[Case Report] Treatment with Antitumor Agents Recommended by Cancer Genome Panel for Uterine Leiomyosarcoma

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Abstract

To date, cancer genomic medicine, using cancer gene panel covered by health insurance in June 2019, has been performed for advanced malignant tumors under public medical insurance. In gynecology, the first-line treatment for uterine leiomyosarcomas, which is a mesenchymal uterine tumor, is surgery. In uterine leiomyosarcoma cases, recurrence is observed within 2 years postoperatively; however, to date, clinical trials have not shown efficacy with existing antitumor agents. Currently, two cases of advanced uterine leiomyosarcomas have been associated with increased tumor mutation burden (TMB) or pathogenic variants (PVs) in the AKT serine/threonine kinase 1 (AKT). Therefore, treatment with pembrolizumab, which is a drug covered by insurance for patients with TMB high, or treatment with kinase inhibitors for patients with PVs in AKT, was considered. Cancer genomic medicine using cancer gene panel provides a new treatment strategy for intractable malignant tumors. This study aimed to discuss the usefulness of cancer genomic medicine by cancer gene panel testing using the case of advanced and recurrence uterine leiomyosarcoma and the latest findings.

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Short title: Cancer genome medicine for advanced leiomyosarcoma

Introduction

Most of the tumors detected in the smooth muscle tissue of the uterine corpus, ovaries, and fallopian tubes are uterine leiomyomas, which are benign mesenchymal tumors [1]. During their lifetime, the prevalence of uterine leiomyoma is approximately 70% and more than 80% in white women and women of African ancestry, respectively [2]. For several uterine leiomyoma cases, regular screening with annual imaging tests is performed [3]. Uterine sarcomas are malignant tumors arising from the smooth muscle tissue or connective tissue of the uterus. Endometrial stromal sarcomas (ESSs) are malignant tumors that develop from the stromal tissue of the uterine lining, and the cells in ESSs contain more epithelial tissue components than smooth muscle tissue components [4]. Uterine leiomyosarcomas are malignant uterine tumors that develop from the smooth muscle layer of the uterus, and the 5-year survival rate for uterine leiomyosarcomas is <20% [5][6]. Uterine carcinosarcomas are malignant tumors wherein a lesion containing malignant tumor cells derived from the epithelial cells of the endometrial lining of the uterine corpus is observed [7]. Uterine carcinosarcomas were also previously called malignant mixed mesodermal/Mullerian tumor.

In actual clinical practice, the cells of uterine mesenchymal tumors have a diverse cell and nuclear morphology; therefore, differential diagnosis between uterine leiomyosarcoma, which is a malignant tumor, and other uterine mesenchymal tumors, including uterine leiomyoma, is difficult [8]. In several cases, uterine leiomyosarcomas coexist with uterine leiomyomas. Furthermore, owing to the high prevalence of uterine leiomyomas, the diagnosis of uterine leiomyosarcoma, especially before surgery, is extremely challenging [8][9]. To date, clinical trials conducted by various medical teams have investigated the effectiveness of antitumor agents on uterine smooth muscle tumors; however, the effectiveness of various antitumor agents against uterine leiomyosarcoma is limited [10][11]. Unfortunately, no common treatment has been established for uterine leiomyosarcomas. Therefore, currently, cases wherein pathogenic variants (PVs) of uterine leiomyosarcomas are detected by cancer gene panel testing such as FoundationOne CDx tissue or liquid are treated by prescribing PV-targeting antitumor drugs [12][13].

Our medical team performed FoundationOne CDx tissue cancer gene panel testing (FoundationOne® CDx's cancer genome test, Foundation Medicine, Inc., Cambridge, MA, USA) on two cases with advanced/recurrent uterine leiomyosarcomas. In our medical institution, the FoundationOne CDx tissue cancer gene panel test detected PVs in the serine-threonine kinase AKT molecule in the cells of advanced/recurrent uterine leiomyosarcoma [14]. Conversely, tumor mutation burden (TMB) high was detected in the cells of advanced/recurrent uterine leiomyosarcoma [15][16]. Therefore,

the multikinase inhibitor pazopanib or pembrolizumab was administered to each patient with advanced/recurrent uterine leiomyosarcoma. Currently, each patient with advanced/recurrent uterine leiomyosarcoma continues to be treated with an antitumor drug selected on the basis of the cancer gene panel test results for each advanced and recurrent uterine leiomyosarcoma.

Materials and Methods

Magnetic resonance imaging (MRI)

To determine the presence, size, and location of the patient's mass, contrast-enhanced MRI was performed to localize the patient's mass using contrast-enhanced MRI equipment (Vantage Centurian: Vantage Galan 3T MRT-3020, Canon Medical Systems, Inc., Ohtawara, Tochigi, Japan).

Cancer genomic testing

In October 2022, the patient had mild hepatic dysfunction following resection of the upper part of the stomach for surgical treatment. Contrast-enhanced computed tomography (CT) revealed a submucosal mass in the body of the stomach and a disseminated metastatic mass in the abdominal cavity. In December 2022, our medical staff resected the tumor site in the stomach using laparoscopic surgery. To determine the diagnosis and treatment strategies, we performed cancer genomic testing (FoundationOne® CDx's cancer genome test, Foundation Medicine, Inc., Cambridge, MA, USA) using tissue sections of the resected tumor.

Results

Case 1

Age: 55 years old, **Sex:** Female, **PS:** 0
Diagnosis: Uterine leiomyosarcoma recurrence, right hydronephrosis
Family history: A grandmother with stomach cancer
Medical history: None

In 2014, uterine leiomyoma development was noted. Therefore, she received regular follow-up at the nearby obstetrics and gynecology clinic; however, no changes were observed until June 2021. However, uterine malignancy was suspected by CT. Therefore, on July 12, 2021, she was referred to our department of gynecological tumor at General Hospital. She was diagnosed with uterine sarcoma stage I by contrast-enhanced MRI and positron emission tomography (PET)–CT.

On July 29, 2021, she underwent total abdominal hysterectomy and bilateral adnexectomy.

She was subsequently diagnosed with uterine leiomyosarcoma stage IB by pathological examination (Supplementary Figure 1). The initial treatment was completed with recommended surgical treatment only according to clinical guidelines. Following hospital discharge, she was followed up in an outpatient visit.

Current medical history: On June 27, 2022, contrast-enhanced CT revealed intraperitoneal radius tumor and metastases to both lungs, and tumor recurrence was diagnosed (intraperitoneal radius: tumor size, 2.1 cm; tumor size in the pelvis, 1.0 cm; multiple lung metastases, including 7-mm tumor in the left lung and 4-mm tumor in the right lung. Contrast-enhanced CT revealed other microlesions) (Supplementary Figures 2 and 3).

From July 11 to September 5, 2022, she received three courses of Adriamycin (Kyowa Kirin Co., Ltd. Chiyoda, Tokyo, Japan) single agent. On September 15, 2022, hydronephrosis, which occurred owing to right ureter obstruction due to intraperitoneal oshitular lesion exacerbation, was observed. Enhance-contrasted CT revealed minimal lung metastatic lesions; however, the treatment effect was judged as progressive disease (PD) by Response Evaluation Criteria in Solid Tumor (RECIST) because the intraperitoneal disseminated tumors were increasing size (Supplementary Figure 2, Supplementary Figure 3). Therefore, the therapeutic drug was changed to pazopanib, a multikinase inhibitor that specifically inhibits vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-Kit; subsequently, cancer genome examination (FundationOne CDx tissue) was performed (tumor content, 50%). The cancer genome examination showed TMB high of 14 Muts/Mb; therefore, pembrolizumab, an immune checkpoint inhibitor (ICI) covered by health insurance, was prescribed and administered to this patient with TMB high as a companion diagnosis (Table 1).

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Table 1. FoundationOne CDx tissue testing results for the 55-year-old patient with advanced and recurrence uterine leiomyosarcomas

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Tumor Mutational Burden – 14 Muts/Mb	Pembrolizumab Dostarlimab	Atezolizumab Avelumab Cemiplimab Durvalumab Nivolumab Nivolumab + Ipilimumab
Microsatellite status - MS-Equivocal	No therapies or clinical trials. see Biomarker Findings section	

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
ARAF - E89K VAF 32.47%	none	none

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES	
MSH6 - F1088fs*5 VAF 1.51%	*MUTYH* - splice site 892-2A>G VAF 50.32%

Based on the Foundation CDx tissue test results, MSH6 - F1088fs*5 (VAF, 1.51%) and MUTYH - splice site 892-2A>G (VAF, 50.32%) were detected as molecules that should be considered for hereditary cancer (Table 1). F1088fs*5, which was detected as a PV in the MSH6 molecule, is a genetic mutation that induces Lynch syndrome onset [17]. However, as the VAF of MSH6 - F1088fs*5 was 1.51%, it was considered a somatic mutation (Table 1). Additionally, splice site 892-2A>G, which was detected as a PV in the MUTYH molecule, is a genetic mutation that induces MUTYH-associated polyposis (MAP) onset [18]. MUTYH - splice site 892-2A>G had a VAF of 50.32%; therefore, it was considered a germinal mutation. However, as no patient or family member developed MAP, investigating the genetic cause of MUTYH was not needed.

Case 2

Age: 82 years old, **Sex:** Female **PS:** 1

Diagnosis: Uterine sarcoma recurrence (epithelioid leiomyosarcoma)

Family history: A brother with kidney and lung cancer

Medical history: hypertension, left ear hearing loss, mitral regurgitation, and cystocele (in pessary placement)

On April 2019, abdominal simple total hysterectomy, bilateral adnexectomy, partial omentectomy, and small mesenteric lesion resection were performed as the recommended surgical treatment.

From May to October 2019, docetaxel plus gemcitabine (DTX + GEM) was administered to the patient (six cycles in total). On October 2020, PET–CT was performed and revealed pelvic recurrence (Supplementary Figure 4). Therefore, pazopanib treatment was started.

On January 2021, the treatment effect was judged as PD by RECIST owing to the increasing size of intraperitoneal disseminated tumors.

On February 2022, doxorubicin (DXR) treatment was initiated.

August 2022, the eighth cycle of DXR was completed. The treatment effect was judged as stable disease (SD) by RECIST as enhance-contrasted CT revealed that the intraperitoneal disseminated tumors were not decreasing size of tumor. Cardiac function was evaluated in conjunction with the Department of Cardiovascular Medicine of our hospital; although mitral regurgitation was noted, cardiac function was judged to be not a problem.

On July 2022, tumor sections were shipped for cancer genome examination (FundationOne CDx tissue) (tumor content, 80%). The results derived from the cancer genome examination showed PVs in the serine-threonine kinase AKT molecule; therefore, the multikinase inhibitor pazopanib, which was covered by health insurance, was prescribed and administered to this patient (Table 2).

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Table 2. FoundationOne CDx tissue testing results for the 82-year-old patient with advanced and recurrence uterine leiomyosarcomas

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	No therapies or clinical trials. See Biomarker Findings section
Tumor Mutational Burden - 2 Muts/Mb	No therapies or clinical trials. See Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
AKT1 - E17K VAF 11.56%	none	Pazopanib
VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES		
ATRX - L1250 VAF 39.98%* *MED12 - G44S VAF 44.88%*		*RB1* - loss exons 18-27 CN0 *TP53* - G187V, K132N VAF 44.89%

Based on the Foundation CDx tissue test results, RB1 - loss exons 18-27 (CN0) and TP53 - G187V, K132N (VAF, 44.89%) were detected as molecules that should be considered for hereditary cancer (Table 2). Loss exons 18-27, detected as a PV in the RB1 molecule, is a germinal mutation that induces retinoblastoma development [19]. However, the copy number of RB1 - loss exons 18-27 was 0, and no retinoblastoma cases were observed under the age of 30 in the family; therefore, investigating the onset of the disease was not needed (Table 2). The VAF of G187V and K132N, which were detected as PVs in the TP53 molecule, was 44.89%; therefore, this TP53 mutation is a germinal mutation that induces Li–Fraumeni syndrome onset [20]. However, as no family members with osteosarcoma, breast cancer, or soft tissue tumors under the age of 30 were noted, considering TP53 - G187V, K132N as a genetic cause of Li–Fraumeni syndrome was not required. The FoundationOne CDx tissue test results indicated that ATRX and MED12 PVs were associated with hereditary cancer onset. However, based on the results of a clinical trial in a Japanese cohort, ATRX and MED12 PVs were not linked to the development of hereditary cancer in Japanese patients.

Discussion

Clinical trials using various antitumor agents are being conducted to establish treatments for uterine leiomyosarcomas; however, the effectiveness of various antitumor agents against uterine leiomyosarcoma is limited [21]. Under these circumstances, advances in cancer genomic medicine have revealed the effectiveness of antitumor agents that target PVs, even for malignant tumors for which no treatment has been established to date [22]. This time, our medical staff experienced treatment with pembrolizumab or pazopanib for uterine leiomyosarcoma with TMB high and uterine leiomyosarcoma with AKT PV detected through cancer genomic medicine.

At present, the results of clinical trials have not shown the effectiveness of ICI against uterine leiomyosarcomas. This result may be because of the absence of biomarkers for ICI, including microsatellite instability (MSI) high and TMB high, in

the uterine leiomyosarcoma of the participants enrolled in the clinical trial [23]. Furthermore, in previous clinical trials, the completed efficacy of serine-threonine kinase inhibitors against uterine leiomyosarcoma has not been confirmed [24]. This result also suggests that biomarkers for kinase inhibitors are not present in the uterine leiomyosarcoma of the participants enrolled in the clinical trial. Personalized medical care for advanced and recurrent malignant tumors can prolong patient survival. In other words, in future cancer medicine, cancer genomic medicine using cancer genome gene panels will be essential in selecting antitumor agents for advanced and recurrent malignant tumors.

The National Cancer Institute (NCI) in the USA announced that a new initiative will evaluate the effectiveness of drug combinations for treating cancers with particular genetic changes [25]. In cancer genomic medicine in Japan, single-agent administration of already approved antitumor agents is prioritized for cases wherein PVs have been detected in multiple molecules in a single patient. Next, an antitumor agent that has been shown effective in clinical trials and case reports is administered as a single agent. To date, in cancer genomic medicine in Japan, in several cases, combination therapy with multiple antitumor agents has not been performed for patients with PVs in multiple molecules. As future cancer genomic medicine, for example, in advanced or recurrent uterine leiomyosarcoma, for cases wherein PV in the *breast cancer 1* (*BRCA1*) or *BRCA2* gene and an active PV in AKT are detected by cancer genomic testing, combination therapy with a poly ADP ribose polymerase (PARP) inhibitor (e.g., olaparib or niraparib) and a tyrosine kinase inhibitor should be considered [11][26]. In Japan, prescriptions of the combination therapy of a PARP inhibitor with tyrosine kinase inhibitor for advanced and recurrent uterine leiomyosarcomas are not covered by health insurance. Therefore, selecting the antitumor agent depends on the results of clinical trials in other countries. NCI's new initiative will be beneficial to cancer genomic medicine in Japan. Currently, in clinical trials, pharmaceutical companies are also examining the efficacy of combination therapy with multiple approved antitumor agents against various advanced and recurrent malignancies. The results of these clinical trials and NCI's new initiative are significant for cancer genomic medicine development.

Advances in cancer genomic medicine are contributing to prolonging the lives of patients with advanced and recurrent malignant tumors. Furthermore, in Japan, if combination therapy with multiple antitumor agents is covered by insurance on the basis of the cancer genome gene panel testing results, it is believed that patients with advanced and recurrent malignant tumors will have longer lives. However, malignant tumor cells acquire resistance mechanisms to various antitumor agents; therefore, treatment using different antitumor agents is required. To elucidate the detailed mechanisms by which malignant tumors acquire resistance to antitumor agents, further basic medical and clinical research is required.

Statements and Declarations

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Competing Interest statement: The authors state No competing interest.

Data Availability: The authors declare that data supporting the findings of this study are available within the article.

Ethics approval and consent to participate: This study was reviewed and approved by the Central Ethics Review Board of the National Hospital Organization Headquarters in Japan (Tokyo, Japan) on November 08, 2019, and Kyoto University School of Medicine (Kyoto, Japan) on August 25, 2023, with approval codes NHO H31-02 and M192. The completion numbers for the authors are AP0000151756, AP0000151757, AP0000151769, and AP000351128. As this research was considered clinical research, consent to participate was required. After briefing regarding the clinical study and approval of the research contents, the participants signed an informed consent form.

Clinical Research: A multi-center retrospective observational clinical study of subjects who underwent cancer genomic medicine at a cancer medical facility in Kyoto, Japan. This study was reviewed and approved by the Central Ethics Review Board of the National Hospital Organization Headquarters in Japan (Tokyo, Japan) on November 18, 2020, and Kyoto University School of Medicine (Kyoto, Japan) on August 24, 2022, with approval codes NHO R4-04 and M237. All participants agreed to take part in the present study. We have obtained Informed Consent Statements from people participating in clinical studies.

Author Contributions: All authors had full access to the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. T.H. and N.K.; Research Conduction, T.H., N.K. and K.A.; Writing-Original Draft, T.H. and I.K.; Writing-Review & Editing, I.K.; Visualization, T.H. and I.K.; Supervision, T.H. and I.K.; Funding Acquisition.

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