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Retreatment with nedaplatin in patients with recurrent gynecological cancer after the development of hypersensitivity reaction to carboplatin

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Abstract

Aim: Platinum is a milestone drug against gynecologic malignancies. The purpose of this retrospective study was to investigate the feasibility of replacing carboplatin with nedaplatin in patients who had developed a hypersensitivity reaction to carboplatin.

Material and Methods: Fifteen patients with recurrent gynecologic cancer (12 ovarian, 1 fallopian tube, 1 endometrial and 1 cervical cancer) who had experienced a hypersensitivity reaction to carboplatin and a possible clinical indication for continuing treatment with platinum were treated with nedaplatin (80 mg/m^2)-containing regimen.

Results: The total number of nedaplatin cycles given was 137 (range 1–29). Four (27%) patients developed hypersensitivity reactions on the second, second, fourth, and ninth administration, respectively. The severities of all the hypersensitivity reactions were grade 3 or less. The other 11 patients (73%) had no nedaplatin-associated hypersensitivity reactions. The incidence of hypersensitivity reactions in the paclitaxel and nedaplatin group (three of four, 75%) was more frequent than the docetaxel and nedaplatin group (none of seven, $P = 0.024$). The objective response rate in eleven patients with measurable disease was 36% (complete response at 9% and partial response at 27%), and the disease control rate was 73% (stable disease at 36%).

Conclusion: Nedaplatin-associated hypersensitivity reactions are not rare in patients who developed allergic reactions to carboplatin. Retreatment of carboplatin-allergic patients with nedaplatin cannot be recommended without careful consideration of the potential risks and benefits.

Key words: carboplatin, cross-reaction, hypersensitivity reaction, nedaplatin, retreatment.

Introduction

Carboplatin is one of the most effective and well-tolerated chemotherapeutic agents for gynecologic malignancies. In addition to a standard first-line regimen, platinum-containing chemotherapy is repetitively administered to patients with platinum-sensitive recurrence in gynecologic cancer.[1–3] However, the repeated treatment with carboplatin is associated with an increased risk of hypersensitivity reactions (HSR). The incidence of HSR has been reported to be 8–44% in patients receiving retreatment with carboplatin.[4–7] Whereas there are several types of drugs available for treatment of recurrent ovarian cancer, platinum is still regarded as the single most active agent. Safety of rechallenge with cisplatin after the development of HSR to carboplatin is controversial. Although there have been several reports suggesting its safety, two

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deaths due to anaphylaxis following rechallenge with cisplatin have been reported.[8,9] So far, 39 of 46 reported cases (85%) were successfully retreated with cisplatin.[10]

Nedaplatin is one of the platinum analogues with the same carrier ligands of ammine as cisplatin and a five-membered ring structure in which glycolate is bound to the platinum ion as a bidentate ligand. Two phase II studies showed its effectiveness against gynecological cancers. The response rate of the nedaplatin monotherapy against cervical and ovarian cancer was 34–46% and 38%, respectively.[11,12]

Retreatment with nedaplatin in patients with hypersensitivity to carboplatin has not been reported yet. The purpose of this study was to evaluate safety and efficacy of rechallenge with nedaplatin in this population.

Patients and Methods

Fifteen patients (12 ovarian, 1 fallopian tube, 1 endometrial, and 1 cervical cancer) who had experienced a hypersensitivity reaction to carboplatin were treated with nedaplatin between 2004 and 2010 after informed consent regarding the potential risks as well as benefits of treatment. All the patients were platinum-sensitive (progression-free interval more than 6 months) at their primary treatment. All had recurrent disease and had experienced HSRs during receiving carboplatin in retreatment. The patient characteristics are summarized in Table 1. Four patients were administrated with single-agent nedaplatin and the other 11 were treated with combination chemotherapy (four with paclitaxel and seven with docetaxel).

Table 1 Patient characteristics

Median age, years (range)	58 (47–67)
Type of cancer (*n*)	
Ovarian cancer	12
Serous	7
Endometrioid	4
Unclassified adenocarcinoma	1
Fallopian tube cancer	1
Endometrial cancer	1
Cervical cancer	1
Prior chemotherapy (*n*)	
One regimen	3
Two regimens	4
>Three regimens	8
Protocol (*n*)	
Nedaplatin	4
Paclitaxel/nedaplatin	4
Docetaxel/nedaplatin	7

In the single-agent protocol, nedaplatin at a dose of 80 mg/m^2 was infused intravenously in 500 mL of normal saline over 2 h. In the paclitaxel/nedaplatin combination protocol, paclitaxel at a dose of 175 mg/m^2 was infused intravenously in 500 mL of normal saline over 3 h, followed by nedaplatin at a dose of 80 mg/m^2 in 500 mL of normal saline over 2 h. In the docetaxel/nedaplatin combination protocol, docetaxel at a dose of 70 mg/m^2 was infused intravenously in 250 mL of 5% glucose over 60 min, followed by nedaplatin at a dose of 80 mg/m^2 in 500 mL of normal saline over 2 h. In all regimens, the patients received intravenous hydration with 1000 mL of 5% dextrose over 4 h after administration of nedaplatin. No patients were administrated a desensitization protocol.

The severity of allergic reactions and anaphylaxis was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Tumor response was assessed in those with measurable disease using radiographic and clinical assessment. Response Evaluation Criteria in Solid Tumors (RECIST) were employed for evaluation of measurable disease.[13]

Results

Hypersensitivity reactions

The management of the patients is summarized in Table 2. A total of 137 cycles of nedaplatin were administered. One hundred and thirty-three cycles (97%) were completed without nedaplatin-associated HSRs. All the 15 patients were successfully treated with nedaplatin on the first administration without experiencing any symptoms suggestive of HSRs. Eleven of the 15 patients (73%) had no nedaplatin-associated HSRs during the nedaplatin-containing chemotherapy (HSR-negative group). Ten of the 11 patients continued the treatment until the disease became progressive (range 1–29 courses), and one patient (#14) periodically receives the chemotherapy without progression of disease (total 23 courses). The other four patients stopped the protocol due to HSRs to nedaplatin (HSR-positive group). One patient (#4) experienced HSRs on the ninth cumulative cycle. She received paclitaxel/nedaplatin against peritoneal dissemination for six cycles without HSRs with a partial response. After a 9-month interval, the disease recurred and she was retreated with nedaplatin. On the third cycle, she developed HSRs with rash, edema, nausea, and vomiting (grade 3 of allergic reaction) immediately after

Table 2 Summary of the management of all patients ($n = 15$)

No.	Disease	Age	Cycles of prior CBDCA	Total CBDCA (mg)	CBDCA HSR grade	Interval to rechallenge (M)	Prior regimen	Regimen	Cycles of nedaplatin	Total nedaplatin (mg)	Premedication	Nedaplatin HSR	Response	Time from infusion start to HSR (min)
1	Ov	64	30	17 175	2	3.9	G	N	2	129	None	Grade 2 (rash)	NE	15
2	Ov	67	9	3 950	3	23.9	T	TN	2	140	D + H + R	Grade 3 (hypotension)	SD	20
3	Ov	47	8	4 455	2	1	TC	TN	4	370	D + H + R	Grade 2 (dyspnea)	NE	44
4	Ov	50	14	8 875	2	1	TC	TN	9	961	D + H + R	Grade 3 (edema)	PR	1
5	Ov	66	12	7 875	3	17.5	TG	DN	1	120	D	(-)	PD	
6	Ov	47	8	5 125	2	3.2	T	DN	4	470	D(x2) + H + R	(-)	NE	
7	Ov	58	11	6 900	3	1	DC	DN	5	600	D′	(-)	PD	
8	Ov	62	8	3 300	2	3.1	TG	DN	6	780	D	(-)	PD	
9	Ov	60	24	12 520	3	9.1	CPT	N	8	1104	D(x2) + R	(-)	SD	
10	Ov	67	20	9 735	2	12.7	T	DN	9	1080	D′	(-)	SD	
11	Ov	52	20	9 080	2	0.7	C	N	15	1800	Cort + R	(-)	PR	
12	Ov	57	8	3 750	3	1	DC	DN	29	3190	D + H	(-)	CR	
13	Tube	59	31	9 660	2	0.7	TC	N	10	1200	D′ + R	(-)	NE	
14	Em	58	10	5 760	2	1.4	TC	DN	23	2845	D′	(-)	PR	
15	Cx	49	26	13 000	2	1.2	TC	TN	10	1100	D(x2) + H + R	(-)	SD	

C, carboplatin; Cort, hydrocortisone 100 mg; CPT, irinotecan; Cx, cervical cancer; D, dexamethasone 20 mg; D′, dexamethasone 6.6 mg; DC, docetaxel/carboplatin; DN, docetaxel/nedaplatin; Em, endometrial cancer; G, gemcitabine; H, diphenhydramine 50 mg; N, nedaplatin; NE, not evaluable; Ov, ovarian cancer; R, ranitidine 50 mg; T, paclitaxel; TC, paclitaxel/carboplatin; TG, paclitaxel/gemcitabine; TN, paclitaxel/nedaplatin; Tube, fallopian tube cancer.

starting infusion of nedaplatin. The other three patients had HSRs on the second, second, and fourth cycle, respectively. In these patients, the reactions occurred more than 15 min after the infusion of nedaplatin had started. Three of the four (75%) patients who received paclitaxel and nedaplatin showed HSRs to nedaplatin, whereas one of the 11 (9%) without paclitaxel ($P = 0.033$ by Fisher's exact test) and none of the seven with docetaxel and nedaplatin ($P = 0.024$) showed HSRs to nedaplatin.

There were no treatment-related deaths. Cycles of nedaplatin, total amount of prior carboplatin, the grade of HSR to carboplatin, and platinum-free interval before the nedaplatin treatment were not significantly distinct between the HSR-positive and the HSR-negative group.

Efficacy

Eleven patients (73%) had measurable disease. We observed one CR (9.1%) and three PRs (27%), for an overall response rate of 36% (95% CI: 11–69%). Stable disease was documented in four (36%) patients, and the disease control rate (CR + PR + SD) was 73% (95%CI: 39–94%). Median progression-free survival was 9.2 months (range: 0.4–42.0 months, 95%CI: 2.1–14.3 months).

In the patients with ovarian or fallopian tube cancer, nine patients had measurable disease. The overall response rate was 33% (one CR and two PRs, 95% CI: 7.5–70%), and the disease control rate was 67% (95% CI: 30–93%). Median progression-free survival was 8.2 months (range: 0.4–38.9 months, 95% CI: 2.1–11.6 months).

Discussion

In this study, we evaluated the safety and efficacy of retreatment with nedaplatin in patients who had developed carboplatin-associated HSRs. Although all the 15 patients were safely treated at first cycle, four (27%) of them experienced HSRs to nedaplatin during their treatment. This incidence suggests that cross-reactions between nedaplatin and carboplatin might occur at substantial frequency, as observed between cisplatin and carboplatin.[10] Our experience supports the risk of delivering any platinum agent following the documentation prior platinum hypersensitivity. However, case 4, who developed HSRs to nedaplatin on the ninth cumulative cycles in the second-line setting, suggests that newly-obtained hypersensitivity to nedaplatin might occur in certain patients.

Table 3 Reported cases of retreatment with carboplatin by desensitization protocol

Authors	Number	Success rate (%)
Gastaminza *et al.*[16]	4	75
Nishio *et al.*[17]	1	100
Gomez *et al.*[18]	7	71
Hesterberg *et al.*[19]	30	97
Confino-Cohen *et al.*[20]	20	95
Lee *et al.*[21]	31	100
Choi *et al.*[22]	8	100
McElroy *et al.*[23]	1	100
Rose *et al.*[24]	33	79
Robinson *et al.*[25]	8	100
Markman *et al.*[26]	3	33
Total	146	90

The mechanism of nedaplatin-associated HSRs remains unclear. Nedaplatin-associated HSRs are likely to be similar to carboplatin-associated HSRs, considering the development of allergic reactions with multiple courses of the therapy and the time from infusion start to the onset of HSRs (≥15 min in three of four patients).[4] Although the exact etiology responsible for carboplatin-associated HSRs is not also clarified, it is believed that both immediate Type I hypersensitivity mediated by IgE and the direct action of platinum on mast cells are involved in the allergic process.

Our study suggests that nedaplatin-associated HSRs in patients with HSRs to carboplatin would be difficult to predict. First, there were no significant differences of the profile between the HSR-positive and the negative group. Second, three of four patients who developed nedaplatin-associated HSRs had premedicated with 20 mg of dexamethasone, 50 mg of diphenhydramine, and 50 mg of ranitidine similar to those of paclitaxel-containing chemotherapy. This indicates that pretreatment with combination of steroids and antihistamines would be insufficient to prevent nedaplatin-associated HSRs. The administration of desensitization protocol may help to reduce the risk of HSRs, as successful rechallenge with carboplatin or cisplatin following desensitization has been reported.[14,15] The result of desensitization to carboplatin is listed in Table 3.[16–25] However, two deaths due to anaphylaxis following retreatment with platinum agents have been reported in spite of using an extensive desensitization protocol.[26] Further study is necessary to evaluate the effect of desensitization to nedaplatin.

It has been reported that the incidence of HSRs depends on a combination drug with platinum. CALYPSO trial showed that carboplatin-associated HSRs occurred significantly less frequently in treatment with pegylated liposomal doxorubicin and carboplatin than that with paclitaxel and carboplatin in patients with platinum-sensitive relapsed ovarian cancer.[27] The result of our study suggests that the combination of paclitaxel and nedaplatin might increase a risk of HSRs to nedaplatin. On the other hand, SCOTROC trial showed that HSRs were more frequent in combination of docetaxel and carboplatin in comparison with that of paclitaxel and carboplatin in first-line setting.[28]

Although the sample size is small, the overall response rate and the disease control rate (CR + PR + SD) in the patients with ovarian or fallopian tube cancer were achieved at 33% and 67%, respectively. A previous report showed that the response rate was 24% and the disease control rate was 59% by treatment with nedaplatin in patients with platinum-resistant ovarian, tubal, and peritoneal cancers.[29] The lower rate of patients with platinum-resistant disease in the present study might lead to slightly higher response rate and disease control rate. Nevertheless, other agents could be as effective as nedaplatin, considering that all the patients had platinum-sensitive disease at their primary treatment.

In conclusion, nedaplatin-associated HSRs are not rare in patients who have developed allergic reactions to carboplatin, indicating that non-platinum agents should be first considered to the patients with HSRs to carboplatin. The use of nedaplatin might be taken into consideration to patients that alternative drugs are not available, as these patients might be still sensitive to platinum. Appropriate informed consent regarding the potential risk and prompt treatment to the HSRs are indispensable for the rechallenge with nedaplatin. And also, the desensitization study of nedaplatin should be needed.

Disclosure

We declare that there are no conflicts of interest.

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Low-grade endometrial stromal sarcoma developing in a postmenopausal woman under toremifene treatment for breast cancer

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Abstract

Low-grade endometrial stromal sarcoma (ESS) is a rare neoplasm that is generally estrogen-receptor- and progesterone-receptor-positive and develops in premenopausal women. Although tamoxifen treatment is associated with an increased risk of ESS, the effect of other selective estrogen receptor modulators, including toremifene, on the risk of ESS is not clear. A 61-year-old postmenopausal woman was treated with toremifene as an adjuvant therapy for breast cancer. A cystic mass developed during the treatment, with gradual growth in the uterine myometrium. The patient was treated with hysterectomy and bilateral salpingo-oophorectomy, and the tumor was diagnosed as low-grade ESS (stage IA) with estrogen-receptor and progesterone-receptor. The patient discontinued toremifene and has been progression-free for 21 months. Our data suggest that toremifene might be associated with the development of ESS in certain patients through its estrogen-like effects in the uterus.

Key words: estrogen-like effect, low-grade endometrial stromal sarcoma, selective estrogen receptor modulator, toremifene, uterine corpus.

Introduction

Selective estrogen receptor modulators (SERM), especially tamoxifen, have been broadly administered as an endocrine treatment for breast cancer.[1] Despite its good reputation, tamoxifen has been associated with a 2–7-fold increased risk of endometrial cancer.[2] In addition, tamoxifen treatment has been associated with elevated risk of uterine sarcomas, including endometrial stromal sarcoma (ESS).[3] Toremifene is another type of SERM commonly used for the treatment of breast cancer.[4,5] Although toremifene might produce comparable estrogenic effects with tamoxifen in the uterus, the risk assessment of toremifene for endometrial cancer and uterine sarcomas is still inconclusive,[4,6] and toremifene-associated ESS has not been reported to date.

ESS is a rare gynecological malignancy accounting for 10% of uterine sarcomas.[7] ESS is classified into two histological subtypes: low-grade ESS (LG-ESS) and undifferentiated uterine sarcoma, depending on the morphology, number of mitoses, cellularity, and necrosis. LG-ESS tends to occur before menopause (mean, 39 years).[8] Estrogen acts as a growth stimulus in LG-ESS, which generally expresses estrogen receptors (ER) and progesterone receptors (PgR). Thus, LG-ESS is thought to be estrogen-dependent.

We report a case of LG-ESS development during treatment with toremifene for breast cancer.

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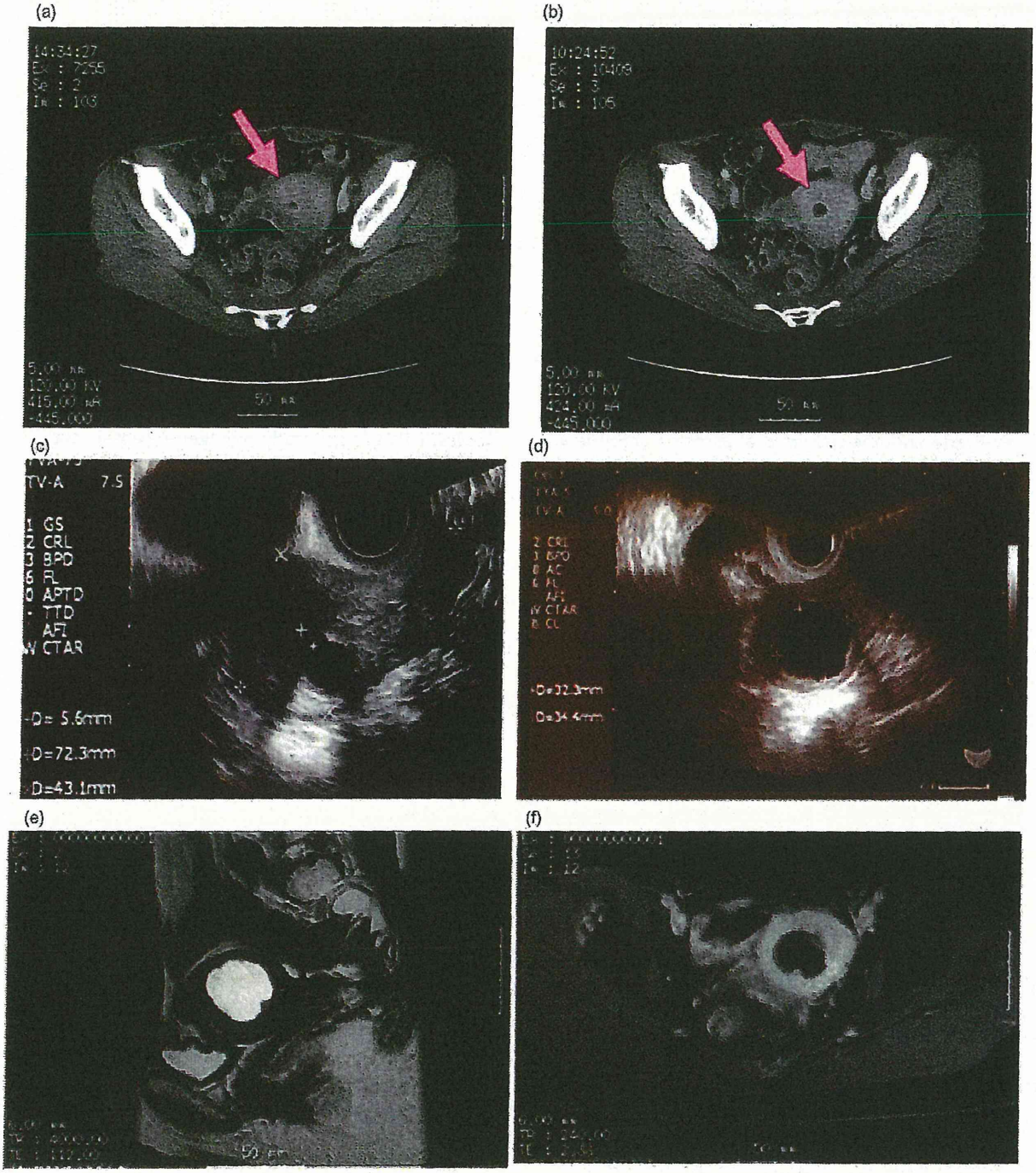

Figure 1 Images of the tumor by (a,b) computed tomography scan, (c,d) transvaginal ultrasonography, and (e,f) magnetic resonance imaging. (a) A cystic mass was first observed in the uterine myometrium 4 months after toremifene treatment in November 2007. (b) The cystic mass was more clearly detected in May 2008. (c) An intramyometrial cystic mass (14 × 16 mm) observed at the patient's first visit. (d) The cystic mass measured 32 × 34 mm 13 months after the first visit. (e) Sagittal T2-weighted image of a cystic tumor 38 mm in diameter located in the posterior myometrium. (f) Gadolinium-enhanced axial T1-weighted image of a homogeneous enhancement of the solid part of the tumor similar to normal myometrium.

Case Report

A 61-year-old woman (gravida 3, para 1) presented to our hospital with brownish discharge in June 2008. She had undergone surgeries for colorectal cancer in March 2007 and for breast cancer in June 2007, and had been treated for breast cancer with toremifene at a daily dose of 120 mg since July 2007. Magnetic resonance imaging (MRI) performed before the start of toremifene treatment in 2007 had revealed no abnormal mass in the uterine myometrium (Fig. S1). A low-density lesion (<1 cm in diameter) was observed in a computed tomography (CT) scan performed in November 2007 and in May 2008 while under treatment with toremifene (Fig. 1a,b). Transvaginal ultrasonography performed in June 2008 revealed a 14 × 12-mm hypoechoic lesion in the posterior myometrium (Fig. 1c). Endometrial cytology and biopsy of the endometrium were negative for malignant cells. The patient was followed up every 3 months, and a gradual enlargement of the hypoechoic lesion in the posterior myometrium was observed. In July 2009, the hypoechoic mass reached a size of 32 × 34 mm (Fig. 1d). In September 2009, MRI revealed a 38-mm tumor, which was presumed to be LG-ESS (Fig. 1e,f). No tumor markers were significantly elevated, including carbohydrate antigen (CA) 125 (11 U/mL), CA19-9 (10 U/mL), carcinoembryonic antigen (CEA) (2.3 ng/mL), neuron-specific enolase (NSE) (13 ng/mL) and lactate dehydrogenase (LDH) (193 U/L), and the biopsy of the endometrium was still negative. The patient discontinued toremifene and underwent total abdominal hysterectomy and right salpingo-oophorectomy in November 2009 (Fig. 2a) (she had received left salpingo-oophorectomy for an ectopic pregnancy when she was 33 years old). She was diagnosed with LG-ESS, International Federation of Gynecology and Obstetrics (FIGO) stage IA (Fig. 2b). The tumor demonstrated strong staining for CD10, ER, and PgR (Fig. 2c–e). The patient has received no postoperative treatment and has been recurrence-free for all of her malignant diseases.

Discussion

LG-ESS develops commonly in premenopausal women (range, 19–58 years).[9,10] In total, nine LG-ESS cases have been diagnosed in our hospital, including the present case (Table 1). The median age of the other eight LG-ESS patients in our hospital was 40 years (range, 28–57 years), and all of them were pre- or perimenopausal. However, in the present case, LG-ESS was diagnosed at the age of 61 (11 years after her menopause). The tumor in the uterine myometrium, which was first detected in a CT scan performed after 4 months of toremifene treatment, showed a gradual enlargement during the treatment period, suggesting that toremifene might be associated with the development of ESS. The reported association between tamoxifen and increased risk of uterine sarcoma and endometrial cancer[2,11,12] implies that other types of SERM, including toremifene, might also be involved in the development of uterine sarcoma through their estrogen-like effects. Whether the estrogenic effect of toremifene can be induced in postmenopausal women remains to be elucidated.

Among the nine LG-ESS cases treated in our hospital, six patients received bilateral salpingo-oophorectomy (BSO) at our hospital as a primary treatment and remain free of recurrence, whereas three patients did not receive BSO and were transferred to our hospital after the diagnosis of recurrence (Table 1). Preservation of the ovaries was associated with recurrence in these nine cases ($P = 0.022$ by log–rank test). Although primary treatment in other hospitals might cause bias in the recurrence rate, these data suggest that continuous exposure to estrogen might increase the risk of LG-ESS development. However, objective responses have been obtained by hormonal therapy with progesterone derivatives or aromatase inhibitors in LG-ESS.[13] As the impact of ovarian preservation and hormonal treatment, including SERM, on the prognosis of LG-ESS is still controversial,[14] further study is necessary to evaluate the potential risks for LG-ESS development.

Figure 2 Macroscopic and microscopic findings of the tumor. (a) Photograph of the cut surface of the excised uterus. The 4 × 4-cm tumor was a relatively soft, polypoid growth in the uterine posterior wall. The cut surface was yellowish-white. (b–e) Histological and immunohistochemical findings of the tumor (high power). (b) Tumor cells in the uterus, demonstrating proliferation of endometrial stromal cells without significant atypia or pleomorphism, diagnosed as low-grade endometrial stromal sarcoma. Tumor cells were strongly positive for (c) CD10, (d) estrogen receptor, and (e) progesterone receptor by immunohistochemistry.