chemoresistant [4]. For these early recurrent patients, multiagent chemotherapy is no more effective than single-agent chemotherapy, and thus a single agent alone is used to treat

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these patients. However, there is only a short response duration in these cases [5]. Moreover, repeating chemotherapy results in a gradual shortening of the progression-free survival (PFS) that the therapy provides [6]. The median PFS obtained after chemotherapy for the second to fifth recurrences were 6.4, 5.6, 4.4, and 4.1 months, respectively. In addition, the chemotherapy response rate (RR) differs depending on the histologic type of the cancer. The RR for patients with clear cell adenocarcinoma (CCC) was found to be 22–56% after the initial chemotherapy and only 8% after the second-line chemotherapy [7–9]. Currently there is no well-established substitute for chemotherapy in cases of early recurrence, a history of repeated chemotherapy, or chemoresistant histological type ovarian cancer. Alternative treatment options are needed for these patients.

While radiation therapy is widely administered for cervical cancer and endometrial cancer, in cases of ovarian cancer it is mainly used to palliate symptoms [10, 11]. In recent years, radiation therapy has also been administered for asymptomatic patients with prospects of prognostic improvement. However, only limited reports are available on the success of this approach [12–15]. In the present study, we investigated the effects and adverse events of radiation therapy for recurrent ovarian cancer.

Materials and Methods

We reviewed the medical records of patients with recurrent epithelial ovarian cancer who were treated with radiation therapy at Jichi Medical University Hospital, Japan, between 2002 and 2010. The presence of epithelial ovarian cancer was confirmed pathologically and was treated with initial debulking surgery and at least 1 regimen of chemotherapy. The administration of radiation therapy for patients with recurrent ovarian cancer was left to the discretion of multiple gynecological oncologists. Chemotherapy was prioritized in principle for patients whose cancers were considered susceptible to chemotherapy on the basis of the duration of the response in the previous chemotherapy cycle, the number of regimens, and the histologic type. Among patients resistant to chemotherapy, suitability for subsequent radiation therapy was determined by taking into consideration factors such as symptoms, the recurrence site, the number of recurrence episodes, and the performance status. Patients with numerous peritoneal metastases or a nonphysiological volume of ascites were excluded. Patients whose lesions were all within the irradiation field were classified into the therapeutic radiation group (TRG). Those with some lesions outside the irradiation field were classified into the palliative radiation group (PRG). Three-dimensional radiation therapy was performed. This study was approved by the Institutional Review Board of Jichi Medical University and meets the standards of the Declaration of Helsinki. Informed consent was obtained from each patient.

The tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors version 1.1 criteria. PFS was defined as the interval between the start of radiation or chemotherapy and recurrence or tumor progression. Overall survival (OS) was defined as the interval between the start of radiation therapy and death or the date of last follow-up contact. Acute and late adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. and Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme, respectively. The Kaplan-Meier method was used to evaluate the patient survival distribution. The significance of the survival distribution in each group was tested by the log-rank test. $p < 0.05$ was considered statistically significant.

Results

A total of 46 subjects comprising 33 and 13 patients in the TRG and PRG, respectively, were enrolled into this study (table 1). The most common histologic type was serous adenocarcinoma, followed by CCC, endometrioid adenocarcinoma, and mucinous adenocarcinoma (MAC). The TRG included 20 patients with a solitary recurrence and 13 patients with multiple recurrences. The most common recurrence site was inside the pelvis, followed by the upper abdomen and the cervical lymph nodes. In the TRG, 18 patients had lesions only in the pelvis. Thirty-two patients (70%) had a history of 2 or more courses of chemotherapy, whereas 14 patients (30%) had a history of only 1 course. Among these 14 patients, 8 were expected to be chemoresistant owing to a histologic diagnosis of CCC, and 3 patients experienced early recurrence after chemotherapy. Platinum-based chemotherapy regimens were used in the majority of cases. There were 31 cases (67%) of recurrence within 6 months after the previous chemotherapy. The median irradiation doses were 60 and 50 Gy in the TRG and PRG, respectively. The radiation doses were not significantly different between the intrapelvic and extrapelvic sites. Generally, the area being irradiated was limited to the local recurrent tumor, except in cases of intrapelvic and para-aortic lymph node recurrence. For intrapelvic recurrence, whole pelvis irradiation was performed in approximately half of the cases (TRG, 12/19; PRG, 1/6). For para-aortic lymph node recurrence ($n = 4$), irradiation included the adjacent lymph node.

In the TRG, the median PFS and OS were 10 and 20 months, respectively (table 2). The PFS of the intrapelvic group (patients with only intrapelvic recurrence) was better than that of the extrapelvic group (patients with some extrapelvic recurrence) ($p < 0.05$). The OS of

Table 1. Patient characteristics

	TRG (n = 33)	PRG (n = 13)	Total (n = 46)
Age, years			
Median	59	53	59
Range	37–79	33–77	33–79
Performance status			
0	23	3	26
1	10	4	14
2	0	6	6
Stage			
1	5	3	8
2	6	1	7
3	17	6	23
4	5	3	8
Histological type			
Serous	16	7	23
Clear	8	2	10
Endometrioid	5	3	8
Mucinous	1	0	1
Adenocarcinoma	2	1	3
Poorly differentiated	1	0	1
Number of recurrence sites			
Solitary	20	0	20
Multiple	13	13	26
Recurrence site (duplicated data)			
Pelvis	19	6	25
Upper abdomen	10	2	12
Neck	5	3	8
Others	4	3	7
Localized in the pelvis	18	0	18
Localized in lymph nodes	10	0	10
Longest diameter			
<4 cm	15	6	21
≥4 cm	18	7	25
Symptom			
Pain	3	4	7
Bleeding	2	4	6
Swelling	1	2	3
Others	3	1	4
No	24	2	26
Number of chemotherapy regimens prior to radiation			
1	12	2	14
2	9	4	13
3	10	4	14
≥3	2	3	5
Regimen			
Paclitaxel/carboplatin	24	11	35
Weekly paclitaxel	11	5	16
Cisplatin/irinotecan	6	8	14
Nedaplatin/irinotecan	8	5	13
Docetaxel/carboplatin	6	0	6
Cisplatin/carboplatin	5	1	6
Others	8	7	15
Duration from the last chemotherapy			
<6 months	24	7	31
≥6 months	9	6	15
Radiation dose, Gy			
Median	60	50	60
Range	42–65	40–60	40–65
1st to 3rd quartiles	58–60	45–56	51–60
Beam (duplicated data)			
10-Mv X-ray	26	8	34
4-Mv X-ray	4	1	5
3-Mv X-ray	2	1	3
6-Mv X-ray	2	3	5
Electron beam	1	1	2

Values are presented as numbers unless otherwise stated.

the intrapelvic group was longer than that of the extrapelvic group, although this difference was not statistically significant ($p = 0.08$). The early recurrence group (patients who experienced recurrence less than 6 months after the last chemotherapy) was compared with the intermediate/late recurrence group (recurrence 6 months or longer after the last chemotherapy). In addition, the CCC/MAC group was compared with the serous adenocarcinoma/other histology group (patients with histologic types other than CCC and MAC, including serous adenocarcinoma). The interval between relapse and the last chemotherapy, histological type, tumor size, and radiation dose were not related to PFS and OS. For the PRG, the median PFS and OS were 2 and 6 months, respectively. The TRG had a better performance status, with more solitary lesions and a higher percentage of tumors localized in lymph nodes compared to the PRG, which presumably accounted for the longer PFS and OS of the TRG compared to the PRG.

The PFS of patients treated with radiation therapy was compared to that of those receiving chemotherapy just before radiation therapy (fig. 1). The median PFS of the former was 10 months, significantly longer than the 5-month PFS of the patients treated with preceding chemotherapy ($p < 0.05$). In cases where an additional chemotherapy regimen was administered, a shorter PFS than that achieved with preceding chemotherapy was anticipated. Thus, radiation therapy is a potential option for chemoresistant ovarian cancer.

For the TRG, the RR limited to lesions within the radiation field was 66%, and the disease control rate (DCR) was 100% (table 3). In one patient with partial remission

Table 2. PFS and OS

	n	PFS, months			OS, months		
		median	range	p value	median	range	p value
TRG							
Total	33	10	1–137		20	5–137	
Recurrence area							
Intrapelvic	18	17.5	4–137		27.5	11–137	
Extrapelvic	15	4	1–36	<0.05	14	5–73	NS
Duration from chemotherapy							
<6 months	24	9.5	2–103		19	5–103	
≥6 months	9	12	1–137	NS	47	10–137	NS
Histological type							
CCC/MAC	9	7	1–137		14	6–137	
SAC/others	24	11	1–103	NS	24.5	5–103	NS
Tumor size							
<4 cm	15	5	1–60		18	5–73	
≥4 cm	18	14.5	3–137	NS	22	6–137	NS
Radiation dose							
<60 Gy	7	18	3–36		36	5–83	
≥60 Gy	26	9.5	1–137	NS	19	8–137	NS
PRG							
Total	13	2	1–10		6	1–26	

NS = Not significant.

in the radiation field, new lesions developed outside the field. When this case was categorized as progressive disease (PD), the RR and DCR were 63% (20/32) and 97% (31/32), respectively. Recurrence area, duration from the last chemotherapy, histological type, tumor size, and radiation dose were not significantly associated with response. However, the number of patients may have been too small to detect a significant association. For the PRG, the RR was 30% and the DCR was 90%. Although the range of radiation doses was similar in both groups, the RR limited to lesions inside the irradiation field was less in the PRG than in the TRG.

In the TRG, changes in carbohydrate antigen 125 (CA125) levels were observed in 25 patients with CA125 values ≥15 U/ml before radiation therapy. CA125 levels decreased to below 50% in 11 patients (44%). Only 2 patients (8%) showed a 2-fold or greater increase in CA125 levels.

Of the 9 patients in the PRG for whom changes in symptoms after therapy could be evaluated, 8 (89%) showed an improvement of symptoms. For the 2 patients who became asymptomatic, the symptom that disappeared was bleeding.

Toxicity was investigated in a total of 46 patients from the TRG and PRG. Acute toxicities included grade 1–2

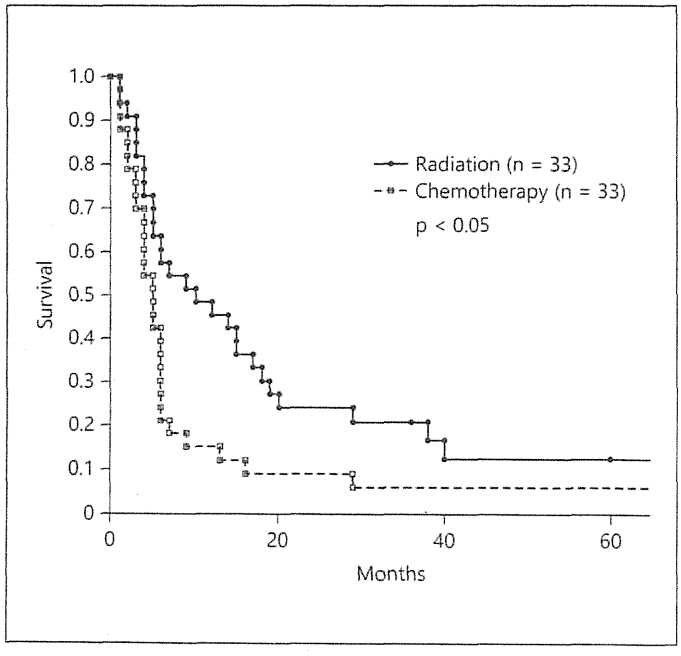

Fig. 1. Comparison of PFS after radiation therapy and chemotherapy received just before radiotherapy in the TRG. The PFS of patients treated with radiation therapy was 10 months (range 1–137), longer than the 5 months (range 1–96) of those treated with previous chemotherapy ($p < 0.05$).

Table 3. Response limited to lesions within the irradiation field

	Complete remission	Partial remission	No change	Progressive disease	Not analyzed	Response rate		
						n	%	p value
TRG								
Total	10	11	11	0	1	21/32	66	
Recurrence area								
Intrapelvic	6	6	6	0	0	12/18	67	
Extrapelvic	4	5	5	0	1	9/14	64	NS
Duration from chemotherapy								
<6 months	8	6	9	0	1	14/23	61	
>6 months	2	5	2	0	0	7/9	78	NS
Histological type								
CCC/MAC	3	0	5	0	1	3/8	38	
SAC/others	7	11	6	0	0	18/24	75	NS
Tumor size								
<4 cm	5	6	3	0	1	11/14	79	
>4 cm	5	5	8	0	0	10/18	56	NS
Radiation dose								
<60 Gy	4	1	2	0	0	5/7	71	
>60 Gy	6	10	9	0	1	16/25	64	NS
PRG								
Total	1	2	6	1	3	3/10	30	

Values are presented as numbers unless otherwise stated. NS = Not significant.

diarrhea in 12 patients (26%), anorexia in 12 patients (26%), nausea in 8 patients (17%), and dermatitis in 5 patients (11%); there were no acute toxicities of grade 3 or higher. Late toxicities included grade 1 radiation enterocolitis in 1 patient (2%) and grade 3 ileus in another (2%).

Discussion

A long PFS was achieved after radiation therapy for chemotherapy-resistant recurrent ovarian cancer, particularly in patients with intrapelvic recurrence. The effects of radiation therapy were at least as good in patients with a response of a short duration from the previous chemotherapy cycle or with a chemoresistant histological type. In addition, the PFS after radiation therapy was longer than that following chemotherapy received just before radiation therapy. Serious adverse events were rare.

Favorable outcomes and an improvement in symptoms after palliative radiation for recurrent ovarian cancer have already been reported [10, 11]. The improvement in symptoms, complete disappearance of symptoms, and duration of the response were reported to be 94–100 and 68–70% and 4.8–11 months, respectively.

Fujiwara et al. [12] administered radiation therapy for recurrent ovarian cancer in patients with a history of chemotherapy without limiting the therapy to symptom palliation. Because the patients without symptoms, with small recurrent tumors, and with recurrent lesions localized to the lymph nodes had a favorable prognosis, it was concluded that radiation therapy may be a potential option for treating localized recurrence without symptoms. Lee et al. [13] conducted radiation therapy on 38 patients with recurrent ovarian cancer and a history of chemotherapy. The RR and median PFS were 65% and 7.2 months, respectively. The median PFS was 10.7 months when it was limited to patients with sporadic recurrent lesions, and this performance was close to that of the TRG in the present study. Brown et al. [14] retrospectively reviewed the records of regionally recurrent ovarian cancer patients treated with definitive involved-field radiation therapy and found that the 5-year OS and PFS rates were 40 and 24%, respectively.

In our study, the effects of radiation therapy were not dependent on the duration of previous chemotherapy. Cmelak and Kapp [16] conducted whole abdominal-pelvic irradiation for recurrence after chemotherapy follow-

ing surgery. The 5-year survival rate limited to early recurrent patients was 50%, showing no significant difference with the 47% 5-year survival rate for all patients. Both studies indicate that radiation sensitivity may be unrelated to chemoresistance, although in other studies early recurrence was found to be associated with a greater relapse risk or a shorter OS [14, 15].

Some studies have also reported the efficacy of radiation therapy for CCC. Brown et al. [14] reported that CCC patients had higher 5-year OS (88 vs. 37%) and PFS (75 vs. 20%) rates than patients with other histological subtypes. Nagai et al. [17] conducted whole abdominal radiotherapy as an additional postoperative therapy for CCC and compared it with chemotherapy, a historical control. Both the OS and the PFS rates were better in the radiation therapy group than in the chemotherapy group, indicating that radiation therapy is likely to be superior to chemotherapy for chemoresistant histologic types. Swenerton et al. [18] investigated whether whole pelvis or whole abdomen irradiation as an adjuvant after postoperative chemotherapy improved the prognosis. Radiation therapy reduced the disease-specific mortality by 40% when the targets were limited to stage I–II CCC, endometrioid adenocarcinoma, and MAC.

New developments in radiation therapy for ovarian cancer have also been reported in recent years, including intensity-modulated radiotherapy and the use of radiation therapy as a chemosensitizer [19–21].

In our study, radiation therapy resulted in a longer PFS than the preceding chemotherapy, which was similar to the findings reported by Brown et al. [14]. The present study was not a prospective study and lacked a clear standard for choosing radiation therapy. In addition, the number of patients was limited because chemotherapy is the standard treatment for recurrent ovarian cancer. We consider it worthwhile to conduct a multicenter and prospective clinical trial in the future to compare radiation therapy with chemotherapy in patients with chemotherapy-resistant recurrent ovarian cancer localized in intrapelvic lesions.

It is also noteworthy that a long PFS could not be achieved for extrapelvic recurrent patients and PRG. This raises the possibility that the symptoms of these patients could be palliated with a shorter and lower dose of radiation, and this is also worthy of further study.

Radiation therapy for recurrent ovarian cancer can be a potential option in cases of chemotherapy-resistant localized recurrences.

Disclosure Statement

None of the authors has any former or present conflict of interest related to this study.

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Successful pregnancy in a Peutz–Jeghers syndrome patient with lobular endocervical glandular hyperplasia

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Abstract

Lobular endocervical glandular hyperplasia (LEGH) is histologically similar to minimal deviation adenocarcinoma (MDA), but classified as a benign disease. Although MDA often develops in Peutz–Jeghers syndrome (PJS) patients, there have been only a few reports on PJS with LEGH. We report a PJS patient who was diagnosed with LEGH by conization and delivered a baby 42 months later. She was referred to our department for multicystic lesions in the uterine cervix at 26 years old. Diagnostic conization was performed, and the histopathological diagnosis was LEGH. As the possibility of MDA could not be ruled out because of concomitant PJS, hysterectomy was considered. However, course observation was selected because the patient strongly wished to preserve fertility. She delivered a baby at 30 years old. The finding that PJS patients may be complicated by LEGH is very important. Loss of fertility by over-treatment should be avoided if patients desire its preservation.

Key words: fertility preservation, lobular endocervical glandular hyperplasia, Peutz–Jeghers syndrome, pregnancy.

Introduction

Peutz–Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by hamartomatous gastrointestinal polyps and mucocutaneous melanin pigmentation. The responsible gene is a tumor suppressor gene, *STK11/LKB1*, on chromosome 19p13.3. PJS is also complicated with malignant tumors in the gastrointestinal tract, pancreas, breast, and elsewhere. In gynecology, minimal deviation adenocarcinoma (MDA) often develops in PJS patients.[1,2]

The clinical symptoms and cytology, histology, and imaging findings of MDA and lobular endocervical glandular hyperplasia (LEGH) are similar, and their differentiation is difficult. Takatsu *et al.* reported that 26 of 54 patients who were led to a diagnosis of LEGH by the central pathological review were overdiagnosed with MDA at their respective medical centers and treated by radical hysterectomy.[3] Reportedly, MDA develops in 15–30% of PJS patients,[1,2] and about 10% of MDA patients have PJS.[2,4] However, there have been only a few reports of PJS patients complicated by LEGH; to our knowledge, only four cases have been reported.[5–8] As the lesions of LEGH and MDA tend to be present near the internal os,[9] hysterectomy, not conization of the cervix, is necessary to diagnose these accurately. Hysterectomy may be readily selected when the patient is postmenopausal or does not wish to have a child, but it cannot be easily selected for patients who want to preserve fertility.

We encountered a PJS patient who was diagnosed with LEGH by conization of the cervix and delivered a baby 42 months later. This is a rare and suggestive case. The clinical course of this patient may provide helpful suggestions when a similar case is encountered.

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Case Report

At the time of the first examination at our department, the patient was 26 years old, unmarried, and nulligravida. She had been diagnosed with PJS based on the presence of melanotic macules on the oral mucosa at 9 years old. At 26 years old, multiple polyps were noted on enteroscopy, swelling of and multiple small cysts in the uterine cervix were observed on abdominal computed tomography (CT), and the patient was referred to our department for close examination. On pelvic examination, mild swelling of the uterine cervix and a large volume of transparent viscous discharge were noted. On transvaginal ultrasonography, the uterine cervix was swollen to about 4 cm, and multiple small cysts were present. On cytology, aggregates of high-columnar glandular cells with a background of endocervical mucous material were observed. The cytoplasm contained yellowish mucus, and the nucleus was small and less atypic. On magnetic resonance imaging (MRI), many cystic lesions showing a high intensity were present in the uterine cervix on T2-weighted imaging (Fig. 1). MDA was suspected based on the findings of pelvic examination, ultrasonography, cytology, and MRI, as well as the complication of PJS, and diagnostic conization of the cervix was performed. Conization was performed using an ultrasonic scalpel with a hook blade. The dimensions of the conization specimen were 55 mm in width and 17 mm in height. On pathological examination of the conization specimen, markedly growing cervical glands formed lobular structures, dilated in a cystic pattern in some regions, and occasionally showed papillary growth. However, no growth beyond the cervical gland region was noted, and glandular cells were small and not atypic, on the basis of which LEGH was diagnosed (Fig. 2). There were LEGH lesions on the surgical margin.

Although the conization specimen led to a diagnosis of LEGH, the possibility of MDA in the residual uterus could not be ruled out because of concomitant PJS, for which hysterectomy was considered, but course observation was selected because the patient strongly wished to preserve fertility. Cervical cytology and biopsy were

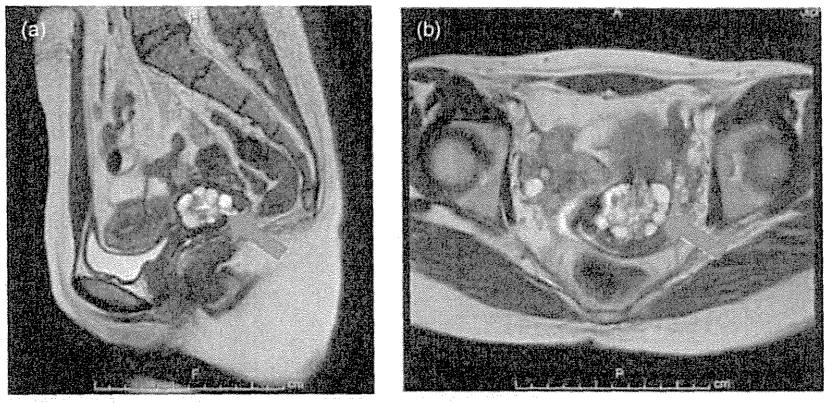

Figure 1 Magnetic resonance imaging on the first examination. T2-weighted image. (a) Sagittal and (b) transverse sections. Many cystic lesions showing a high intensity (arrow) were present in the uterine cervix.

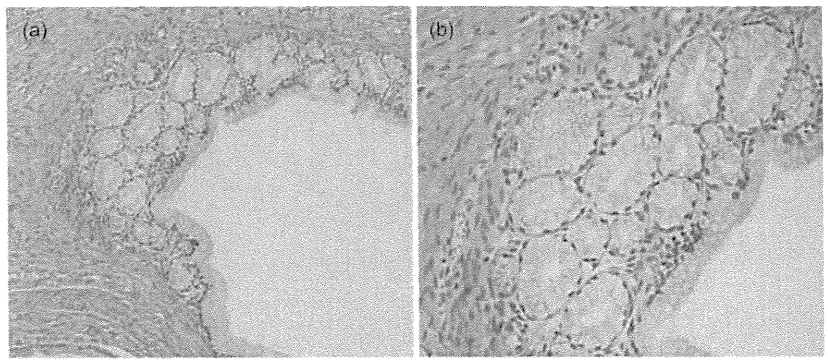

Figure 2 Photographs of the histopathology on conization of the cervix. Hematoxylin–eosin stain, original magnification (a) 100× and (b) 200×. Markedly growing cervical glands formed lobular structures and dilated in a cystic pattern in some regions.

performed every 3 months until pregnancy, and the course was carefully followed to identify whether MDA and adenocarcinoma developed. Cells and tissues were collected from the closest possible region to the internal os. After conization, atypical glandular cells continuously appeared on cytological and histological examinations, but no finding suggested malignancy. Furthermore, we performed transvaginal ultrasound every 3 months and MRI every year and confirmed that there were no changes in the size and appearance of the uterine cervical lesion. During pregnancy, cervical biopsy was not performed, but cervical cytology and transvaginal ultrasound were performed every 3 months. Because MRI had been performed 1 month before her pregnancy became evident, the next MRI was performed 3 months after delivery.

The patient married at 29 years old, became pregnant by infertility treatment, and gave birth at 30 years old by normal vaginal delivery at 39 weeks of gestation. Fortunately, the patient had no symptoms or signs of threatened abortion or threatened premature labor, so she required no special care during pregnancy. In addition, as her cervical length measured 48 mm, she did not undergo cervical cerclage. As atypical glandular cells were persistently detected on cervical cytology after delivery, and there was a possibility that LEGH was a precursor of MDA or adenocarcinoma,[9,10] after discussion with her and her family, she underwent modified radical hysterectomy at 31 years old. Gross examination of the resected, opened uterus revealed multiple mucus-filled cysts in a portion of the cervix, measuring 35 mm in length and 15 mm in depth. On postoperative pathological examination, many gland ducts forming lobular structures were noted around the gland ducts, which were dilated in a cystic pattern. Nuclear atypia of epithelial cells comprising the ducts was weak, and the polarity was retained. These epithelial cells were arranged in a lobular pattern without desmoplastic stromal reactions. LEGH accounted for the majority of cervical lesions (Fig. 3a). However, glandular dysplasia (Fig. 3b) and adenocarcinoma *in situ* (AIS) with a clear nucleolus and severe nuclear atypia (Fig. 3c) were partially noted. Glandular dysplasia and AIS accounted for a few percent of the lesions. No evidence of vascular invasion was seen. On the basis of these findings, the patient was diagnosed with 'LEGH with AIS'.

As of about 3 years after surgery, no recurrence had been noted, and the child's development has been normal. However, labial melanotic macules began to become prominent at about 2 years and 9 months of age.

Discussion

This is the first report of a PJS patient who was diagnosed with LEGH by conization and could deliver a baby. The present case suggests the following two points: (i) as well as MDA, PJS patients may have LEGH; and (ii) follow-up must be carefully performed in PJS patients with LEGH.

Our patient with PJS had LEGH, and not MDA. A search of the PubMed database using the keywords 'Peutz–Jeghers syndrome' and 'lobular endocervical glandular hyperplasia' revealed that there have been four case reports on PJS with LEGH.[5–8] Two of these were diagnosed by hysterectomy[6,8] and one by simple trachelectomy.[5] In the fourth case, conization was performed and the patient was followed for 12 months, but no recurrence was noted.[7] None of them had a child. In our patient, pregnancy was established 34 months after conization, and she gave birth by normal vaginal delivery at 39 weeks and 3 days of gestation. Table 1 summarizes the characteristics of the five patients, including the present case.

As it is known that MDA complicates PJS, and LEGH has been suggested to be a precursor of MDA and adenocarcinoma,[9,10] hysterectomy was also considered for our patient. Lesions of LEGH and MDA tend to be present near the internal os, rather than the squamocolumnar junction.[9] The surgical margin of the conization specimen was positive, suggesting the presence of MDA in regions not removed by conization, which was also a reason to consider hysterectomy. However, course observation was selected because the patient strongly wished to preserve fertility. Finally, she was able to deliver a baby. The present case may provide useful information when similar patients select treatment in the future.

However, follow-up should be carefully performed when preserving fertility in PJS patients with LEGH. Although LEGH is a benign disease, patients with concomitant LEGH with MDA or adenocarcinoma have been reported.[9,10] Therefore, total excision of the uterus and its close pathological examination are now considered desirable as the primary treatment. Course observation is an option for patients who want to have a child, like our patient, but prolonged course observation is accompanied by risk. In our patient, modified radical hysterectomy was performed 50 months after she had been diagnosed with LEGH. It was unclear when AIS appeared, but the possibility of MDA or adenocarcinoma development may increase with prolongation of course observation of LEGH, to

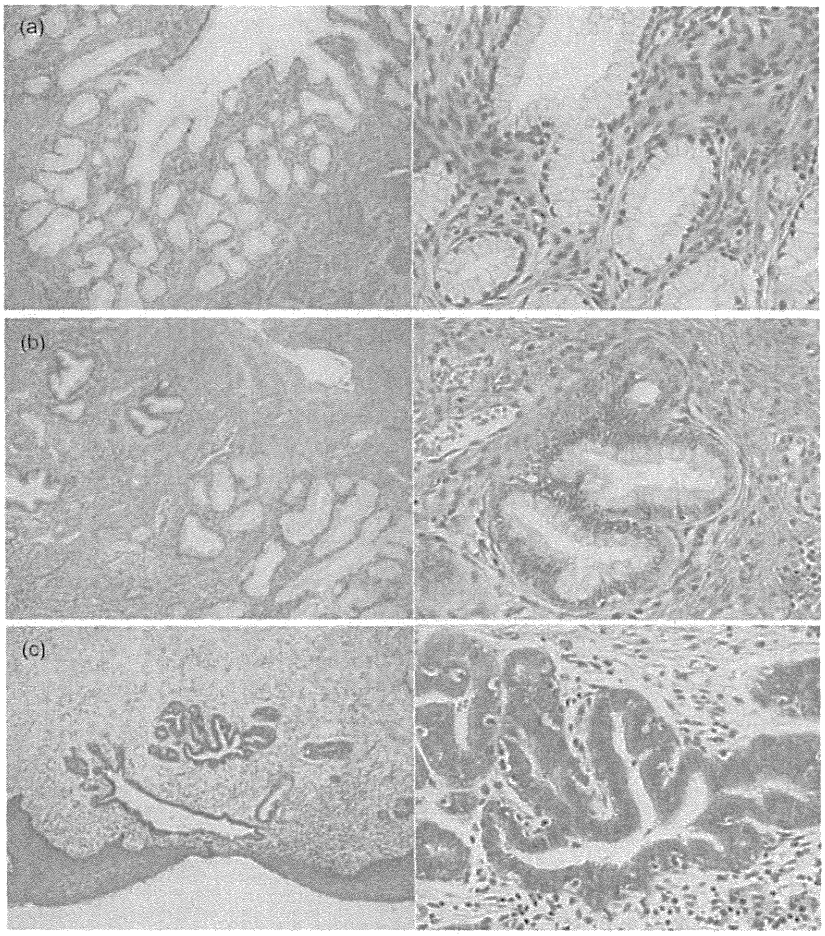

Figure 3 Photographs of the histopathology of the excised uterus: (a) lobular endocervical glandular hyperplasia (LEGH) region; (b) glandular dysplasia region; and (c) adenocarcinoma *in situ* (AIS) region. Hematoxylin–eosin stain, original magnification (left) 100× and (right) 400×. LEGH accounted for the majority of cervical lesions. However, partial glandular dysplasia and AIS with a clear nucleolus and severe nuclear atypia were noted.

Table 1 Characteristics of the five Peutz–Jeghers syndrome patients who were diagnosed with lobular endocervical glandular hyperplasia

Authors	Age (years)	Pregnancy history	Surgery	Delivery after surgery	Follow-up (months)	Recurrence
Hahn *et al.* 2012[5]	30	0 para	Simple trachelectomy	No	12	No
Hirasawa *et al.* 2012[6]	42	1 para	Hysterectomy	Impossible	—	—
Ito *et al.* 2012[7]	27	0 para	Conization	No	12	No
Yasumoto *et al.* 2012[8]	41	0 para	Hysterectomy	Impossible	—	—
Takei *et al.* (present case)	26	0 para	Conization	Yes	50	No

which attention should be paid, particularly in PJS patients. MRI may be useful for follow-up. According to Takatsu *et al.*, on MRI, LEGH appears as a characteristic multicystic lesion with an inner solid component, whereas MDA shows a predominantly solid pattern. For the differential diagnosis of LEGH from MDA, cervical cytology or the appearance of gastric mucin alone is insufficient. The accuracy of diagnosis is increased by combining MRI with these procedures.[3] Actually, we performed not only cervical cytology and transvaginal ultrasonography but also MRI every year to confirm that there were no changes in the size or features of the uterine cervix.

The present patient was diagnosed as having LEGH with AIS. The histological differences among LEGH, LEGH with AIS, MDA, and common adenocarcinoma are as follows:[11] LEGH is defined as non-invasive proliferation of endocervical glandular cells without any adenocarcinoma component. LEGH may show mild nuclear enlargement, but the degree of cellular atypia is not as high as that of AIS or MDA. LEGH with AIS literally refers to a condition in which LEGH and AIS coexist. The area of AIS is usually smaller than that of LEGH. Indeed, in the present patient, the former was about 1% of the latter. MDA is defined as highly differentiated endocervical-type mucinous adenocarcinoma with well-formed glands resembling LEGH, but accompanied by a component of obviously invasive adenocarcinoma.[4] Common adenocarcinoma refers to a condition in which most of the tumor area is composed of frank invasive adenocarcinoma. The area of well-formed glands resembling LEGH is smaller and that of frank invasive adenocarcinoma is larger in common adenocarcinoma than in MDA. Cellular atypia is also more marked than in MDA.

The course after the diagnosis of LEGH by conization was followed for the longest period in our patient among the reported cases. Hysterectomy was performed 50 months after conization, and AIS was present in some of the specimen. The disease had not progressed to adenocarcinoma despite the long-term course observation. However, the natural history of LEGH is unclear, and it may progress to MDA or adenocarcinoma earlier. According to the recent literature,[12,13] LEGH is considered to be a precancerous lesion of MDA. Therefore, LEGH may eventually transform into MDA. In the future, it will be necessary to collect data on LEGH patients whose fertility has been preserved and who have been followed-up in multicenter studies. A detailed analysis of the outcome of such patients is expected to elucidate the natural history of LEGH, thereby providing useful information for patients who wish to preserve their fertility. Interestingly, Mikami *et al.* reported that, among 14 MDA cases, six had LEGH components.[14]

The initiation of infertility treatment was late because the patient was unmarried when she was diagnosed with LEGH. When a patient is married and wants to have a child, it may be necessary to establish pregnancy earlier using fertility treatment. We recommended that this patient undergo infertility treatment promptly after marriage. Finally, pregnancy was achieved through *in vitro* fertilization.

The finding that PJS may be complicated by LEGH, as noted in this patient, is important information for patients who want to preserve fertility. It is also necessary to follow the course carefully until hysterectomy. In particular, caution is needed in PJS patients. In the future, patients in whom LEGH is followed up after conization should be accumulated to clarify the natural history of LEGH. This may provide useful information for patients who wish to preserve fertility.

Disclosure

We declare no conflicts of interest.

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ORIGINAL ARTICLE

Feasibility study of gemcitabine plus docetaxel in advanced or recurrent uterine leiomyosarcoma and undifferentiated endometrial sarcoma in Japan

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Abstract
Background Uterine leiomyosarcoma (LMS) and undifferentiated endometrial sarcoma (UES) are rare, aggressive malignancies. Both are treated similarly; however, few chemotherapy agents are effective. Recently, the combination of gemcitabine (900 mg/m^2, days 1 and 8) plus docetaxel (100 mg/m^2, day 8) with granulocyte colony-stimulating factor (G-CSF, 150 μg/m^2, days 9–15) has been shown to have activity in LMS. In Japan, neither prophylactic G-CSF at a dose of 150 μg/m^2 nor docetaxel at a dose of 100 mg/m^2 are approved for use. For this reason, we evaluated the combination of 900 mg/m^2 gemcitabine plus 70 mg/m^2 docetaxel regimen without prophylactic G-CSF support in advanced or recurrent LMS and UES in Japanese patients.
Methods Eligible women with advanced or recurrent LMS and UES were treated with 900 mg/m^2 gemcitabine on days 1 and 8, plus 70 mg/m^2 docetaxel on day 8, every 3 weeks. The primary endpoint was overall response rate, defined as a complete or partial response.
Results Of the eleven women enrolled, 10 were evaluated for a response. One complete response and 2 partial responses were observed (30 %) with an additional 4 (40 %) having stable disease. Mean progression-free survival was 5.4 months (range 1.3–24.8 months), and overall survival was 14 months (range 5.3–38.4 months). Grade 4 neutropenia was the major toxicity (50 %). The median number of cycles was 5 (range 2–18). Twenty-two cycles (44 %) employed G-CSF.
Conclusion The gemcitabine plus docetaxel regimen without prophylactic G-CSF support was tolerable and highly efficacious in Japanese patients with advanced or recurrent LMS and UES.

Keywords Chemotherapy · Uterine leiomyosarcoma · Gemcitabine · Docetaxel · G-CSF · Japanese patients

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Introduction

Uterine leiomyosarcoma (LMS) and undifferentiated endometrial sarcoma (UES) together account for approximately 1 % of all uterine malignancies [1–3] and thus are diagnosed in only a few hundred women each year in Japan [4]. Systemic therapy for LMS and UES is similar [5]. Women who present with advanced disease and those with recurrence have a poor prognosis [6]. Median

survival among women with advanced disease is less than 1 year.

Single-agent doxorubicin remains the standard first-line therapy in many treatment settings, with first-line response rates of approximately 25 %. The combination of doxorubicin plus ifosfamide (response rate 28–30 %) has not been shown to improve outcomes among patients with soft tissue sarcoma compared with doxorubicin alone [7, 8] (Table 1). Other single agents with moderate activity in leiomyosarcoma include ifosfamide (response rate 17.2 %) [9], gemcitabine (bolus infusion achieved a 20 % response rate) [10], trabectedin (response rate of 8 % among patients without prior treatment, and 45 % second-line treatment) [11, 12] and temozolomide (15.5 % objective response with daily oral treatment) [13]. Multiple chemotherapy agents, including cisplatin [14–16], liposomal doxorubicin [17], intravenous etoposide [18], oral etoposide [19], paclitaxel [20, 21], topotecan [22], trimetrexate [23], sunitinib malate [24], and thalidomide [25] have been tested in the first- and second-line settings with negligible activity demonstrated.

Docetaxel disrupts mitosis by the promotion of abnormal microtubular assembly and suppression of the depolymerization of microtubular bundles to free tubulin [26]. Gemcitabine is an S-phase-specific, fluorine-substituted pyrimidine analog, which is phosphorylated by deoxytidine kinase to the active diphosphate and triphosphate metabolites. This metabolite inhibits ribonucleotide reductase and DNA synthesis [27]. The clinical development of the gemcitabine–docetaxel regimen is outlined, and data demonstrating the efficacy of this regimen in soft tissue sarcoma are reviewed [28–30].

Table 1 Responses of chemotherapeutic trials in LMS

Drugs	Treatment lines	Response rate	Progression-free survival (months)
Doxorubicin [7]	First/second	7/28 (25 %)	3.5
Doxorubicin [36]	First	5/26 (19 %)	5
Cisplatin [16]	First	1/33 (3 %)	Not reported
Ifosfamide [9]	First	6/35 (17 %)	Not reported
Liposomal doxorubicin [17]	First	5/32 (16 %)	4.1
Etoposide IV [18]	First	0/28 (0 %)	2.1
Etoposide PO [19]	First/second	2/29 (7 %)	2.1
Paclitaxel [20]	First/second	3/33 (9 %)	Not reported
Topotecan [22]	First	4/36 (11 %)	Not reported
Trimetrexate [23]	Second	1/24 (4.3 %)	2.2
Paclitaxel [21]	First	4/48 (8 %)	1.5
Gemcitabine (bolus infusion) [10]	First/second	9/42 (20 %)	Not reported
Gemcitabine (fixed-dose rate, 10 mg/m^2/min) [37]	Second	4/21 (19 %)	5.5
Sunitinib malate [24]	Second	2/23 (8.7 %)	1.5
Temozolomide [13]	Second	1/13 (8 %)	Not reported
Thalidomide [25]	Second	0/29 (0 %)	1.7
Trabectedin [11]	Second	6/35 (17.1 %)	Not reported
Trabectedin [12]	Second	5/11 (45 %)	Not reported
Vincristine/dactinomycin/cyclophosphamide [38]	First	29 %	Not reported
Doxorubicin/dacarbazine [7]	First/second	24 %	Not reported
Doxorubicin/cyclophosphamide [36]	First	5/26 (19 %)	Not reported
Doxorubicin/ifosfamide [8]	First	10/33 (30 %)	4
Mitomycin/doxorubicin/cisplatin [39]	First	8/35 (22.8 %)	Not reported
DMAP, sargramostim (GM-CSF) [40]	First	5/18 (28 %)	5.9
Doxorubicin/ifosfamide [41]	First	12/25 (48 %)	Not reported
Gemcitabine + docetaxel [31]	First	18/34 (53 %)	5.6
Gemcitabine + docetaxel [33]	Second	13/48 (26 %)	5.6+
Gemcitabine + docetaxel [34]	First	15/42 (36 %)	4.4
Gemcitabine + docetaxel [37]	Second	5/21 (24 %)	4.7
Gemcitabine + docetaxel (this study)	Second/third	3/10 (30 %)	5.4

LMS Leiomyosarcoma, *DMAP* dacarbazine, mitomycin, doxorubicin, and cisplatin, *GM-CSF* granulocyte–macrophage colony-stimulating factor

A single-institution study of gemcitabine plus docetaxel yielded high objective response rates among patients with advanced LMS in both the second-line [31] and first-line settings [32]. Recently, gemcitabine plus docetaxel has been shown to yield higher response rates, and longer progression-free and overall survivals than single-agent gemcitabine in a randomized trial for patients with soft tissue sarcoma who had received up to three prior regimens [30]. In a Gynecologic Oncology Group (GOG) phase II trial for women with advanced leiomyosarcoma who had received one prior cytotoxic regimen, gemcitabine plus docetaxel achieved objective responses in 28 % of patients, with an additional 50 % having stable disease (SD). The high dose of docetaxel (100 mg/m$^{2)}$ in this study, however, produced profound myelosuppression necessitating the use of growth factor support [33].

A prospective study of gemcitabine plus docetaxel has been eagerly anticipated in Japan. However, such studies have not been conducted because the GOG regimen, as either prophylactic G-CSF at a dose of 150 μg/m^2 or docetaxel at a dose of 100 mg/m^2, is not approved in Japan. The maximum approved dose of docetaxel in Japan is 70 mg/m^2.

Therefore, the aim of this single-institution study was to evaluate the efficacy and toxicity of a regimen of gemcitabine 900 mg/m^2 plus dose-reduced docetaxel 70 mg/m^2 without prophylactic G-CSF support in Japanese patients with advanced or recurrent LMS and UES.

Patients and methods

Patients

Women with measurable advanced or recurrent LMS and UES with non-resectable disease were eligible. All tumors were histologically confirmed. Patients were permitted to have had prior chemotherapy and pelvic radiotherapy; however, patients previously treated with either docetaxel or gemcitabine were excluded. Patients were required to have an ECOG performance status of 0–2, and adequate bone marrow function [absolute neutrophil count (ANC) greater than or equal to 1500/μl, and platelets greater than or equal to 100,000/μl]; renal function (creatinine less than or equal to 1.5 × the institutional upper limit of normal); hepatic function (bilirubin less than or equal to 1.5 × the institutional upper limit of normal, and serum glutamic oxaloacetic transaminase [sGOT] and alkaline phosphatase less than or equal to 2.5 × the institutional upper limit of normal); and neurological function [baseline neuropathy, sensory and motor, less than or equal to National Cancer Institution Common Toxicity Criteria version 3.0 (CTC 3.0) grade 1]. Patients with a history of another invasive malignancy within the past 5 years were not eligible. All patients provided written, informed consent. The protocol and consent were reviewed and approved annually by Institutional Review Boards of Tohoku University Hospital.

Treatment

All participants had baseline imaging with a computed tomography (CT) scan of the chest, abdomen, and pelvis, within 4 weeks of starting therapy. CT imaging was repeated following every other cycle of treatment to assess response. A history was taken, and a physical examination and assessment of toxicities were performed at each cycle. Complete blood counts and comprehensive metabolic panels were monitored weekly. Participants received gemcitabine 900 mg/m^2 on days 1 and 8 intravenously infused over 90 min, followed by docetaxel 70 mg/m^2 on day 8 intravenously infused over 60 min. Treatment cycles were repeated approximately every 3 weeks, and patients continued on the study treatment until disease progression, achievement of discontinuation criteria as defined in the study protocol, or at the discretion of the investigator. Recommended pre-medication for the docetaxel was dexamethasone 8 mg orally twice a day starting the day prior to docetaxel. Early intervention with diuretics was encouraged for signs of docetaxel-related fluid retention. Patients received the day 1 treatment of each cycle provided the ANC was greater than or equal to 1500/μl and the platelet count was greater than or equal to 100,000/μl. Patients received full-dose day 8 treatment provided the ANC was greater than or equal to 1000/μl and platelet count greater than or equal to 100,000/μl. Seventy-five percent of the planned day-eight dose was given if the ANC was between 500 and 1000/μl or the platelet count was between 50,000 and 100,000/μl, and provided bilirubin levels from day 1 or after were within institutional normal limits. Day-8 treatment with docetaxel was omitted if the bilirubin remained above normal on day 8. Day-8 gemcitabine and docetaxel were both omitted if the day-8 ANC was under 500/μl or the platelet count was less than 50,000/μl. Patients were given therapeutic and second-line prophylactic G-CSF if they had grade 4 neutropenia. Doses of both docetaxel and gemcitabine were reduced by 25 % in subsequent cycles if a patient experienced grade 3 elevations in sGOT, serum glutamic pyruvic transaminase (sGPT), or alkaline phosphatase, and treatment was not resumed until such grade 3 elevations had resolved to grade 1 or less. Patients who experienced grade 2 or worse neurotoxicity had treatment held for a maximum of 2 weeks and could resume treatment at 75 % of the prior docetaxel dose if the neuropathy had improved. Other non-hematological toxicities with an impact on organ function of grade 2 (or greater) required 25 % dose reduction and delay in subsequent therapy for a maximum of 2 weeks until it recovered to no worse than grade 1.