EJGO European Journal of Gynaecological Oncology

Prolonged stable disease using pazopanib in recurrent and refractory uterine leiomyosarcoma: a proposal of "pazopanib beyond progression"

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Summary

Background: To date, there is no standard therapy in patients with recurrent or refractory uterine leiomyosarcoma (LMS). A case with LMS that achieved prolonged stable disease using pazopanib beyond progression (PBP) is reported. *Case Report:* A 49-year-old patient with recurrent and refractory LMS that achieved long-term stable disease is reported. The patient had previously received three regimens before pazopanib therapy: combination chemotherapy with ifosfamide, doxorubicin, and cisplatin (IAP), gemcitabine monotherapy, and combination therapy with bevacizumab, temozolomide, and cabozantinib. Subsequently, oral administration of pazopanib was initiated at a dose of 400 mg daily. At the third week, the dose was reduced to 200 mg daily due to grade 1 hypothyroidism. At the ninth week, a new lesion in liver was detected; however, continuation of pazopanib was selected. At the 15th week, the patient developed moderate genital bleeding and received palliative radiotherapy (30 Gy) in addition to pazopaznib. The patient occasionally developed toxicities such as hypetension and diarrhea, which were manageable. At the 59th week, her general condition was suddenly worsened due to disease progression, and pazopanib treatment was discontinued. During the period of pazopanib, recurrent tumors showed stable disease, in spite of occurrence of new lesion at liver. Subsequently, the patient died of the disease 16 months after the initiation of pazopanib monotherapy. *Conclusion:* PBP could be a candidate for the patients with recurrent or refractory LMS.

Key words: Uterus; Leiomyosarcoma; Pazopanib beyond progression (PBP).

Introduction

Uterine sarcomas comprise 8% of all uterine corpus cancers. Among them, uterine leiomyosarcoma (LMS) is the most common histological subtype form [1]. Median progression-free survivals and overall survivals (OS) of uLMS at Stage IV were 7.7 and 23.5 months, respectively [2]. The PALLETE study demonstrated that pazopanib, a multi-tyrosine kinase inhibitor, showed anti-tumor activity to soft tissue sarcomas including uterine LMS [3]. In general, pazopanib treatment was continued until disease progression or unmanageable toxicities. So far, there has been no report that demonstrated the effectiveness of pazopanib after judgement of progression. The hypothesis "pazopznib beyond progression (PBP)" might be clinically useful, as the drug is an anti-angiogenesis agent like bevacizumab [4]. Herein, the authors report a case that showed sustained clinical usefulness of PBP for recurrent and refractory uterine LMS.

Case Report

A 49-year-old woman, gravida 3, para 4, presented with lower abdominal pain. In serological test, LDH 332 IU/l was slightly elevated. CA125, CA19-9, and CEA were within normal limits. MRI showed 11 cm uterine necrotic tumors with low signal area in T2-weighed and high signal area in diffusion weighted image, which suggested that the tumors were uterine LMSs. CT scan revealed several nodules in lung and liver. Pathological findings by transvaginal needle biopsy enabled the authors to diagnose as uterine leiomyosarcoma (uLMS). The patient's diseases were diagnosed as uLMS at Stage IVB. During the first course of the combination chemotherapy with ifosfamide, doxorubicin, and cisplatin (IAP), grade 3 pulmonary edema developed subsequently. She underwent five courses of gemcitabine and a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial sigmoidectomy, which complete resection in the peritoneal cavity was achieved. Four courses of gemcitabine were performed as adjuvant chemotherapy. Pulmonary metastatic lesion by chemotherapy decreased in size. Although the size of pulmonary tumor did not change two months later, the new tumor recurred at vaginal stump. She received the combination chemotherapy of bevacizumab, temozolomide, and cabozantinib. After three courses, tumors at pelvic and pulmonary lesion were diagnosed progressive disease. Next, 400 mg of pazopanib per day was administrated (Figure 1). Three weeks later from the initial treatment of

Revised manuscript accepted for publication September 22, 2016

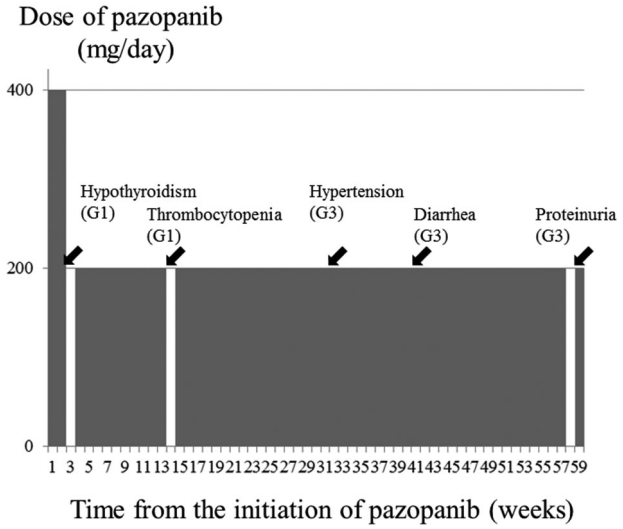

Figure 1. — Doses of pazopanib and side effects observed during pazopanib treatment.

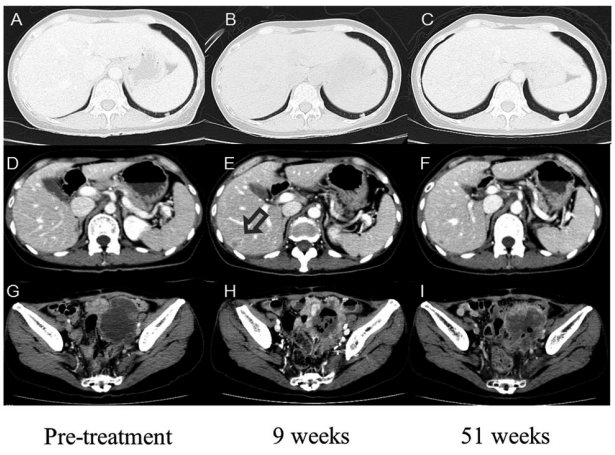

Figure 2. — CT images during pazopanib treatment. At nine weeks from the initiation of pazopanib treatment, a new lesion in liver was detected (E, shown by arrow). At 51 weeks, pelvic and lung tumors increased in size (C and I), however, liver tumor further decreased in size (F). A, B, C: lung tumor; D,E,F: Liver tumor (D: no tumor at pre-treatment); G, H, I: pelvic tumor; A, D, G: images at pre-treatment; B,E,H: images at nine weeks; C, F, I: images at 51 weeks.

pazopanib, 200 mg of pazopanib was decreased for grade 1 hypothyroidism. Nine weeks later, a new lesion in liver with a size of 9.1 mm diameter was observed (Figure 2), but continuation of pazopanib treatment was selected. Fourteen weeks later, the administration of pazopanib had been suspended for one week due to grade 1 thrombocytopenia. Vaginal stump bleeding from pelvic tumor occurred at 17 weeks. Whole pelvic radiotherapy (30 Gy/ten fractions) was performed for palliation in addition to the pazopanib treatment. Pelvic tumor reduced in size by radiotherapy and vaginal bleeding decreased. Anti-hypertension drug was administrated for grade 3 hypertension at 33 weeks and blood pressure was stabilized. Forty weeks later, the treatment was discontinued for one week due to grade 3 diarrhea. Grade 3 proteinuria was observed 58 weeks later, but pazopanib treatment was continued. Fifty-nine weeks later, the patient's performance state (PS) was judged to be three due to progression of disease (PD), and the patient obtained progression-free survival time of 59 weeks when the progression judged by a new lesion in liver at nine weeks was omitted (Figure 3). Subsequently, she and her families elected best supportive care only. The patient died of disease 12 weeks after the discontinuation of pazopanib. Survival durations from the initial administration of pazopanib were 71 weeks. OS time from the first chemotherapy was 36 months.

Discussion

The treatment for advanced or metastatic uterine LMS is limited in systemic chemotherapy, such as gemcitabine or temozolomide, and trabectedin. The indication of surgical resection of metastatic lesion in LMS cases is limited, and mainly for palliation [5]. The present case obtained extremely longer duration of stable disease using pazopanib treatment, and pelvic irradiation.

The importance of vascular endothelial growth factor (VEGF) pathway for LMS has been investigated. Immunochemical analysis demonstrated that VEGF, VEGFR-1, and VEGFR-2 are frequently expressed in LMS [6, 7] and high expression of VEGF is associated with poor prognosis [6]. In vitro and vivo experiments, anti-angiogenesis by VEGF receptor and growth factor receptor inhibitor induced apoptosis in LMS [8]. Thus, anti-angiogenesis targeting VEGF or VEGF receptor could be promising for LMS. In phase III trial, the addition of Bev to the combination with Gem and docetaxel for LMS did not improved prognosis [9]. In general, complete remission of LMS using the combination of Bev and temozolomide was reported [10]. Therefore, this patient received the regimen including Bev and temozolomide, but clinical activity was not observed.

PALETTE trial demonstrated pazopanib improved progression-free survivals [median 4.6 months (95% CI: 3.7-4.8)], but OS was not improved [median 12.5 months (95%CI: 10.6-14.8)] compared with placebo [3]. Recently, in vivo analysis demonstrated tumors accelerated metastasis after short-term treatment with an inhibitor of tumor angiogenesis [11]. Actually, in a clinical setting, PBP was effective for improving OS in colon cancer and breast cancer [12, 13]. In ovarian cancer trials, bevacizumab was used until progression and the treatment was usually changed to other regimens without bevacizumab [13, 14]. In PALETTE trial, treatment was continued until PD or unmanageable toxicities. In this case, a new lesion in liver was detected at nine weeks from the initial pazopanib treatment, and the patient was usually judged as PD using RECIST criteria. In the present case, continuation of pazopznib was selected, and the patient obtained progression-free survival time of 59 weeks when the progression

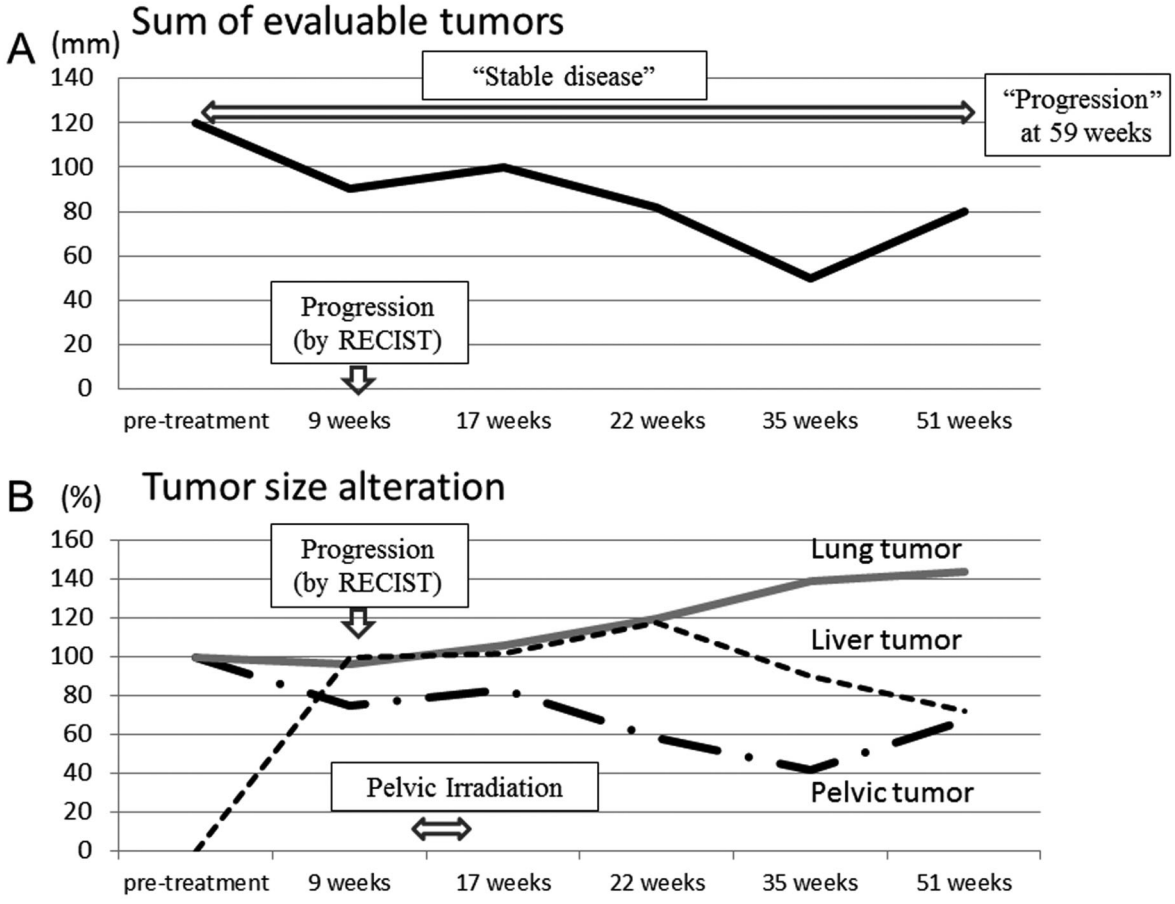

Figure 3. — A. Sum of evaluable tumors. B. Tumor size alteration.

judged by a new lesion in liver at nine weeks was omitted. It was unclear whether pazopanib treatment only induced longer duration of disease stabilization, as radiotherapy was added for palliative therapy for vaginal bleeding. However, a new lesion in liver detected at nine weeks definitely showed tumor shrinkage during administration of pazopanib, suggesting PBP was effective in some tumors including recurrent uterine LMS.

The analysis for the Japanese subgroup in PALLETE trial demonstrated the clinical benefit of pazopanib was observed in Japanese population similar to the global population. The incidence of side effects such as hypertension, decreased weight, and decreased appetite, was higher in Japanese population, and the dose reduction of pazopanib was more frequently needed in Japanese compared with the global population [15]. In this case, initial dose was 400 mg/day; however, dose reduction to 200 mg/day was needed due to several toxicities for further continuation of the drug.

Conclusion

The present case report clearly shows the effectiveness of PBP for recurrent and refractory uterine LMS. This treatment should be evaluated for further studies including biomarker analyses.

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