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Real-world experience of Doxorubicin Monotherapy for Advanced or Metastatic Retroperitoneal Sarcoma: A Single Institutional Study of 16 Cases

RYO SATO[1], YUTO MATSUSHITA[1], ASUKA SANO[1], KYOHEI WATANABE[1], HIROMITSU WATANABE[1], KEITA TAMURA[1], DAISUKE MOTOYAMA[1,2], ATSUSHI OTSUKA[1] and HIDEAKI MIYAKE[3]

[1]*Department of Urology, Hamamatsu University School of Medicine, Hamamatsu, Japan;*
[2]*Department of Developed Studies for Advanced Robotic Surgery, Hamamatsu University School of Medicine, Hamamatsu, Japan;*
[3]*Division of Urology, Kobe University Graduate School of Medicine, Kobe, Japan*

Abstract. *Background/Aim: Anthracycline-based chemotherapies including doxorubicin monotherapy are recommended in major guidelines for patients with advanced or metastatic retroperitoneal sarcoma (RPS); however, few studies have reported the outcomes of doxorubicin monotherapy for these patients. We herein investigated the oncological efficacy and safety of doxorubicin monotherapy for patients with advanced or metastatic RPS in real-world clinical practice. Patients and Methods: Sixteen patients diagnosed with advanced or metastatic retroperitoneal sarcoma, receiving doxorubicin monotherapy as first-line treatment between February 2017 and March 2023 at our Institution were analyzed. Response rate, progression-free survival (PFS) periods, overall survival (OS) period, and adverse event (AE) profiles were retrospectively investigated. Results: The median age of patients was 69.5 years. Best responses to doxorubicin were as follows: complete response, 0 patients (0.0%); partial response, 3 (18.8%); stable disease, 9 (56.3%); and progressive disease, 4 (25.0%). The objective response rate and disease control rate were 18.8 and 75.0%, respectively. During the observation period (median, 22 months, range=2-53 months), median PFS and OS periods were 8.0 and 24.0 months, respectively. The following AEs Grade ≥3 occurred: neutropenia in 14 patients (87.5%), febrile neutropenia in 5 (31.3%), leukopenia in 2 (12.5%), thrombocytopenia in 1 (6.3%), and heart failure in 1 (6.3%). Grade ≥3 nausea and vomiting did not occur and there was no treatment-related death. Conclusion: The oncological outcomes of doxorubicin monotherapy for RPS in real-world clinical practice were not inferior to those of the EORTC trial. The incidence of hematological AEs was higher; however, severe gastrointestinal AEs were prevented by prophylactic antiemetics and there were no treatment-related deaths. Collectively, doxorubicin monotherapy with appropriate prophylactic agents is a valid option for patients with advanced or metastatic RPS.*

Correspondence to: Ryo Sato, Department of Urology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Chuo-ku, Hamamatsu, Shizuoka 431-3192, Japan. Tel: +81 534352306, Fax: +81 534352305, e-mail: rsato02@hama-med.ac.jp

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Soft tissue sarcoma (STS) is a rare tumor accounting for less than 1% of all malignancies in adults (1). It arises throughout the body, such as the extremities, viscera, and retroperitoneal area, and retroperitoneal sarcoma (RPS) accounts for approximately 15% of STS (2). In a previous study, median age at diagnosis of RPS was 60 years and more than 50% of patients were female (3). The representative histological types of RPS are predominantly dedifferentiated liposarcoma (37%), well-differentiated liposarcoma (26%), and leiomyosarcoma (19%) (4). Surgical therapy is the mainstay for patients with localized and clinically resectable RPS because it represents the only approach for a potential cure, in particular, surgery with achieving textbook outcomes is important (5). However, 8.2% of newly diagnosed RPS patients did not undergo surgery because of unresectable or metastatic disease (6). In addition, the local recurrence rate was reportedly 23-39% and distant metastatic recurrence was observed in 21-24% of surgically resected cases (3, 4, 7). Although there is a report of favorable efficacy and safety of intensity-modulated carbon-ion radiotherapy for unresectable STS

(8), anthracycline-based chemotherapies, particularly doxorubicin monotherapy, is recommended in major guidelines for patients with advanced or metastatic RPS (9, 10). However, this recommendation is based on findings of a phase III trial on patients with STS (11); therefore, further evidence for doxorubicin monotherapy for advanced or metastatic RPS is needed. Retrospective studies previously reported the oncological outcomes of chemotherapy for advanced or metastatic RPS; however, not only doxorubicin monotherapy, but also other regimens were used (12, 13). Therefore, we herein investigated the oncological outcomes and safety profiles of doxorubicin monotherapy for patients with advanced or metastatic RPS.

Patients and Methods

Declarations. The design of the present study was approved by the Research Ethics Committee of our Institution (No.20-099). The need to obtain informed consent from patients was waived because of the retrospective design of the study; however, an opportunity to opt out was provided through the website of our institution.

Patients. The present study included 16 consecutive Japanese patients diagnosed with locally advanced and/or metastatic RPS and receiving doxorubicin monotherapy at our Institution between February 2017 and March 2023.

Drugs. Doxorubicin was intravenously administered at a dose of 75 mg/m^2 once every 3 weeks with prophylactic antiemetics: dexamethasone, 5-HT3 receptor antagonists and aprepitant or fosnetupitant. The dose was modified or withdrawn in consideration of age, medical history, and treatment-related adverse events (AEs). All patients received treatment with doxorubicin until disease progression, death, or the total dose reached 500 mg/m^2.

Follow-up. All of the data examined in this study were obtained from the medical records of each patient. The following clinicopathological characteristics were collected: age, sex, the Eastern Cooperative Oncology Group performance status (ECOG PS), histology, the resection of primary lesions, and metastatic organs. In addition, the total dose of doxorubicin, follow-up data on the prognostic outcomes, and AE profiles were investigated. Prior to treatment with doxorubicin, all patients underwent radiological examinations by CT. As a rule, tumor measurements after the introduction of treatment with doxorubicin were performed by CT every 6 to 12 weeks. Responses to systemic therapy were evaluated using RECIST version 1.1 (14). All doxorubicin-induced AEs were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (15).

Statistical analyses. All statistical analyses were conducted using EZR software (Saitama Medical Center, Jichi Medical University, ver. 1.40) and p-values <0.05 were considered to be significant. Progression- free survival (PFS) and overall survival (OS) periods were defined as the time from the initiation of doxorubicin to disease progression or death and the initiation of doxorubicin to death, respectively. PFS and OS rates were calculated using the Kaplan-Meier method.

Table I. *Patient characteristics*.

Variables	N=16
Median age, years (range)	69.5 (34-84)
Sex, n (%)	
Male	10 (62.5)
Female	6 (37.5)
ECOG PS, n (%)	
0	11 (68.8)
1	2 (12.5)
2	3 (18.8)
Histology, n (%)	
Dedifferentiated liposarcoma	8 (50.0)
Leiomyosarcoma	5 (31.3)
Synovial sarcoma	1 (6.3)
Undifferentiated pleomorphic sarcoma	1 (6.3)
Malignant peripheral nerve sheath tumor	1 (6.3)
Resection of the primary lesion, n (%)	11 (68.8)
Metastatic sites, n (%)	
Lung	10 (62.5)
Liver	4 (25.0)
Lymph node	2 (12.5)
Other	10 (62.5)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Results

Patient characteristics. Clinicopathological characteristics are shown in Table I. Dedifferentiated liposarcoma was the most common histology (n=8, 50.0%) and the prevalence of lung metastasis was the highest (n=10, 62.5%).

Details of doxorubicin monotherapy and prognosis. As shown in Table II, the median number of cycles was 6 and the median dose of doxorubicin was 330.5 mg/m^2. Fifteen patients (93.8%) needed a dose reduction. Best responses to doxorubicin were as follows: a complete response, partial response, stable disease, and progressive disease (PD) in 0, 3 (18.8%), 9 (56.3%), and 4 (25.0%) patients, respectively. Collectively, the overall response rate (ORR) and disease control rate were 18.8 and 75.0%, respectively. During the follow-up period (median, 22 months, range 2-53 months), 13 (81.3%) patients showed disease progression and 9 (56.3%) died. As shown in Figure 1, median PFS and OS were 8.0 months (95%CI=2-11) and 24.0 months (95%CI=17-not reached), respectively.

Toxicity. AEs related to doxorubicin are shown in Table III. All patients developed at least one AE and ≥Grade 3 AEs occurred in 14 patients (87.5%). Most ≥Grade 3 AEs were hematological toxicities and there were no gastrointestinal ≥Grade 3 AEs. One patient (6.3%) discontinued treatment due to febrile neutropenia and thrombocytopenia and no treatment-related deaths occurred in this series.

Table II. *Details of doxorubicin monotherapy and prognosis of 16 patients.*

Case	Age	Sex	Histopathology	Cycles of doxorubicin	Total dose of doxorubicin (mg/m^2)	Best response to doxorubicin	PFS (months)	OS (months)	Outcome
1	67	Male	Dedifferentiated liposarcoma	6	450	SD	11	17	Dead
2	76	Male	Dedifferentiated liposarcoma	4	247	SD	5	53	Dead
3	76	Male	Undifferentiated pleomorphic sarcoma	4	238	PD	2	22	Dead
4	29	Male	Malignant peripheral nerve sheath tumor	2	114	PD	1	2	Dead
5	72	Female	Leiomyosarcoma	8	455	SD	8	24	Dead
6	67	Male	Dedifferentiated liposarcoma	2	123	PD	1	3	Dead
7	81	Male	Dedifferentiated liposarcoma	11	500	PR	1	21	Dead
8	34	Male	Synovial sarcoma	7	498	PR	8	28	Dead
9	38	Male	Leiomyosarcoma	6	328	SD	5	35	Alive
10	62	Female	Dedifferentiated liposarcoma	6	333	SD	11	28	Alive
11	62	Female	Leiomyosarcoma	7	394	SD	10	22	Alive
12	73	Female	Dedifferentiated liposarcoma	6	409	SD	12	22	Dead
13	72	Male	Dedifferentiated liposarcoma	3	182	SD	21	21	Alive
14	43	Male	Dedifferentiated liposarcoma	6	396	SD	15	15	Alive
15	74	Female	Leiomyosarcoma	6	326	PR	9	10	Alive
16	84	Female	Leiomyosarcoma	3	132	PD	3	7	Alive

PFS, Progression-free survival; OS, overall survival; PR, partial response; SD, stable disease; PD, progression disease.

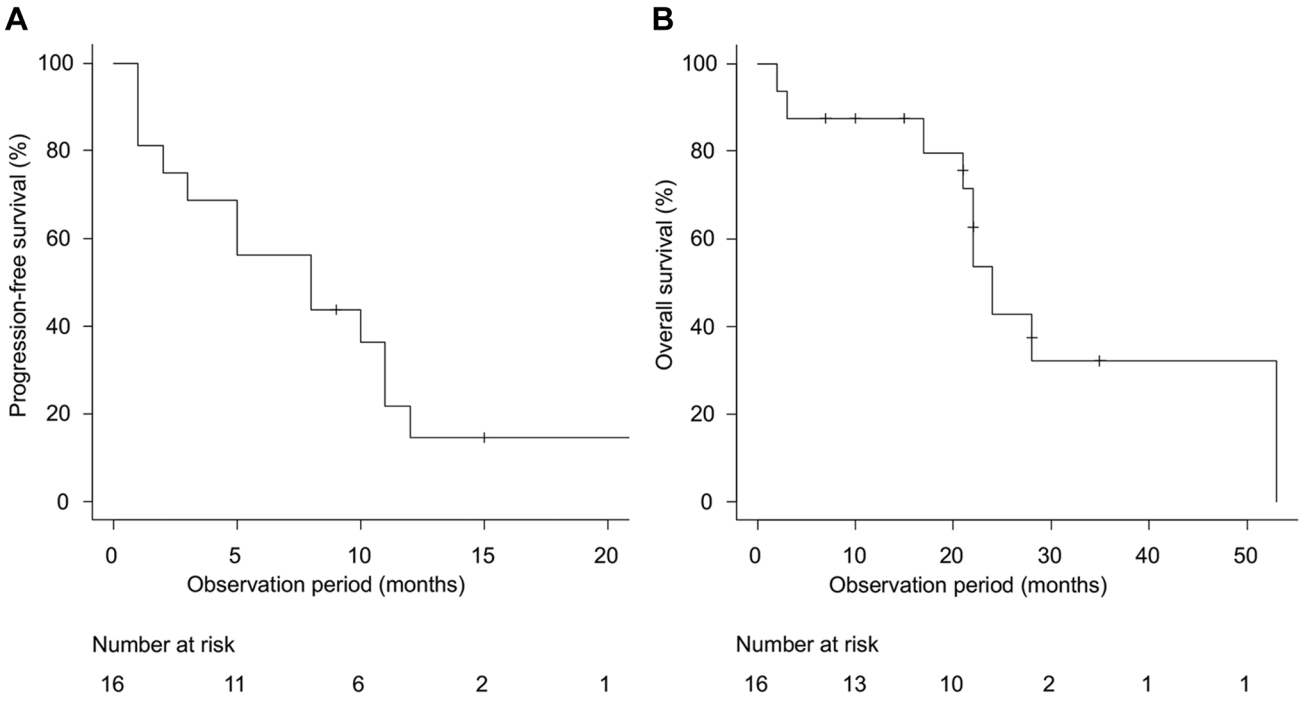

Figure 1. *Kaplan-Meier curves of (A) PFS and (B) OS of 16 patients in the present study. PFS: Progression-free survival; OS: overall survival.*

Subsequent therapies after doxorubicin monotherapy. After discontinuation due to PD or the completion of doxorubicin, 10 patients (62.5%) were administered second-line therapy, while 6 (37.5%) received best supportive care.

Discussion

In newly diagnosed RPS patients, 3.1 and 5.1% did not undergo surgery because of non-resectability and metastatic

disease (6). RPS has higher local recurrence and distant metastatic recurrence rates than STS in the limbs because it is often difficult to resect with a R0 margin status for anatomical reasons (3, 4, 7). Treatment for advanced or metastatic RPS was decided based on the findings of the EORTC trial: a randomized phase III trial comparing the efficacy and safety of doxorubicin monotherapy and doxorubicin plus ifosfamide for advanced or metastatic STS (11). The results obtained showed that PFS was significantly longer with doxorubicin plus ifosfamide than with doxorubicin monotherapy (7.4 months *vs*. 4.6 months, hazard ratio=0.74, p=0.003), whereas OS was not significantly different between the two groups (14.3 months *vs*. 12.8 months, HR=0.83, p=0.076). In addition, ≥Grade 3 AEs, including hematological, neurological, and gastrointestinal toxicities, were more frequent in the doxorubicin plus ifosfamide group. Based on findings on OS and AEs, doxorubicin monotherapy has been recommended as the standard treatment in major clinical guidelines (9, 10). However, the participants of the EORTC trial included not only RPS patients, but also patients with STS arising from another site; therefore, there is no prospective clinical trial on chemotherapy for advanced or metastatic RPS. Two retrospective observational studies that included RPS patients were previously conducted; however, multiple systemic chemotherapy regimens were used, with doxorubicin monotherapy accounting for 8.5-31% (12, 13). Limited information is currently available on doxorubicin monotherapy for RPS. Therefore, we retrospectively reported the oncological outcomes and safety profiles of doxorubicin monotherapy for patients with advanced or metastatic RPS.

In comparison of the characteristics of participants with the doxorubicin monotherapy cohort of the EORTC trial and previous retrospective studies, there were more elderly patients and the prevalence of ECOG PS ≥2 was higher in the present study than in the other studies (11, 13). However, the breakdown of histology, particularly the percentage of cases of liposarcoma and leiomyosarcoma, was equivalent between the present study and the previous study on RPS (13). Despite the regimens widely differing, a larger number of cycles was performed in this study than in the other studies (11, 13); however, a dose reduction was more frequently needed in our cohort than in the doxorubicin monotherapy cohort of the EORTC trial (93.8% *vs*. 32%) (11).

Oncological outcomes, including ORR, median PFS, and median OS, in the present study were 18.8%, 8.0 months, and 24.0 months, respectively, while they were 13.6-16%, 4.6-5.9 months, and 12.8-15.2 months in the previous studies (11, 13). In our cohort, ORR was equal, whereas PFS and OS were slightly longer despite the older age of patients and poor PS, which are significant factors associated with OS (16). Although the reasons for this remains unclear, differences in race and variability in subsequent lines of therapy may have contributed to these discrepancies (12).

Table III. *Profiles of adverse events of the 16 patients included in the study.*

Events, n (%)	Any Grade	Grade ≥3
Neutropenia	16 (100)	14 (87.5)
Febrile neutropenia	–	5 (31.3)
Leukopenia	3 (18.8)	2 (12.5)
Thrombocytopenia	5 (31.3)	1 (6.3)
Heart failure	1 (6.3)	1 (6.3)
Nausea	6 (37.5)	0 (0.0)
Fatigue	5 (31.3)	0 (0.0)
Anemia	3 (18.8)	0 (0.0)
Peripheral neuropathy	2 (12.5)	0 (0.0)

Another point of interest is the assessment of AEs related to doxorubicin monotherapy in real-world clinical practice. The prevalence of grade ≥3 neutropenia and grade ≥3 febrile neutropenia was 37 and 13%, respectively, in the doxorubicin monotherapy cohort of the EORTC trial, while they were 87.5 and 31.3%, respectively, in the present study despite dose reductions being more common (11). We attributed the higher incidence of hematopoietic AEs to the older age of patients and poor PS, which are risk factors for febrile neutropenia (17). On the other hand, grade ≥3 nausea and grade ≥3 vomiting were not observed in our cohort, but were detected in 6 and 3% of patients, respectively, in the EORTC trial (11). This may be because of the use of the prophylactic antiemetic, aprepitant in the present study, which was not administered in the EORTC trial. All patients in the present study were routinely administered aprepitant during chemotherapy, and after 2023, fosnetupitant was used instead of aprepitant. Hematological AEs frequently occurred in practice because of the older age of patients and poor PS, whereas the administration of prophylactic antiemetics prevented severe gastrointestinal AEs.

Study limitations. This was a retrospective study with a small number of patients. While PFS and OS events were observed in more than 50% of patients, the observation period was comparatively short. Furthermore, protocols regarding dose adjustments to and the discontinuation of doxorubicin were not strictly standardized. In addition, the retrospective design of this study may have led to a limited ability to accurately capture AEs; therefore, AEs may have been underreported.

In conclusion, we herein reported the oncological outcomes and AE profiles of doxorubicin monotherapy for patients with advanced or metastatic RPS in real-world clinical practice. The incidence of hematological AEs was higher because of the older age and poor PS; however, oncological outcomes were not inferior to those in previous

studies and the routine use of prophylactic antiemetics prevented severe gastrointestinal AEs. In addition, no treatment-related death was observed. Our results suggest doxorubicin monotherapy with appropriate prophylactic drugs is a beneficial treatment for advanced or metastatic RPS patients.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

Research conception and design: Ryo Sato. Data acquisition: Ryo Sato. Statistical analysis: Ryo Sato. Data analysis and interpretation: Asuka Sano, Kyohei Watanabe, Yuto Matsushita, Hiromitsu Watanabe, and Keita Tamura. Drafting of the manuscript: Ryo Sato. Critical revision of the manuscript: Yuto Matsushita and Hideaki Miyake. Supervision: Daisuke Motoyama, Atsushi Otsuka, and Hideaki Miyake.

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