Original Article

Efficacy and Safety of Trabectedin for Patients With Unresectable and Relapsed Soft-Tissue Sarcoma in Japan: A Japanese Musculoskeletal Oncology Group Study

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BACKGROUND: Although initial trabectedin (1.2 mg/m^2) is safe and effective for patients with translocation-related sarcoma (TRS) in Japan, its efficacy in other types of soft-tissue sarcomas (STSs) remains unknown. This study retrospectively investigated its efficacy and safety through postmarketing surveillance of trabectedin in patients with unresectable and relapsed STS. **METHODS:** One hundred forty patients received intravenous trabectedin (1.2 mg/m^2 on day 1 every 21 days) over the course of 24 hours. The primary endpoint was the efficacy and safety of trabectedin. **RESULTS:** Grade 3 or higher adverse events occurred in 100 patients (71%) and included hepatotoxicity (37.8%), neutropenia (32.8%), and rhabdomyolysis (3.6%). Patients at high risk for grade 3 or higher rhabdomyolysis (36%) were classified by height (≥170.3 cm) and age (≤32 years) through a classification and regression tree model (area under the curve, 0.9). The overall median progression-free survival (PFS) was 3.7 months; with respect to the histological type, the median PFS was 17.4 months for myxoid liposarcoma, 4.9 months for leiomyosarcoma, 5.6 months for synovial sarcoma, and 3.7 months for dedifferentiated liposarcoma. Histological type (liposarcoma/leiomyosarcoma [L-sarcoma] and TRS) and grade 3 neutropenia (but not grade 4) were associated with significantly improved PFS after trabectedin treatment ($P = .003$, $P = .04$, and $P = .001$). The median growth modulation index (GMI) was 0.91; 37 patients (36.7%) experienced a GMI > 1.33, and among patients with solitary fibrous tumors and undifferentiated pleomorphic sarcoma, 60% and 42.9%, respectively, had a GMI > 1.33. The median overall survival (OS) was 16.4 months. A GMI > 1.33 was associated with significantly improved OS ($P = .0006$). **CONCLUSIONS:** Initial trabectedin at 1.2 mg/m^2 has clinically meaningful benefits for patients with L-sarcoma and certain histological subtypes of TRS. ***Cancer* 2020;126:1253-1263**. © *2019 American Cancer Society*.

KEYWORDS: adverse drug event, rhabdomyolysis, soft-tissue sarcoma, trabectedin, treatment efficacy.

INTRODUCTION

Soft-tissue sarcoma (STS) is a rare cancer; its annual incidence rate is estimated to be between 3 and 5 cases per 100,000. There are more than 50 histological types of STS, which can develop almost anywhere in the body. Surgical resection is the primary treatment for STS; however, local recurrence and distant metastases occur in 9% to 15% and 21% to 29% of patients, respectively.[1,2] In unresectable and metastatic cases of STS, systemic chemotherapy is a mainstay of treatment. Anthracycline-based chemotherapy is the gold standard for the treatment of STS.[3] After the failure of anthracycline-based chemotherapy, drugs approved in recent years, such as pazopanib, trabectedin, and eribulin, are used as second or subsequent lines of chemotherapy.[4-7]

Trabectedin is a marine-derived antineoplastic drug and multitarget agent that induces apoptosis and cell cycle arrest through binding to the minor groove of DNA and affecting DNA-binding proteins; it activates the immune microenvironment by inhibiting monocyte differentiation, tumor-associated macrophages, and cytokine production.[8] The efficacy and safety of trabectedin in patients with STS have been demonstrated in phase 2 and 3 studies.[6-12] A randomized phase 3 study

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that compared trabectedin with dacarbazine in patients with advanced liposarcoma/leiomyosarcoma (L-sarcoma) revealed the efficacy and safety of trabectedin.[7] Moreover, a retrospective study demonstrated the efficacy of trabectedin in histological types of STS other than L-sarcoma, especially translocation-related sarcoma (TRS).[13]

In Japan, a phase 1 pharmacokinetic study of trabectedin administered to patients with advanced STS resulted in a recommended dose of 1.2 mg/m^2 as a 24-hour continuous infusion, which differs from the recommended dose of 1.5 mg/m^2 as a 24-hour continuous infusion in the United States and Europe.[14] In this dose setting, a phase 2, randomized, open-label study revealed the efficacy of trabectedin in comparison with best supportive care in patients with advanced TRS after standard chemotherapy.[6] In 2015, on the basis of this result, trabectedin was approved in Japan for the treatment of all histological types of STS. However, the efficacy and safety of trabectedin in Japanese patients with advanced STS remain unknown in a real-world clinical setting. We aimed to clarify the clinical outcomes of Japanese patients with advanced STS, especially histological types other than TRS, treated by physicians from the Japanese Musculoskeletal Oncology Group (JMOG) in a real-life setting with a more diverse patient population than the populations recruited in the clinical trials. Moreover, the response rates and time-to-event endpoints were compared with those reported in other clinical trials, and risk factors for adverse events were investigated.

MATERIALS AND METHODS

Patients and Treatment

We retrospectively reviewed the postmarketing surveillance (PMS) data, and an independent questionnaire, which was not included in the PMS data, was administered to JMOG members. In Japan, PMS data include verification of the safety of new medicines after approval and market release. As a requirement for its approval, a presentation of the PMS data from all patients who had received trabectedin since December 7, 2015, was required by the Ministry of Health, Labor, and Welfare of Japan. At the cutoff date of December 2, 2016, 425 patients were enrolled in the PMS system. All investigations were approved by the institutional review boards of each participating center and were performed in accordance with the Declaration of Helsinki.

One hundred forty-three patients who underwent trabectedin treatment at 29 JMOG institutions were identified among all patients registered in the PMS system. The inclusion criterion was the receipt of trabectedin for an unresectable and/or metastatic lesion. After the application of the inclusion criterion, 3 patients were excluded from the study because of a resectable lesion; therefore, 140 patients were analyzed.

Trabectedin (1.2 mg/m^2) was administered continuously for 24 hours by intravenous infusion through central venous access every 3 weeks. Treatment continued until disease progression or discontinuation for other reasons, such as unacceptable toxicity or consent withdrawal.

To clarify the efficacy of trabectedin for the treatment of STS, especially histological types other than L-sarcoma and TRS, we analyzed the progression-free survival (PFS), objective response rate, and overall survival (OS). The radiological responses to trabectedin were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Stable disease (SD) was defined as a lack of disease progression for >8 weeks. The schedule of radiological evaluation was dependent on each institutional protocol. For intrapatient comparisons, the growth modulation index (GMI) was calculated as the ratio of PFS with trabectedin treatment to PFS with the previous treatment line.[15] We also evaluated the safety of trabectedin. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

Associations between patients' clinical parameters were analyzed with the Mann-Whitney U test for quantitative data and with the chi-square test for qualitative data. PFS was defined as the time from the initial administration of trabectedin to either radiological tumor progression (according to RECIST, version 1.1) or death from any cause. OS was defined as the time from the initial administration of trabectedin to the date of either death or the last follow-up examination. Associations of the patients' clinical parameters with PFS and OS were analyzed with Kaplan-Meier curves and the log-rank test. The multivariate analysis was performed with a Cox proportional hazards model. Factors identified as significant in the univariate analysis were included as variables in the multivariate analysis. P values <.05 were considered statistically significant. The JMP Pro 14 software program (SAS Institute, Inc, Cary, North Carolina) was used to perform all statistical analyses.

We used a classification and regression tree (CART) model to build trees by patient characteristics and adverse events. Recursive partitioning, a nonparametric statistical

TABLE 1. Patients and Clinical Characteristics

Characteristic	Value
Age, mean (range), y	48.5 (17-77)
Sex, No.	
Female	61
Male	79
WHO performance status, No.	
0	67
1	61
2	9
3	2
4	1
Lines of chemotherapy, No.	
1	17
2	43
≥3	80
Target lesion of trabectedin, No.	
Unresectable and/or local recurrence	17
Metastasis	106
Both	17
Histology, No.	
Myxoid/round liposarcoma	22
Leiomyosarcoma	20
Synovial sarcoma	18
Dedifferentiated liposarcoma	15
Undifferentiated pleomorphic sarcoma	10
Extraskeletal Ewing sarcoma	7
Solitary fibrous tumor	6
Alveolar soft-part sarcoma	5
Malignant peripheral nerve sheath tumor	4
Spindle cell sarcoma	4
Clear cell sarcoma	4
Other	25
TRS, No.	
TRS	70
Non-TRS	70
L-sarcoma, No.	
L-sarcoma	60
Non–L-sarcoma	80

Abbreviations: L-sarcoma, liposarcoma/leiomyosarcoma; TRS, translocation-related sarcoma; WHO, World Health Organization.

method for multivariable data, uses a series of dichotomous splits to create a decision tree to correctly classify members of the population by choosing the best predictor. We generated receiver operating characteristic curves to assess the overall diagnostic accuracy of the CART models.

RESULTS

Patient Characteristics

Patient characteristics are presented in Table 1. A total of 140 patients with STS who received trabectedin, including 61 women and 79 men, with a mean age of 48.5 years (range, 17-77 years) were included. The mean follow-up after the initiation of trabectedin treatment was 14.7 months (range, 0.2-34.7 months). Trabectedin was administered to patients with a local recurrence or unresectable primary tumor (n = 17), a metastasis (n = 106), or both a local recurrence and a metastasis (n = 17).

TABLE 2. Common Adverse Events

	No. of Patients (%)		
Adverse events	All Grades	Grade 3	Grade 4
All	135 (96)	100 (71)	32 (23)
Hematologic adverse event			
Leukopenia	56 (40)	22 (16)	9 (6)
Neutropenia	62 (44)	27 (19)	19 (14)
Anemia	60 (43)	13 (9)	5 (4)
Thrombocytopenia	31 (22)	3 (2)	5 (4)
Febrile neutropenia	5 (4)	3 (2)	2 (1)
Nonhematologic adverse event			
Hepatotoxicity	89 (64)	49 (35)	4 (3)
Nausea	17 (12)	3 (2)	0 (0)
Appetite loss	7 (5)	2 (1)	0 (0)
Rhabdomyolysis	5 (4)	4 (3)	1 (1)
CK elevation	20 (14)	4 (3)	0 (0)

Abbreviation: CK, creatinine kinase.

The treatment lines were as follows: first line (n = 17), second line (n = 43), and third or higher line (n = 80). Most patients (128 of 140 [91.4%]) had a good performance status (PS; 0 or 1).

Histological diagnoses included myxoid liposarcoma (MLS; n = 22), leiomyosarcoma (LMS; n = 20), synovial sarcoma (SS; n = 18), dedifferentiated liposarcoma (DDLS; n = 15), undifferentiated pleomorphic sarcoma (UPS; n = 10), and others (n = 55).

Exposure and Safety

All 140 patients were included in the safety analysis; 673 cycles were evaluable for trabectedin toxicity. Most cases received initial trabectedin at a dose of 1.2 mg/m^2; only 3 cases received 0.9 mg/m^2. The median number of treatment cycles was 3 (range, 1-24). Patients received a median dose intensity of 0.33 mg/m^2/wk (range, 0.13-0.41 mg/m^2/wk) and a median cumulative dose of 3.3 mg/m^2 (range, 1-27 mg/m^2) over a median treatment duration of 9.8 weeks (range, 3-151.4 weeks).

Adverse events occurred in 135 patients (96%) and included hepatotoxicity (64%), neutropenia (44%), and creatinine kinase (CK) elevation (14%). Grade 3 or higher adverse events occurred in 100 patients (71%; Table 2). Major grade 3 or higher adverse events included hepatotoxicity (n = 53 [37.9%]), neutropenia (n = 46 [32.9%]), febrile neutropenia (n = 5 [3.6%]), and rhabdomyolysis (n = 5 [3.6%]). Younger patients were more likely to develop grade 3 or higher neutropenia and rhabdomyolysis or CK elevation (P = .03 for both; Mann-Whitney U test). Lower neutrophil counts (P < .0001; area under curve, 0.69; Youden index, 2960) and white blood cell counts (P = .009;

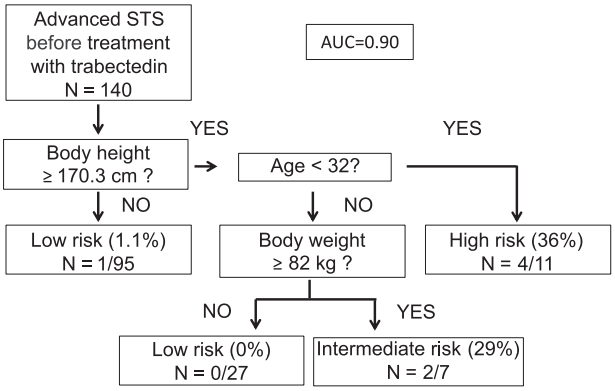

Figure 1. Classification and regression tree analysis for predicting the risk of rhabdomyolysis equal to or greater than grade 3 or a creatinine kinase elevation equal to or greater than grade 3. AUC indicates area under curve; STS, soft-tissue sarcoma.

area under curve, 0.7; Youden index, 4430) were associated with grade 3 or higher neutropenia (Mann-Whitney U test). Taller body height was associated with grade 3 or higher rhabdomyolysis or CK elevation ($P = .03$; Mann-Whitney U test). To classify low- and high-risk patients with rhabdomyolysis after treatment with trabectedin, we developed CART models using several variables, including patient characteristics and other adverse events (Fig. 1). The risk of rhabdomyolysis was classified by body height and age into 4 nodes: high (36%), intermediate (25%), and low (0.2% and 1.1%). The area under the receiver operating characteristic curve was 0.90. Chemotherapy-related death caused by gastrointestinal bleeding was observed in 1 case. One hundred thirty-seven patients discontinued treatment with trabectedin because of disease progression (n = 96); adverse events (n = 16); subsequent treatment, including surgery, radiotherapy, and embolization (n = 9); patient refusal (n = 7); and other reasons (n = 9). Eleven patients (7.9%) required a dose reduction at an average of 3.2 cycles (range, 2-6 cycles). Hepatotoxicity was the most common toxicity (82%) and was followed by neutropenia (27%), rhabdomyolysis (10%), and vomiting (10%). A dosing delay related to toxicities was needed in 49 patients (35%); 20% had 1 delay, and 15% needed more than 1 delay because of hepatotoxicity (50%) and neutropenia (45.2%).

Efficacy of Trabectedin

Tumor response

One hundred twenty-nine cases were evaluable by RECIST; 11 were excluded because of tumor progression before the evaluation. Table 3 describes the efficacy of trabectedin in this cohort. Eleven cases (7.9%), including 7 cases of MLS, 3 cases of SS, and 1 case of a solitary fibrous tumor (SFT), achieved a partial response (PR). Fifty-four cases (41.9%) achieved SD. Long SD (ie, SD for more than 6 months) was observed in 25 of the 54 cases of SD. A PR plus long SD was observed in 36 cases: 17 of the MLS cases (77.3%), 6 of the SS cases (33.3%), 5 of the LMS cases (25%), and 3 of the DDLS cases (20%).

Progression-free survival

The median PFS was 3.7 months (95% confidence interval [CI], 2.8-5.7 months; Fig. 2), and the PFS of each histological type was as follows: MLS, 17.4 months; LMS, 4.9 months; SS, 5.6 months; and DDLS, 3.7 months. Patients with TRS and L-sarcoma had better PFS than those with non-TRS (5.6 months [95% CI, 3.5-8.9 months] for TRS vs 2.5 months [95% CI, 1.6-3.7 months] for non-TRS; $P = .004$) and non–L-sarcoma (8.4 months [95% CI, 2.9-13.8 months] for L-sarcoma vs 3.2 months [95% CI, 2.3-4.5 months] for non–L-sarcoma; $P = .004$; Fig. 2). However, the PFS of patients with TRS except for MLS was equivalent to that of patients with non-TRS ($P = .3$; Fig. 2). Sex, lines of chemotherapy, body mass index (BMI), and serum albumin level were not correlated with PFS (Table 4); however, younger age (≤65 years) and better PS (≤2) were correlated with improved PFS (hazard ratio [HR] for age ≤ 65 years, 0.57; 95% CI, 0.33-0.99; $P = .046$; HR for PS ≤ 2, 0.49; 95% CI, 0.25-0.98; $P = .043$). Moreover, patients with grade 3 or higher neutropenia experienced significantly better PFS according to the multivariate analysis (HR for grade 3 vs grade 0-2, 0.37; 95% CI, 0.20-0.68; $P = .001$; HR for grade 4 vs grade 0-2, 0.62; 95% CI, 0.34-1.14; $P = .13$). The HR for PFS depending on the histological subtype in the multivariate Cox proportional hazards model (adjusted for age and PS) was 0.62 (95% CI, 0.39-0.99; $P = .04$) for TRS and 0.52 (95% CI, 0.33-0.8; $P = .003$) for L-sarcoma.

To investigate the efficacy of trabectedin according to the histological type, we calculated the GMI. The GMI was evaluable in 98 cases (Table 3); the median GMI was 0.91 (range, 0.03-11.86). Thirty-seven patients (37.8%) experienced a GMI > 1.33, which is considered to be a sign of drug activity according to a previous report.[15] Among the histological types with more than 4 cases, rates for a GMI > 1.33 were 43.8% for SS, 31.8% for MLS, 36.4% for DDLS, 42.9% for UPS, 31.3% for LMS, and 60% for SFT.

TABLE 3. PFS, OS, GMI, and Best Overall Response According to Histological Subtypes

Histology	No. of Patients	Median PFS, mo	Median OS, mo	Median GMI	GMI > 1.33, %	PR		PR + Long SD	
						No.	%	No.	%
Unknown	1	1.2	2.9	0.35	0	0	0	0	0
Malignant ossifying fibromyxoid tumor	1	NA	17.5	0.10	NA	0	0	0	0
Malignant peripheral nerve sheath tumor	4	4.5	11.9	0.03	0	0	0	0	0
Synovial sarcoma	18	5.6	19.3	0.93	43.8	3	16.7	6	33.3
Mesenchymal chondrosarcoma	2	9.1	NA	NA	NA	0	0	1	50
Angiosarcoma	2	2.7	NA	1.95	100	0	0	0	0
Solitary fibrous tumor	6	2.3	NA	1.58	60	1	16.7	1	16.7
Spindle cell/sclerosing rhabdomyosarcoma	1	NA	2.1	NA	NA	0	0	0	0
Sclerosing epithelioid fibrosarcoma	1	6.3	16.6	1.26	0	0	0	0	0
Well-differentiated liposarcoma	2	1.4	NA	1.50	100	0	0	0	0
Extraskeletal Ewing sarcoma	7	1.3	9.1	0.42	20	0	0	0	0
Extraskeletal myxoid chondrosarcoma	2	NA	NA	NA	NA	0	0	0	0
Endometrial stromal sarcoma	2	NA	NA	NA	NA	0	0	1	50
Desmoplastic small round cell tumor	1	NA	NA	NA	NA	0	0	1	100
Fibrosarcoma	1	1.6	3.4	NA	NA	0	0	0	0
Pleomorphic rhabdomyosarcoma	2	1.9	6.5	2.17	50	0	0	0	0
Dedifferentiated liposarcoma	15	3.7	11.8	1.23	36.4	0	0	3	20
Myxoid liposarcoma	22	17.4	27.6	1.52	54.5	7	31.8	17	77.3
Myxofibrosarcoma	3	5.3	10.6	0.54	33.3	0	0	1	33.3
Leiomyosarcoma	20	4.9	18.0	1.02	31.3	0	0	5	25
Alveolar rhabdomyosarcoma	1	3.7	NA	NA	NA	0	0	0	0
Alveolar soft-part sarcoma	5	5.6	16.4	0.44	20	0	0	0	0
Spindle cell sarcoma	4	1.4	7.4	0.71	0	0	0	0	0
Undifferentiated round cell sarcoma	1	0.7	3.6	0.35	0	0	0	0	0
Undifferentiated pleomorphic sarcoma	10	1.3	8.4	1.05	42.9	0	0	0	0
Clear cell sarcoma	4	3.0	11.3	0.26	0	0	0	0	0
Dermatofibrosarcoma protuberance	1	0.5	23.1	0.54	0	0	0	0	0
Epithelioid sarcoma	1	1.1	NA	1.14	0	0	0	0	0
Total	140	3.7	16.4	0.91	36.7	11	7.9	36	25.7

Abbreviations: GMI, growth modulation index; NA, not applicable; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

Overall survival

The median OS was 16.4 months (95% CI, 11.5-21.2 months; Fig. 3). At the final follow-up, 3 patients were still receiving trabectedin. After treatment with trabectedin, 79 patients (56.4%) underwent subsequent chemotherapy: 53 patients underwent 1 regimen, 18 underwent 2 regimens, 7 underwent 3 regimens, and 1 underwent 4 regimens. Grade 3 or higher adverse events did not affect the rate of patients undergoing subsequent therapy (data not shown). Twenty-nine patients (20.7%) underwent subsequent radiation therapy. Forty-nine patients received eribulin, and 33 received pazopanib. Eighty-nine patients died of their sarcoma. The median OS according to the histological type was as follows: MLS, 23.2 months; LMS, 12.2 months; SS, 14.3 months; and DDLS, 9.3 months. Poor prognostic factors for patients undergoing trabectedin treatment were a PS $\geq$ 2 ($P < .0001$), 3 or more lines of chemotherapy ($P = .03$), a BMI < 18 kg/m^2 ($P = .02$), and an albumin level < 4 g/dl ($P = .0001$) according to the Cox univariate analysis. The multivariate analysis revealed a PS $\geq$ 2 (HR, 2.68; 95% CI, 1.25-5.78; $P = .01$), an albumin level < 4 (HR, 2.23; 95% CI, 1.31-3.78; $P = .003$), and a BMI < 18 kg/m^2 (HR, 2.73; 95% CI, 1.1-6.76; $P = .03$) as significant poor prognostic factors (Table 5).

Similarly to the results for PFS, the histological type was correlated with OS. Patients with TRS had better OS than those with non-TRS (21.6 months [95% CI, 15.4-29.7 months] vs 11.8 months [95% CI, 7.5-16.6 months]; $P = .007$), although L-sarcoma was not associated with significantly better OS than non–L-sarcoma (21.3 months [95% CI, 13.6-29.4 months] vs 13.5 months [95% CI, 9.1-17.5 months]; $P = .19$; Fig. 3).

Finally, the median OS was 22.4 months (95% CI, 13.9-32.5 months) with a GMI > 1.33 and 11.8 months (95% CI, 7.0-16.3 months) with a GMI $\leq$ 1.33, and a GMI > 1.33 was associated with significantly improved OS ($P = .0006$; Fig. 3 and Table 5).

DISCUSSION

Our retrospective, multicenter study, using PMS data of prospectively registered patients and retrospectively collected outcomes of trabectedin for patients with unresectable and relapsed STS in routine clinical practice, represents real-world data that include clinical demographics, efficacy, and adverse events of trabectedin.

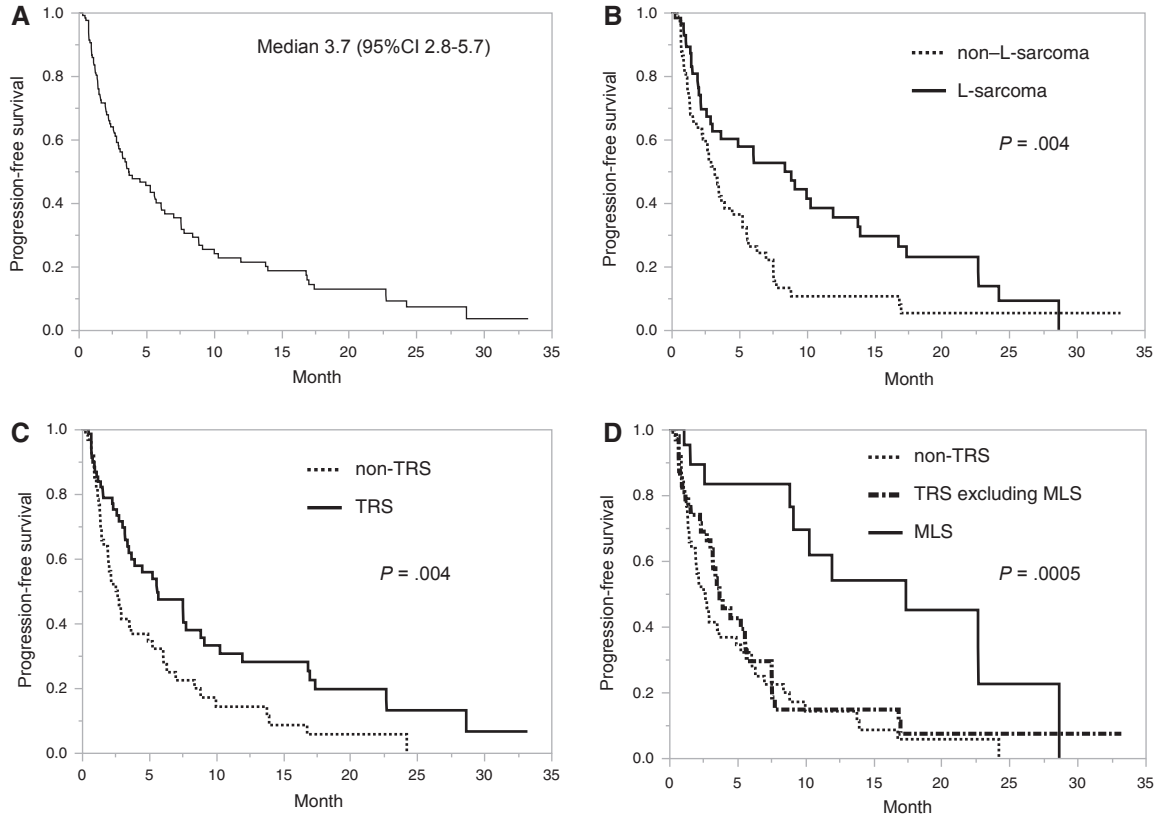

Figure 2. Kaplan-Meier survival curves for progression-free survival: (A) all 129 patients in the current study, (B) L-sarcoma versus non–L-sarcoma, (C) TRS versus non-TRS, and (D) MLS versus TRS (excluding MLS) versus non-TRS. CI indicates confidence interval; L-sarcoma, liposarcoma/leiomyosarcoma; MLS, myxoid liposarcoma; TRS, translocation-related sarcoma.

TABLE 4. Univariate and Multivariate Analyses of Prognostic Factors for Progression-Free Survival

		Univariate Analysis			Multivariate Analysis		
	No.	Median Survival, mo	95% CI, mo	*P*	HR	95% CI	*P*
Age							
≥65 y	22	2.8	1.2-4.9	.006	0.57	0.33-0.99	.046
<65 y	106	5.3	3.0-7.6				
Sex							
Female	54	3.7	2.8-7.5	.48			
Male	75	4.5	2.3-6.1				
PS							
0 or 1	118	4.5	2.9-6.1	.047	0.49	0.25-0.98	.043
≥2	11	2.2	0.7-3.0				
Lines of chemotherapy							
1 or 2	57	5.3	3.0-7.8	.16			
≥3	72	2.8	2.1-2.0				
BMI							
<18 kg/m^2	9	1.6	0.9-4.5	.62			
≥18 to <25 kg/m^2	86	3.5	2.7-6.1				
≥25 kg/m^2	33	6.1	2.6-8.9				
Albumin							
≥4 g/dl	64	5.6	3.2-7.6	.31			
<4 g/dl	64	2.9	2.0-4.9				
Neutropenia							
Grade 0-2	85	2.6	1.9-3.9	.002			
Grade 3	25	10.3	3.5-22.7		0.37	0.2-0.68	.001
Grade 4	19	4.9	3.2-5.7		0.62	0.34-1.14	.125

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; PS, performance status.

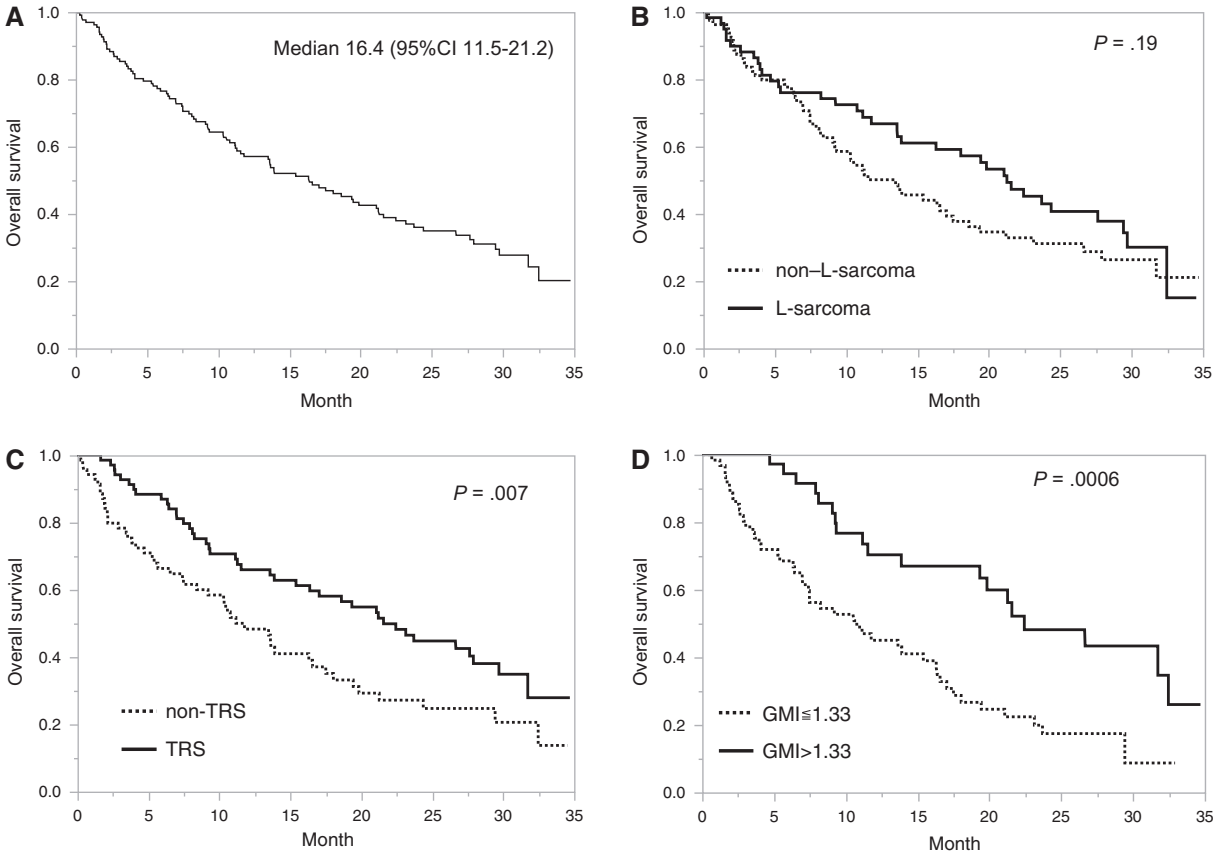

Figure 3. Kaplan-Meier survival curves for overall survival: (A) all 140 patients in the current study, (B) L-sarcoma versus non–L-sarcoma, (C) TRS versus non-TRS, and (D) GMI > 1.33 versus GMI ≤ 1.33. CI indicates confidence interval; GMI, growth modulation index; L-sarcoma, liposarcoma/leiomyosarcoma; TRS, translocation-related sarcoma.

Furthermore, our data are based on the clinical outcomes of an initial dose of 1.2 mg/m^2, which is different from the initial dose in other countries, which use 1.5 mg/m^2. We have found that trabectedin is effective for unresectable and relapsed L-sarcoma and TRS as previously reported; however, there are differences in efficacy among histological subtypes of TRS. Furthermore, the GMI (which allows for intrapatient comparisons) suggests that trabectedin could have possible benefits for patients with DDLS and UPS. Inhibition of tumor progression and extension of OS were equivalent to those in previous clinical trials. In addition, the number of grade 3 or higher adverse events and the rate of dose reduction were lower than those in previous reports. Our results indicate that trabectedin at an initial dose of 1.2 mg/m^2 is an effective treatment option for patients with unresectable and relapsed STS.

The median PFS for the entire study cohort was 3.7 months with a 6-month PFS rate of 44%. The benefits for disease control demonstrated in this study were consistent with those of previous studies (Table 6).[6-13] Moreover, these results indicate that an initial dose of 1.2 mg/m^2 can provide benefits in daily clinical practice. As for histological types, the PFS of patients with L-sarcoma and TRS was longer than that of patients with other types. Although patients with MLS benefitted significantly from trabectedin treatment, the PFS of patients with TRS (except for MLS) and non-TRS was not correlated. This result indicates that some histological types of TRS have a poor response to trabectedin. Among TRS cases, 7, 5, and 4 cases of extraskeletal Ewing sarcoma (EES), alveolar soft-part sarcoma (ASPS), and clear cell sarcoma (CSS), respectively, occurred; none achieved long SD, and the GMI of each type was <1.33. In contrast, 16 and 6 cases of SS and SFT, respectively, occurred; a PR plus long SD was achieved in 33.3% and 16.7%, respectively, and the GMI values were 0.93 and 1.58, respectively. Although the number of patients with SFTs was limited, the GMI was similar to that reported previously

TABLE 5. Univariate and Multivariate Analyses of Prognostic Factors for Overall Survival

		Univariate Analysis			Multivariate Analysis		
	No.	Median Survival, mo	95% CI, mo	*P*	HR	95% CI	*P*
Age							
≥65 y	24	11.2	5.4-19.8	.07			
<65 y	115	17.5	11.8-23.1				
Sex							
Female	61	18.0	13.5-21.6	.62			
Male	79	13.9	10.3-23.1				
PS							
0 or 1	128	18.6	13.6-23.1	<.0001			
≥2	12	3.9	1.6-9.3		2.68	1.25-5.78	.01
Lines of chemotherapy							
1 or 2	60	21.6	13.9-27.9	.03			
≥3	80	11.8	7.5-17.5		1.12	0.65-1.94	0.68
BMI							
<18 kg/m^2	10	8.0	0.2-11.5	.02	2.73	1.1-6.76	.03
≥18 to <25 kg/m^2	96	16.6	11.3-21.6		1.09	0.61-1.97	.77
≥25 kg/m^2	34	19.4	10.6-29.7		1		
Albumin							
≥4 g/dl	66	26.7	17.5-32.5	.0001	2.23	1.31-3.78	.003
<4 g/dl	73	9.3	6.3-13.9				
Neutropenia							
Grade 0-2	95	13.5	9.2-18.6	.12			
Grade 3	26	23.7	15.4-NR				
Grade 4	19	24.4	9.1-31.7				
GMI							
>1.33	36	22.4	13.9-32.5	.0006	0.38	0.21-0.66	.0007
≤1.33	62	10.8	7.0-16.3				

Abbreviations: BMI, body mass index; CI, confidence interval; GMI, growth modulation index; HR, hazard ratio; PS, performance status.

(1.49 in 11 cases).[16] These results indicate that trabectedin could have a clinical benefit for those with SFTs. Only 2 patients had mesenchymal chondrosarcoma (MCS), which reportedly responds to trabectedin[17]; the median PFS was 9.1 months, and 1 case achieved long SD. A subgroup analysis of a previous phase 2 study showed no significant benefit of trabectedin in comparison with best supportive care for patients with EES and ASPS,[7] and this is consistent with our results. These results indicate that there were responders (SS, SFT, and MCS) and nonresponders (EES and ASPS) to trabectedin among the patients with TRS. We also observed prolonged PFS for those with DDLS (36.4%) or UPS (42.9%) and a GMI > 1.33. UPS is an aggressive and relatively chemoresistant tumor; therefore, the result could be helpful in selecting better chemotherapeutic agents for this histological type. However, the GMI is a preliminary variable used in evaluating the efficacy of a chemotherapeutic agent, and the PFS of patients with UPS and DDLS was relatively short (1.3 and 3.7 months, respectively). Therefore, further analysis is required to clarify the clinical benefit of trabectedin in patients with UPS and DDLS. Although these results support drug selection depending on histological types, differences in the efficacy of trabectedin were observed among the same histological types. Previous reports indicated that high activity of nuclear excision repair genes, including *ERCC1* and *ERCC5*, and low activity of the *BRCA* gene were associated with better PFS and OS after trabectedin treatment.[18] Therefore, a combination of histological types and biomarkers for drug response could be helpful for selecting candidates for trabectedin treatment.

In our study, 19% of the patients experienced grade 3 neutropenia, and 14% experienced grade 4. Prophylactic use of pegfilgrastim was considered by each physician according to the risk factors of each patient (eg, age >65 years and comorbidity profile) and according to the guideline in Japan because the risk of febrile neutropenia associated with trabectedin is approximately 15%. In our study, pegfilgrastim was used for 20 patients: 11 patients during the first course and 9 patients after an episode of severe myelosuppression during the prior course of trabectedin treatment. Interestingly, grade 3 neutropenia but not grade 4 neutropenia during trabectedin treatment was significantly associated with better PFS. In many cancer types, grade 3/4 neutropenia is associated with increased survival.[19] Although neutropenia during chemotherapy could be influenced by the pretreatment neutrophil count,[20] as shown in our cases, this result indicates that

TABLE 6. Comparison of the Results of Trabectedin Treatment for Unresectable and Relapsed STS

Study Design	Country	No. of Patients	Histology	L-Sarcoma, %	PFS, mo	ORR, %	6-mo PFR, %	Recommended Initial Dose	Dose Reduction, %	Cycle Median	Hepatotoxicity (Grade 3/4), %		Neutropenia, %		CK Increase (>Grade 3), %
											AST	ALT	Grade 3	Grade 4	
This study	Japan	140	Advanced STS	42	3.7	7.9	44	1.2 mg/m^2, 24 h	7.9	3		37.8	19	14	3.6
Phase 2	United States	36	Advanced STS	64	1.7	8	NA	1.5 mg/m^2, 24 h	14	2	23.3	14.6	23	11	3
Phase 2	France	54	Advanced STS	52	1.9	3.7	24	1.5 mg/m^2, 24 h	NA	3	48	57		61	3.7
Phase 2	EORTC	104	Advanced STS	57	3,5	8	29	1.5 mg/m^2, 24 h	34	3	35.3	44.5		52	NA
Phase 2	Japan	39	TRS	NA	5.6	8	44	1.2 mg/m^2, 24 h	19	3	47	33	31	36	6
Phase 3	United States	345	L-sarcoma	100	4.2	9.9	37	1.5 mg/m^2, 24 h	35	4	25	12	21	16	5.3

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CK, creatinine kinase; EORTC, European Organisation for the Research and Treatment of Cancer; L-sarcoma, liposarcoma/leiomyosarcoma; NA, not applicable ORR, objective response rate; PFR, progression-free rate; PFS, progression-free survival; STS, soft-tissue sarcoma; TRS, translocation-related sarcoma.

sufficient drug exposure is important to gain clinical benefits. However, grade 3 neutropenia was not associated with better OS, and we did not evaluate the quality of life. Further investigations to reveal the correlation between severe trabectedin-induced neutropenia in advanced STS cases and survival and quality of life are required.

The median OS was 16.4 months, which is in line with a previous phase 3 study (12.4 months in the trabectedin group).[7] As for the pretreatment conditions of patients, a PS $\geq$ 2, a BMI $<$ 18 kg/m^2, and a serum albumin level $<$ 4 g/dl were unfavorable prognostic factors for OS. Ploner et al[21] also reported 3 or more lines of prior trabectedin to be a poor prognostic factor. Notably, PS, BMI, and serum albumin reflect a patient's condition, and more advanced cases usually have worse PS, BMI, and serum albumin. In contrast, a GMI $>$ 1.33 was the most significant favorable prognostic factor for OS. This result is supported by the findings of Sanctis et al, who found that a GMI $>$ 1.33 was associated with significantly improved OS.[15,22] Therefore, the growth-inhibitory effect of trabectedin may have a significant impact on longer patient survival.

In our cases with an initial dose of 1.2 mg/m^2, grade 3 or higher adverse events, including hepatotoxicity and neutropenia, were fewer in comparison with extensive previous phase 2 and 3 studies (Table 6). Notably, this study was retrospective and depended on spontaneous reporting; therefore, low-grade adverse events might have been underreported. However, the main purpose of PMS is to survey adverse events, and hepatotoxicity, neutropenia, and rhabdomyolysis were included as key elements. Thus, our results of adverse events could be reliable and comparable with those of previous phase 2 and 3 studies. Furthermore, the rate of dose reduction was 7.9%, which is less than half of other reports. Most adverse events leading to dose reductions were hepatotoxicities, and this is consistent with other reports.[11,13,16] The hepatoprotective effect of dexamethasone has been reported,[23] and most of our cases were treated with 16.5 mg of dexamethasone. Thus, an initial trabectedin dose of 1.2 mg/m^2 and sufficient premedication with dexamethasone reduced hepatotoxicity and lowered the rate of dose reduction, and this resulted in good tolerability of trabectedin.

Rhabdomyolysis is a devastating adverse event of trabectedin, but its risk factors have not been reported. However, the CART analysis revealed that the high-risk group had a combination of tall body height ($\geq$170.3 cm) and young age ($<$32 years). The reason for the high rate of rhabdomyolysis or CK elevation (grade 3 or higher) in these patients is unclear. A lot of other factors, including

the pharmacokinetics of the drug and any other concomitant drugs, could be related to rhabdomyolysis. Therefore, further analysis using a larger sample size is needed to verify this result. More precise periodic monitoring of creatine phosphokinase and symptoms such as muscle pain and fatigue are recommended for timely intervention in high-risk patients.

This study had some limitations. The small number of patients limited the analysis of the association between different histological types and clinical outcomes. The retrospective design made comparisons with previous clinical trials difficult because the eligibility criteria and follow-up procedures may differ from this study. Furthermore, the scheduled time points for tumor evaluations, dose reductions, and treatment delays depended on the physician's decision. The GMI was influenced by the frequency of response assessment in the daily clinical practice of each institution or each physician. We used RECIST criteria only for tumor responses not based on the Choi criteria, which are preferable to RECIST to prevent misdiagnoses in tumor progression evaluations after trabectedin treatement.[24] Despite these limitations, this study based on PMS data is representative of the general population because it included patients with a variety of medical conditions, and the results could support daily clinical decision making.

In conclusion, we have confirmed that trabectedin is effective and that its effectiveness depends on the histological types of STS. L-sarcoma and TRS are expected to have a good response to trabectedin, as reported previously, and MLS, SS, SFT, and MCS are responsive; however, ASPS, EES, and clear cell sarcoma were unresponsive to trabectedin among TRS cases. In addition, trabectedin could possibly be clinically beneficial for patients with DDLS and UPS, but further investigation is warranted. Our data revealed that initial trabectedin at a dose of 1.2 mg/m^2 led to fewer adverse events in comparison with previous clinical trials using 1.5 mg/m^2; however, the efficacy was identical. Moreover, this dose setting is favorable for patients with unresectable and relapsed STS.

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AUTHOR CONTRIBUTIONS

Hiroshi Kobayashi: Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing–original draft, and visualization. **Shintaro Iwata:** Resources and writing–review and editing. **Toru Wakamatsu:** Resources and writing–review and editing. **Keiko Hayakawa:** Resources and writing–review and editing. **Tsukasa Yonemoto:** Resources and writing–review and editing. **Junji Wasa:** Resources and writing–review and editing. **Hiroyuki Oka:** Methodology, software, formal analysis, and data curation. **Takafumi Ueda:** Conceptualization, methodology, writing–review and editing, supervision, and project administration. **Sakae Tanaka:** Writing–review and editing, supervision, and project administration.

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