useful to examine the antitumor effects of anticancer drugs, as it takes only a short time for the effects of the agents to be assessed. In this study, we presented the data regarding single-agent administration of GEM and CBDCA. We are currently conducting a study on the combination, and will report the results in a future paper.

This report provides valid findings that would contribute to improvement of the prognosis of patients with CCC. We anticipate that our findings would also promote the development of further in vitro studies.

Disclosure

The authors report no conflicts of interest in this work.

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CASE REPORT

Monochorionic twin fetus with VACTERL association after intracytoplasmic sperm injection

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ABSTRACT   We report a rare case of a monochorionic twin gestation after intracytoplasmic sperm injection (ICSI) in which one of the fetuses had VACTERL association. A 27-year-old woman became pregnant by ICSI and was found to have monochorionic twin fetuses. One fetus was noted to have the following anomalies: a multicystic, dysplastic left kidney with a hydroureter, and a dilated colon. A normal-sized stomach and normal amount of amniotic fluid were observed during the prenatal period with no other anomalies. The postnatal examination revealed hypospadias, and anal, esophageal, and duodenal atresia; thus, a diagnosis of VACTERL association was established. Although the prenatal diagnosis of this disorder is a challenge, even in a singleton, some of the characteristic features observed during antepartum ultrasonography may be a clue to the diagnosis, especially in a twin pregnancy after ICSI.

Key Words: fetal ultrasound, intracytoplasmic sperm injection, monochorionic twin, prenatal diagnosis, VACTERL association

INTRODUCTION

VACTERL association (V, vertebral defects; A, anal atresia; C, cardiac anomaly; TE, tracheal-esophageal fistula with esophageal atresia; R, renal defects; and L, radial limb dysplasia) is a spectrum of fetal anomalies with an incidence of 1–9/100 000 infants (Botto et al. 1997; Solomon 2011). Patients are considered to have VACTERL association if three or more organ systems are involved. This disorder generally occurs sporadically in an otherwise normal healthy family. The etiology of VACTERL remains unknown. A familial pattern of VACTERL association also occurs in 8–10% of patients (Solomon et al. 2010). Although antepartum ultrasonography can demonstrate some of the characteristic findings, the prenatal diagnosis of VACTERL association is not always possible because it is very difficult to detect all of the symptoms associated with this disorder during the prenatal period. However, patients with VACTERL association require considerable postnatal surgical treatment and care, and thus the perinatal management of an affected infant is essential for obstetricians and neonatologists although the prenatal diagnosis of this disorder is a challenge.

Reports on fetuses with VACTERL association in twin pregnancies have been limited and there is a paucity of data in the literature regarding the incidence of this disorder in twin fetuses (Camacho et al. 2008; Athwal et al. 2010). We herein report a rare case of a

monochorionic twin fetus with VACTERL association conceived by intracytoplasmic sperm injection (ICSI).

CLINICAL REPORT

A 27-year-old Japanese nulligravida underwent ICSI and frozen embryo transfer as treatment for idiopathic spousal oligospermia and achieved a pregnancy. She was found to have monochorionic diamniotic twin fetuses in the first trimester and was referred to our hospital for perinatal management of this condition. An ultrasound at 20 weeks of gestation revealed the following in fetus A: a multicystic, dysplastic left kidney (Fig. 1); normal-sized stomach; no abdominal cysts; no cardiac anomalies; and no limb abnormalities. No congenital anomalies were detected in fetus B. At 31 weeks of gestation, fetus A developed a left hydroureter (Fig. 2). Moreover, dilatation of the colon progressed in fetus A (Fig. 3). Both of the fetuses grew normally with a normal amniotic fluid volume.

Preterm rupture of membranes occurred at 36 weeks of gestation and a cesarean section was performed. Infant A was a male weighing 2024 g and infant B was a male weighing 2208 g. Histologic examination of the placenta confirmed a monochorionic, diamniotic twin pregnancy. Infant B was healthy and no cardiac, renal, or congenital anomalies were demonstrated on ultrasound and physical examination. Infant A had hypospadias, and anal, esophageal (gross C type), and duodenal atresia. An X-ray did not reveal vertebral abnormalities except six lumber vertebrae which might merely reflect lumbarization of S1 (Fig. 4). No limb deficiencies were evident on X-ray. Postnatal ultrasound confirmed a left ureterocele, hydroureter, and a multicystic, dysplastic kidney without cardiac anomalies. The chromosomal analysis showed a normal karyotype (46, XY). Therefore, a postnatal diagnosis of VACTERL association was established in infant A. Repairs of the esophageal and duodenal atresia, and a colostomy for the anal atresia were successfully performed.

DISCUSSION

VATER association has been defined as the presence of at least three of the five classic VATER anomalies (vertebral defects, anal atresia, tracheoesophageal fistula, renal defects, and radial ray limb deficiency). Additional defects associated with VATER association include genital defects, cardiovascular anomalies, and small intestinal atresia, as well as rotary malpositioning of the hand, clinodactyly, or syndactyly. The expanded VATER association, including cardiac and limb defects, is referred to as VACTERL association (Temtamy and Miller 1974; Khoury et al. 1983; Czeizel and Ludanyi 1985). Herein we report monozygotic twins, one fetus of which had VATERL association based on the presence of anal atresia, tracheoesophageal fistula (gross C type esophageal atresia),
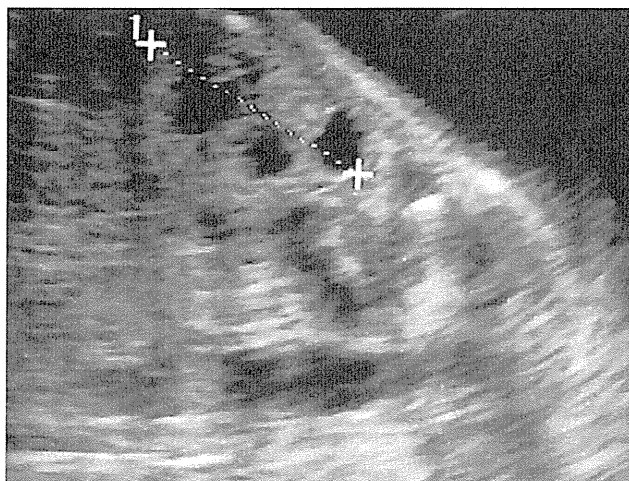
Fig. 1 Ultrasound at 20 weeks of gestation revealed a left multicystic, dysplastic kidney in fetus A.
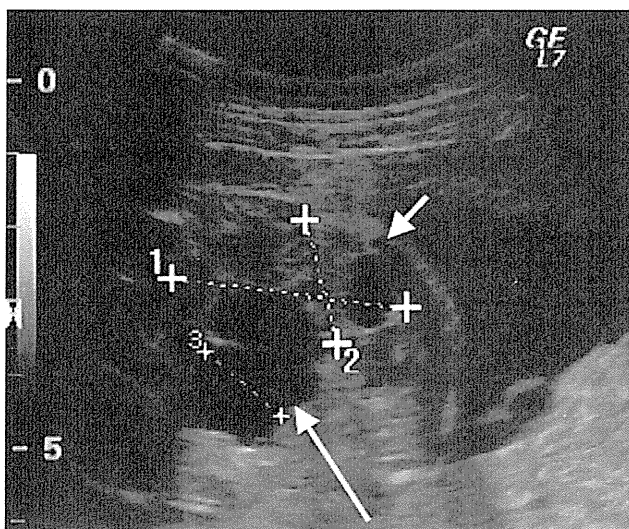

Fig. 2 Ultrasound at 31 weeks of gestation revealed a left hydroureter (long arrow) and a multicystic, dysplastic kidney (short arrow) in fetus A.

Fig. 3 Ultrasound sagittal view of the abdomen in fetus A revealed a remarkable dilatation of the colon.
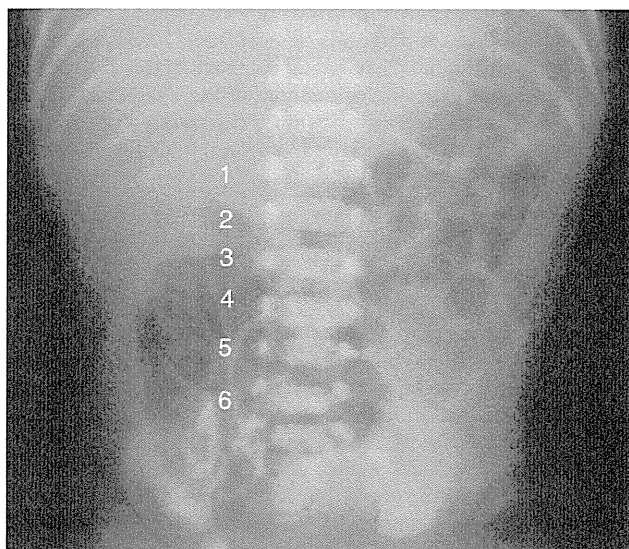

Fig. 4 Abdominal X-ray of infant A revealed six lumbar vertebrae.

a left ureterocele, hydroureter, and a multicystic, dysplastic kidney. The presence of these three defects of the six categories supports the diagnosis.

The differential diagnosis of VACTERL association is broad, and includes a number of conditions for which genetic testing is available. The presence of other features not typically observed in VACTERL association may suggest other disorders, such as pigmentary abnormalities in Fanconi anemia or hypocalcemia in deletion 22q11.2 syndrome. Ruling out these disorders includes evaluation for features that are not typical of VACTERL association, such as brain malformations, ophthalmologic anomalies, and hearing deficits (Solomon 2011). Infant A had duodenal atresia, which is a feature not typically present in VACTERL association;

however, no other findings were noted in our case that would affect the differential diagnosis, including a chromosomal abnormality.

The embryology of VACTERL association is unknown. VACTERL association may result from a single early defect in fetal blastogenesis or mesoderm formation. It has been shown that the defects in VACTERL association are all due to defects in blastogenesis. Martinez-Frias et al. (1998) suggested that the entire embryo represents the developmental field during blastogenesis. Such a single 'hit' during blastogenesis may produce an association of anomalies, while later in gestation a similar hit would produce only a single anomaly.

The majority of studies comparing the prevalence of congenital anomalies at birth in singleton and plural births have observed an increased risk in the latter. Among twins, a higher prevalence of

congenital anomalies occurs in monochorionic twins compared to dichorionic twins (Glinianaia et al. 2008). The incidence of congenital anomalies in a twin pregnancy is approximately 1.5 times that of a singleton fetus, and the incidence of congenital anomalies in a monochorionic twin is approximately 1.5 times that of a dichorionic twin (Layde et al. 1980).

Machin (1996) reported that most monozygotic twin pairs are not identical. Indeed, there may be major differences in birth weight, genetic diseases, and congenital anomalies in monozygotic twin pairs. These facts indicate that post-zygotic events may lead to the formation of two or more cell clones in the inner cell mass and the early embryo that actually stimulates the monozygotic twinning event. There is also evidence that there may be an unequal allocation of the number of cells to the monozygotic twin; this may have widespread implications for the cascade of developmental events during embryogenesis, formation, and vascularization of the placenta.

Many studies suggest that infants resulting from ICSI pregnancies have an increased risk of major congenital anomalies compared with infants born after spontaneous conception. ICSI is a more invasive procedure than routine *in vitro* fertilization. When a spermatozoon is injected through the oocyte membrane, problems involving the technique of ICSI itself, chromosomal aberrations of sperm, and hereditary abnormalities may be transmitted to the conceptus (Bonduelle et al. 2002); however, there have been no reports demonstrating a relationship between VACTERL association and ICSI. Sunagawa et al. (2007) reported the first and only case in which both dichorionic twin fetuses conceived after ICSI had VACTRL association. Although Sunagawa et al. (2007) suggested a possible relationship between VACTERL association and ICSI, they concluded that their case might be explained by the natural occurrence rate of this association in twins, not by the ICSI procedure. Therefore, we do not know the exact basis for the etiology of this disorder in our monochorionic twin. Only a few cases with VACTERL association in a monochorionic twin pregnancy have been reported and there is a paucity of data in the literature describing the incidence of this disorder in a twin (Camacho et al. 2008; Athwal et al. 2010). Although Botto et al. (1997) reviewed 286 VATER infants, there was no mention of twins. Czeizel and Ludanyi (1985) reviewed 43 infants that included two sets of twins; however, they were not monozygotic.

Reports on the prenatal diagnosis of VACTERL association are rare. Tongsong et al. (1999) mentioned that the existence of several sonographic markers of the VATER complex allows this disorder to be detected on prenatal sonography. Of note, antepartum ultrasonography only revealed a multicystic, dysplastic kidney, a hydroureter, and enteric expansion in our case. Although the prenatal diagnosis of VACTERL association is not always possible because it is very difficult to detect all of the symptoms associated with this disorder during the prenatal period, antenatal suspicion of this disorder should be helpful for early postnatal definitive diagnosis and care of the affected infant.

In conclusion, we managed a rare case of a monochorionic twin fetus with VACTERL association conceived by ICSI. Whether or not the VACTERL association is a specific congenital anomaly among twin pregnancies after ICSI is more frequent than other anomalies is not known. Although the prenatal diagnosis of this disorder is still a challenge, even in a singleton fetus some of the characteristic features observed with prenatal ultrasonography may be a clue to the diagnosis, especially in a twin pregnancy through ICSI.

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Picture of the Month

Towards improved ultrasound-based analysis and 3D visualization of the fetal brain using the 3D Slicer

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Magnetic resonance imaging (MRI) provides useful three-dimensional (3D) information; however, there are some restrictions on its use during pregnancy due to safety concerns. In addition, fetal movements can create artifacts on MR images, as image quality depends on position of the fetus and placenta. In the past decade, 3D ultrasound imaging has been used in clinical practice to investigate the formation and volumetric size of critical anatomical structures of the fetus. However, current techniques rely mainly on analysis of sections of interest that do not integrate anatomical information concerning the shape of these structures.
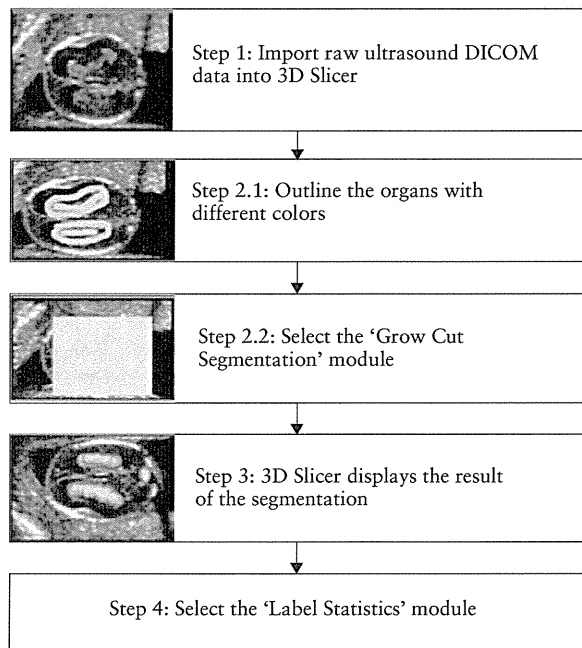

Figure 1 Flowchart describing the 3D Slicer workflow used in this study. DICOM, digital imaging and communications in medicine.
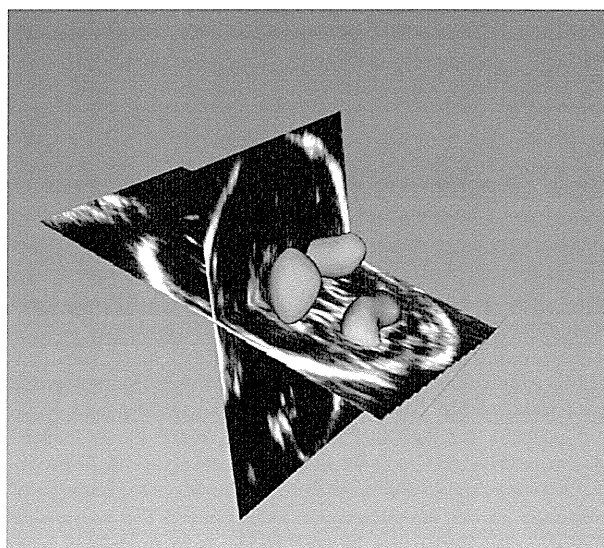
Figure 2 Result of 'Grow Cut Segmentation' of the fetal brain using the 3D Slicer. The blue structure represents the choroid plexus, and the yellow structure the cerebrum at 14 weeks of gestation (axial and coronal views).

We provide a brief description of a workflow for semi-automated segmentation and 3D visualization of fetal ultrasound volumes in the second trimester using the 3D Slicer open source software[1,2]. Our workflow allowed quantitative image analysis of the choroid plexus and cerebrum from 3D ultrasound images.

We acquired 3D ultrasound volumes from five healthy pregnant women at 12 (n = 2), 14 (n = 2) and 19 (n = 1) weeks of gestation. Informed consent was obtained in each case. We used a Voluson E6 (GE Medical Systems, Zipf, Austria) ultrasound machine with a RAB4-8-D/OB D/4D 8-MHz transabdominal transducer. Our workflow consisted of four steps (Figure 1). Firstly, we imported DICOM (digital imaging and communications

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PICTURE OF THE MONTH

in medicine) ultrasound volumes into the 3D Slicer. We then used the 'Grow Cut Segmentation' algorithm[3] of the interactive Editor module to extract critical structures from the ultrasound volumes. We reconstructed 3D surface models from segmented regions using the 'Marching Cubes' algorithm[4], and finally computed the volume of 3D anatomical models using the 'Label Statistics' module of the software.

Figure 2 shows a 3D surface model of the choroid plexus and cerebrum reconstructed from the original 3D ultrasound volumes. The corresponding volumes of these structures at 12, 14 and 19 weeks' gestation were, respectively: 431.1 mm³, 698.9 mm³ and 1203.3 mm³ for the choroid plexus and 183.6 mm³, 282.8 mm³ and 469.8 mm³ for the cerebrum.

Using the 3D Slicer, we were able to obtain patient-specific quantitative information and 3D visualization of anatomical structures within the fetal brain. We anticipate being able to perform segmentation that accurately matches the anatomy using different methods. We believe this method, combined with ultrasound or MRI data, will be helpful in monitoring fetal development and detecting anomalies of the brain as well as other anatomical structures.

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Investigation of the clinicopathological features of fallopian tube malignancy

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Abstract. The present study investigated the clinico-pathological features of fallopian tube malignancy (FTM) and elucidated the biological behavior of this disorder. Data were compiled concerning FTM from 68 patients from 7 institutes. The patients included 60 cases with fallopian tube carcinoma and 8 cases with fallopian tube carcinosarcoma. The clinical stage was stage III or higher in 72% of the cases. A complete response or partial response was achieved in 56 and 10 of the 68 patients with FTM, respectively, indicating a response rate of 97.1%. The median observation period for FTM was 41 months (3 to 126 months). Three of the 19 patients with stage I/II disease (16%) and 31 of the 49 patients with stage III/IV disease (63%) experienced recurrence, with a median progression-free survival of 17.5 months, and a 3-year overall survival of 77.2%. Regarding the site of recurrence, local intraperitoneal recurrence (26.2%) and solitary recurrences in lymph nodes (19.0%) and in the liver (16.7%) were relatively frequent. Secondary debulking surgery (SDS) was performed in 15 patients (44%) out of the 34 recurrent FTMs. Conversely, recurrence was associated with ascites (carcinomatous peritonitis) in 4 of the 34 recurrent patients, but all 4 patients died. The median survival period after recurrence was 28 months: 7.5 and 30 months with and without ascites, respectively (P<0.001). A univariate analysis showed that prognosis was significantly correlated only with whether SDS could be performed. These results suggest that since FTM frequently results in solitary recurrence, aggressive recurrence treatment including SDS could improve prognosis.

Introduction

Fallopian tube malignancy (FTM) is a rare disease that comprises only 0.14 to 1.8% of female genital malignancies (1). The incidence rate in the United States is estimated to be on average 3.6/million/year (2). Although rare, FTM is a disease that has increased 4.5-fold over the past 40 years (3). Even though the staging and therapeutic strategy for fallopian tube carcinoma are based on those of ovarian carcinoma, it is difficult to conduct a large-scale clinical study exclusively on fallopian tube carcinoma because of its rarity, and the pattern of metastasis as well as time to recurrence are not clear. Wethington *et al* (4) compared the outcome of fallopian tube carcinoma and ovarian carcinoma based on the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute, and showed that fallopian tube carcinoma was associated with a more favorable long-term outcome than ovarian carcinoma. However, the biological behaviors of fallopian tube carcinoma such as location of recurrence and time to recurrence remain unknown (4).

This study was a retrospective, multicenter study that aimed to investigate the clinicopathological features of FTM and to elucidate the biological behaviors of this disease.

Materials and methods

All patients with FTM treated between January 2001 and December 2011 were eligible for this study. Institutional review board approval was obtained at each of the 7 participating academic centers prior to data acquisition, and informed

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consent was obtained from the patients or the guardians. Cases were defined as FTM using diagnostic criteria as documented by Sedlis (5). Briefly, these criteria were as follows: i) the main tumor arises from the endosalpinx; ii) the histological pattern reproduces the endothelium of the tube mucosa; iii) transition from benign to malignant tubal epithelium is demonstrable; iv) the ovaries or endometrium are either normal or contain a tumor smaller than the tumor in the tube. In addition, we also adopted the definition of fallopian tube carcinoma of WHO classification which states that there is a primary lesion in the lumen or fimbriae of the fallopian tube and a lesion does not exist in the ovary and the uterine or it is different from the fallopian tube clearly even if it exists (6). All slides were reviewed by expert pathologists from each institution. A common database form was designed to be utilized by all participating centers. The medical records included information regarding age, gravidity and parity, clinical presentation, disease stage, type of surgery performed, treatment rendered, histological type, progression-free survival (PFS), overall survival (OS), and sites of recurrence. Patients of all stages were eligible. Staging was based on the International Federation for Obstetrics and Gynecology (FIGO) criteria. Procedures included in the standard surgery consisted of bilateral salpingo-oophorectomy, hysterectomy and greater omentectomy with or without cytoreduction. Staging laparotomy included retroperitoneal (pelvic, para-aortic) lymph node dissection (or biopsy) and intraperitoneal biopsies in addition to standard surgery. The 1-cm cutoff was used as a threshold for optimal cytoreduction (7). When adjuvant chemotherapy was indicated, patients generally received platinum/taxan-based combination chemotherapy. Cases that received neoadjuvant chemotherapy also were included in this retrospective study.

Clinical response was assessed in the enrolled patients with lesions that could be measured according to the revised RECIST guideline (version 1.1) (8). A complete response (CR) was defined as the complete disappearance of all measurable lesions. A partial response (PR) was defined as a 30% or greater decrease in the sum of the measurable lesions. Stable disease was defined as a steady state of response less than PR or an increase in <20% in the sum of the measurable lesions. Progressive disease was defined as an increase of 20% or more in the sum of the measurable lesions or the appearance of new lesions.

PFS was calculated from the date of the start of treatment to the date of recurrence or progression. OS was calculated from the date of the start of treatment to the date of death or last follow-up. The cumulative survival curve and median PFS time were estimated by use of the Kaplan-Meier method. Comparison between survival curves was carried out using the log-rank test. Difference in response rate between predictive variables was analyzed using the Chi-square test. Statistical significance was set at P<0.05.

Results

Patient characteristics. Patient characteristics are shown in Table I. Sixty-eight patients with FTM were enrolled for this retrospective analysis. The 68 patients with this disease included 60 cases with fallopian tube carcinoma and 8 cases with fallopian tube carcinosarcoma. The median age of the patients

Table I. Patient characteristics.

Clinical factors	No. of patients
Fallopian tube malignancy	
Carcinoma of the fallopian tube	60
Carcinosarcoma of the fallopian tube	8
Median age (range), in years	60 (38-85)
History of delivery	
Yes	64
No	4
Menstruation	
Premenopause	14
Postmenopause	54
Chief complaint	
Lower abdominal pain or distension	27
Atypical genital bleeding	21
Feeling of abdominal mass	5
Bloody bowel discharge	2
Asymptomatic	10
Others	3
Serum CA-125, median (range), U/ml	338.5 (4-16,000)
Preoperative diagnosis	
Ovarian carcinoma	45
Fallopian tube carcinoma	9
Endometrial carcinoma	9
Colon carcinoma	2
Others	3
Neoadjuvant chemotherapy	
Yes	10
No	58
FIGO stage	
I	11
II	8
III	40
IV	9
Histological type	
Serous	50
Endometrioid	6
Undifferentiated	2
Clear cell	1
Transitional	1
Carcinosarcoma	8
Debulking surgery	
Complete or optimal	44
Suboptimal	24
Type of surgery	
With staging	34
Without staging	34
Chemotherapy	
Paclitaxel + carboplatin	57
Docetaxel + carboplatin	3
Ifosfamide + epirubicin + cisplatin	4
Paclitaxel alone	1
None	3

Table II. Patient outcome.

Outcome	No. of patients
Response evaluation	
Complete response	56
Partial response	10
Stable disease	1
Progressive disease	1
Recurrence	
Yes	34
No	34
Secondary debulking surgery	
Yes	15 (44.1%)
No	19
Progression-free survival (median, months)	17.5
Three-year survival rate	77.2%

Table III. Sites of recurrence.

Recurrent site[a]	No. of patients (%)
Intraperitoneal (with ascites)	4 (9.5)
Intrapertitoneal (without ascites)	8 (19.0)
Pelvic cavity	11 (26.2)
Lymph nodes	8 (19.0)
Liver	7 (16.7)
Lung	3 (7.1)
Increase in CA-125 alone	1 (2.5)

[a]Included are 30 recurrent carcinomas and 4 recurrent carcinosarcomas of the fallopian tube. Several relapsed patients had one or more recurrent sites.
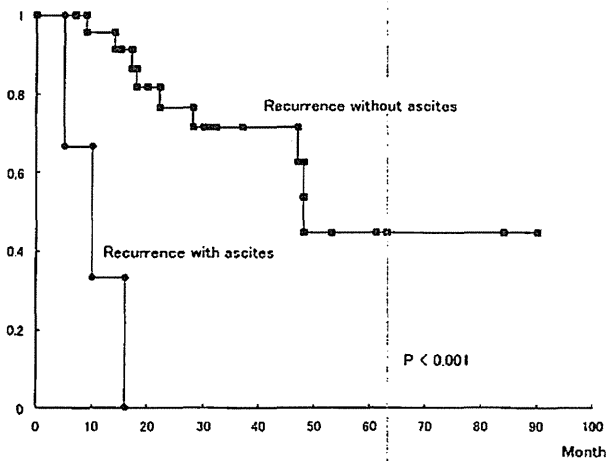

Figure 1. Survival time after recurrence. The median survival time after recurrence was 28 months: 7.5 and 30 months with and without ascites, respectively (P<0.001).

was 60 years (range, 38-85 years); initial symptoms included so-called Latzko's triad of lower abdominal pain (including bloating) in 27 patients (39.7%), atypical genital bleeding in 21 patients (30.9%), and the sensation of an abdominal mass in 5 patients (7.4%). Melena due to infiltration of the bowel was the initial symptom in 2 patients. Preoperative diagnoses included a suspected ovarian carcinoma in 45 patients (66.2%); fallopian tube carcinoma was suspected before surgery in just 9 patients (13.2%). Endometrial carcinoma was suspected and treatment for this condition was started in 9 patients (13.2%). Histological types were serous adenocarcinoma in 50 patients, endometrioid adenocarcinoma in 6 patients, and other types in 4 patients. All of the 8 carcinosarcomas were heterologous. The clinical stages were: stage I in 11 cases, stage II in 8 cases, stage III in 40 cases, and stage IV in 9 cases, indicating that

stage III or more comprised 72% of the cases. All of the 68 patients underwent standard surgery, and additionally staging surgery was performed in 34 patients. Optimal surgery was achieved in 44 patients (64.7%) (including 10 patients who underwent associated intestinal resection) and suboptimal surgery was achieved in 24 patients. The median number of chemotherapy cycles was 6 (range, 1-12). Postoperative chemotherapy included platinum-based combination treatment in 64 patients (94%).

Patient outcome. Patient outcome is summarized in Table II. The initial therapeutic effect in 68 patients with this disease was CR in 56 patients and PR in 10 patients, indicating that a response rate as high as 97.1% was achieved. The median observation period for FTM was 41 months (8-126 months). Three of 19 patients with stage I/II disease experienced recurrence and one patient died. The patient who died was a patient who received incomplete chemotherapy due to the presence of chronic renal failure. Recurrence occurred in 31 of 49 stage II/IV patients (63%), with a median PFS of 17.5 months, and a 3-year OS of 77.2%.

While the most frequent site of recurrence was intraperitoneal dissemination, local pelvic peritoneal recurrence (26.2%) and solitary recurrences in the lymph nodes (19.0%) and the liver (16.7%) were relatively frequent (Table III). Secondary debulking surgery (SDS) such as resection of the relapsed abdominal/pelvic mass or lymph nodes, or partial hepatectomy was performed in as many as 44% of patients with recurrence (Table II). Conversely, recurrence was associated with ascites (carcinomatous peritonitis) in just 4 of the relapsed 34 patients, but all 4 patients died. The median survival time after recurrence was 28 months: 7.5 and 30 months with and without ascites, respectively (P<0.001) (Fig. 1).

Determination of factors predicting poor outcome in fallopian tube malignancies. Univariate analysis by histological type, FIGO stage, age, CA-125 level, operative procedure, completion rate, recurrent site, presence or absence of SDS performance, and time to recurrence was performed to assess predictive factors related to the prognosis of FTM. Prognosis was significantly correlated solely with whether SDS could be performed (Table IV).

Table IV. Determination of factors predicting poor outcome in fallopian tube malignancy.

Factors	No. of patients	Death events from this disease	P-value
Histology			
Carcinoma of the fallopian tube	60	12	
Carcinosarcoma of the fallopian tube	8	2	ns
Stage			
I/II	19	2	
III/IV	49	12	ns
Age, years			
≥60	33	8	
<60	35	6	ns
CA-125 value			
≥330	33	7	
<330	35	7	ns
Completion of surgery			
Complete or optimal	44	10	
Suboptimal	24	4	ns
Staging laparotomy			
Yes	34	7	
No	34	7	ns
Recurrent sites			
Intraperitoneal	12	6	
Others	30	8	ns
Ascites in recurrence			
Yes	4	4	
No	30	10	ns
Secondary debulking surgery			
Yes	15	1	
No	19	13	<0.01
Time to recurrence			
≥6 months	30	13	
<6 months	2	1	ns

ns, not significant.

Discussion

This study revealed that, although intraperitoneal recurrence occurred in fallopian tube carcinoma and carcinosarcoma, recurrence presented as carcinomatous peritonitis was noted in only 4 of the 34 patients with relapsed disease; isolated metastases to the abdominal/pelvic cavity or lymph nodes and sole metastasis to the liver were relatively frequent. Therefore, it appears that post-recurrence survival was prolonged since in many patients SDS such as excision of the relapsed abdominal/pelvic mass or the relapsed lymph node or partial hepatic resection was indicated. This fact was also supported by the univariate analysis which revealed that prognosis was significantly correlated solely with whether SDS was performed. Previous studies have shown that FTM easily infiltrates surrounding organs and progresses aggressively (1), and that

lymph node metastasis occurs more frequently than that in ovarian carcinoma (9). The present study, however, showed that only 4 of the 34 patients with recurrent disease developed carcinomatous peritonitis, demonstrating for the first time that carcinomatous peritonitis is uncommon. It is already known in cases of ovarian carcinoma that the prognosis of a solitary recurrence in the liver is significantly improved by partial hepatic resection (10). Thus, the results of the present study suggest that SDS should be positively introduced to recurrent FTMs unless patients develop carcinomatous peritonitis.

With regard to the initial site of recurrence, FTM shows contrasting findings with those for ovarian carcinoma (Table III). While the present results demonstrated a high frequency of lymph nodes recurrence (19.0%) and solitary liver metastasis (16.7%), Ushijima reported that lymph node metastases (7.1%) and solitary liver metastases (6.3%) occur

infrequently in ovarian carcinoma (11). FTM is richly permeated with lymphatic channels that drain into the para-aortic lymph nodes through infundibulopelvic lymphatics (12), and indeed a more frequent rate of lymph node metastasis than ovarian carcinoma has been reported (9,11). In addition, Ajithkumar *et al* (13) found that metastasis to the retroperitoneal lymph nodes was observed at the initial visit in ~50% of patients, irrespective of the stage of disease advancement. In this study as well, metastasis to the retroperitoneal lymph nodes was observed in 16 of the 34 patients (47.1%) on whom staging surgery was conducted initially (data not shown).

It has been reported that platinum-based chemotherapy for advanced or recurrent fallopian tube carcinoma resulted in CR in 75% of patients (14) and that an 82.2% response rate was obtained in progressive fallopian tube carcinoma (9). In this study, the combination therapy with platinum and a taxane was chosen as a postoperative chemotherapeutic regimen for most patients, and CR to postoperative chemotherapy was 82% in the present patients, although suboptimal surgery accounted for ~35% of all patients. There was no difference in the number of deaths between patients who received optimal surgery and those who received suboptimal surgery, suggesting that aggressive postoperative chemotherapy was mandatory and the combination of platinum and a taxane was effective, even in patients undergoing suboptimal surgery. The results of the present study were compatible with those of Baekelandt *et al* (15) and Gemignani *et al* (16), in which an 87.5% response rate and significant prolongation of PFS were observed. These reports and this study suggest that combination therapy with platinum and a taxane is effective against FTM. Given that the response rate to chemotherapy in epithelial ovarian carcinoma was found to be 56% (17) and that the rate for ovarian carcinosarcoma was 20 to 68% (18,19), the favorable effect of initial therapy in FTM is noteworthy. This favorable therapeutic effect may be attributed to the histological type of fallopian tube carcinoma, which is largely composed of serous and endometrioid adenocarcinoma.

Within Latzko's triad, atypical genital bleeding was observed in ~30% of patients in this study. If an adnexal tumor is detected in patients with atypical genital bleeding or a watery vaginal discharge, FTM should be considered as a differential diagnosis. Nevertheless, a definitive preoperative diagnosis of FTM is difficult in many patients. It has been reported that FTM is diagnosed preoperatively in 0 to 10% of patients (20-22). Moreover, Meng *et al* (23) reported that in 50% of patients, even intraoperative findings fail to identify that the primary site is the fallopian tube. In this study, preoperative diagnosis was feasible in 13.2% of patients, probably by virtue of advances in imaging diagnosis. Transvaginal ultrasonography has been reported to be more effective than abdominal ultrasonography (24), and the presence of a sausage-like mass and/or multilobular mass with a 'cog-and-wheel' appearance is considered to be the basis for suspecting a FTM (25-27). Diagnostic ability has improved with the development of color Doppler and three-dimensional Doppler transvaginal ultrasonography (28). However, findings that clearly discriminate FTM have not been identified, even with full use of CT and MRI. Although this provides no clinical specificity, the CA-125 level is increased in 80% or more of patients with fallopian tube carcinoma (13,29). Although it

has been reported occasionally that the preoperative CA-125 level is an independent predictive factor for the prognosis of fallopian tube carcinoma (13,30) and that this level correlates with responsiveness to chemotherapy (31,32), such a correlation with the prognosis and therapeutic effect was not observed in this study. More cases need to be accumulated to establish the clinical significance of the CA-125 level in fallopian tube carcinoma.

A retrospective multicenter study was conducted recently to clarify the prognosis of fallopian tube carcinoma. Moore *et al* (33) used matched, case-controlled methods to compare the prognosis of fallopian tube carcinoma in 96 patients and epithelial ovarian carcinoma in 189 patients. Comparison of stage I/II with a median observation period of 57 months for fallopian tube carcinoma and 42 months for ovarian carcinoma showed a 5-year survival rate of 95% for fallopian tube carcinoma and 76% for ovarian carcinoma (P=0.02); a similar comparison in stage III/IV disease with a median observation period of 33 months for fallopian tube carcinoma and 35 months for ovarian carcinoma, showed a 3-year survival rate that was comparable (59%) for both diseases. Accordingly, Moore *et al* (33) re-evaluated the concept that therapy for fallopian tube carcinoma could be similar to that for ovarian carcinoma. Conversely, Pectasides *et al* (34) analyzed 64 patients with fallopian tube carcinoma and reported that advanced stage and residual tumor diameter correlated significantly with prognosis. In stage III/IV fallopian tube carcinoma, while the 5-year survival in patients whose residual tumors could be debulked to less than 1 cm was 55%, the 5-year survival of patients with larger residual tumor deposits was 21% (9). Thus, optimal debulking and subsequent platinum/taxan therapy were concluded to confer a favorable prognosis. In addition, a large population-based tumor registry study in which 416 patients with fallopian tube carcinoma were included showed that the 5-year survival rate was 95% for stage I, 75% for stage II, 69% for stage III, and 45% for stage IV, respectively, indicating that the prognosis was better than the 5-year survival rate for each stage of ovarian carcinoma evaluated at around the same time (35). More recently, using SEER database, the outcome of 1,576 women with fallopian tube carcinoma and 54,249 with epithelial ovarian carcinoma was compared (4). Five-year cancer-specific survival was 54 and 36% in women with stage III and IV fallopian tube carcinoma, respectively, vs. only 30 and 14% in those with the same stage epithelial ovarian cancer, respectively (4). However, initially relapsed locations and time to recurrence were not clarified in the SEER database (4). The present results suggest that there are many isolated recurrences and few recurrences of carcinomatous peritonitis for FTMs. Thus, because there are many cases of FTMs for which recurrent tumors can be extracted by surgery, even if the disease relapsed, prognosis would be improved. Although a hypothesis for the origin of ovarian and peritoneal carcinoma has been proposed, based on the concept of transport and implantation of malignant cells from the fallopian tube to the ovary and peritoneum (36), the results of this study suggest that FTM has a different biological behavior when compared to ovarian carcinoma.

The present study suggests that FTM frequently results in solitary recurrence, and that aggressive recurrence treatment including SDS would improve the prognosis of this disease.

However, several limitations must be acknowledged in this study. While differentiation of fallopian tube and ovarian carcinoma for women with advanced stage disease is sometimes difficult (37), a central pathology review was not performed as a retrospective nature. Although clinical features of fallopian tube carcinoma are not distinct from those of ovarian carcinoma as reported using case-control analysis (38), this study did not adopt a case-control method. Further study to elucidate the molecular mechanisms involved in the development of FTM and to improve decision-making for disease treatment is warranted.

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ORIGINAL ARTICLE

A pilot study of oxaliplatin with oral S-1 as second-line chemotherapy for patients with recurrent adenocarcimona of the uterine cervix

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Abstract

Background The efficacy and safety of S-1/oxaliplatin (SOX) therapy in patients with recurrent adenocarcinoma of the uterine cervix were examined in a pilot study.

Patients and methods S-1 was orally administered for 14 days at a dose of 80–120 mg/body/day to 7 patients with recurrent adenocarcinoma of the uterine cervix, with oxaliplatin being administered intravenously at a dose of 100 mg/m^2 on day 1. Each therapy cycle was 21 days, and the patients received 6 cycles at most. The antitumor effect, adverse events, progression-free survival (PFS), and overall survival (OS) were investigated.

Results The median age of the patients was 49 years. The antitumor effect was rated as a complete response in 2 patients, partial response in 2, and stable disease in 3. The overall response rate was 57.1 %, and the disease control rate was 100 %. Regarding hematological toxicities of grade 3 or more, leukopenia, neutropenia and thrombocytopenia occurred in 42.9, 28.6 and 14.3 %, respectively; regarding non-hematological toxicities, grade 3 rectovaginal fistula occurred in 14.3 %, as well as grade 2 fatigue in 14.3 % of the patients. The median PFS and OS were 5 months (range 3–9 months) and 7 months (range 4–43 months), respectively.

Conclusions These results suggest that SOX therapy is useful for the treatment of recurrent adenocarcinoma of the uterine cervix, having a promising antitumor effect and minimal adverse effects. It was also suggested that SOX therapy may contribute to improving the prognosis for patients with adenocarcinoma of the uterine cervix.

Keywords Oxaliplatin · S-1 · SOX · Cervical adenocarcinoma · Chemotherapy

Introduction

Currently, adenocarcinoma of the uterine cervix accounts for about 20–25 % of all uterine cervix cancers, and its frequency is rising [1]. It has been reported previously that adenocarcinoma of the uterine cervix carries a poorer prognosis than squamous cell carcinoma [2–4]. The reasons cited for this poorer prognosis include the occurrence of lymph node metastasis at a relatively early stage [5] and low sensitivity to radiation therapy [6]. Therefore, chemotherapy is expected to be more effective for improving the prognosis than radiation or chemoradiotherapy. Although new therapeutic strategies should be tried, few studies have focused on adenocarcinoma, and thus no high-level evidence has yet been obtained.

Katsumata et al. used S-1 therapy (80–120 mg/day) in 37 patients with advanced or recurrent carcinoma of the uterine cervix; each cycle of S-1 therapy consisted of 4-weeks' continuous administration followed by a 2-week rest period. They reported that the response rate was 30.6 %, the median time to progression was 5.2 months, and the median survival time was 15.4 months. Although adverse events of grade 3 or more, including diarrhea, anemia and anorexia, occurred in 22, 16 and 16 % of patients, respectively, the severity of these symptoms was within an acceptable range [7]. At present, a phase-III clinical study using S-1 (cisplatin 50 mg/m^2 on day 1 + S-1 80–120 mg/day on days 1–14 vs. cisplatin 50 mg/m^2 on day

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1) in patients with advanced or recurrent carcinoma of the uterine cervix is underway on a global scale. S-1 is considered to be a promising drug that may serve as a new therapeutic strategy for carcinoma of the uterine cervix. In addition, with regard to chemotherapy for colorectal carcinoma, it was reported that 39.5 % of patients with inoperable advanced or metastatic colorectal carcinoma responded to S-1 [8]. The results of phase-I and phase-II studies of S-1 in combination with L-OHP (oxaliplatin) (S-1 + oxaliplatin; SOX therapy) showed a high response rate of 56 % [9], attracting considerable attention to this combination regimen as an alternative to FOLFOX therapy. In Japan, an intergroup phase-II clinical study of the efficacy and safety of SOX therapy for mucinous adenocarcinoma of the ovary has been underway since 2008, and the results are currently awaited.

We conducted a pilot study of the SOX regimen in patients with adenocarcinoma of the uterine cervix. Here, we describe the efficacy and safety of this therapy as evaluated in the present study.

Subjects and methods

The subjects were 7 patients, diagnosed with recurrent adenocarcinoma of the uterine cervix between April 2007 and September 2012, who gave informed consent to participate in this study. They had evaluable lesions that were histologically confirmed to be adenocarcinoma of the uterine cervix. All 7 patients had a history of chemotherapy, and ranged in age from 20 to 75 years, had a performance status (PS) of 0–2, and had well-maintained function of their major organs. Patients who were judged to be unsuitable for safe implementation of this treatment, such as those with intestinal paralysis, intestinal obstruction, diarrhea, interstitial pneumonia, pulmonary fibrosis, and/or uncontrolled diabetes mellitus, were excluded from the study.

S-1 was orally administered twice daily for 14 consecutive days (from the evening of day 1 until the morning of day 15). Oxaliplatin was administered on day 1. The S-1 dosing regimen was 80–120 mg/body/day, per os. More specifically, the S-1 dose was 80 mg/body/day for patients whose body surface area (BSA) was less than 1.25 m^2, 100 mg/body/day for those who had a BSA of 1.25 to less than 1.5 m^2, and 120 mg/body/day for those with a BSA of 1.5 m^2 or more. Oxaliplatin, 100 mg/m^2 dissolved in 250 mL of 5 % glucose, was administered intravenously by drip infusion over 120 min. Each cycle of combination therapy consisted of 21 days, and patients received 6 cycles at most (Fig. 1).

The requirements for therapy initiation were as follows: neutrophil count, 1500/mm^3 or more; platelet count, 75000/mm^3 or more; AST/ALT, less than 100 IU/L (less
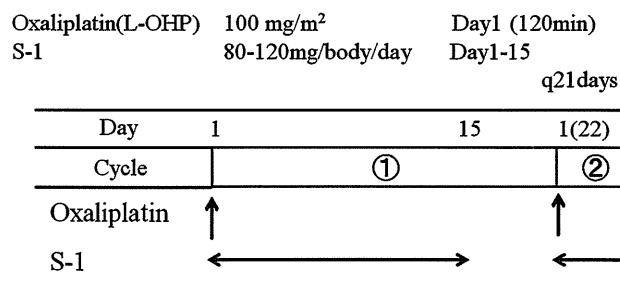

Fig. 1 Oxaliplatin, 100 mg/m^2 dissolved in 250 mL of 5 % glucose, was administered on day 1 by intravenous drip infusion over 120 min. S-1 was orally administered twice daily for 14 consecutive days (from the evening on day 1 until the morning on day 15). The dose of S-1 was 80 mg/body/day in patients with a body surface area (BSA) of less than 1.25 m^2, 100 mg/body/day in those with a BSA of 1.25 m^2 or more and less than 1.5 m^2, and 120 mg/body/day in those with a BSA of 1.5 m^2 or more. Each cycle of therapy consisted of 21 days

than 150 IU/L when there was liver metastasis); total bilirubin, less than 1.5 mg/dL; serum creatinine, less than 1.5 mg/dL; and no signs of diarrhea or infection. The requirements for initiation of a second cycle were: neutrophil count, 1500/mm^3 or more; platelet count, 75000/mm^3 or more; and the absence of non-hematological toxicities of grade 2 or more excluding nausea, vomiting, anorexia, fatigue, and hair loss.

In patients with grade 4 thrombocytopenia in the previous cycle or whose platelet count did not reach 75,000/mm^3 on the day scheduled for initiation of the next cycle but who showed a restored count within 14 days, the dose of oxaliplatin was reduced from 100 to 75 mg/m^2. When the platelet count did not reach 75,000/mm^3 even after 14 days, the therapy was discontinued. When grade 4 neutropenia persisted for at least 5 days, or when febrile neutropenia of grade 3 or more occurred, the dose of oxaliplatin was reduced from 100 to 75 mg/m^2, and the dose of S-1 was reduced by one level (e.g., a previous dose of 120 mg/body/day was decreased to 100 mg/body/day; similarly, 100 was reduced to 80 mg/body/day and 80 to 50 mg/body/day). When grade 2 sensory nerve disorder occurred and did not improve to grade 1 by the day scheduled for initiation of the next cycle, the oxaliplatin dose was reduced from 100 to 75 mg/m^2. When the same symptoms developed a second time, the oxaliplatin dose was reduced from 75 to 50 mg/m^2. If the same symptoms were observed a third time, the therapy was discontinued. When sensory nerve disorder of grade 3 occurred but had improved to grade 1 by the day scheduled for initiation of the next cycle, the oxaliplatin dose was reduced as described above. If the symptoms did not improve to grade 1, the therapy was discontinued.

The antitumor effect, adverse events, progression-free survival (PFS), and overall survival (OS) were investigated. The antitumor effect was evaluated using the Response

Evaluation Criteria in Solid Tumor (RECIST). The National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) version 3.0 was used for evaluation of adverse events. PFS and OS were calculated by the Kaplan–Meier method.

Results

Patient characteristics

The median age of the patients was 49 years (range 43–58 years), and PS was 0 in 5 patients, 1 in 1, and 2 in 1. The disease was clinical stage I in 1 patient, stage II in 2, stage III in 1, and stage IV in 3. The histological type was mucinous adenocarcinoma in all 7 patients. The median number of previous therapeutic regimens was 2 (range 1–4), and the treatment-free interval was less than 6 months in 6 patients and 6 months or more in 1. All patients had received taxane or platinum therapy. The median number of cycles of SOX therapy was 5 (range 4–6) (Table 1).

Antitumor response

The antitumor effect in terms of the response to therapy was rated as a complete response (CR) in 2 patients, partial response (PR) in 2, and stable disease (SD) in 3. The overall response rate was 57.1 %, and the disease control rate was 100 % (Table 2).

Toxicity

Regarding hematological toxicities of grade 3 or more, leukopenia occurred in 42.9 %, and neutropenia in 28.6 %, of patients. Both patients with grade 4 neutropenia showed improvement before initiation of the next cycle, without administration of granulocyte-colony stimulating factor (G-CSF). Thrombocytopenia of grade 3 or more developed in 1 (14.3 %) patient during the 5th cycle of therapy. In this patient, the platelet count was restored to more than $75,000/mm^3$ on day 28 without platelet transfusion, but the therapy was discontinued because of progressive disease (PD). Anemia of grade 3 or more occurred in 2 (28.6 %) patients during the 4th and 3rd cycles, respectively, and both received erythrocyte transfusion. As for non-hematological toxicities, grade 3 rectovaginal fistula occurred in 1 (14.3 %) patient, and therapy was discontinued after 5 cycles. This patient underwent a colostomy. Grade 2 fatigue was the only other non-hematological toxicity of grade 2 or more, and occurred in only 1 (14.3 %) patient. Sensory nerve disorder of grade 1 developed in all (100 %) patients (Table 3).

Table 2 Response

Response	No. of patients	(%)
CR	2	28.6
PR	2	28.6
SD	3	42.9
PD	0	0
Overall response rate	4	57.1
Disease control rate	7	100

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

Table 1 Patient characteristics (*N* = 7)

Age, years		Treatment-free interval, months	
Median	49	<6	6 (85.7 %)
Range	43–58	≥6	1 (14.3 %)
Performance status (PS)		Cell type	
0	5 (71.4 %)	Mucinous	7 (100 %)
1	1 (14.3 %)	Site of metastasis	
2	1 (14.3 %)	Lymph nodes	4 (57.1 %)
No. of previous regimens		Vaginal stump	4 (57.1 %)
1	3 (42.9 %)	Bone	2 (28.6 %)
2–3	3 (42.9 %)	Others	3 (42.9 %)
≥4	1 (14.3 %)	No. of cycles	
FIGO stage		4	2 (28.6 %)
I	1 (14.3 %)	5	2 (28.6 %)
II	2 (28.6 %)	6	3 (42.9 %)
III	1 (14.3 %)		
IV	3 (42.9 %)		

Table 3 Adverse events of SOX therapy (*n* = 7)

	Grade				
	1	2	3	4	≥3 (%)
Leukopenia	2	2	3	0	3 (42.9)
Neutropenia	3	2	0	2	2 (28.6)
Thrombocytopenia	3	2	1	0	1 (14.3)
Anemia	3	2	1	1	2 (28.6)
Nausea	5	0	0	0	0
Vomiting	0	0	0	0	0
Diarrhea	0	0	0	0	0
Sensory neuropathy	7	0	0	0	0
Mucositis	1	0	0	0	0
Fatigue	3	1	0	0	0
Vaginal fistula	0	0	1	0	1 (14.3)

Status of therapy

Three (42.9 %) of the 7 patients completed 6 cycles of therapy. PD occurred during therapy in 3 (42.9 %) of the 7 patients. In 2 of these 3, therapy was discontinued after 4 cycles and the regimen was altered. In the other patient with PD, the therapy was switched to a palliative regimen after 5 cycles. The aforementioned adverse events necessitated discontinuation of the therapy after 5 cycles in 1 (14.3 %) of the 7 patients.

In total, 36 cycles of this therapy were administered to the 7 patients. Thirteen (44.8 %) of 29 cycles were delayed by 1 week. The reason for the delay was unrestored neutrophil count for 1 cycle, and onset of peritonitis and pyelitis for 1 cycle each. Another cycle was delayed at the physicians discretion because there was a downward trend in the patient's platelet count although it remained over 75,000/mm^3. As for the other 9 cycles, the delay was at the patient's request because of fatigue, nausea, etc. Ultimately, only 1 (3.4 %) cycle was delayed by 1 week because of failure to satisfy the requirements for initiation of the next cycle of therapy. No dose reductions of oxaliplatin or S-1 occurred in any of the patients due to adverse events.

Survival

The median follow-up period was 7 months (range 4–43 months), the median PFS was 5 months (range 3–9 months), and the median OS was 7 months (range 4–43 months).

Discussion

Cisplatin (CDDP) has been used as monotherapy or in combination with other drugs as chemotherapy for adenocarcinoma of the uterine cervix [10, 11]. Chemotherapy with taxanes has been studied in recent years [12, 13]. In the GOG 204 study, which was a randomized controlled study involving 435 patients with stage-IVB or recurrent carcinoma of the uterine cervix including 54 with adenocarcinoma and 36 with adenosquamous carcinoma, vinorelbine/CDDP therapy, gemcitabine/CDDP therapy, and topotecan/CDDP therapy failed to show a therapeutic effect superior to that of paclitaxel (PTX)/CDDP therapy [14]. Therefore, at present, combination chemotherapy with taxane plus a platinum agent is generally considered to be the most effective regimen for the treatment of adenocarcinoma of the uterine cervix. However, there is no established second-line chemotherapy for patients who have recurrent disease after receiving first-line therapy with taxane plus a platinum agent. The histological type of adenocarcinoma of the uterine cervix is mucinous adenocarcinoma in a high proportion of patients with this disease, and it carries a poor prognosis in comparison with other histological types [15]. Uterus and ovary have the same embryological origin: the mullerian duct. Mucinous adenocarcinomas of both cervix and ovary show very similar histological characteristics. Moreover, cervical and ovarian mucinous adenocarcinomas consist of endocervical and intestinal types. We considered that both carcinomas had a similar chemosensitivity for the SOX regimen. Thus, we carried out a pilot study of the SOX regimen that is used for mucinous adenocarcinoma of the ovary in clinical study, and examined its efficacy and safety in patients with recurrent adenocarcinoma of the uterine cervix.

The important elements requiring serious attention when considering chemotherapy for recurrent cancer include: (1) minimal toxicity, (2) quality of life (QOL) maintenance, and (3) simplicity, in addition to a promising antitumor effect. Although the SOX therapy response rate was 57.1 % in this study, there were 2 (28.6 %) cases with CR (Fig. 2).
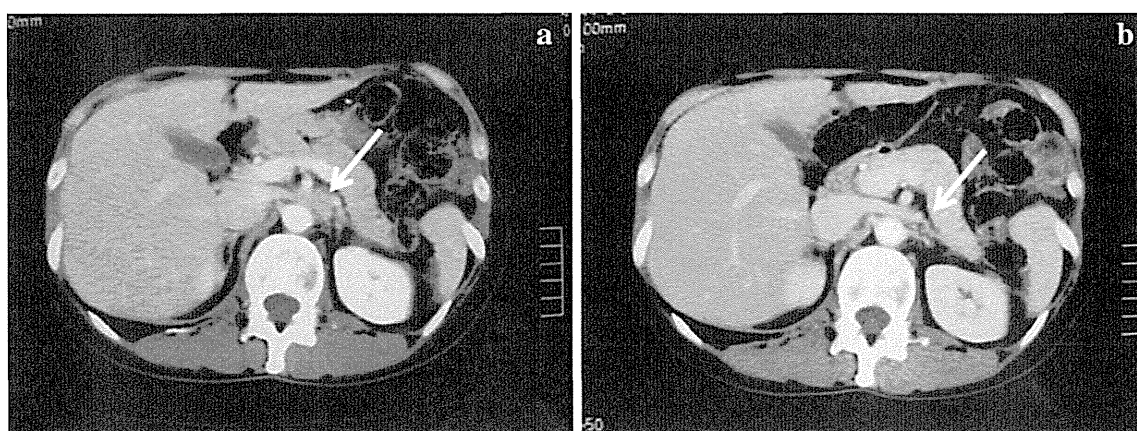

Fig. 2 a Before SOX therapy: para-aortic lymph nodes were enlarged to 1.5 cm × 1.5 cm, confirming lymph node involvement. b After 6 cycles of SOX therapy: para-aortic lymph node metastasis had disappeared

In addition, the disease control rate was 100 %, showing a sufficient chemotherapeutic effect in patients with recurrent disease. The hematological toxicities observed were mild and treatable. Although grade 3 or 4 anemia occurred in 1 patient each, no platelet transfusion or G-CSF was required. As for non-hematological toxicity, sensory nerve disorder of grade 1, which is peculiar to oxaliplatin therapy, developed in all 7 patients, but did not require discontinuation of therapy.

Although the initiation of therapy was delayed by 1 week in 13 (44.8 %) cycles, there was only 1 cycle in which the reason for the delay was failure to satisfy the requirements for initiation of the next cycle of therapy; specifically, the reason was an unrestored neutrophil count. In this study, the S-1 dose was set at 80–120 mg/body/day, and the oxaliplatin dose at 100 mg/m². S-1 at a dose of 80 mg/m² and oxaliplatin at a dose of 130 mg/m² are reported to be common in SOX therapy for colorectal carcinoma. In these previous reports, S-1 or oxaliplatin therapy was completed without dose reductions in 57 and 81 %, respectively, showing rather low rates of complete treatment [9, 16]. In our study, PD occurred in 3 of the 7 patients, requiring discontinuation of therapy. However, none of the criteria for reduction of the oxaliplatin dose were met in any of the patients, and the rate of complete treatment was 100 %. SOX therapy using an oxaliplatin dose of 100 mg/m² appears to promote good compliance. The time required for intravenous administration of oxaliplatin on day 1 was 135 min including premedication, allowing outpatient management of patients. Thus, the patients maintained their QOL while being treated.

The results of this pilot study suggest that the SOX regimen is an effective antitumor therapy for recurrent adenocarcinoma of the uterine cervix, and is associated with minimal adverse effects. This therapy deserves further investigation in a phase-II clinical study to examine its potential as a second-line therapy for recurrent adenocarcinoma of the uterine cervix, a malignancy that is difficult to treat in daily clinical practice. The present pilot study has provided important findings that may contribute to improving the prognosis for patients with adenocarcinoma of the uterine cervix.

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Neoadjuvant chemotherapy using platinum- and taxane-based regimens for bulky stage Ib2 to IIb non-squamous cell carcinoma of the uterine cervix

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Abstract

Purpose There are no reports on the use of neoadjuvant chemotherapy (NAC) in non-squamous cell cervical carcinoma. We examined the effectiveness and safety of paclitaxel/carboplatin (TC) and docetaxel/carboplatin (DC).

Methods Stage Ib2 to IIb disease was present in 23 patients scheduled for radical hysterectomy. We administered 1–3 courses of either the TC or the DC regimen. Antitumor effects were found superior by Response Evaluation Criteria in Solid Tumors. Safety was assessed with National Cancer Institute Common Terminology Criteria for Adverse Events.

Results Median age was 50 years (range 32–63 years), with stage Ib2 in 6 cases (26.1 %) and IIb in 17 cases (73.9 %). Complete response was achieved in 5 cases (21.7 %), partial response in 13 (56.5 %), stable disease in 5 (21.7 %); the response rate was 78.3 %, and surgery completion rate was 78.3 %. Leukopenia or neutropenia ≥grade 3 was seen in 12 (52.2 %) and 21 (91.3 %) cases, respectively, with grade 3 febrile neutropenia in 2 cases (8.7 %) and no anemia or thrombocytopenia ≥grade 3. Median progression-free survival was 26 months (95 % CI, 13.5–38.5 months); median overall survival was 35 months (95 % CI, 20.9–49.1 months).

Conclusion NAC for non-squamous cell cervical carcinoma showed potent anti-tumor effects and manageable adverse events.

Introduction

The methods used to treat bulky stage Ib2 to IIb cervical cancers differ between Japan and Western countries. In Western countries, concurrent chemoradiation therapy (CCRT) has been recommended as a standard treatment for such tumors, based on the results of multiple large-scale randomized trials and meta-analyses [1–7]. In Japan, Korea, and Italy, among other countries, the neoadjuvant chemotherapy (NAC) approach has been introduced to clinical practice and is extensively utilized [8, 9]. An Italian phase III, controlled study involving patients with locally advanced stage Ib2 to IIb squamous cell carcinoma of the cervix showed that NAC prior to radical hysterectomy improves patient outcomes compared with conventional radiation therapy alone [10].

There are no previous reports on the use of NAC for bulky non-squamous cell carcinoma of the cervix. We present the results of an ongoing pilot study on its efficacy and safety.

Subjects and methods

Subjects

We studied 23 patients with locally advanced non-squamous cell carcinoma of the uterine cervix (clinical stage Ib2 to IIb) between January 2002 and September 2011. All patients were scheduled to undergo radical hysterectomy and gave informed consent for this study.

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Inclusion criteria

The following inclusion criteria were employed: (1) histologically verified non-squamous cell carcinoma of the uterine cervix; (2) locally advanced disease, stage Ib2–IIb; (3) between 20 and 74 years of age; (4) Eastern Cooperative Oncology Group performance status 0–2; (5) no prior treatment; (6) presence of a measurable bulky mass in the uterine cervix on magnetic resonance imaging (MRI); (7) hematologic and biochemical findings within the following parameters, WBC count $\geq$4,000/mm^3, neutrophil count $\geq$2,000/mm^3, platelet count $\geq$100,000/mm^3, hemoglobin $\geq$10.0 g/dL, AST and ALT levels $\leq$2 times the upper limit of normal reference range, serum total bilirubin level $\leq$1.5 mg/dL, serum creatinine $\leq$1.5 mg/dL, and creatinine clearance $\geq$60 mL/min; (8) life expectancy $\geq$6 months; and (9) written informed consent personally given by the subject.

Exclusion criteria

Exclusion criteria were as follows: (1) overt infection; (2) serious complication(s), for example, cardiac disease, poorly controlled diabetes mellitus, malignant hypertension, bleeding tendency; (3) multiple active cancers; (4) interstitial pneumonia or pulmonary fibrosis; (5) pulmonary effusions; (6) history of unstable angina or myocardial infarction within 6 months after registration, or a concurrent serious cardiac arrhythmia requiring treatment; (7) contraindications to treatment with paclitaxel, docetaxel, or carboplatin; (8) intestinal paralysis or ileus; (9) pregnancy, breast-feeding, or desire for future pregnancy; (10) history of serious drug hypersensitivity or drug allergy; and (11) judged unsafe for participation by the attending physician.

Medication administration and criteria for modification

Regimen

The choice of regimen was left to the attending physician. Paclitaxel/carboplatin (TC) therapy was administered to 4 patients and DC therapy to 19 patients. Courses of treatment were administered 21 days apart, with a intravenous paclitaxel dose of 175 mg/m^2 or a docetaxel dose of 70 mg/m^2 administered on Day 1, and intravenous carboplatin with area under the curve (AUC) 6 mg/mL per min also administered on Day 1. As a rule, maximum 3 courses of treatment were administered to each patient.

Criteria for initiating the second course of treatment

The second course was postponed by a maximum of 2 weeks when blood analysis performed within 2 days

prior to the planned start did not satisfy the following criteria: (1) neutrophil count $\geq$1,000/mm^3; (2) platelet count $\geq$75,000/mm^3.

Carboplatin dose-reduction criteria

The carboplatin dose for the second course was reduced from AUC 6 mg/mL per min to AUC 5 mg/mL per min if the patient experienced grade 4 thrombocytopenia or grade 3 thrombocytopenia accompanied by bleeding. If signs of toxicity remained after this dose reduction, the third course of treatment was reduced to AUC 4.

Paclitaxel dose-reduction criteria

The paclitaxel dose for the second course was reduced from 175 to 135 mg/m^2 in patients exhibiting grade 2 or higher severe peripheral nerve toxicity during the first course. If this grade of nerve toxicity persisted after the dose reduction, the paclitaxel dose for the third course was reduced to 110 mg/m^2.

Docetaxel dose-reduction criteria

The docetaxel dose for the second course was reduced from 70 to 60 mg/m^2 if the patient experienced grade 4 neutropenia lasting 7 days or longer or febrile neutropenia lasting 4 days or longer. If signs of toxicity remained after this dose reduction, the docetaxel dose for the third course was reduced to 50 mg/m^2.

Supportive therapy

A granulocyte colony-stimulating factor (G-CSF) preparation was administered to patients who developed grade 4 neutropenia during the first course of NAC. These patients were permitted prophylactic G-CSF during the second and subsequent courses of NAC. Anti-emetics were used for the preventive purpose.

Primary treatment

Patients with stage Ib2–IIb cervical carcinoma underwent radical hysterectomy unless the tumor responded to preoperative treatment with progressive disease (PD), at which time the tumor was up-staged. In cases in which surgery was not possible, CCRT was adopted.

Postoperative therapy

Postoperative radiotherapy, postoperative chemotherapy, or CCRT was additionally administered in patients with a positive surgical margin at the vaginal stump,

lymphadenopathy, invasion of the cardinal ligament, or evident invasion of the vasculature.

Outcome evaluation

The primary endpoint was anti-tumor response. Secondary endpoints comprised adverse events, the surgery completion rate, the progression-free survival (PFS) period, and the overall survival (OS) period. Hematologic tests and urinalysis were performed before the start of treatment and, as a rule, once weekly after starting treatment. Electrocardiograms and chest radiographs were obtained before the start and at the end of treatment.

Evaluation of anti-tumor response

Anti-tumor response was evaluated using Response Evaluation Criteria in Solid Tumors guidelines. The baseline MRI findings were compared with the findings at the conclusion of treatment. For our efficacy evaluation, we adopted the best rating, without incorporating the response period.

Evaluation of adverse events

Adverse events were evaluated employing the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Statistical analysis

Progression-free survival (PFS), defined as the time from the start of the study treatment to documented tumor progression or death, and overall survival (OS), defined as the time from the start of treatment to the date of death, were calculated by the Kaplan–Meier method. The statistical data were obtained using StatMate III.

Results

Background variables

The median age of the 23 patients was 50 years (range 32–63 years). The performance status was 0 in 18 patients (78.3 %), and in 5 patients, the performance status was 1 (21.7 %). The clinical stage was Ib2 in 6 cases (26.1 %) and IIb in 17 cases (73.9 %). The histological type was mucinous adenocarcinoma in 10 cases (43.5 %), endometrioid adenocarcinoma in 5 (21.7 %), clear cell adenocarcinoma in 1 (4.3 %), and adenosquamous carcinoma in 7 (30.4 %). One course of NAC was administered in

1 patient (4.3 %), 2 courses in 17 patients (73.9 %), and 3 courses in 5 patients (21.7 %). The regimens comprised TC therapy in 4 cases (17.4 %) and DC therapy in 19 cases (82.6 %) (Table 1).

Anti-tumor response

A complete response was noted in 5 cases (21.7 %), partial response in 13 (56.5 %), and stable disease in 5 (21.7 %), with a overall response rate of 78.3 %. In subgroup analysis, the overall response rate of TC therapy and DC therapy was 100 and 73.7 %, respectively (Table 2).

Adverse events

Grade 3 or higher severe leukopenia or neutropenia was seen in 12 (52.2 %) and 21 (91.3 %) cases, respectively. Grade 3 febrile neutropenia was noted in 2 cases (8.7 %). The G-CSF preparation was used in 13 (56.5 %) of the 23 patients; it was administered during 19 (38.8 %) of the 49 total cycles. The mean duration of G-CSF treatment during each course was 2.6 days. No patients experienced grade 3 or higher severe anemia or thrombocytopenia. The only sign of grade 3 or higher severe non-hematologic toxicity was nausea, seen in 1 case (4.3 %). No patients had signs of grade 2 or higher severe neurotoxicity (Table 3).

In 3 cases (13.0 %), the second course of treatment was postponed due to a low neutrophil count; in all 3 patients, the second course was initiated within 7 days of its scheduled time. Both patients (10.0 %) with grade 3 febrile neutropenia for 4 days or longer had received DC therapy prior to the development of this complication. In these 2 cases, doses were reduced for the second course of treatment: docetaxel from 70 to 60 mg/m^2 and carboplatin from AUC 6 to AUC 5.

Table 1 Patient characteristics ($n = 23$)

Median age years [range]		Cell type	
50 [32–63]		Mucinous	10 (43.5 %)
Performance status at entry		Endometrioid	5 (21.7 %)
0	18 (78.3 %)	Clear cell	1 (4.3 %)
1	5 (21.7 %)	Adenosquamous	7 (30.4 %)
2	0 (0 %)	Regimen	
FIGO stage at initial diagnosis		DC	19 (82.6 %)
Ib2	6 (26.1 %)	TC	4 (17.4 %)
IIa	0 (0 %)	Number of cycles	
IIb	17 (73.9 %)	1	1 (4.3 %)
		2	17 (73.9 %)
		3	5 (21.7 %)

DC docetaxel + carboplatin, *TC* paclitaxel + carboplatin