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Eribulin as a first-line treatment for soft tissue sarcoma patients with contraindications for doxorubicin

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Doxorubicin is a first-line therapy for patients with unresectable advanced soft tissue sarcoma (STS). However, because of cardiotoxicities, it is not used for patients with cardiac problems. Eribulin has exhibited efficacy for advanced STS in second- or later-line treatments. In the present study, we retrospectively analyzed the efficacy and safety of first-line eribulin therapy for patients with advanced STS unable to receive doxorubicin. Six of 28 patients who received eribulin as any line treatment received eribulin as a first-line treatment. The reasons for avoiding doxorubicin were as follows: cardiac problems for four patients and advanced age for two. Median progression-free survival (PFS) of the patients who received eribulin as first-line and, second or later-line therapy were 9.7 months (95% CI: 1.0-not reached) and 3.9 months (95% CI: 2.7–5.9), which were not significantly different. The reasons for discontinuation of eribulin were disease progression and adverse events (2 fatigue and 1 neuropathy) for three patients each. No treatment-related cardiotoxicity was observed. The findings of this study indicated that eribulin exhibits meaningful efficacy for the patients with contraindications for doxorubicin as a first-line treatment without cardiac adverse events. However, appropriate safety management is necessary because older patients are typically among those intolerable of doxorubicin.

Soft tissue sarcomas (STS) are heterogenous tumors with over 50 subtypes[1]. Doxorubicin is globally applied as a first-line therapy for patients with unresectable advanced STS. However, doxorubicin has a side effect of cardiotoxicity and is generally contraindicated for patients with current or previous abnormal cardiac function[2]. Clinical trials on doxorubicin have excluded patients with abnormal left ventricular or cardiac ejection fraction[3,4]. STS is common in older patients, and the proportion of patients with STS aged > 60 years exceeds 50% in Japan[5,6]. Older patients have an increased risk of doxorubicin-induced heart failure[7], and old age is reported to be associated with increased hematological toxicity by anthracyclines[8]. Accordingly, the use of doxorubicin tends to be avoided in older populations. Thus, the treatment strategy for the patients with STS with cardiac comorbidities or the aged remains unclear, and is therefore an important issue.

Other chemotherapies for advanced STS are histology-driven, and the application of each drug differs slightly between countries. In Japan, eribulin, pazopanib, trabectedin and ifosfamide are applied[1,9–12]. Eribulin is a microtubule inhibitor that inhibits the growth of microtubules, causing G2/M cell cycle arrest. Eribulin significantly prolonged overall survival (OS) in previously treated patients with advanced liposarcoma (L-sarcoma) or leiomyosarcoma (LMS) compared with dacarbazine in a phase III trial. A phase II trial in Japan also showed the efficacy of eribulin for patients with advanced STS[9,12]. In Japan, eribulin is approved for any kinds of soft tissue

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sarcoma. On the other hand, for example, eribulin is approved only for liposarcoma in the U.S. based on the data preplanned, exploratory subgroup analyses of OS. Eribulin has been also applied for patients with metastatic breast cancer and its safety and efficacy have been confirmed for older patients[13].

In the present study, we retrospectively investigated the safety and efficacy of first-line eribulin in patients with STS who were unable to receive doxorubicin because of cardiac comorbidities or advanced age.

Patients and methods

Patients. We collected data from 28 patients who started eribulin treatment between April 2016 and December 2018 at our institution. The cutoff date was November 2019. Six of 28 patients who received eribulin as any line treatment received eribulin as a first-line treatment. The eligibility criteria were age ≥ 20 years, histologically proven metastatic or recurrent STS, and receiving eribulin and having sufficient organ function tolerable to chemotherapy.

Treatments. All patients received 1.4 mg/m^2 eribulin as a 5-min intravenous infusion on days 1 and 8 every 3 weeks. Initial dose reduction was allowed according to patient status at the discretion of the investigators. Outpatients generally visited the investigators on days 1 and 8 every 3 weeks. At each visit, physical examinations, laboratory tests, and assessments for adverse events (AEs) were performed. The treatment was continued until disease progression, unacceptable toxicity, or a decision to discontinue by the patient or investigator. Dose reduction and treatment delay were performed according to the manufacturer's instructions.

Assessment. Medical information of each patient was retrospectively obtained by electronic records. Tumor lesions were assessed by computed tomography (CT) every 2–3 months. In cases of worsening symptoms or laboratory findings, CT was performed. Progression-free survival (PFS) and OS were defined as the period from the initiation of eribulin to the day of tumor progression or the day of death from any cause, respectively. Tumor responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Adverse events during the therapy were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analysis. PFS and OS of two specific patients groups were estimated using the Kaplan–Meier method, compared wth the log-rank test. Other comparisons of two specific patient groups were performed using chi-squared test and Fisher's exact test. Hazard ratios were calculated using a Cox proportional hazard model. Values of $p < 0.05$ were considered significant. Relative dose intensity was the percentage of actual cumulative dose compared with the amount of planned cumulative dose. All statistical analyses were carried out using JMP software (SAS Institute Japan, Tokyo, Japan).

Ethics approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of Kyushu University Hospital (Approval No. 2019-618).

Informed consent. Informed consent was not obtained from each patient due to the retrospective nature of the present study. The consent was waived by the Ethics Committee of Kyushu University Hospital.

Results

Patients' characteristics. A total of 28 patients with STS were analyzed. Six and twenty-two patients received eribulin as a first-line treatment and, a second or later-line treatment, respectively. The patients' characteristics are shown in Table 1. The median age of the patients who received eribulin as a first-line therapy was 76 years (range: 58–82 years), which is significantly older than 62 years (range: 20–76 years) for the patients who received eribulin as a second or later-line therapy. Five patients (83%) were male. Performance status 0 or 1 was observed in three patients (50%). Histology was L-sarcoma, LMS, and others for two patients each. The reason for avoiding doxorubicin therapy was cardiac problems for four patients and advanced age for two.

Treatment and efficacy. The median follow-up time was 16 months for patients who received first-line eribulin therapy. At the data cutoff, no patients received eribulin. The reasons for discontinuation of eribulin were disease progression and adverse events (2 fatigue and 1 neuropathy) for three patients each. The median number of cycles of eribulin treatment was 7.5 (range: 2–15). The median relative dose intensity was 93% (range: 49–99%). The reasons for cessation of eribulin treatment were progressive disease and AEs in 50% of the patients each. These AEs were two cases of fatigue and one of neuropathy. Median PFS in the six patients treated with eribulin as a first-line treatment was 9.7 months (95% confidence interval [CI]: 1.0 month–not reached) (Fig. 1a). The PFS rate at 12 weeks was 67%. OS was 39.4 months (95% CI: 1.7–39.4 months) (Fig. 1b). The response rate for the five patients with measurable lesions was 0%, and the disease control rate was 66.7%. On the other hand, the median number of cycles of eribulin treatment for the patients who received second or later-line eribulin therapy was 7.7 (range: 2–22). The median relative dose intensity was 79% (range: 31–100%). The reasons for cessation of eribulin treatment were progressive and surgery in 91% and 9.0% of the patients each. Median PFS was 3.9 months (95% CI: 2.7–5.9 months) (Fig. 1a). The PFS rate at 12 weeks was 65% for twenty patients except for two patients who received surgery. Within twenty-two patients who received eribulin as a second or later-line treatment, twelve patients were initially diagnosed as unresectable or metastatic and received first-line chemo-