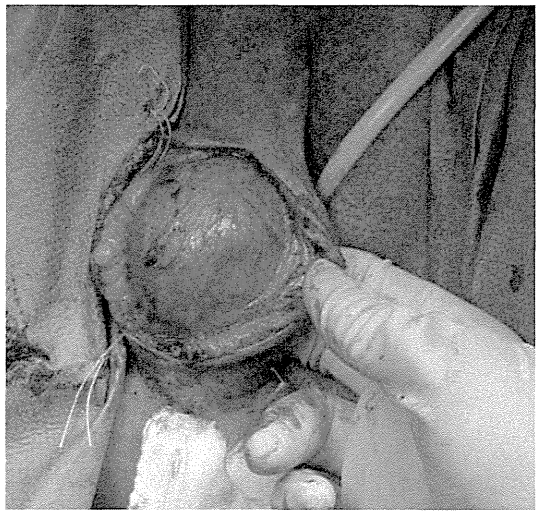

Fig. 3 At surgery, the tumor was easily separated from adjacent normal tissue

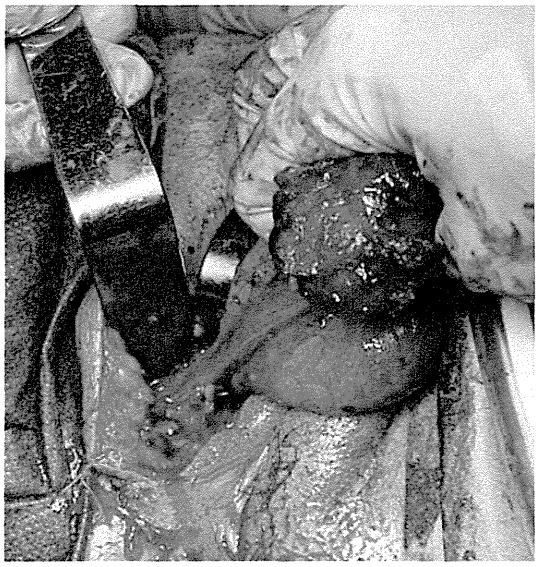

Fig. 4 The tumor was fed by vessels arising from the pelvic floor

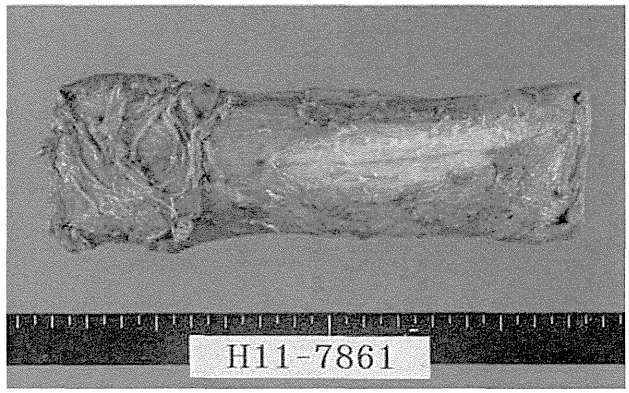

Fig. 5 The tumor was soft and gelatinous and its cut surface was white and uniform

tumor. They concluded that inappropriate expression of this DNA-binding protein may be important in the pathobiology of AAM.

Although AAM is a benign tumor, recurrence often occurs. Smith [4] reported the incidence of recurrence to be approximately 70 %. The pattern of recurrence is mainly repeated local recurrence. The characteristic of this neoplasm is slow growth, as Smith et al. [4] experienced one case of recurrence 23 years after the original resection. However, some cases of mortality have also been reported. Blandamura et al. [5] reported a death due to pulmonary metastasis, and Smith [4] reported a death from a urinary bladder invasion. Clinical symptoms depend on the lesion where AAM grows. Patients are sometimes asymptomatic, even if they have a visible peripheral mass. Patients often report experiencing pelvic fullness and pressure, perinea swelling, vulvovaginal pain, dysmenorrhea, and dyspareunia. When AAM infiltrates the intestine or bladder, patients have bowel or bladder dysfunction. Because of its rarity, it is misdiagnosed in more than 80 % cases, and most are misdiagnosed as a bacterial abscess.

Behcet's disease causes chronic inflammation if blood vessels throughout the body. Although the exact cause of Behcet's disease is unknown, both genetic and environmental factors are thought to be responsible for the disease. Behcet's disease leads to numerous symptoms, e.g., oral and genital ulcers, dermal rashes and lesions, and ocular inflammation. Vaginal ulcer is the most often observed gynecological lesion in patients with Behcet's disease, and this ulceration can often cause vulvar lymphedema. Because our patient had Behcet's disease, we initially misdiagnosed her mass as this commonly associated lymphedema. Conversely, because of their similar clinical features, some researchers have misdiagnosed lymphedematous pseudotumors as AAM and have even reported them as thus [6, 7]. Therefore, it follows that the differential diagnosis of vulvovaginal enlargement is important. Diseases included in the category of similar diseases are AAM, myxoma, lymphedema, neurofibroma, angiomyofibroblastoma, myxoid liposarcoma, dermato fibrosarcoma protuberans, malignant fibrous histiocytoma, and malignant peripheral nerve sheath tumor, as summarized in Table 1.

Diagnostic imaging CT, particularly MRI, are useful tools for determining the extent of the tumor, better enabling us to plan our surgical approach. On CT imaging, AAM has low attenuation relative to muscle. When we used enhanced CT, it revealed a swirling pattern within the tumor. On MRI, the tumor was isointense relative to muscle on the T1-weighted image, and hyperintense on a T2-weighted image. Also, avid and heterogeneous enhancement was observed after

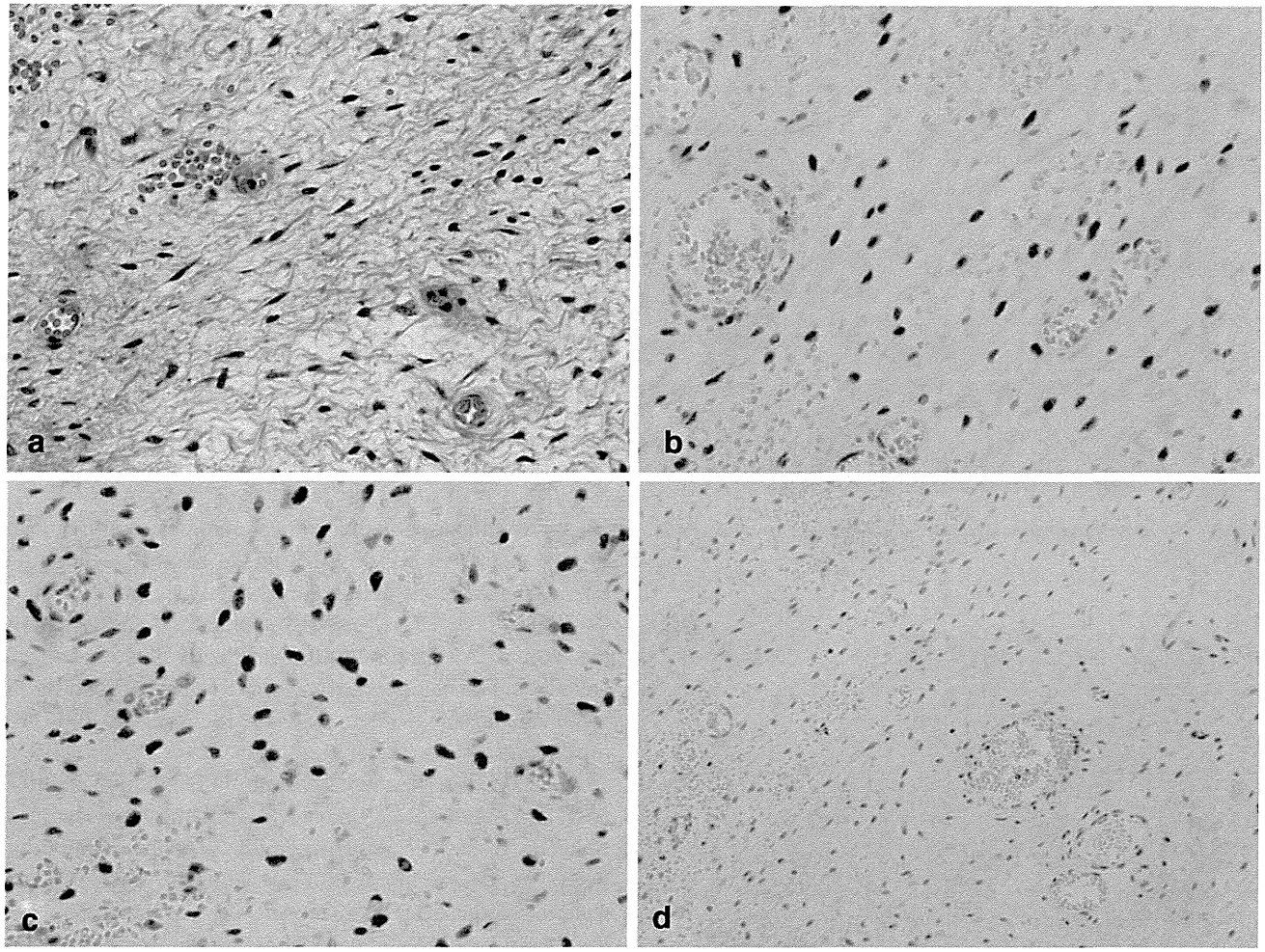

Fig. 6 H&E staining revealed spindle and stellate cells without atypia (**a**, ×400). Immunohistochemistry was positive for both estrogen receptor (**b**, ×400) and progesterone receptor (**c**, ×400). The Ki-67 labeling index was <1 % (**d**, ×200)

administration of intravenous contraction, with a characteristic "swirling" or "layering internal" pattern [8]. It is thought that the hypodensity on CT and the hyperintensity on T2-weighted MRI are because of the high water content and loose myxoid matrix of the tumor; enhancement is believed to be because of its high vascularity. The "swirling" or "layering strand" pattern is a characteristic feature from imaging studies and is found in approximately 83 % of patients [8].

AAM has bland histological features on H&E staining: spindled and stellate cells without atypia, and abundant myxoid stroma with areas of numerous vessels. Immunohistochemistry staining for desmin, SMA, vimentin, CD34, S100 protein, and particularly for estrogen and progesterone receptors, is useful [9, 10]. In our case, the estrogen and progesterone receptor statuses were positive, and S100 protein was negative, indicative of the typical features of AAM.

Resection is regarded as the initial treatment of choice for AAM. The objective of resection is to remove the tumor completely to prevent recurrence, although it is very difficult to achieve the necessary negative margins because of the infiltrative nature of AAM and the absence of a defined capsule. Chan et al. reported that patients who received radical surgery with clear resection margins have similar chances of remaining disease-free as those with tumor-involved resection margins. They concluded that incomplete or partial resection is acceptable, especially when high operative morbidity is expected and preservation of fertility is desired [11].

AAM occurs mainly in females of reproductive age who often desire preservation of their fertility. Incomplete surgery is acceptable when operative morbidity is expected with a radical approach and preservation of fertility is an issue [11]. Chemotherapy and radiation therapy are not preferable because of the low mitotic activity of the tumor [2], but use of radiotherapy for local control or alleviation of symptoms has been described [12]. Angiographic embolization was also attempted by Nyam et al. [13], who performed angiographic embolization 2 days before the

Table 1 Differential diagnosis of vulvar edematous diseases

Tumor type	Refs.	Clinical or imaging features	Pathologic features
Aggressive angiomyxoma	[8]	Usually larger than 10 cm, high recurrence. Swirled pattern (MRI)	Low mitotic activity. Positive IHC for ER and PR
Myxoma	[16]	High signal intensity, similar to that of fluid (MRI)	Circumscribed, typically hypocellular and hypovascular
Lymphedema	[7]	Related to obesity, trauma, infection, or associated inflammatory skin disease	Dilated and tortuous, lymphatic
Neurofibroma	[17]	Usually do not exceed 3 cm, vulvar neurofibroma can be seen in as many as 18 % of patients with von Recklinghausen's disease	Wavy spindle, wire-like, collagen bundles, Wagner–Meissner body
Angiomyofibroblastoma	[18, 19]	Usually <6 cm, has not been associated with increased body mass index or immobilization. Heterogeneous signal intensity observed on T2-weighted MRI and fast and persistent inhomogeneous enhancement on dynamic gadolinium-enhanced MRI	Circumscribed lesion with plump, plasmacytoid to spindled cell arranged predominantly around capillary-sized vessels
Myoid liposarcoma	[20]	Commonly occurs in lower extremities within the intramuscular fat planes in middle-aged people who present with a painless slow growing mass. Homogenous enhancement after administration of contrast material (MRI)	Plexiform vasculature, lipoblasts which are bland rounded to fusiform cells
Dermato fibrosarcoma protuberans (DFSP)	[21]	Fibrous tumor of intermediate grade malignancy, with a tendency to local recurrence; rarely metastasizes. Survival is 91–100 %, and local recurrence is 20–49 %	Composed of fascicles of fibroblast like cells arranged in a herringbone pattern and associated with a degree of nuclear pleomorphism and mitotic activity
Malignant fibrous histiocytoma (MFH)	[22]	Usually present as a large solitary mass, occurs mainly in elderly postmenopausal women	At least 50 % of tumor has highly vascularized myxoid stroma
Malignant peripheral nerve sheath tumor (MPNST)	[23]	Extremely rare, especially in the vulva	Resembles fibrosarcoma or MFH that arise from nerve or neurofibroma or that express S-100 protein or other neural markers

MRI magnetic resonance imaging, *IHC* immunohistochemistry, *ER* estrogen receptor, *PR* progesterone receptor

resection operation. During the operation they confirmed the discolored embolized area, which enabled them to visualize the border between normal tissue and tumor.

Because AAM has both estrogen and progesterone receptors, hormonal therapy, for example administration of a GnRh agonist or tamoxifen, has been conducted successfully [14, 15]. Also, for patients with a completed family, oophorectomy may be potential useful, although the efficacy of conducting a prophylactic oophorectomy is still under investigation. Adjuvant hormonal therapy including GnRh agonist and tamoxifen may be an option.

Conclusion

AAM is very rare disease and is often misdiagnosed as an infection or edema. When a vulvovaginal enlargement is found in patients still of reproductive age, the physician should consider the possibility of AAM. Complete surgical resection does not guarantee cure of the tumor. Because of its positive estrogen receptor and progesterone receptor status, hormonal therapy may be a crucial treatment for control of the disease.

Conflict of interest There are no conflicts of interest to declare in relation to this article.

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ORIGINAL PAPER

WT1 peptide immunotherapy for gynecologic malignancies resistant to conventional therapies: a phase II trial

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Abstract
Objective The aim of the present study was to analyze the long-term survival effects of WT1 peptide vaccine, in addition to its anti-tumor effects and toxicity.
Methods A phase II clinical trial was conducted during the period of 2004–2010 at Osaka University Hospital, Osaka, Japan. The patients who had gynecologic malignancies progressing against previous treatments received WT1 peptide vaccine intradermally at 1-week intervals for 12 weeks. The vaccination was allowed to further continue, unless the patient's condition became significantly worse due to the disease progression.
Results Forty out of 42 patients, who met all the inclusion criteria, underwent WT1 peptide vaccine. Among these 40 patients, stable disease was observed in 16 cases (40 %). Skin toxicity of a grade 1, 2 and 3 occurred in 25 cases (63 %), 9 cases (23 %) and a single case (3 %), respectively, and liver toxicity of grade 1 in a single case (3 %). The overall survival period was significantly longer in cases positive for the WT1 peptide-specific delayed-type hypersensitivity (DTH) reaction after the vaccination, compared to those negative for the DTH reaction ($p = 0.023$). Multivariate Cox proportional hazards analysis demonstrated that the adjusted hazard ratio for the

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negative DTH reaction was 2.73 (95 % CI 1.04–7.19, $p = 0.043$).
Conclusion WT1 peptide vaccine may be a potential treatment, with limited toxicity, for gynecologic malignancies that have become resistant to conventional therapies. Larger scale of clinical studies is required to establish the efficacy of the WT1 peptide vaccine for gynecologic malignancies.

Keywords WT1 peptide immunotherapy · Gynecologic malignancy · Anti-tumor effect · Survival · Stable disease · Toxicity

Abbreviations

CR	Complete response
CT	Computed tomography
HLA	Human leukocyte antigen
HPV	Human papillomavirus
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PS	Performance status
RECIST	Response evaluation criteria in solid tumor
RR	Responsive rate
SD	Stable disease
TC	Paclitaxel and carboplatin

Introduction

The Wilms tumor gene, *WT1*, was first identified as a tumor suppressor gene responsible for Wilms tumors of the kidney. However, a series of investigations demonstrated that *WT1* possesses an oncogenic, rather than a tumor-suppressive, function, and WT1 protein is expressed in various kinds of hematological and solid malignancies, indicating that immunotherapy targeting WT1 could potentially be used for treatment of a variety of such malignancies (Oka and Sugiyama 2010). In fact, WT1 has been regarded as one of the most promising target antigens for cancer immunotherapy by an American National Cancer Institute pilot project (Cheever et al. 2009). It has already been demonstrated that WT1 vaccination is safe, and encouraging reports that showed its efficacy for several kinds of tumors have been accumulated (Oka and Sugiyama 2010; Hashii et al. 2010; Oji et al. 2010; Izumoto et al. 2008). A previous phase I study empirically determined a safe dose of the WT1 peptide, which was intradermally injected with Montanide ISA 51 adjuvant for patients with solid tumors, as 3 mg per injection, and this dose was shown to have little toxicity except skin reaction of the vaccination sites (Morita et al. 2006).

Ovarian carcinoma accounts for 5 % of all cancers among women and will eventually develop in 1 of every 58 women. It has an extremely high mortality rate; consequently, aggressive cytoreductive surgery followed by chemotherapy with taxane and platinum is the gold standard for its therapy. Endometrial carcinoma is an even more common malignant neoplasm of the female pelvis and is the fourth most common cancer of women today. Endometrial carcinoma is usually confined to the uterus or pelvis, has a lower mortality rate than ovarian cancer and is commonly treated by resection of the uterus and adnexae, with or without co-resection of the regional lymph nodes. Another common gynecological tumor, uterine cervical carcinoma, is mostly associated with a human papilloma virus (HPV) infection, and its incidence appears to vary from one locality to another. It is important to note that in some Asian and South American countries, cervical carcinoma accounts for the largest percentage of cancer deaths in women. Cervical carcinoma is usually treated by radical surgery and/or radiation therapy. And lastly, yet another kind of uterine tumor, the leiomyosarcoma, although rare, has an extremely poor prognosis (DiSaia and Creasman 2002).

Tumors in the early stage of all these diseases are usually treated relatively successfully, while the advanced and recurrent forms of these diseases are often very difficult to treat. Salvage, second-line and third-line chemotherapies are effective in only a fraction of the cases, and the best available supportive care is usually proposed to the patients whose tumors have become resistant to prior therapies.

An immunotherapeutic approach that is less toxic than available chemotherapies might be a more promising option for those whose gynecologic malignancies continue to progress despite conventional chemotherapy and radiation treatments. A previous small study showed that disease stabilization was achieved in 3 (25 %) of 12 gynecologic malignancies by vaccination with an antigenic WT peptide (Ohno et al. 2009). There is only one case report on the effect of WT1 peptide for the survival elongation in a ovarian cancer case (Dohi et al. 2011). In the present phase II trial, we have analyzed for the first time the long-term survival effect of the WT1 peptide vaccine, as well as its anti-tumor effects, evaluated by the usual response evaluation criteria in solid tumor (RECIST) and toxicity.

Materials and methods

Eligibility

This phase II trial was conducted at Osaka University Hospital, Osaka, Japan, during the period of 2004–2010. Major inclusion criteria were as follows: having a gynecologic malignancy progressing despite previous treatments;

WT1 protein expression in the primary or metastatic tumor tissue using anti-WT1 rabbit polyclonal antibody C-19 (Santa Cruz Biotechnology) or anti-WT1 mouse monoclonal antibody 6F-H2 (Dako Cytometry); positive status for human leukocyte antigen (HLA)-A*2402; performance status (PS) of 0–2; and life expectancy >3 months.

Vaccination schedule

The HLA-A*2402-restricted, 9-mer modified WT1 peptide (amino acids 235–243: CYTWNQMNL) emulsified with Montanide ISA 51 adjuvant, was used for the vaccination, as previously described (Hashii et al. 2010). The dose of WT1 peptide injected was 3 mg per body. The WT1 vaccination was scheduled to be performed intradermally every week for 12 weeks but was allowed to continue even after 12 weeks, unless the patient's condition became significantly worse due to the disease progression.

Evaluation of the WT1 vaccine effects

The primary endpoints of the WT1 vaccine study were its anti-tumor effect and its toxicity. Computed tomography (CT) was performed every 4 weeks to evaluate tumor size. The anti-tumor effect was evaluated by the RECIST (version 1.1) (Eisenhauer et al. 2009) after the vaccination during 12 weeks. Adverse effects were graded based on the National Cancer Institute's Common Toxicity Criteria (version 2.0). A test for delayed-type hypersensitivity (DTH) reaction specific to the WT1 peptide used for vaccination was performed at week 4 and 8. We regarded the patient as DTH positive, if the DTH reaction of the patient was positive either at week 4 or at week 8.

Secondary endpoints were progression-free survival (PFS) and overall survival (OS). PFS was defined as the period from the date of the start of WT1 vaccination to the date of the radiologic or pathologic relapse, or to the date of the last follow-up. OS was defined as the period from the start of the vaccination to the patient's death or to the date of the last follow-up. OS was analyzed for its association with DTH.

Cancellation or termination of WT1 vaccination

If grade 3 toxicity was observed, the next injection of the WT1 vaccine was postponed until the toxicity returned to grade 2 or less. The vaccination was permanently terminated if grade 4 toxicity was detected or if a performance status of 3 or worse was observed.

Statistical analysis

MedCalc (MedCalc Software, Mariakerke, Belgium) was used for statistical analysis. The association between DTH induction and anti-tumor effect, including RECIST evaluation, PFS and OS, was analyzed by Fisher's exact test. OS curves were constructed using the Kaplan–Meier method and evaluated for statistical significance by the log-rank test. Multivariate Cox proportional hazards model (stepwise method) for the factors including age, origin of the disease, histology, evaluation of the previous therapy and number of recurrence was calculated to evaluate whether DTH was a significantly important factor on OS. Results were considered to be significant when the p value was <0.05.

Statements of ethics

This study was approved by the Institutional Review Board and the Ethics Committee of the Osaka University Hospital. All patients provided written informed consent. (Approval of this analysis: #10302, approved on March 11, 2011).

Results

Clinical characteristics of the patients and completion rate of the study schedule

During the study period, 42 patients entered the study. Among these, 2 patients were excluded from the present analysis due to protocol violation. The clinicopathological characteristics of these patients are shown in Table 1. The median age was 56 (35–75). The histological diagnosis was obtained as ovarian carcinoma in 24 cases, cervical carcinoma in 11 cases, uterine sarcoma (leiomyosarcoma and carcinosarcoma) in 5 cases. These patients had already received 1–11 (median: 3) kinds of treatments prior to the WT1 vaccination and were considered to have disease

Table 1 Clinical characteristics of patients enrolled in the phase II study

Characteristics	
Number (cases)	40
Median age (years) (range)	56 (35–75)
Type of malignancy	
Ovarian carcinoma	24 (60 %)
Cervical carcinoma	11 (28 %)
Uterine leiomyosarcoma/carcinosarcoma	5 (13 %)
Performance status	
0	35 (88 %)
1	4 (10 %)
2	1 (3 %)
Median number of previous treatment regimens (range)	3 (1–11)

resistant to conventional therapies such as chemotherapy and radiotherapy.

Injection of the WT1 vaccine was performed weekly for 1–50 (median: 14.5) times. The 12 injections prescheduled upon entry to this trial were completed in 32 of the 40 cases (80 %). Vaccination was terminated prior to the 12th injection due to progression of the disease including worsening of PS in 8 cases (20 %).

Anti-tumor effect of the WT1 peptide vaccine evaluated by RECIST

Among the 40 patients who received the WT1 vaccination, neither complete response (CR) nor partial response (PR) was obtained. Encouragingly, however, stable disease (SD) of 3 months or more was observed in 16 cases (40 %), including 10 cases of ovarian carcinoma, 5 cases of cervical carcinoma and a single case of uterine leiomyosarcoma, respectively.

The WT1 peptide-specific DTH reaction appeared after the vaccination in 27 cases (68 %); however, the vaccine's anti-tumor effect evaluated by RECIST was not correlated to the appearance of DTH (data not shown).

Toxicity of the WT1 vaccination

An adverse effect was observed in 36 cases (90 %): grade 1, 2 and 3 of skin reaction in 25 cases (63 %), 9 cases (23 %) and a single case (3 %), respectively, and grade 1 liver toxicity in a single case (3 %). The skin reactions had definite relationship with WT1 injection because the reactions were observed only in WT1 injected area. The liver toxicity occurred after first injection of WT1, and the relationship between WT1 vaccine and liver toxicity was probable. Postponement of the next injection due to adverse effects occurred in one case with grade 3 of skin reaction. However, termination of the WT1 vaccine injection due to adverse effects was never required.

Prognosis of the patients treated with WT1 peptide vaccine: the vaccines' survival effect

The PFS was 84 days (11–497). Surprisingly, among these WT1-vaccinated cases, which had been already resistant to conventional therapies and the disease had exhibited continuous progression against various other treatments for 40–1,198 days (median: 185 days), progression-free survival for a range of 67–427 days (median: longer than 160 days) was achieved in 16 SD cases (Table 2). The median OS of all the patients was 193 days (29–941).

Although an association between an anti-tumor effect evaluated RECIST and an appearance of DTH reaction was not observed, the PFS tended to be longer in DTH-positive cases than DTH-negative ones ($p = 0.23$ by the log-rank test), and the OS was significantly longer in DTH-positive cases than DTH-negative ones ($p = 0.023$ by the log-rank test) (Fig. 1).

Table 2 Duration of disease progression before WT1 vaccination was begun and progression-free period afterward in stable disease (SD) cases

Case number	Duration of disease progression before WT1 vaccine (days)	Progression-free survival after WT1 vaccine (days)
1	40	105[a]
2	55	67
3	61	427[a]
4	81	320
5	97	126
6	142	145
7	155	92
8	178	273
9	192	140[a]
10	324	84
11	405	175
12	434	196
13	439	84[a]
14	655	196
15	737	219
16	1,198	180[a]
Median	185	160[a]

The duration of disease progression before the WT1 vaccine, and the progression-free period after the start of WT1 vaccination in 16 SD cases, is demonstrated

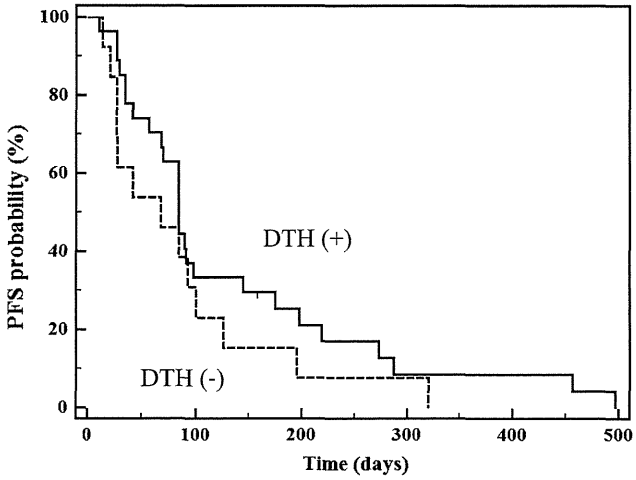
[a] The cases in which the disease was stable after WT1 vaccination without progression

Multivariate Cox proportional hazards analysis

We utilized the multivariate Cox proportional hazards model in order to find evidence to further support our belief that the DTH reaction was significantly associated with the survival. The DTH reaction was demonstrated to be an independent factor for overall survival of the patients (Table 3). The adjusted hazard ratio (HR) for the DTH reaction (− vs. +) was 2.73 (95 % CI 1.04–7.19, $p = 0.043$).

Discussion

A National Cancer Institute pilot project recently suggested that WT1 was one of the most promising targets for cancer immunotherapy (Cheever et al. 2009), and it has been demonstrated that WT1 vaccination is safe and has therapeutic potential for at least several kinds of tumors (Oka and Sugiyama 2010; Hashii et al. 2010; Oji et al. 2010;



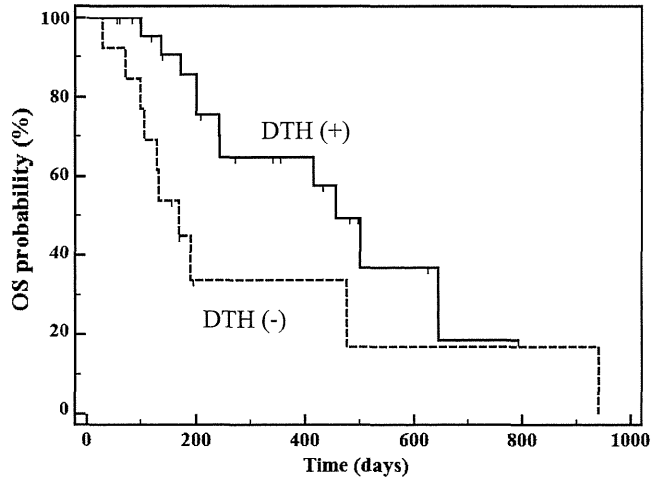


Fig. 1 PFS and OS association with DTH after WT1 vaccination. **a** The PFS tended to be longer in positive DTH cases than in DTH-negative cases ($p = 0.23$ by the log-rank test). **b** The OS was significantly longer in positive DTH cases than in DTH-negative cases ($p = 0.023$ by the log-rank test). *Solid line*: DTH (*plus*), *broken line*: DTH (*minus*)

Izumoto et al. 2008; Ohno et al. 2009). In this current phase II trial, we have tested the efficacy and safety of WT1 immunotherapy for gynecologic malignancies that were progressing, that is, resistant against conventional therapies.

In general, gynecologic tumors, including ovarian, endometrial and cervical carcinomas and uterine sarcomas, are very difficult to further treat, once the disease become resistant to conventional therapies such as chemotherapy or radiotherapy. For example, when ovarian carcinoma is first treated with cytoreductive surgery, the surgery is immediately followed by combination chemotherapy with paclitaxel and carboplatin (TC). If there is a failure of this first-line treatment, a single drug or combination chemotherapy for the recurrent disease, chosen based on the patient's treatment-free interval, can still be performed effectively in some cases (Koensgen et al. 2008; Markman et al. 2003; Harries and Gore 2002; Dizon et al. 2003). However, even though some third-line regimens have been reported to be occasionally effective for second relapses of some of these advanced stage diseases (Vergote et al. 2009; Chiyoda et al. 2010); the efficacy of each attempt becomes progressively lower as the number of previous treatment failures increases.

In the present study, the median number of the previous treatment regimens was 3 (range 1–11 treatments). Since all of the patients in the present trial had exhibited resistance to previous therapies, normally supportive care would have been considered as the only remaining option for them; however, the experimental WT1 vaccination immunotherapy was offered to them as an alternative.

A previous small study showed that stable disease was achieved by WT vaccination in 3 (25 %) of 12 gynecologic malignancies (Ohno et al. 2009). However, that study was so small that a survival effect was not analyzed. The response rate (CR + PR/all) in our study was 0 % (0 of 40 cases). However, the disease control rate (CR + PR + SD/all), which corresponds to disease stabilization lasting at least 3 months from the start of the vaccination, was 40 % (16 of 40 cases). The median PFS was 84 days (11–497), and the median OS of all the patients was 193 days (29–941). Considering that these cases were resistant to various kinds of therapies, and the diseases were progressing prior to the vaccination, these results of disease control rate and PFS time may be favorable, and were consistent with results of the previous smaller study that suggested the therapeutic potential of WT1 vaccine for gynecologic malignancies. Furthermore, surprisingly, in these SD cases, whose tumors had continuously progressed against previous therapies during the median of 185 days of treatments (range 40–1,198 days), the disease was durably controlled, without significant progression of the disease, for the median of longer than 160 days (range 67–427 days) after starting the WT1 immunotherapy (Table 2), implying an improved survival effect of the WT1 peptide vaccine. The adverse effect by the WT1 peptide-based immunotherapy with the dosage and schedule adopted here was limited and largely tolerable.

We next investigated the association of DTH and the efficacy of the WT1 immunotherapy. The OS of the patients with a positive DTH reaction was significantly better than that of those with a negative DTH reaction ($p = 0.023$ by the log-rank test) (Fig. 1). Moreover, the DTH reaction was demonstrated to be an independent factor for overall survival of the patients by multivariate Cox proportional hazards analysis (Table 3). These findings suggested that the induction of WT1-specific immune response, that is, the peptide-specific DTH, is a potential

Table 3 Multivariate Cox proportional hazards analysis on overall survival

Variable	Number of cases	Adjusted HR	95 % CI	*p* value
Age (years)				0.44
<60	24	1		
≥60	16	0.64	0.21–1.96	
Origin of the disease				0.75
Uterus	16	1		
Ovary	24	1.17	0.44–3.14	
Histology				0.98
Carcinoma	35	1		
Sarcoma, carcinosarcoma	5	0.99	0.28–3.42	
Evaluation of the previous therapy				0.39
SD	4	1		
PD	36	1.88	0.46–7.71	
Number of previous therapy regimens				0.034
<3	12	1		
≥3	28	4.28	1.12–16.37	
DTH				0.043
+	27	1		
−	13	2.73	1.04–7.19	

Multivariate Cox proportional hazards analysis (stepwise method) for the factors including age, origin of the disease, histology, evaluation of the previous therapy, number of previous therapy regimens and DTH was performed to evaluate whether DTH was an independently significant factor on OS

SD stable disease, *PD* progressive disease

predictor for the induction of clinical response, leading to a better prognosis.

The number of previous treatment regimens was also demonstrated to be an independent factor for survival prognosis after WT1 immunotherapy. The response rate of the first-line chemotherapy was quite high for ovarian carcinoma, however, that of second-line and the third-line chemotherapy was 34.5 and 27.5 %, respectively (Nishio et al. 2006). Effectiveness of WT1 was demonstrated to be associated with the number of previous treatment regimens, which was similar to that of the cell toxic chemotherapy. As the number of chemotherapy regimen increases, the tumor cells are considered to become resistant to the next line therapy. Furthermore, immunological potentials of the patients treated by chemotherapy with many courses might be dampened, leading to the poor response to the administered cancer vaccine. WT1 peptide vaccination soon after the first-line therapy, including the vaccination to prevent relapse after the operation, chemotherapy or radiation therapy, may be a favorable setting for the next clinical trial.

In the present phase II prospective study with a single arm, we have, for the first time, analyzed the survival effect of the WT1 vaccine for gynecologic malignancies, in addition to its anti-tumor effect conventionally evaluated by RECIST and toxicity, which had previously been reported in a smaller pilot study (Ohno et al. 2009). It was strongly suggested that WT1 peptide vaccination could induce the peptide-specific immune response in patients whose gynecological tumors have become resistant to conventional therapies, leading to a better survival. Larger two-arm randomized studies will be required to confirm the efficacy and clinical usefulness of the WT1 peptide vaccine for gynecologic malignancies.

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Conization using the Shimodaira-Taniguchi procedure for adenocarcinoma *in situ* of the uterine cervix

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ABSTRACT

Objective: The Shimodaira-Taniguchi conization procedure addresses the disadvantages of the loop electrosurgical excision procedure (LEEP) by using a high frequency current and a triangular probe with a linear excision electrode to extract the tissue as a single informative specimen, without incurring accompanying thermal trauma. The aim of the present study was to analyze the surgical efficacy of the Shimodaira-Taniguchi conization procedure for adenocarcinoma *in situ* (AIS) of the uterine cervix.
Study design: At the Osaka University Hospital, conization using the Shimodaira-Taniguchi procedure has long been routinely performed for AIS. Medical records of patients during the period from 2005 to 2011, whose post-conization diagnosis was AIS, were retrospectively analyzed. A literature review was conducted of the PubMed database to clarify the surgical outcome efficacy of the Shimodaira-Taniguchi procedure compared to other procedures.
Results: During the study period, a post-conization diagnosis of AIS was made in 10 patients. A positive resection margin was detected in 4 of the 10 cases (40%), and residual disease was observed in 3 cases (30%). A review of the relevant literature indicates that the rate of positive margin and residual disease by the Shimodaira-Taniguchi procedure, including our cases, was not significantly different from the cold knife, LEEP or laser procedures ($p = 0.32$, 0.99, and 0.40, respectively, for positive margin, and $p = 0.76$, 0.94, and 0.063, respectively, for residual disease).
Conclusion: AIS was demonstrated to be efficaciously treated, with a low risk of residual disease, by the Shimodaira-Taniguchi conization procedure. Further study is still needed to establish a standard of conservative treatment for AIS.

1. Introduction

Adenocarcinoma *in situ* (AIS), a non-invasive neoplastic lesion widely regarded as a precursor of adenocarcinoma of the uterine cervix, has been increasing. Although a hysterectomy is a definitive treatment for AIS, the condition often occurs in women still of reproductive age, who may desire fertility preservation [1]. There remains controversy regarding the ideal less-radical treatment of AIS. Achievement of a negative margin after conization is required for adequate treatment, but residual disease is sometimes later detected even in patients with a negative margin. Young et al. reported that 13% of their patients with a negative margin had residual or recurrent AIS disease [1].

Currently, conization is the standard option for treatment of a squamous lesion of the cervical intraepithelial neoplasia (CIN) type, a precursor of squamous cell carcinoma (SCC) of the uterine cervix. The loop electrosurgical excision procedure (LEEP) has largely replaced the cold knife procedure because it overcomes several of the former's drawbacks (including significant blood loss, longer operation times, and a higher rate of postoperative hemorrhage). Laser conization is another option. The Shimodaira-Taniguchi conization procedure was introduced in 1992; it addresses the disadvantages of LEEP by using a high frequency current and a triangular probe with a 0.25 mm linear excision electrode to extract the tissue as a single informative specimen, without incurring accompanying thermal trauma [2,3]. The electrodes for the Shimodaira-Taniguchi conization procedure are illustrated in Fig. 1. After excision by the cutting electrode, the coagulation electrode is used at the cut surface to achieve hemostasis. The efficacy of Shimodaira-Taniguchi conization procedure for CIN 3 lesions was reported previously [4].

Many previous studies have demonstrated the rates of positive margin and residual disease after conization for AIS [1,2,5–23]. For example, a positive margin was detected in 22 (30%) of 74 patients,

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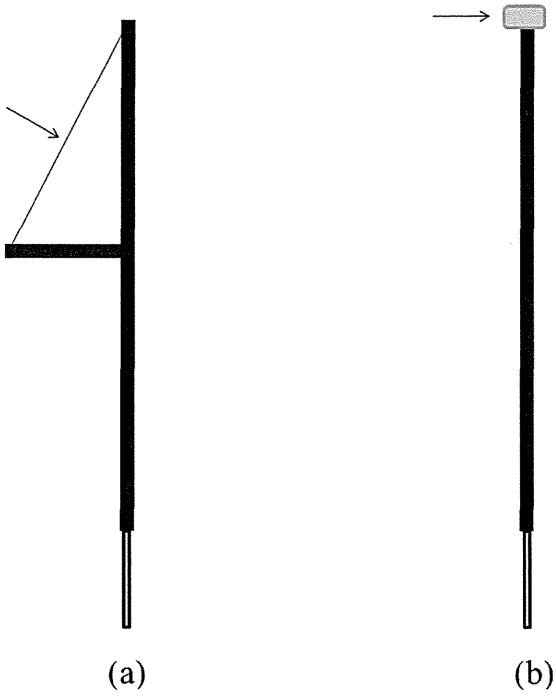

Fig. 1. The two probes used in the Shimodaira-Taniguchi conization, Cutting electrode (arrow), Coagulation electrode (arrow).

including 52 patients (70%) who received conization by cold knife, 9 patients (12%) by LEEP, 2 patients (3%) by laser, 9 patients (12%) by Fischer excisor, and 2 patients (3%) by unspecified procedures [1]. A comprehensive analysis of the efficacy of each procedure, however, including the rate of positive margin and that of residual disease, has never been properly conducted. In particular, only the rate of positive margin was reported for the Shimodaira-Taniguchi conization procedure in a previous report [2].

In the present study, reports showing the rate of positive margin and residual disease of each conization procedure, such as cold knife, LEEP, laser and Shimodaira-Taniguchi, were reviewed, and by adding our own data with Shimodaira-Taniguchi conization, we have made comparisons of efficacy.

2. Materials and methods

In the Department of Obstetrics and Gynecology of the Osaka University Hospital in Osaka, Japan, conization using the Shimodaira-Taniguchi procedure has been routinely performed for some time for patients diagnosed with AIS of the uterine cervix, after endocervical biopsy or cytology has been used to rule out invasive adenocarcinoma. Conization resected cervical tissue was carefully divided into 12 specimens for pathological diagnosis.

During the six-year period from 2005 to 2011, a post-conization diagnosis of AIS was made in 10 patients. Medical records of these 10 patients, including pathology reports, were retrospectively analyzed. Hysterectomy was usually indicated for the patients whose post-conization diagnosis was AIS, irrespective of their margin status. For those who desired a fertility-sparing option, however, no further treatment was performed after conization, if the conization resection margin was negative. For some patients with a positive resection margin who had a strong desire for fertility-sparing management, re-conization was performed. In the cases where hysterectomy was not performed, tight follow-up was conducted, with endocervical cytology every 3 months for the first year after conization, every 6 months in the second year, and then annually thereafter. Whenever a case displayed a positive cytological test, a colposcopic observation and biopsy or endocervical curettage was performed.

2.1. Literature review

The PubMed database was searched for papers related to AIS margin status and residual disease after conization using specified procedures including cold knife, loop electrosurgical excision procedure (LEEP), including the variant large loop excision of the transformation zone (LLETZ), laser, and the Shimodaira-Taniguchi procedure, using combinations of the following keywords: AIS, conization, margin, residual, persistent, cold knife, loop electrosurgical excision procedure, laser, and Shimodaira-Taniguchi.

2.2. Statistical analysis

MedCalc (MedCalc Software, Mariakerke, Belgium) was used for the statistical analysis. The rates of positive margin of conization and of residual disease after conization were compared by four procedures, including cold knife, LEEP, Laser and Shimodaira-Taniguchi, and were analyzed by Fisher's exact test. Bonferroni's correction was used to assess differences among the four groups and a value of $p < 0.0125$ was considered statistically significant.

2.3. Statements of ethics

This study was approved by the Institutional Review Board and the Ethics Committee of the Osaka University Hospital. All patients provided written informed consent.

3. Results

3.1. Clinical characteristics of patients whose post-Shimodaira-Taniguchi conization diagnosis was AIS

During the study period, a post-conization diagnosis of AIS was made in 10 patients (Table 1). Their median age was 44 (29–55) years. Co-existence of CIN3 was observed in 3 cases. Following conization using the Taniguchi-Shimodaira procedure, 7 patients (70%) underwent hysterectomy, and 2 patients (20%) received conization again. One patient, whose conization margin was free of disease, did not agree to further treatment.

3.2. Cases of positive margin or persistence after Shimodaira-Taniguchi conization

Among the 7 hysterectomy cases (including 3 patients with a positive margin and 4 cases of negative margin), residual AIS was detected in one case whose margin was positive, and an adenocarcinoma was found in 2 positive-margin cases and in one negative-margin case. Among the 2 re-conization cases (including a patient of positive margin and another case of negative margin), no residual disease was detected in re-conization samples and, till now, these two cases have been followed by cytology for 15 months and 7 months, respectively.

Table 1
Clinical characteristics of patients whose post-conization diagnosis was AIS.

Characteristic	
Number (cases)	10
Median age (years) (range)	44 (29–55)
Treatment following conization	
Hysterectomy	7 (70%)
Re-conization	2 (20%)
None	1 (10%)

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Table 2
Studies demonstrating the rates of positive margin and residual disease after conization for AIS, including case from the present study.

Author (year)	Cold knife		LEEP		Laser		Shimodaira-Taniguchi	
	Margin	Residue	Margin	Residue	Margin	Residue	Margin	Residue
Kennedy et al. (1995)	–	–	0/1	1/1	–	–	–	–
Widrich et al. (1996)	8/24	5/24	9/18	4/18	1/3	–	–	–
Wolf et al. (1996)	18/47	15/47	3/7	5/7	0/1	0/1	–	–
Houghton et al. (1997)	–	–	8/19	1/19	–	–	–	–
Denehy et al. (1997)	5/11	8/11	5/5	4/5	0/1	0/1	–	–
Tay et al. (1999)	0/2	–	–	–	6/17	–	–	–
Azodi et al. (1999)	6*/25	–	6/8	–	–	–	–	–
	* endocervix							
Krivak et al. (2000)	1/1	0/1	–	–	–	–	–	–
Östor et al. (2000)	16/73	11/73	–	–	–	–	–	–
Kennedy et al. (2002)	9/37	–	28/49	–	0/4	–	–	–
Andersen et al. (2002)					17/60	3/60	–	–
Schorge et al. (2003)	1/5	0/5	2/4	0/4	–	–	–	–
Hwang et al. (2004)	9/20	–	9/23	–	11/41	–	–	–
Bryson et al. (2004)	–	–	7/22	0/22	-	–	–	–
Cohn et al. (2005)	0/1	1/1	–	–	–	–	–	–
Bull-Phelps et al. (2007)	13/69	–	11/32	–	–	–	–	–
Young et al. (2007)	15/52 –	–	–	–	–	–	–	
Dalrymple et al. (2008)	8/38	3/38	6/44	1/44	–	–	–	–
Matsumura et al. (2010)	–	–	–	–	–	–	–	3/28
DeSimone et al. (2011)	–	–	20/41	18/41	–	–	–	–
van Hanegem et al. (2012) 11/58 3/58	11/58	3/58	14/54	3/54	–	–	–	–
The present study (2012)	–	–	–	–	–	–	4/10	3/10

Margin: positive margin, Residue: residual disease.

The single patient with a negative margin who did not agree to further treatment was followed by endocervical cytology every 3 months for 12 months, till now, with so far no evidence of persistence or recurrence of the disease.

In total, a positive resection margin was detected in 4 of 10 cases (40%), and residual disease was observed in 3 of 10 cases (30%), as shown in Table 2.

3.3. Review of the previous studies reporting margin status and persistent disease after conization using specified procedures

The PubMed database search was done to review previous studies reporting margin status and residual disease after conization, using specified procedures, including cold knife, loop electro surgical excision procedure (LEEP), laser and the Shimodaira-Taniguchi procedure. Data from reports in which the procedure of conization was not clearly described were excluded from the analysis. The relevant results are listed in Table 2. Results from our own retrospective study are included. In total, a positive margin was observed in 26% by cold knife conization, 40% by LEEP, and 28% by Laser conization, and 40% by Shimodaira-Taniguchi procedure (Table 3). The rate of positive margin by the Shimodaira-Taniguchi procedure was not significantly different from cold knife, LEEP and laser ($p = 0.32$, 0.99, and 0.40, respectively). Cold knife conization tended to provide a relatively low frequency of positive margin, but a statistically significant difference was not detected.

Table 3
The rates of positive margin and residual disease by the types of conization procedures.

Procedure	Positive margin	Residual disease
Cold knife	120/463 (26%)	46/258 (18%)
LEEP	130/327 (40%)	35/215 (16%)
Laser	35/127 (28%)	3/62 (5%)
Shimodaira-Taniguchi	4/10 (40%)	6/38 (16%)

Margin: positive margin, Residue: residual disease, The rates of positive margin and residual disease by the Shimodaira-Taniguchi conization procedure were not significantly different from those by any other procedures (Fisher's exact test with Bonferroni's correction).

Residual disease following cold knife conization was observed in 18% of combined study cases, 16% by LEEP, 5% by laser conization, and 16% by the Shimodaira-Taniguchi procedure. The rate of residual disease after the Shimodaira-Taniguchi procedure was not significantly different from cold knife, LEEP or laser ($p = 0.76$, 0.94, and 0.063, respectively). Laser conization tended to provide a relatively low frequency of residual disease, but a significant difference was not detected.

4. Comments

Currently, conization is the standard option selected for treatment of CIN 3, a precursor of SCC of the uterine cervix. Cervical conization does not necessarily increase the risk of preterm delivery in subsequent pregnancy [24]. The status of the conization resection margin has been found to be fairly predictive of a persistence or recurrence of CIN lesions [4], so choice of cervical method should consider which gives the most consistent negative margins. LEEP and laser conization have largely replaced the original cold knife procedure, based on their efficacy and safety. The Shimodaira-Taniguchi procedure is also been found to be useful for conization for CIN 3 [2–4].

The gold standard for the successful treatment of AIS is hysterectomy. Many women of child-bearing age weigh the risks and opt for a conservative, fertility-sparing management for their AIS, but the choice of surgical procedure is still quite controversial. One of the reasons for this is the high rate of disease residue found not only in positive margin cases but also in the negative margin cases. According to a review article, persistent disease was detected in 149 (55%) of 272 positive margin cases and in 45 (23%) of 196 negative margin cases [1]. In the present study of our own cases, we first analyzed the rate of positive margin and that of residual disease after Shimodaira-Taniguchi conization. Positive resection margin was detected in 4/10 cases (40%), and residual disease was observed in 3/10 cases (30%). This is the first demonstration of both these rates

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following the Shimodaira-Taniguchi procedure, with the exception of a report by Matsumura et al. of a disease residue rate of 3 of 28 [2].

Next, we compared the rate of positive margin and that of residual disease after conization by four procedures, including cold knife, LEEP, laser and the Shimodaira-Taniguchi procedure. In total, a positive margin was observed in 26% by cold knife conization, 40% by LEEP, and 28% by laser conization, and 40% by the Shimodaira-Taniguchi procedure (Table 3). The rate of positive margin after the Shimodaira-Taniguchi procedure was not significantly different from cold knife, LEEP and laser ($p = 0.32$, 0.99, and 0.40, respectively). Residual disease was observed in 18% by cold knife conization, 16% by LEEP, and 5% by laser conization, and 16% by the Shimodaira-Taniguchi procedure. The rate of residual disease after the Shimodaira-Taniguchi procedure was also not significantly different from cold knife, LEEP and Laser ($p = 0.76$, 0.94, and 0.063, respectively). These results suggested that the types of procedure of conization did not affect the efficacy, as measured by the rates of positive margin and residual disease.

In the present study, all three cases with later residual disease after Shimodaira-Taniguchi conization had a positive margin at the initial conization. No residual disease was observed in the negative margin cases. These results may imply that negative margin cases after Shimodaira-Taniguchi conization can be followed without any further treatment, including hysterectomy. One possible reason is the more accurate diagnosis of margin status attributed to the Shimodaira-Taniguchi procedure. The Shimodaira-Taniguchi conization procedure also addresses the disadvantages of LEEP, which causes thermal damage to the tissues, by using a high frequency current and a triangular probe with a 0.25 mm linear excision electrode to extract the cone of tissue as a single informative specimen, and does so without incurring any undue thermal trauma [2]. Matsumura et al. demonstrated the benefits of the procedure: that the number of excised specimens needed was only one per patient in 79% of the cases they studied (358 of 455 cases), that the mean operation time was 11 min, and that the average blood loss was only 9.9 ml. In fact, the number of the excised specimens needed in our present study was only one per patient in 8 (80%) of 10 cases. Another reason may be the necrotizing effect to residual disease caused by the coagulation electrode.

In our present study, we feel we have further demonstrated the usefulness of the Shimodaira-Taniguchi conization procedure for AIS, which gives a high cure rate. The Shimodaira-Taniguchi conization procedure can be adequately used for the patients suspected of AIS who express a desire for fertility sparing. Further study is still needed to establish a standard of conservative treatment for AIS.

Conflict of interest statement

The authors state that there are no conflicts of interest.

Condensation

Adenocarcinoma *in situ* was demonstrated to be well treated, with low-risk of residual disease, by Shimodaira-Taniguchi conization.

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臨床腫瘍プラクティス

子宮体がん，子宮頸がんの薬物治療

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ヴァンメディカル

特集 子宮体がん，子宮頸がんの薬物治療

3．子宮体がんに対する薬物療法の実際

1）術後補助化学療法・化学放射線療法の進め方

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View Points !

▶子宮体がんの場合，子宮限局例の５年生存率は85%以上であるが，子宮外進展を伴う高リスク群の予後は不良である。欧米では術後補助療法として放射線療法が広く用いられるが，日本では術後化学療法が一般的である。

▶本邦での術後化学療法は，2005年２月に保険適用となったAP療法が標準治療だが，新規抗がん薬の登場により，TC（パクリタキセル＋カルボプラチン）療法などのレジメンが開発されてきた。

▶JGOG2043等の試験にて，TC療法やDP療法，さらにはTEC療法・TAC療法・ddTC療法といった，新たな治療法の開発が進みつつある。

導 入

- 子宮体がんは年々増加傾向にあり，2005年の国立がん研究センターの報告によると年間8,000人が新規発症し，毎年1,800人が死亡している。
- 子宮体がんの初回治療は原則手術であり，子宮全摘術，両側付属器摘出術，腹腔細胞診に加え骨盤・傍大動脈リンパ節郭清/生検を行い，進行期を決定する。この手術進行期に加え，腫瘍進展度，組織型，分化度，筋層浸潤，脈管侵襲などの病理学的所見から再発リスクを推定し術後補助療法を行う。
- 子宮体がんは子宮に限局していれば５年生存率85%以上と良好であるが子宮外進展を伴う高リスク群の予後は不良である。欧米では術後補助療法として放射線療法が広く用いられているが，日本では術後化学療法が一般的である。
- Ⅲ期，Ⅳ期症例を対象として全腹部照射と化学療法をランダム化比較したGOG122試験の結果は化学療法が無再発生存・全生存共に全腹部照射を上回っており，化学療法の有効性を示唆するものであった。
- 今後子宮体がんにおける術後補助化学療法の重要性は増していくものと思われ，現在大規模臨床試験が進行中である。現在の子宮体がん術後化学療法における知見について述べる。

進行・再発化学療法の変遷（表１）

- これまで子宮体がんに対し，単剤で効果が認められているのは，シスプラチン（CDDP），カルボプラチン（CBDCA），ドキソルビシン（DXR（ADM）），エピルビシン（EPI），シクロホスファミド（CPA），トポテカン等であった。
- その後パクリタキセル（PAC）やドセタキセル（DOC）も単剤で30%を超える奏効

表1 進行・再発子宮体がんに対する臨床試験

試験名	デザイン	期間	対象	症例数	RR	PFS(m)	OS(m)
EORTC55872		1988～1994	Ⅲ/Ⅳ期再発	177			
	A(60mg/m²)monthly 7コース				17	7	7
	AP(60/50mg/m²)monthly 7コース				43*	8	9
GOG107			Ⅲ/Ⅳ期再発	281			
	A(60mg/m²)tri-weekly 7コース				25	3.8	9.2
	AP(60/50mg/m²)tri-weekly 7コース				42*	5.7*	9.0
GOG177		1998～2000	Ⅲ/Ⅳ期再発	273			
	AP(60/50mg/m²)tri-weekly 7コース				34	5.3	12.3
	TAP(150/45/50mg/m²), G-CSF サポート, tri-weekly 7コース				57*	8.3*	15.3

A: ドキソルビシン/P: シスプラチン/T: パクリタキセル
RR: response rate / m: month / PFS: progression free survival / OS: overall survival
G-CSF: granulocyte-colony stimulating factor
GOG: Gynecologic Oncology Group
EORTC: European Organization for Research and Treatment of Cancer
*統計学的有意差あり

率が報告されている。

- 奏効率の向上を目指しこれらの薬剤を組み合せた多剤併用化学療法が試みられCAP療法(CPA+DXR+CDDP)やAP療法(DXR+CDDP)等の有効性が示された。
- 再発・進行子宮体がんに対しDXR単剤とAP療法を比較検討したランダム化第Ⅲ相試験(GOG107)では,AP療法がDXR単剤治療に対し奏効率42% vs 25%,無増悪生存期間5.7ヵ月 vs 3.8ヵ月と有意に優れていた[1]。
- さらに同様にDXR単剤とAP療法を比較したランダム第Ⅱ/Ⅲ相試験(EORTC55872)も同様にAP療法の有効性・安全性を示し,AP療法が再発・進行子宮体がんの標準治療と考えられるようになった[2]。
- 本邦では2005年2月にAP療法は保険適用となっている。その後タキサン系の登場により,AP療法とPACを加えたTAP療法との比較試験GOG177が行われ,奏効率34% vs 57%,無増悪生存期間5.3 vs 8.3ヵ月,全生存期間12.3 vs 15.3ヵ月とTAP療法群が有意に優れている結果であった[3]。しかしTAP療法群は末梢神経障害grade 2が27%,grade 3が12%,心不全grade 3が2%,治療関連死が5例など重篤な有害事象を認め,毒性の点から標準治療には至らなかった。
- TAP療法では毒性が問題となったが,タキサン系が今後新たなkey drugとなる可能性を踏まえ,このタキサン系を加えた多剤併用療法を用いたランダム化第Ⅱ相試験(JGOG2041)が実施された[4]。進行・再発子宮体がんに対してTC療法 vs DP療法

vs DC療法について検討し，奏効率はTC療法が60%，DP療法が52%，DC療法が48%と，3つのレジメンとも先述のGOG 177におけるAP療法の奏効率34%を上回るものであった。

- 卵巣がんの標準化学療法として確立しているTC（PAC＋CBDCA）療法の進行・再発子宮体がんに対する報告では奏効率は63～87%と高く[5~7]，2005年にJGOGが行った全国調査では標準治療とされているAP療法は少数派にとどまっていた。子宮体がん術後に補助化学療法を施行すると答えた施設のうち80%がTC療法を第一選択としている[8]。しかし，現在有効性を支持するエビデンスは十分でなく，今後の臨床試験の結果が待たれる状況である。

子宮体がんにおける術後補助化学療法の位置づけ

- 欧米では歴史的に術後補助療法として放射線治療を主体に検討されてきており，現在も放射線治療が中心的な役割を果たしている。
- Ⅲ期，Ⅳ期の残存腫瘍2 cm以下の症例を対象に術後全腹部照射とAP療法を比較したGOG122においてAP療法は血液毒性が強いものの，全生存期間はAP療法が全腹部照射に有意に勝る効果（ハザード比0.71，95%CI，0.55-0.91：$p<0.01$）が示され，術後再発高リスク群における化学療法の有用性を示した[9]。しかしMaggiらの報告ではⅠC期/G3，ⅡA～ⅡB/G3（筋層浸潤≧1/2），Ⅲ期に対し放射線療法とCAP療法の第Ⅲ相試験を行った結果PFS，OSには有意差は認められていない[10]。
- これらを受け，NCCNの診療アルゴリズムにおいてⅢ・Ⅳ期症例における化学療法の役割は支持されたが，子宮限局例での治療指針を変えるほどのインパクトになっていない。
- 子宮体がんⅠ期を対象としたランダム化比較試験のメタアナリシスでは手術のみの群と比較し術後放射線治療施行群では局所再発は有意に減少したが生存率に差は認められなかった。しかしサブセット解析にて中リスク群（筋層浸潤1/2以上，G3）では生存期間の延長が認められている[11,12]。
- 過去の報告より子宮に限局するがリスク因子，すなわち筋層浸潤1/2以上，G3，高度な脈管侵襲等の因子を有する場合，初回手術による完全摘出後でも再発・死亡の転帰をたどる場合があり，また術後放射線療法後でも遠隔転移のリスクを有する。これらの術後再発中リスク群における術後補助療法についてまだ明らかなコンセンサスはない。
- 本邦ではJGOG2033において中リスクを有する類内膜腺癌に対する術後補助療法として全骨盤照射とCAP療法の比較がなされている。無増悪生存期間，全生存期間は両群で同等であったが，高/中リスク群(high-intermediate risk；stageⅡ/腹部細胞診positive)でのサブセット解析ではCAP療法が無増悪生存期間，全生存期間共に優れていた。
- エビデンスとなるには足らないが今後高リスク群のみならず高/中リスク群における術後補助療法として化学療法が全骨盤照射に変わりうる可能性を示唆しさらに大規模なランダム化比較試験が求められるとの結論となった[13]。

今後のstudy（表2）

- 本邦では子宮体がんに対してTC療法が多くの施設において使用されているが，本療法の検証はこれからである。本邦にて現在進行中の第Ⅲ相試験としてJGOG2043があ

表2 現在進行中の臨床試験

試験名	デザイン	対 象	症例数
GOG209	TAP（160/45/50mg/m²），G-CFSサポート，tri-weekly 7コース vs TC（175mg/m²/AUC＝6），tri-weekly 7コース	Ⅲ/Ⅳ期，再発	692 689
JGOG2043	AP(60mg/m², 50mg/m²)tri-weekly 6コース vs DP(70mg/m², 60mg/m²)tri-weekly 6コース vs TC(180mg/m², AUC＝6)tri-weekly 6コース	残存腫瘍2 cm以下，筋層浸潤1/2を超えるⅠ～Ⅱ期G2～G3，予後不良の組織型，Ⅲ期，腹腔内に留まるⅣ期	232 228 228
PORTEC-3	pelvic radiotherapy（48.6Gy） vs pelvic radiotherapy/cisplatin 50 mg/m²（day 1，day22）＋TC（175 mg/m², AUC＝6）tri-weekly 6コース	IB期/G3/LVSI，IC/II期/G3 III期の類内膜腺癌 IB/IC/II/III期の漿液性または明細胞腺癌	500 500
GOG258	volume-directed radiotherapy（45 Gy）cisplatin 50mg/m²（day 1，day29）＋TC（175mg/m²，AUC＝6）tri-weekly 6コース vs TC(175mg/m², AUC＝6)tri-weekly 6コース	Ⅲ/Ⅳ期 Ⅰ/Ⅱ期でかつ腹水細胞診陽性の漿液性または明細胞腺癌	804 804
ENGOT-EN2-DGCG	経過観察 vs TC（175mg/m²，AUC 5）tri-weekly 6コース	I/II期 術後中・高リスク	678 678

T：パクリタキセル/A：ドキソルビシン/P：シスプラチン/C：カルボプラチン/D：ドセタキセル

る[14]。単純子宮全摘術＋両側付属器切除＋骨盤リンパ節郭清を施行された残存腫瘍2 cm以下，筋層浸潤1/2を超えるⅠ～Ⅱ期G2～G3，予後不良の組織型，Ⅲ期，腹腔内に留まるⅣ期を対象としてAP療法，DP療法，TC療法の比較を行う。現在すでに登録が終了し解析待ちである。

- 本試験はAP療法を標準治療アームとしたタキサン系薬剤を含む併用療法の臨床試験であり，結果が大いに期待される。またTC療法はTAP療法に比し，奏効率も良好で末梢神経障害も少ない点が考慮され，米国でⅢ/Ⅳ期，再発症例に対する第Ⅲ相試験(GOG209)が施行され，現在解析中である[15]。
- 現在までに示されているように術後化学療法は進行がんに対し有意に生存率を改善させるが，化学療法単独では局所制御は十分でなく，GOG122でも化学療法群では全体で50%に再発を認め，内骨盤・腹腔内は32%であった。このため局所制御と遠隔転移を改善できる化学療法/放射線療法に期待が寄せられている。