Uterine leiomyosarcoma well-controlled with eribulin mesylate

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Abstract

Uterine leiomyosarcoma is a rare type of malignant gynecological tumor and has a poor prognosis; therefore, this tumor is often difficult to treat. Some new drugs have been approved during the past several years in Japan and are expected to be efficacious. Eribulin, one of these drugs, is a natural product of halichondrin B, which is isolated from a marine sponge. A recent clinical trial comparing eribulin with dacarbazine to target liposarcoma and leiomyosarcoma indicated that overall survival (OS) was prolonged by treatment with eribulin. We report a case of uterine progressive leiomyosarcoma that responded to eribulin. A 57-year-old woman was suspected of having leiomyosarcoma based on an endometrial biopsy and imaging examinations. Although the tumor grew toward the uterine artery on the right side of the uterine cervix, we performed a total abdominal hysterectomy and bilateral salpingo-oophorectomy to obtain an outcome of no gross residual disease. However, the margin of the right side of the uterine cervix was histologically positive, so leiomyosarcoma stage IIB (pT2bcN0cM0, FIGO2008) was diagnosed. Gemcitabine and docetaxel therapy was administered postoperatively. However, after three cycles, the residual tumor progressed. Other anticancer drugs were administered but were ineffective. We administered eribulin (1.4 mg/m^2) as a fourth-line regimen, and the mass decreased by 32% after four cycles. However, the residual tumor continued to grow after eight cycles. The only adverse event associated with eribulin treatment was mild, grade 2 neutropenia. For our patient, eribulin was effective for her recurrent leiomyosarcoma. In selecting chemotherapy, there are currently no fixed guidelines; we should consider the characteristics and adverse events associated with each drug and patient performance status and comorbidities. In this patient, eribulin was associated with few adverse events, an easy route of administration and a good quality of life. Therefore, eribulin is expected to be efficacious for the treatment of gynecologic sarcoma.

Keywords Eribulin · Uterine leiomyosarcoma · Quality of life

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Introduction

Uterine leiomyosarcoma is a rare malignant gynecologic tumor and has a poor prognosis; therefore, it is difficult to establish standard therapy. Although doxorubicin has been administered as a first-line therapy in patients with advanced unresectable or metastatic soft tissue sarcoma, no further therapy has been established. Three new drugs have been approved during the past several years in Japan. Eribulin, one of these drugs, is expected to be efficacious. A recent clinical trial comparing eribulin with dacarbazine to target liposarcoma and leiomyosarcoma indicated that overall survival (OS) was prolonged by treatment with eribulin [1]. We report a case of progressive uterine leiomyosarcoma that responded to eribulin as a fourth-line therapy.

Case report

A 57-year-old multigravida, pluriparous woman with no significant medical or family history consulted a doctor with a chief complaint of lower abdominal pain prior to her visit with us and was told she had swelling of the uterus and thickening of the endometrium. Her endometrial biopsy showed uterine leiomyosarcoma. Therefore, she was referred to our hospital for further examination and treatment. Magnetic resonance imaging revealed an irregularly enhanced mass that was 76 mm in diameter (Fig. 1). Positron emission tomography-computed tomography indicated no metastasis

Fig. 1 Preoperative sagittal T2-weighted MRI showing a 76-mm diameter mass in the front wall of the uterine body and cervix

or lymph node swelling. Therefore, stage I leiomyosarcoma was suspected. Although the tumor grew toward the uterine artery on the right side of the uterine cervix, we performed a total abdominal hysterectomy and bilateral salpingo-oophorectomy to obtain an outcome of no gross residual disease. However, the margin of the right side of the uterine cervix was histologically positive, so leiomyosarcoma stage IIB (pT2bcN0cM0, FIGO2008) was diagnosed (Figs. 2, 3). She received adjuvant chemotherapy, which included intravenous gemcitabine (1000 mg/m² on days 1 and 8) and docetaxel (70 mg/m² on day 8 every 3 weeks). After two cycles, the residual tumor grew slightly, and the tumor continued to grow after the third cycle; therefore, the patient was diagnosed with progressive disease (Fig. 4). Although trabectedin (1.2 mg/m² administered through a central venous line over 24 h every 3 weeks) was administered as a second-line regimen, the mass continued to grow and invaded the right ureter, causing hydronephrosis (Fig. 5). Oral pazopanib

Fig. 2 Resected uterus and bilateral adnexa. There was a 10×8 cm diameter mass mainly in the front wall of the uterus

Fig. 3 Pathological findings (hematoxylin and eosin (HE) staining, low-power field). There was severe nuclear atypia and coagulative necrosis in tumor cells and fascicular hyperplasia of the spindle cells

Fig. 4 After three cycles of gemcitabine and docetaxel, a horizontal T2-weighted MRI showed a recurrent tumor in the right pelvis

Fig. 5 After two cycles of trabectedin, a horizontal T2-weighted MRI showed a recurrent tumor in the right pelvis that had grown up to 42 mm in diameter

(800 mg/day) was administered as a third-line regimen; the mass remained stable for at least four cycles, although some growth was noticed. After six cycles, the mass increased in size by 33%, and we diagnosed the patient with progressive disease. The adverse events the patient experienced associated with pazopanib treatment were grade 1 hypertension, grade 1 liver damage, grade 1 edema, grade 2 hematuria, grade 3 proteinuria, grade 3 hypoalbuminemia and grade 3 anemia (Fig. 6). Surgery was planned to evaluate

the right pelvic mass and assess for any invasive bladder lesions because no other metastasis or masses were identified (Fig. 7). At surgery, some dissemination was observed in the intestines and mesentery that could not be detected before surgery. Therefore, we resected only the omentum including the disseminated disease. After surgery, the patient's hematuria worsened due to bladder invasion, and she underwent right internal iliac artery embolization, after which the hematuria was resolved. Intravenous eribulin was administered as a fourth-line regimen (1.4 mg/m² on days 1 and 8) after her general condition improved. The mass decreased in size by 32% until the fourth cycle (Fig. 8) but then gradually progressed after eight cycles (Fig. 9). The patient experienced only grade 2 neutropenia and was treated immediately as an outpatient without the use of granulocyte colony-stimulating factor.

Discussion

We describe our experience with a patient who had recurrent uterine leiomyosarcoma and responded to treatment with eribulin as a fourth-line regimen. Although eribulin usually caused neutropenia, it was associated with fewer adverse events and had a shorter administration time than other drugs in this patient. Therefore, we believe that eribulin can maintain patients' quality of life.

Uterine leiomyosarcoma is a rare tumor that accounts for 1–2% of malignant uterine tumors [2]. Because of its rarity, it is difficult to plan a clinical trial to develop an appropriate treatment; therefore, no standard therapy has been established. Although half of uterine sarcomas are confined to the uterus at the time of diagnosis, the 5-year survival rate is 55.4% even after complete resection. Overall, uterine leiomyosarcoma has a poor prognosis compared with other gynecological tumors [3]. Although the principal treatment for unresectable and recurrent disease is resection, doxorubicin and ifosfamide have also been used as key drugs for treatment. The response rate of monotherapy is 25% for doxorubicin [4], 21% for gemcitabine [5], and 17% for ifosfamide [6]. Regarding combination therapy, the response rate is 30% for both doxorubicin/dacarbazine

Fig. 6 Adverse events (according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0)

	GD	Trabectedin	Pazopanib	Eribulin
neutropenia	4	4	2	2
thrombopenia	1	2	1	0
liver damage	1	2	1	1
hypertension	0	0	2	0
proteinuria	0	0	3	0

Fig. 7 After six cycles of pazopanib, a sagittal T2-weighted MRI showed that the mass had grown up to 73 mm in diameter and invaded the bladder

Fig. 8 After four cycles of eribulin, a horizontal T2-weighted MRI showed that the mass had reduced to 45 mm in diameter

Fig. 9 After eight cycles of eribulin, a horizontal T2-weighted MRI showed that the mass had grown up to 88 mm in diameter, and we diagnosed disease progression

Fig. 10 Treatment and the change in tumor size. The mass responded to eribulin as a fourth-line regimen after 4 cycles

[4] and doxorubicin/ifosfamide [7]. This suggests favorable outcomes, but because these drugs are associated with an increased number of adverse events, combination therapy can be administered, but it is important to pay close attention to the patient's general condition. In addition, the response rate for gemcitabine and docetaxel for unresectable leiomyosarcoma is 35.8% as a first-line therapy [8] and 27.1% as a second-line therapy [9], which suggests favorable outcomes. Therefore, gemcitabine and docetaxel therapy is preferred for unresectable and recurrent leiomyosarcoma according to the 2017 National Comprehensive Cancer Network (NCCN) guidelines [10]. However, a randomized controlled phase III trial that compared gemcitabine and docetaxel with doxorubicin alone as a first-line treatment for unresectable or metastatic soft tissue sarcomas (GeDDiS) [11] showed similar progression-free survival at 24 weeks (46.4% vs 46.3%), and the median OS (67.3 versus 76.3 weeks) did not differ between the two groups. Further subgroup analyses showed no differential effects between the two groups or between those with uterine leiomyosarcoma and those with other sarcomas. Therefore, gemcitabine and docetaxel therapy has not been established as a first-line regimen for those with uterine leiomyosarcoma.

In this case, we selected gemcitabine and docetaxel as first-line therapy after recurrence based on the 2015 NCCN guidelines [12]. Although we offered the patient doxorubicin and two new drugs when choosing a second-line therapy, she selected trabectedin, which she responded poorly to. Adverse events occurred with the continued use of pazopanib, which made it difficult to maintain a general state of health, and the mass continued to grow after six cycles. We administered eribulin as a fourth-line regimen, which reduced the size of the mass by 32% and provided 6 months of progression-free survival (Fig. 10). Considering that the phase III trial evaluating advanced or recurrent malignant soft tissue tumors (liposarcoma and leiomyosarcoma) [1] reported that the progression-free survival was 2.6 months

in the eribulin group, our patient had a favorable outcome. Approximately 66% of cases in this were leiomyosarcomas, of which 44% were uterine leiomyosarcomas (131 cases, 29% of the total). Clinical trials enrolling this many patients with uterine leiomyosarcoma are rare; therefore, this significant trial supports the good outcome of our patient. Furthermore, the patient's satisfaction was high because she experienced only grade 2 neutropenia and was treated as an outpatient, which was financially beneficial for her.

Although three new drugs including pazopanib [13], trabectedin [14] and eribulin [1] have been proven to be effective, there are currently no fixed guidelines regarding which medication to choose first. We should consider the characteristics of the medications including the route of administration and adverse events of each drug, and the performance status and comorbidities of patients when choosing drugs [15].

Eribulin combines with the plus end of microtubules, which inhibits microtubule dynamics and induces apoptosis to exert anticancer effects. Taxanes and vinblastine are also known to be tubulin-binding anticancer drugs, and taxanes bind to the inner surface of microtubules to exert their anticancer effects. In a study using human ovarian cancer cells, tumor growth was suppressed by administering eribulin, although these cells were resistant to paclitaxel [16]. Additionally, in our case, the patient responded to eribulin after resistance to docetaxel and gemcitabine, which were used as first-line treatments. Regarding peripheral sensory neuropathy, because the functional region of eribulin in microtubules is different from that of taxane, eribulin can be used after taxane-induced peripheral sensory neuropathy has occurred. Furthermore, a study of human breast cancer models in which a control group was compared with eribulin and capecitabine treatment revealed that there was improvement in perfusion and hypoxia in tumor cells due to vascular remodeling, which allowed the drug to be easily delivered drug to cancer cells to help increase the anticancer efficacy in the eribulin group [17].

Based on the aforementioned findings and considering vascular remodeling, eribulin was effective and had increased anticancer effects during and after administration. Therefore, knowing when to administer eribulin is important. The clinical trial evaluating treatments of liposarcoma and leiomyosarcoma did not recommend eribulin as a first-line chemotherapy because of the low response rate of 4% [1]. In our case, the patient responded to eribulin, and even though this was a fourth-line treatment, our findings suggest that eribulin can be administered after resistance to some other drugs.

However, we think that OS may be prolonged by administering eribulin early after the second-line regimen for microenvironmental control. Whether eribulin should be administered early after the second-line treatment or later after

resistance to some other drugs has developed to prolong OS and improve quality of life remains to be determined.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

References

- Schöffski P, Chawla S, Maki RG et al (2016) Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma. *Lancet* 387:1629–1637
- WHO classification of tumors of Female Reproductive Organs; 2014:139–141
- Seagle BL, Sobecki-Rausch J, Strohl AE et al (2017) Prognosis and treatment of uterine leiomyosarcoma: a National Cancer Database study. *Gynecol Oncol* 145:61–70
- Omura GA, Major FJ, Blessing JA et al (1983) A randomized study of Adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. *Cancer* 52:626–632
- Look KY, Sandler A, Blessing JA et al (2004) Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: a Gynecologic Oncology Group (GOG) Study. *Gynecol Oncol* 92:644–647
- Sutton GP, Blessing JA, Barrett RJ et al (1992) Phase II trial of ifosfamide and mesna in leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. *Am J Obstet Gynecol* 166:556–559
- Sutton G, Blessing JA, Park R et al (1996) Ifosfamide treatment of recurrent or metastatic endometrial stromal sarcoma previously unexposed to chemotherapy: a study of the Gynecologic Oncology Group. *Obstet Gynecol* 87:747–750
- Hensley ML, Blessing JA, Mannel R et al (2008) Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine sarcoma: a Gynecologic Oncology Group phase II trial. *Gynecol Oncol* 109:329–334
- Hensley ML, Blessing JA, Degreest K et al (2008) Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. *Gynecol Oncol* 109:323–328
- NCCN guideline 2017: <https://www.tri-kobe.org/nccn/guideline/gynecological/english/uterine.pdf> (accessed on 1 August 2017)
- Seddon B, Strauss S, Whelan J et al (2017) Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. *Lancet Oncol* 18:1397–1410
- NCCN guideline 2015: <https://www.tri-kobe.org/nccn/guideline/gynecological/english/uterine.pdf> (accessed on 1 September 2015)
- Van der Graaf WT, Blay JY, Chawla SP et al (2012) Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 379:1879–1886
- Kawai A, Araki N, Sugiura H et al (2015) Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study. *Lancet* 16:406–416

15. Kawai A, Yonemori K, Takahashi S et al (2017) Systemic therapy for soft tissue sarcoma: Proposals for the optimal use of pazopanib, trabectedin, and eribulin. *Adv Ther* 34:1556–1571
16. Kuznetsov G, TenDyke K, Yu MJ et al (2007) Antiproliferative effects of halichondrin B analog eribulin mesylate (E7389) against paclitaxel-resistant human cancer cells in vitro. [abstract C58]. *Proc Am Assoc Cancer Res* 48:275
17. Funahashi Y, Okamoto K, Adachi Y et al (2014) Eribulin mesylate reduces tumor microenvironment abnormality by vascular remodeling in preclinical human breast cancer models. *Cancer Sci* 105:1334–1342