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Case report

Therapeutic efficacy of a four-year treatment with eribulin in a patient with uterine leiomyosarcoma: A case report

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ABSTRACT

Uterine leiomyosarcoma (LMS) is a gynecological malignancy with an extremely poor prognosis. Multiple new therapeutic agents, including pazopanib, trabectedin, and eribulin, have been clinically applied to treat uterine LMS, and their therapeutic effects are expected. We encountered one patient with advanced recurrent uterine LMS who achieved a partial response to a four-year treatment with eribulin. A 31-year-old woman was diagnosed with stage 2B LMS. After the first recurrence, Gemcitabine, Docetaxel (GD) therapy was administered, and complete response (CR) was achieved. However, 2 years and 10 months later, recurrence occurred at the vaginal cuff, and GD therapy and doxorubicin hydrochloride were administered, resulting in CR. Five months later, she experienced another recurrence at the same location and was treated with eribulin. To date, 53 courses of eribulin have been administered and are currently ongoing. Maintaining low neutrophil-to-lymphocyte ratio and low platelet-to lymphocyte ratio in this manner is considered to be one of the reasons why eribulin continues to be effective. We encountered a rare case in which eribulin was administered for the longest period of time, and produced an observable effect in uterine LMS.

1. Introduction

Uterine leiomyosarcoma (LMS) is a rare gynecologic malignancy with an extremely poor prognosis and accounts for 1–3% of uterine malignant tumors (WHO Classification of Tumors of Female Reproductive Organs, 2014; Seagle et al., 2017). In recent years, multiple novel therapeutic agents such as pazopanib, trabectedin, and eribulin have been clinically used to treat uterine LMS and are expected to have therapeutic potential. However, the efficacies of these agents for uterine LMS are limited (Schöffski et al., 2016; Kawai et al., 2015).

Eribulin was approved for the treatment of malignant soft tissue tumors in Japan in 2016. Eribulin is a synthetic analog of halichondrin B, which is a marine natural product that interferes with microtubule dynamics (Huyck et al., 2011). In a Phase 3 clinical trial of eribulin in patients with advanced or recurrent malignant soft tissue tumors (liposarcoma or leiomyosarcoma) who had received at least two prior therapies, including anthracycline chemotherapy, a statistically significant improvement was demonstrated in the primary endpoint of overall survival compared with the comparator dacarbazine (Schöffski et al., 2016).

Although the existence of tissue necrosis and an increase in the number of mitotic figures have been included as pathological malignancy evaluations of uterine LMS and are considered to be important prognostic indicators, they cannot predict the therapeutic effect of treatment (Patil et al., 2011).

Miyagawa et al. demonstrated that the neutrophil-to-lymphocyte ratio (NLR), which is a marker of systemic immunity, was significantly associated with progression-free survival (PFS) in patients with metastatic breast cancer treated with eribulin but not in those treated with nab-paclitaxel (Miyagawa et al., 2018). In addition, Miyoshi et al. proposed a baseline NLR cut-off value of 3.0 as a general prognostic marker of overall survival (OS) in patients with breast cancer but not as a specific predictor of OS in eribulin-treated patients (Miyoshi et al., 2020).

Herein, we report the case of a patient with advanced recurrent uterine LMS who achieved a partial favorable response over four-year treatment with eribulin, which is the longest eribulin treatment regimen that produced an observable effect in uterine LMS to date.

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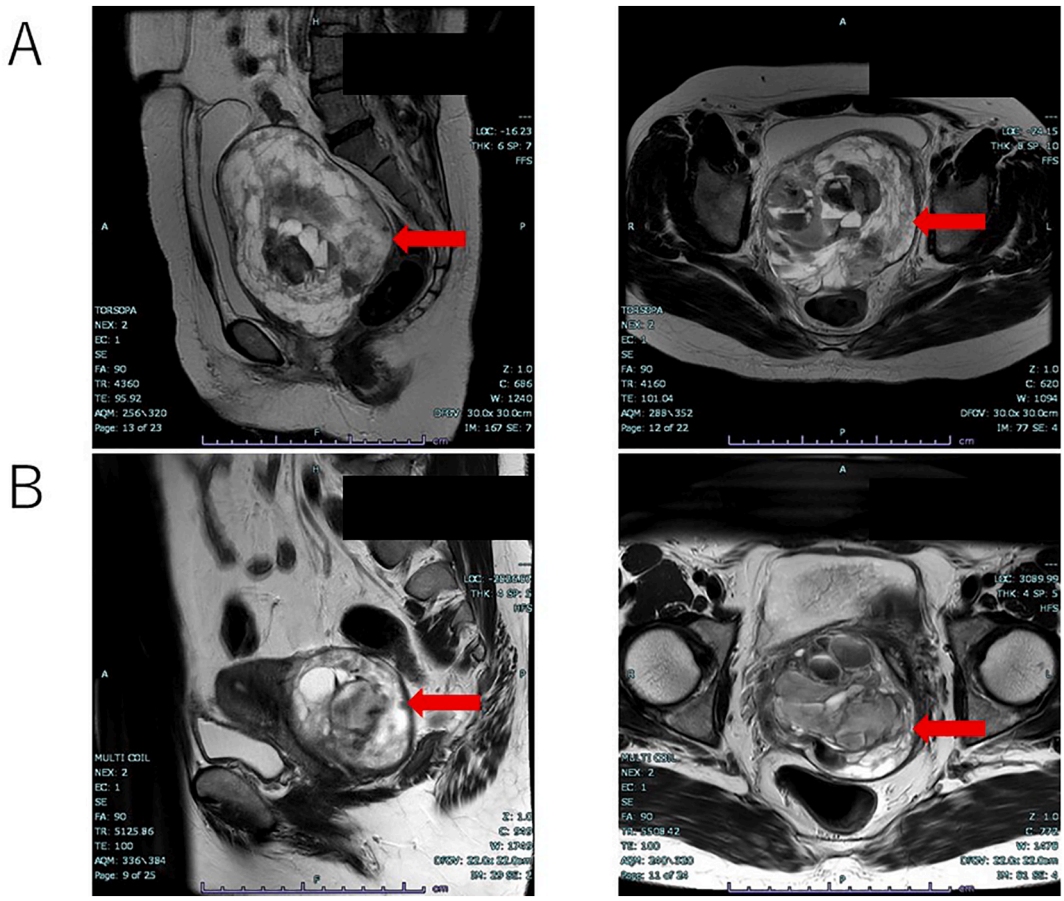

Fig. 1. Pelvic magnetic resonance imaging findings at first visit and first recurrence. (A) At the first visit, a tumor suspected of degenerative myoma was found in the pelvis. (B) The tumor recurred in the posterior wall of the uterine cervix.

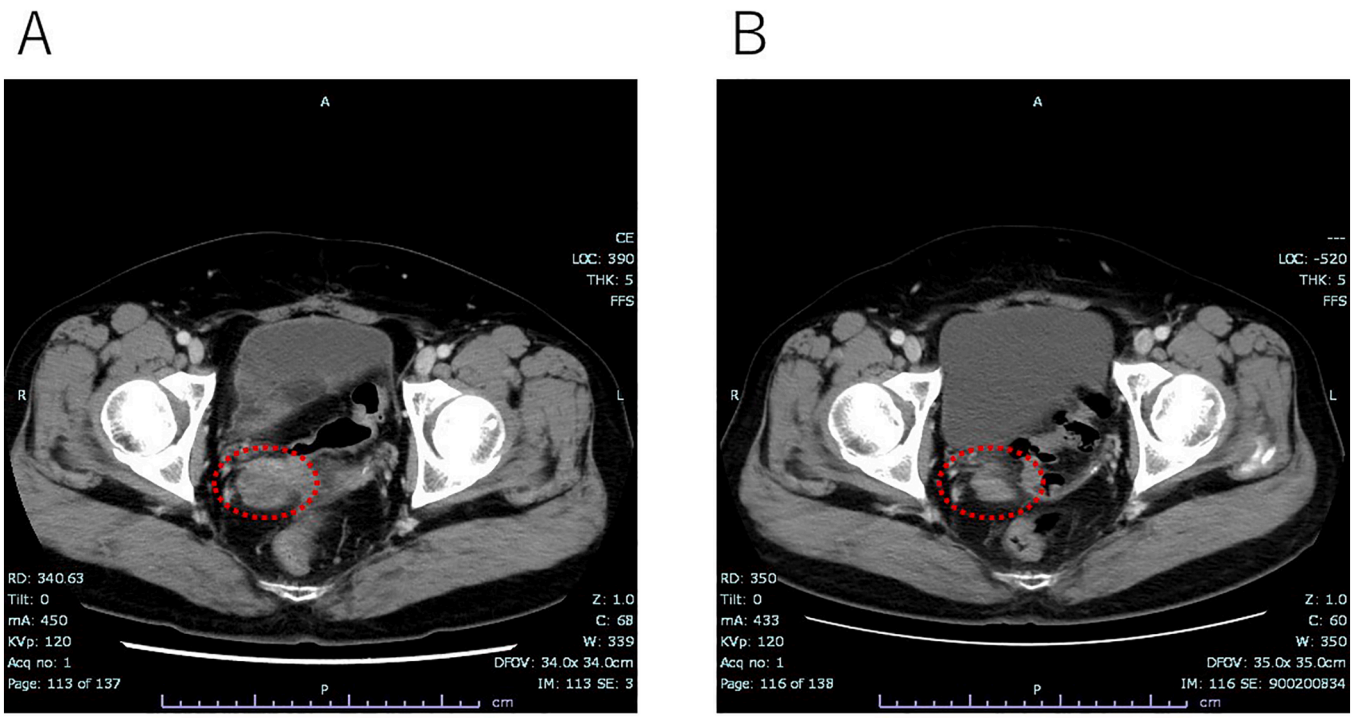

Fig. 2. Comparison of computed tomography findings at the start of eribulin administration and at present. (A) The tumor was present at the vaginal cuff, and the size was 26 × 25 × 15 mm at the start of eribulin treatment. (B) The tumor has gradually decreased to 20 × 12 × 11 mm at present.

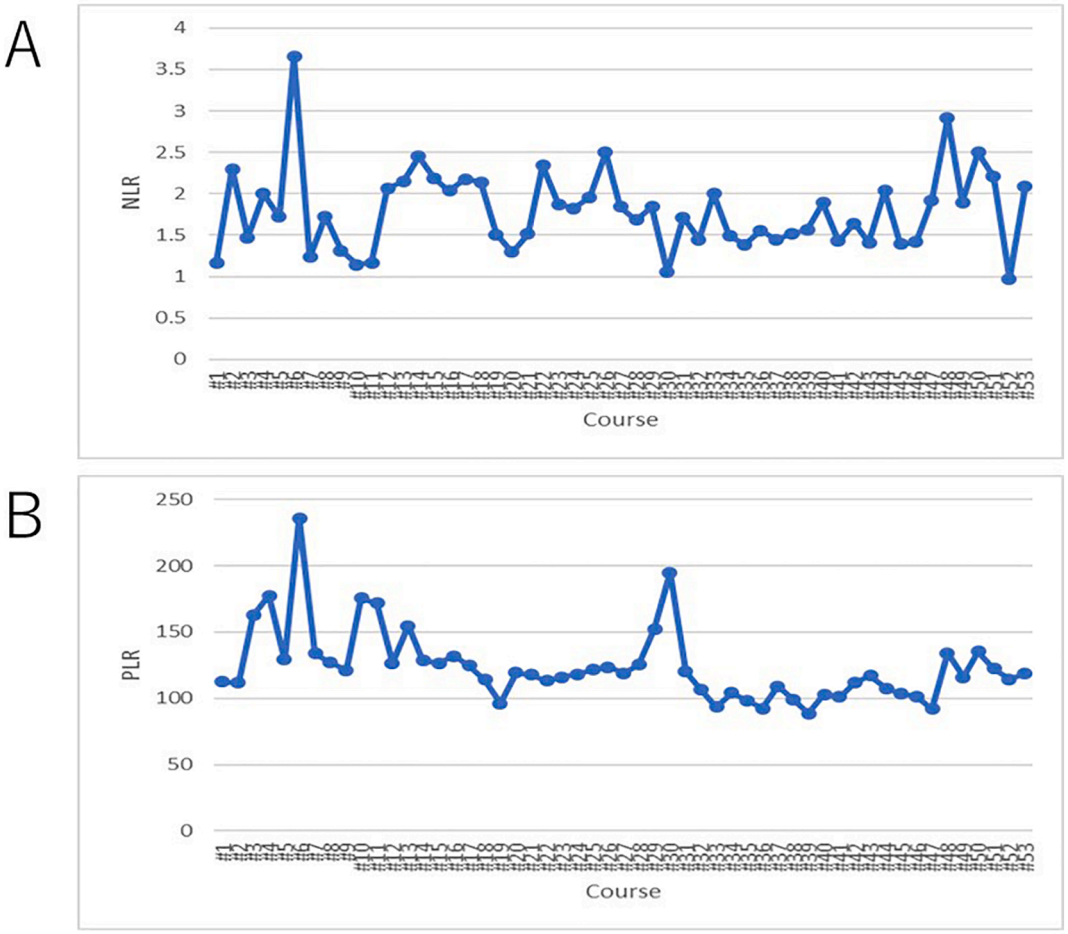

Fig. 3. Time series of neutrophil-to-lymphocyte ratio (NLR) and platelet-to lymphocyte ratio (PLR) from the start of eribulin administration to the present. (A) The patient's pre-treatment NLR was low at 1.17 and remains low at present. (B) The patient's pre-treatment PLR was low at 112 and remains low at present.

2. Case presentation

A 31-year-old woman was referred to our hospital after an abnormality was identified during a cervical-cancer screening. Transvaginal ultrasonography and magnetic resonance imaging revealed a degenerative uterine leiomyoma of the pelvis (Fig. 1A). The patient was unmarried and desired uterine preservation; therefore, tumorectomy was performed. Pathological evaluation suggested a smooth muscle tumor of uncertain malignant potential and careful follow-up was considered.

Ten months after the initial surgery, the tumor recurred in the posterior wall of the uterine cervix, and malignancy could not be ruled out; therefore, total hysterectomy and bilateral adnexectomy were performed (Fig. 1B). The patient was diagnosed with stage 2B LMS.

After the first recurrence, Gemcitabine, Docetaxel (GD) therapy was administered, and complete response (CR) was achieved. However, 2 years and 10 months later, recurrence occurred at the vaginal cuff, and GD therapy alongside doxorubicin hydrochloride were administered, resulting in CR. Five months later, computed tomography (CT) was performed. The patient experienced another recurrence in the same location and received eribulin (Fig. 2A). Eribulin was administered intravenously at a dose of 1.4 mg/m^2 during a 2–5-min infusion on days 1 and 8 of the 21-day cycle. The main side effects were myelosuppression, peripheral neuropathy, hepatic dysfunction, interstitial pneumonia, hair loss, nausea, stomatitis, taste disturbance, and fatigue, and the patient was carefully followed-up.

At the start of eribulin treatment, the tumor size was 26 mm × 25 mm × 15 mm, which gradually decreased to 20 mm × 12 mm × 11 mm, and the state of PR continued (Fig. 2B). The patient had low pretreatment neutrophil-to-lymphocyte ratio (NLR) (1.17) and platelet-to lymphocyte ratio (PLR) (112), which remained at this level throughout treatment, with the median NLR value of 1.72 (interquartile range [IQR]: 1.44–2.07) and a PLR of 118 (IQR: 107–128), as shown in Fig. 3A and 3B. To date, 53 courses of eribulin have been administered and are ongoing. Regarding side effects due to long-term use, grade 2 liver dysfunction occurred after 5 cycles of eribulin; however, the administration could be continued without side effects. Although grade 3 or higher non-hematological toxicity requires dose reduction, this case did not require dose reduction.

3. Discussion

To our knowledge, this is a rare case in which eribulin was administered for the longest reported period of time to a patient with LMS, and a positive therapeutic effect was observed. In 2016, eribulin was approved for the treatment of patients with unresectable LMS and liposarcoma who received prior chemotherapy (Schöffski et al., 2016). Although we focused on NLR and PLR to predict the effect of eribulin, we identified that maintaining low NLR and PLR could be considered to underlie the efficacy of eribulin after 53 cycles. Some previous reports have suggested that low NLR and PLR reflect the antitumor immunity status and is associated with the long-term survival of cancer patients (Sato et al., 2021).

Sato et al. conducted a retrospective analysis of 53 patients treated with eribulin for recurrent or metastatic soft-tissue sarcoma (STS). They identified a low baseline NLR (<3.0) as an independent predictive marker of durable clinical benefits and better PFS in patients with STS

treated with eribulin (Sato et al., 2021). NLR and absolute lymphocyte count are attracting attention as predictors of the effect of eribulin on metastatic breast cancer (Miyagawa et al., 2018; Miyoshi et al., 2020; Takahashi et al., 2021). A combination of NLR and PLR has been reported to be able to predict survival in patients with STS (Shimada et al., 2021). Moreover, peripheral immune-related markers reflect not only the anti-oncogenicity status of the immune system but also the pro-oncogenicity status, making NLR and PLR useful biomarkers for assessing the efficacy of STS treatment (Shimada et al., 2021).

However, no studies have yet investigated the effects of eribulin in a large cohort of patients with uterine LMS, with the literature limited to case reports (Ethier et al., 2017; Omichi et al., 2017). In addition, as far as the literature is concerned, there are no cases of patients with uterine LMS who have been treated for over 4 years, as in our case.

NLR is an indicator of systemic inflammation and an elevated NLR is recognized as a poor prognostic factor in various malignancies (Ethier et al., 2017; Omichi et al., 2017). One possible underlying mechanism of peripheral immune-related markers as useful references is the effect of drugs on the tumor microenvironment (Shimada et al., 2021; Ito et al., 2017). Eribulin affects intratumoral vascular remodeling, resulting in improved drug delivery and immune cell trafficking (Shimada et al., 2021; Ito et al., 2017). This indicates that the anti-tumor effect of eribulin is potentially enhanced by a high lymphocyte ratio in the tumor microenvironment (Shimada et al., 2021; Ito et al., 2017).

4. Conclusions

This report presents a rare case wherein a patient with uterine LMS was treated with eribulin for the longest reported period of time (4 years), and a therapeutic effect was observed. Furthermore, we investigated the factors associated with the eribulin monotherapy administered to the patient, including NLR and PLR. We propose that maintaining low NLR and PLR can be considered as the reasons why eribulin treatment maintained therapeutic effectiveness. We plan to accumulate data from a larger number of patients to confirm this hypothesis.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the consent is available for review by the Editor-in-Chief of this journal upon request.

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Ethical approval

This study was approved by the Ethical Review Board of Sapporo Medical University (342-73, Sapporo, Japan).

CRediT authorship contribution statement

Motoki Matsuura: Investigation, Data curation, Writing – original draft, Visualization. **Kazuma Yorozu:** Writing – review & editing. **Sachiko Nagao:** Writing – review & editing. **Shoko Kurokawa:** Writing – review & editing. **Masato Tamate:** Writing – review & editing. **Taishi Akimoto:** Writing – review & editing. **Tsuyoshi Saito:** Writing – review & editing.

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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