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Case report

Efficacy of pazopanib in *FGFR1*-amplified uterine carcinosarcoma: A case report

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1. Introduction

Uterine carcinosarcoma (UCS) is a rare malignancy, accounting for approximately 5% of uterine cancers, 15% of all deaths caused by corpus uteri malignancies, and more than 50% of recurrent cases (Cantrell et al., 2015). Moreover, its prognosis is poor. Recent studies suggest that UCS is of monoclonal origin, and these tumors are best classified as de-differentiated carcinomas of the endometrium rather than as sarcomas. The standard treatment is combination therapy with platinum-based cytotoxic chemotherapy, similar to that for high-grade uterine cancer; however, there is no specialized treatment for UCS. In recent years, the combination of pembrolizumab and lenvatinib has been introduced for the treatment of advanced-stage uterine cancer after demonstrating its efficacy. However, the efficacy of this combination therapy against UCS has not yet been established in comparison with conventional chemotherapy (Hunt et al., 2021). The development of new molecular-targeted therapies is desirable for UCS.

Recently, the individual analysis of cancer genes using next-generation sequencing and other methods has made it possible to select molecularly targeted therapies based on genetic mutations, regardless of the organ. Although the frequency of therapeutic adaptation is only 10% (Sunami et al., 2019), treatment options for malignant diseases with limited standard treatments are expanding. However, the pathological significance of the genetic abnormality and the level of evidence for the efficacy of treatment targeting the specific genetic abnormality are difficult to assess; thus, the interpretation of the results needs to be discussed and reviewed by experts in each case. Particularly, off-label use of anticancer drugs based on genomic abnormalities may be an effective tool for rare cancers such as UCS, although randomized trials cannot be applied.

Herein, we report a case of recurrent UCS in which an oncogenomic genetic test showed *Fibroblast Growth Factor Receptor1 (FGFR1)* amplification. *FGFR1*, a tyrosine kinase involved in cell proliferation, activates the downstream *MAPK* and *PI3k/Akt/mTOR* signaling pathways. Activating mutations or amplification of *FGFR1* have been frequently reported in the lung and breast (Dieci et al., 2013). Amplification and overexpression of *FGFR1*, which are significant contributors to poor prognosis, promote growth and survival signals in tumor cells (Turner et al., 2010). Tyrosine kinase inhibitors targeting the *FGFR* family have recently proven efficacious against *FGFR*-alternated advanced cancers in the biliary tract and urothelial cancers. Pazopanib is an oral multi-targeted tyrosine kinase inhibitor that inhibits *c-KIT*, *FGFR*, *PDGFR*, and *VEGFR*. Moreover, it prevents the progression of tumor growth in renal cell carcinoma and malignant soft tissue tumors. We encountered a case in which off-label administration of pazopanib, recommended as evidence level D (Naito et al., 2021) at an expert tumor board meeting, was effective for a certain period and as palliative care while maintaining the quality of life.

2. Case report

A 54-year-old gravida 4 para 3 woman presented to our hospital with

Abbreviations: UCS, uterine carcinosarcoma; FGFR, Fibroblast Growth Factor Receptor.

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a chief complaint of irregular genital bleeding. She attained menopause at age 49, and her medical history included hyperlipidemia, liver cysts, and thyroid adenoma. Her family history included colorectal and gastric cancer in her maternal grandmother and uncle, respectively. The patient was diagnosed with carcinosarcoma with endometrioid carcinoma grade 3 and sarcoma of the homologous type by dilation and curettage. With no evidence of myometrial invasion on magnetic resonance imaging, distant metastasis, or enlarged lymph nodes on computed tomography (CT), we diagnosed it as preoperative stage IA equivalent. She underwent abdominal hysterectomy, bilateral adnexal resection, pelvic and para-aortic lymph node dissection, and partial omentectomy for UCS. Surgery was performed and the patient was no evidence of disease. The postoperative pathological diagnosis was endometrioid carcinoma grade 3, with no sarcomatous component, stage IA (pT1aN0M0) according to the FIGO 2008 staging system.

Eight months after the first surgery, recurrence in the vaginal wall and distant pulmonary metastases were detected. Secondary surgical resection was performed for each organ, and postoperative chemotherapy with paclitaxel plus carboplatin was administered for six cycles. The postoperative pathology of the vaginal tumor and recurrent lung lesion were sarcoma and adenocarcinoma, respectively. Six months after completion of paclitaxel plus carboplatin chemotherapy, CT revealed multiple new lung metastases, and adriamycin was initiated as a second-line chemotherapy.

An oncogene panel test (OncoGuide™ NCC Oncopanel System) for 114 cancer-related genes was performed while the patient was receiving adriamycin therapy. The specimens were the lung lesions removed at the time of previous recurrence. The results showed a 4.13-fold amplification of the *FGFR1* gene, and genetic point mutations in *PIK3CA* and *RET* were observed. The expert tumor board meeting discussed the indication of pazopanib for *FGFR1* amplification based on case reports that showed the effectivity of pazopanib in breast cancer (Cheng et al., 2017) and small cell lung cancer (Alessandro et al., 2019) with *FGFR1* amplification, and concluded that pazopanib treatment should be recommended as evidence D (Naito et al., 2021). After adriamycin was terminated due to progressive disease, pazopanib therapy was initiated as an off-label use at the patient's expense, and written informed consent was obtained to publish this case.

Pazopanib was started at 800 mg, and the dose was reduced to 600 mg and 400 mg according to incidence of adverse events, including grade 3 fatigue and grade 2 thrombocytopenia (according to the Common Terminology Criteria for Adverse Events v6.0). Chest X-ray scans were performed every 2–3 weeks and CT scans were performed as needed. Right lower and left upper lung tumors were observed to determine the treatment effect. A 28% reduction in the size of lung metastases was observed on day 26 of treatment, and the reduction was maintained thereafter (Fig. 1). CT performed 109 days after treatment showed a 67-mm, mild enlargement of the lower right lung tumor; however, the interior was necrotic. Tumor resection was scheduled, aimed at controlling the lower right lung tumor, and pazopanib was withdrawn 1 week before surgery.

Preoperative CT showed no evidence of mediastinal invasion; however, intraoperative findings with a thoracoscope showed that the right lower lung tumor had invaded the inferior vena cava and mediastinum. Therefore, removal was not feasible, and only a biopsy was performed. Postoperative pathology revealed sarcoma. CT performed 14 days after withdrawal showed a rapid enlargement occupying the entire lower lung field. (Fig. 2) The patient received 20 Gray (Gy)/5 Fractions (Fr) as palliative radiotherapy. A tumor shadow occupied half of the right lung on a chest radiograph on day 152 of treatment, and 600–800 mg pazopanib therapy was resumed on day 154. On day 191 of treatment, a chest radiograph showed that the tumor had decreased in size to one-third of the right lung. The tumor of the left upper lung was also reduced in size, suggesting the efficacy of pazomanib. (Fig. 3).

Two months after resuming pazopanib administration, on day 230 of treatment, the patient developed respiratory failure, and CT showed right pleural effusion and left pneumothorax. The pneumothorax was thought to be caused by a tumor found in the left lung apex, and pazopanib was discontinued. She died of respiratory failure due to UCS 1 month after pazopanib was discontinued.

3. Discussion

This case showed that individual oncogene analysis allowed pazopanib use for refractory UCS, and that the treatment was effective for a certain period. Standard treatments for UCS had been unsuccessful, and there seemed to be no other treatment options. Individual analysis of the cancer genome panel test showed *FGFR1* amplification, and an expert tumor board meeting recommended pazopanib treatment at the level of evidence D. During the treatment period of 7.5 months with oral pazopanib 400–800 mg/day, there were no adverse events above grade 3. Appetite and activities of daily living could be maintained while visiting the hospital. The disease was under control for a total of approximately 7 months, excluding the 24-day withdrawal period, until day 230, when pneumothorax resulted in drug withdrawal. This was an effective treatment in palliative care. We believe that pazopanib contributed to tumor control, based on the marked increase in tumor size after preoperative withdrawal of pazopanib and tumor shrinkage after

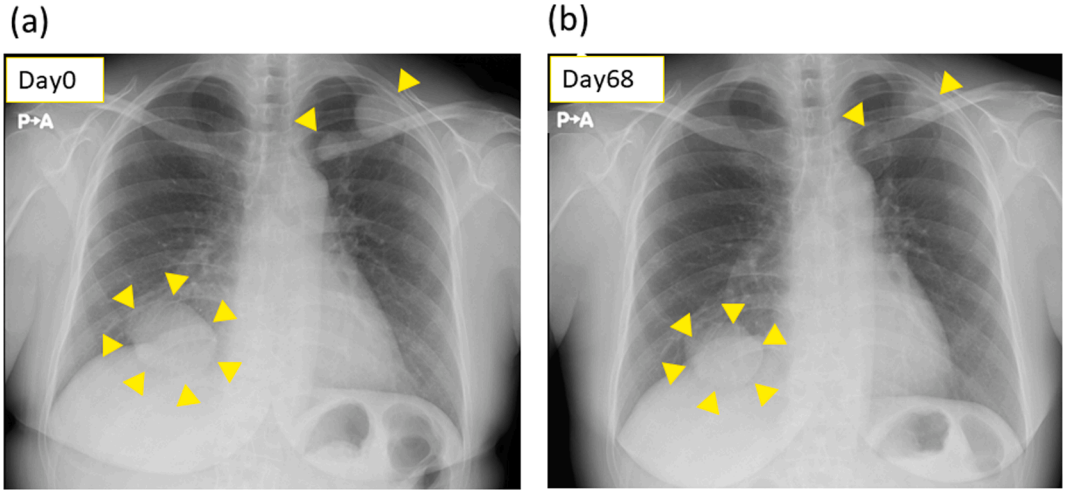

Fig. 1. Tumor shrinkage observed in lung metastatic lesions with pazopanib treatment. Chest X-rays (a) before and (b) 68 days after the start of pazopanib treatment.

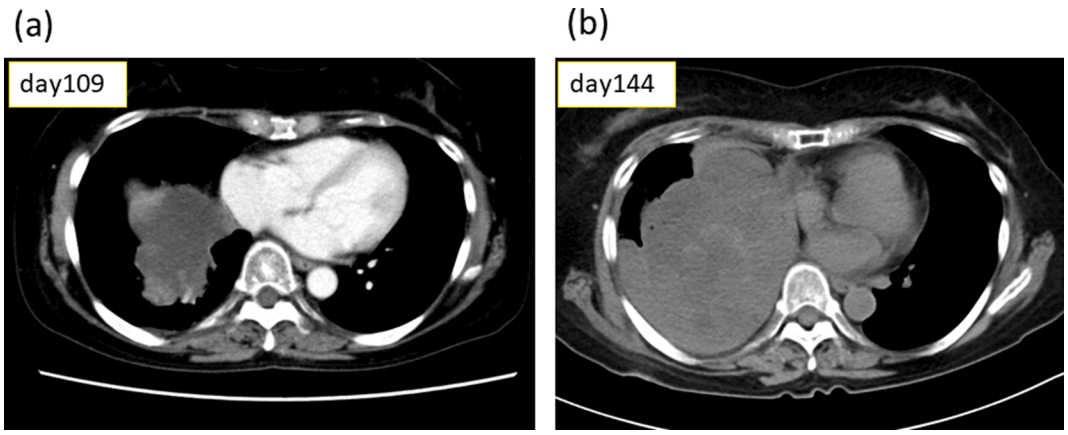

Fig. 2. Rapid tumor growth after pazopanib withdrawal. Chest computed tomography (CT) scan (a) during pazopanib treatment and (b) 14 days after pazopanib withdrawal showing rapid tumor growth.

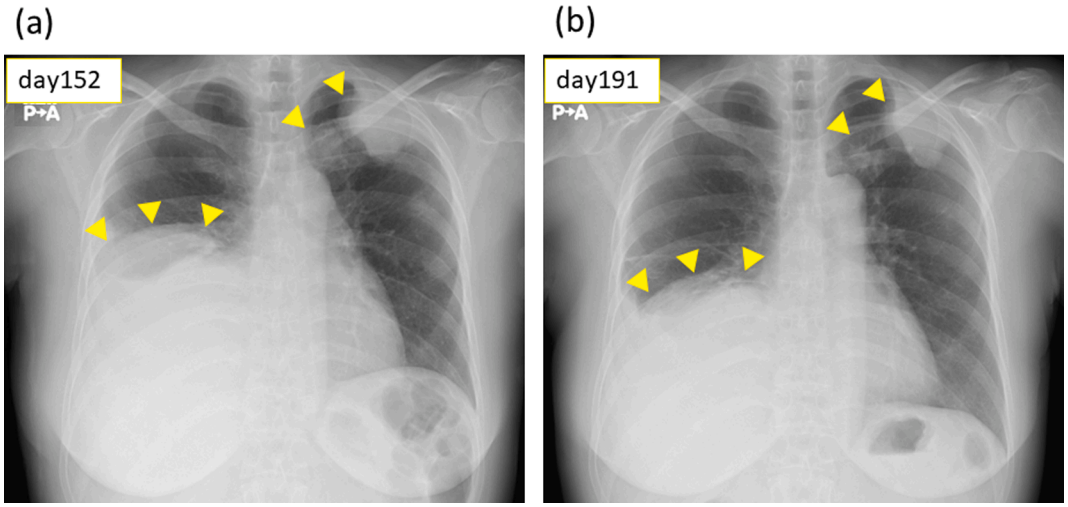

Fig. 3. Effect of pazopanib resumption on lung metastatic tumors. Chest X-rays (a) before and (b) 37 days after resuming pazopanib treatment.

resumption of pazopanib. Although there is a report on the effectiveness of pazopanib in UCS (Nishikawa et al., 2017), to our knowledge, this is the first case in which pazopanib treatment was applied based on *FGFR1* amplification and was effective against UCS.

In a report on pazopanib treatment of small cell lung cancer with *FGFR1* amplification, remarkable tumor shrinkage was observed after 2 months of pazopanib treatment. To perform real-time monitoring of the disease a second liquid biopsy was performed after 3 months of treatment and *FGFR1* amplification was no longer detectable. This suggests a molecular response to treatment with a significant decrease in the molecular tumor burden (Russo et al., 2019). In our case, pazopanib withdrawal caused a rapid increase in tumor size, and re-administration of pazopanib caused a decrease in tumor size inside and outside of the palliative radiation field. Currently, only one genomic test is required, and a second genetic test cannot be performed by the national health insurance in Japan. Metastatic lesions of UCS have an adenocarcinoma component (Sreenan and Hart, 1995). In this case, tissue was collected from the lung metastasis twice, at the time of the first recurrence and after the start of pazopanib treatment. The diagnosis of lung metastasis differed between the two rounds of surgery—it was diagnosed with a carcinoma component at the first time and sarcoma at the second. Therefore, recurrent lesions at the same site could show characteristics of histological changes, while genomic alterations might have also been found if a second genetic test had been examined. The second genetic test might have allowed us to verify whether pazopanib contributed to the reduction in *FGFR*-amplified tumor volume.

The therapeutic development of small molecule FGFR inhibitors was preceded by non-selective inhibitors, including ponatinib, nintedanib, and pazopanib. Of these, pazopanib was approved by the FDA in October 2009 and has been used in clinical practice for $>$ 10 years. Therefore, its safety has been well studied. However, selective FGFR inhibitors, including pemigatinib, infigratinib, erdafitinib, and futibatinib, were developed several years after non-selective FGFR inhibitors. Reasons for choosing a non-selective FGFR inhibitor for this case include selective inhibitors not being approved in Japan for all indications then and the safety profile of pazopanib. However, cost and safety must be taken into consideration for off-label use when it is not possible to participate in clinical trials, as in this case.

FGFR mutations and amplifications have been reported in several solid tumors, and the probability of detecting *FGFR* gene abnormalities in malignant tumors is 3–7%, of which approximately half are *FGFR1* amplifications (Helsten et al., 2016). In UCS, the rate of *TP53* mutations varies from 62% to 91%, whereas that of *PTEN* mutations varies from 18% to 48%, and the frequency of *FGFR* abnormalities is low (Matsuzaki et al., 2021). The *FGFR2* mutation is noted in about 11–15% of uterine cancers and is a poor prognostic factor (Jeske et al., 2017). However, there have been few reports about clinical studies using FGFR inhibitors for uterine malignancy. The multi-kinase inhibitor dovitinib, a non-selective FGFR inhibitor, showed some clinical activity, but they could not confirm the clinical benefits for recurrent and advanced-stage

uterine cancer patients with or without *FGFR2* mutations (Konecny et al., 2015). Therefore, the relationship between *FGFR* gene abnormalities and response rates remains unclear in UCS. The correlation between the presence of *FGFR1* amplification and the response rate to FGFR inhibitors warrants further clarification in UCS.

4. Conclusion

In our patient with UCS and *FGFR1* amplification, pazopanib was effective in reducing the tumor size, although only for a limited period. She was able to walk independently and continue oral intake at home without respiratory disturbance, preserving the patient's quality of life. Thus, pazopanib and other FGFR inhibitor therapies may be effective options for UCS and other malignancies with *FGFR1* amplification. The widespread use of cancer genome testing with expert tumor board knowledge will further expand treatment options for refractory malignancies.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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