

CASE SERIES

Four Cases with FUS/CHOP Fusion Gene Products Positive Myxoid Liposarcoma Responding Effectively to Trabectedin Monotherapy

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Background: Myxoid liposarcoma, a rare type of tumor, accounts for approximately 30% of all liposarcomas. Myxoid liposarcomas harboring the FUS/CHOP fusion gene have shown promising results with trabectedin in basic research and some clinical experiments. However, the efficacy and safety of trabectedin in chemotherapy-naive soft tissue sarcomas or FUS/CHOP fusion gene-positive myxoid liposarcomas have not yet been established. Therefore, we evaluated the effectiveness and safety of trabectedin monotherapy in four cases of myxoid liposarcoma harboring the FUS/CHOP fusion gene at our hospital.

Patients and Methods: We analyzed four patients with metastatic myxoid liposarcoma who underwent surgery at Okayama University and received chemotherapy at Kawasaki Medical School. These patients had positive test results for the FUS/CHOP fusion gene as an aid to pathological diagnosis by RT-PCR. RNA was extracted from tumor tissue sliced from frozen tumor specimens. Following reverse transcription, PCR was performed using TLS/FUS-CHOP primers. The resulting products were electrophoresed, and then the nucleotide sequences were confirmed.

Case Presentation: Case 1: A 44-year-old male started trabectedin as second-line therapy after initial chemotherapy, which included doxorubicin. To date, he has completed 9 cycles, showing a response for 6 months. Case 2: A 71-year-old male, deemed intolerant to doxorubicin, started trabectedin as his first-line treatment. He has undergone 50 cycles to date, maintaining a response for 56 months. Case 3: A 59-year-old female began trabectedin as second-line therapy after initial chemotherapy, including doxorubicin. She responded for 6 months before experiencing disease progression. Case 4: A 79-year-old male developed new lesions after one course of initial chemotherapy, including doxorubicin. He then began trabectedin and has maintained a response for 10 months to date.

Conclusion: Compared to other chemotherapies, trabectedin demonstrated potentially higher efficacy and a favorable safety profile for patients with myxoid liposarcoma harboring the FUS/CHOP fusion gene.

Keywords: Trabectedin mono-therapy, efficacy, toxicity, myxoid liposarcoma

Introduction

Myxoid liposarcoma accounts for about 30% of liposarcomas,¹ which are rare cancers with an incidence rate of six or fewer cases per 100,000 people per year.² On the other hand, the FUS/CHOP fusion gene is formed by the translocation of the FUS gene located on the short arm of chromosome 16 (16p11.2) and the CHOP gene located on the long arm of chromosome 12 (12q13.3). The FUS/CHOP fusion gene products are presumed to be strongly associated with the development of myxoid liposarcoma as a tumor-specific transcription factor.³ Among human soft tissue malignancies,

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approximately 95% of patients with myxoid liposarcoma, which commonly occurs in adults, are positive for the FUS/ CHOP fusion gene.4

Several reports suggest that trabectedin is expected to be effective against myxoid liposarcoma with the FUS/CHOP fusion gene, based on basic research into its mechanism of action.^{5–8} Currently, it is used as a salvage chemotherapy after initial treatment, including doxorubicin, worldwide. However, the role of trabectedin in the actual clinical treatment of untreated myxoid liposarcoma has not yet been established. Since prospective clinical trials for rare diseases are challenging, it is meaningful to review and compile data on prognosis, safety, and efficacy from existing cases. Therefore, we examined and reported the efficacy and safety of trabectedin monotherapy in four patients with myxoid liposarcoma harboring the FUS/CHOP fusion gene at our hospital.

Materials and Methods

Patients

We analyzed four patients with metastatic myxoid liposarcoma who underwent surgery at the Department of Medical Materials for Musculoskeletal Reconstruction, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and received chemotherapy at the Department of General Internal Medicine 4, Kawasaki Medical School. The status of the FUS/CHOP fusion gene was confirmed using RT-PCR at Okayama University, and it was positive in all four cases.

Detection of FUS/CHOP Fusion Gene

The detection of the FUS/CHOP fusion gene was performed as follows: RNA was extracted from tumor tissue sliced from frozen tumor specimens. Following reverse transcription, PCR was performed using TLS/FUS-CHOP primers. The resulting products were electrophoresed on a polyacrylamide gel, where bands were detected. The bands were excised, cloned, and the nucleotide sequences were confirmed.

Case Presentation

Case I

A 44-year-old male noticed a mass in his right thigh around 2012. The mass gradually increased in size, and in 2017, he consulted a local physician. A magnetic resonance imaging (MRI) scan suggested liposarcoma, and he was referred to the department of orthopedic surgery at another hospital. A needle biopsy and incisional biopsy diagnosed myxoid liposarcoma, and wide excision surgery was performed. In April 2021, a computed tomography (CT) scan suggested metastasis to the left thigh, and MRI revealed multiple bone metastases (C7 vertebra, right ilium, and left femur). Initial chemotherapy, including doxorubicin, was administered starting in June 2021, and after six cycles, progressive disease (PD) was confirmed. The patient was positive for the FUS/CHOP fusion gene products, and trabectedin was initiated as a second-line therapy. After four cycles, partial response (PR) was achieved, and to date, nine cycles have been administered, maintaining efficacy for 9 months. (Figure 1)



Figure I Changes in imaging of Case I patient before and after trabectedin administration (Chest CT) The pulmonary metastasis showed a significant reduction after nine cycles of trabectedin monotherapy compared to the findings of pre-treatment.

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Case 2

A 71-year-old male was suspected of having a tumor in the left thigh, and was referred to the department of orthopedic surgery at another hospital in September 2017. A pathological examination by needle biopsy led to a diagnosis of myxoid liposarcoma. Preoperative radiation therapy and wide excision surgery were performed in January 2018. However, metastasis to the right thigh was observed 4 months later, and another surgery was performed in May 2018. In June 2018, a CT scan revealed a small nodule about 1 mm in the right buttock, which gradually increased in size. In November 2018, metastases appeared in the left gluteus medius muscle, and contrast-enhanced CT revealed further metastases around the left retroperitoneal gallbladder and left axillary lymph nodes. Curative reoperation was deemed impossible, and the patient was referred to our department in November 2018 for systemic chemotherapy. Due to decreased cardiac function and intolerance to doxorubicin, and because of FUS/CHOP fusion gene positivity, trabectedin was selected as the initial chemotherapy. Adverse events included grade 2 nausea and vomiting and grade 3 neutropenia. The patient obtained stable disease (SD) up to six cycles and PR after eight cycles. To date, 50 cycles have been administered, maintaining efficacy for 56 months (Figure 2).

Case 3

A 59-year-old female noticed an enlarging nodule in the groin area in 2019 and consulted a local physician. Initially, she was placed under observation, but in March 2020, the nodule showed further enlargement, and she was referred to the department of orthopedic surgery at another hospital. After further examinations, including abdominal CT and needle biopsy, she was diagnosed with primary retroperitoneal myxoid liposarcoma with inguinal lymph node metastasis.

Initial chemotherapy, including doxorubicin, was started in April 2020. After three courses of initial chemotherapy, heavy ion radiotherapy was added. However, in August 2021, a new metastatic lesion was found in the lumbosacral spine, and local therapy with stereotactic radiotherapy was added, temporarily controlling the disease. Eight months later, both the primary and metastatic lesions showed progression again. It was determined that local therapy alone was insufficient for disease control, and she was referred to our department for chemotherapy. Due to FUS/CHOP fusion gene positivity, trabectedin was started as second-line chemotherapy. Eight cycles of chemotherapy were administered, maintaining SD and efficacy for 6 months (Figure 3).

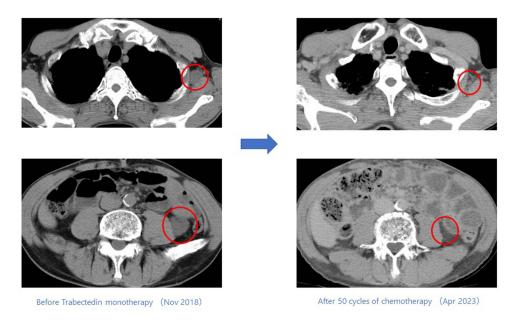


Figure 2 Changes in imaging of Case 2 patient before and after trabectedin administration (Chest and abdominal CT) Metastatic site of left axillary lymph node and retroperitoneal metastasis showed a complete remission after 50 cycles of trabectedin monotherapy compared to the findings of pre-treatment.

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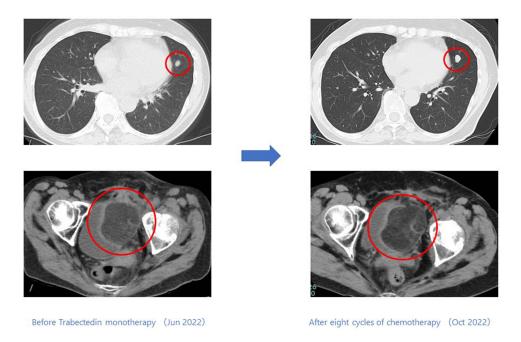


Figure 3 Changes in imaging of Case 3 patient before and after trabectedin administration (Chest and abdominal CT) Metastatic site of lung and primary site of retroperitoneal lesion showed a stable disease with slight increase after eight cycles of trabectedin monotherapy compared to the findings of pre-treatment.

Case 4

A 79-year-old male presented with right knee joint pain in April 2021 and consulted a local physician. MRI revealed a mass in the right thigh, and he was referred to the department of orthopedic surgery at another hospital in August 2021. A needle biopsy of the mass in the right thigh pathologically diagnosed myxoid liposarcoma. Preoperative radiotherapy was administered, followed by wide excision and intramedullary nailing in December 2021.

Four months later, in April 2022, chest and abdominal CT images confirmed metastatic recurrence in the right retroperitoneum, and MRI showed multiple bone metastases. The patient was referred to our department for chemotherapy in August 2022.

Initial chemotherapy, including doxorubicin, was administered, but new lesions appeared after just one cycle. Due to the positivity of the FUS/CHOP fusion gene products, trabected in was initiated as second-line therapy. After four cycles of trabectedin, PR was achieved. Although 11 cycles of trabectedin monotherapy had been administered to date, CT image showed that while the retroperitoneal lesions had further shrunk, the chest wall lesions had exacerbated again. (Figure 4)

Patient's background characteristics were shown in Table 1. The ages of the patients ranged from 44-year-old to 79year-old, with three males and one female. The primary sites were the extremities in three cases and the retroperitoneum in one case, and all cases had undergone surgery or radiation therapy, or both. Chemotherapy with trabectedin was administered as the first-line chemotherapy in one case with cardiac dysfunction caused by myocardial infarction, but in the other three cases, it was administered as the second-line salvage chemotherapy after an initial anthracycline containing regimen. All cases had evaluable lesions, and the presence of the FUS/CHOP fusion gene product was confirmed using reverse transcription-polymerase chain reaction (RT-PCR) method in all cases.

Discussion

Among the four cases with myxoid liposarcoma harboring FUS/CHOP fusion gene product treated with trabectedin monotherapy, three showed significant tumor reduction and achieved PR. Additionally, these three cases exhibited a delayed response, and the one case that has shown SD so far may potentially show further therapeutic effects in the future. Considering that the response rate of trabectedin in the past clinical trials targeting fusion gene-positive soft tissue sarcoma, or so called L-sarcomas (liposarcoma or leiomyosarcoma) was 5.6–8%, 10–12 the fact that three out of four cases Dovepress Kirishi et al

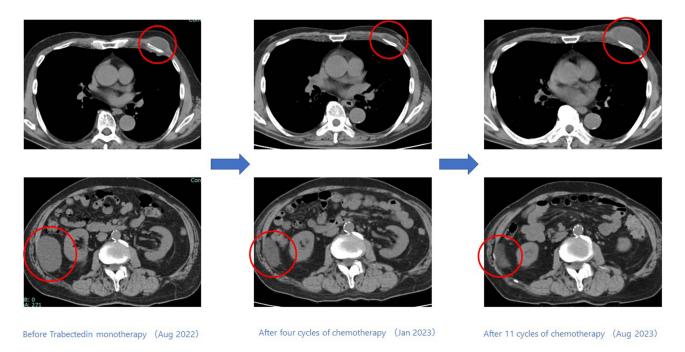


Figure 4 Changes in imaging of Case 4 patient before and after trabectedin administration (Chest and abdominal CT) Metastatic site of left chest wall and retroperitoneal metastatic lesion showed a partial response after four cycles of trabectedin monotherapy compared to the findings of pre-treatment. After 11 cycles of chemotherapy, CT image showed that while the retroperitoneal lesions had further shrunk, the chest wall lesions had exacerbated again, leading to an overall assessment to be disease progression.

in this study showed a clear tumor reduction suggests that the response rate of trabectedin in patients with FUS/CHOP fusion gene-positive myxoid liposarcoma might be considerably high. A Phase II trial had been conducted targeting only pre-treated patients with myxoid liposarcoma in past. This study demonstrated remarkably good results, with a response rate of 51%, including two cases of complete response (CR). Unfortunately, testing for the FUS/CHOP fusion gene was performed in only 64.7% (33/51) of the patients. Consequently, no definitive conclusions can be drawn regarding the relationship between the presence of the FUS/CHOP fusion gene and the superior efficacy of trabectedin. On the other hand, preclinical studies have suggested that trabectedin may have particularly strong efficacy in patients with myxoid liposarcoma harboring the FUS/CHOP chromosomal translocation. The specific mechanism of its antitumor effect are hypothesized to be twofold: first, trabectedin binds to DNA and alkylates the N2 position of guanine, thereby damaging the transcription-coupled nucleotide excision repair complex and promoting the degradation of RNA polymerase II,

Table I Characteristics of All Four Patients

Patient's number	Age	Sex	Primary site	Operation	Radiation	Treatment line	Metastatic site	FUS/CHOP fusion gene products
1	44	М	Rt thigh	(+)	(-)	Second line	Lung, Lt thigh, Bone	Positive
2	71	М	Lt thigh	(+)	(-)	First line	Lt axillary LN, Subcutaneous tissue Lt gluteus medius muscle, Retroperitoneum	Positive
3	59	F	Retroperitoneum	(-)	(+)	Second line	Lung, Inguinal LN	Positive
4	79	М	Rt thigh	(+)	(+)	Second line	Retroperitoneum, Bone, Chest wall	Positive

Abbreviation: LN, Lymph node.

G4

G2

G2

Patient's number **AST/ALT** increased Neutropenia **Thrombocytopenia A**nemia Nausea/ **Vomiting** G3 G١ G4 G4 G3 2 GΙ GΙ G2 G2 3 G3 G2

Table 2 Toxicity Profile of Trabectedin Monotherapy

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leading to the collapse of the DNA double helix;^{5,6,14} second, trabectedin inhibits the transcription factor activity of the FUS/CHOP fusion gene products, efficiently regulating the expression of cancer-related genes under its control.⁶

G١

Among past clinical studies, Kawai et al reported the results toward the antitumor effect of trabectedin in patients with fusion gene-positive soft tissue sarcomas that could act as oncogene drivers. In their study, the overall response rate to trabectedin in patients with translocation-related sarcomas was 8% (3/37), and progression-free survival was 5.6 months. When limited to the patients with myxoid round cell liposarcoma, the response rate was elevated to 21% (3/14), and the progression-free survival was 7.3 months, showing a favorable trend. Although it is unclear how many patients with myxoid round cell liposarcoma were positive for the FUS-CHOP fusion gene in their study, we consider this result to support the findings from our case studies. However, it is regrettable that myxoid liposarcoma and myxoid round cell liposarcoma are examined on almost the same level. Although it is assumed that the patients who achieved PR according to RECIST criteria were all myxoid round cell liposarcoma patients, this is not clearly described in their study.

Due to its rarity, large-scale clinical trials targeting myxoid liposarcoma harboring FUS/CHOP fusion gene have not been conducted to date, and unfortunately, the clinical efficacy of trabectedin toward these patients has not been demonstrated by the results of large-scale clinical study.

As a new approach, a European group has reported a phase II clinical trial that added surgery after a combination of radiotherapy and chemotherapy. ¹⁵ Although they were non-randomized clinical trials targeting resectable cases, they demonstrated favorable anti-tumor effects, suggesting that trabectedin could be incorporated into multimodal therapy. However, the result is not enough for a large-scale clinical trial, and outcomes from future studies are eagerly anticipated.

Therefore, we report the clinical course of four cases of myxoid liposarcoma with confirmed FUS/CHOP fusion gene products as a case series. All cases showed favorable antitumor effects with minimal toxicity within durable range, (Table 2 and Figure 5) and we believe that the use of trabectedin should be actively considered in patients with FUS/

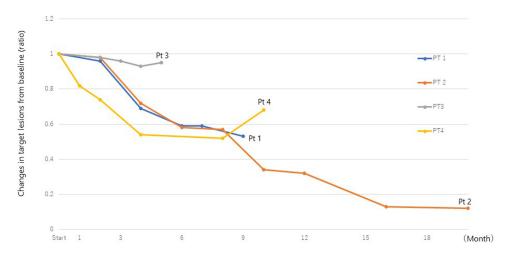


Figure 5 The anti-tumor effects of all four patients up to 20 months using a spider plot all four cases showed favorable antitumor effects by trabectedin monotherapy. The maximum effect was observed with partial remission in 3 out of 4 cases, and stable disease in 1 case. Additionally, all three cases that achieved partial remission demonstrated a duration of effect lasting over eight months, and one case achieved complete remission after undergoing up to 50 cycles of treatment (Pt2).

Abbreviations: Pt, patient.

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CHOP fusion gene-positive myxoid liposarcoma. Nevertheless, there are issues related to the diagnostic methods and costs for FUS/CHOP chromosomal translocation, and generally, FUS (TLS)-DDIT3 (CHOP) mRNA analysis using RT-PCR is used as a substitute for diagnosing FUS/CHOP chromosomal translocation. In our study, we judged FUS/CHOP fusion gene positivity based on the detection of mRNA, which was the FUS/CHOP fusion gene product, but it is possible that these testing methods may influence the results of clinical efficacy, requiring cautious handling in future investigations.

When trabectedin is used for malignant soft tissue tumors, it has been reported that there is some delay in the emergence of clinical effect in cases of good response, and that the effect persists for a long duration, which is not seen with other drugs such as eribulin, and pazopanib. As described above, a delayed response was observed in three out of four cases, and long-term persistence of effects over 8 months was observed in three out of four cases, (Figure 5) suggesting that this clinical course may be due to the diverse mechanisms of action of trabectedin in patients with FUS/CHOP chromosomal translocation-positive myxoid liposarcoma.

Recent basic research conducted by an Italian group has revealed that trabectedin acts primarily as a transcriptional regulator. In addition, trabectedin regulates the transcription of 4883 genes involved in processes that sustain adipocyte differentiation. Genomic analysis has also shown that prolonged trabectedin treatment leads to the loss of cytobands 4p15.2, 4p16.3, and 17q21.3, which results in drug resistance. These findings elucidate the complex mechanism of action of trabectedin and provide a foundation for developing novel combinatorial therapies to overcome the drug resistance.¹⁷

Despite many problems, the prognosis of patients with myxoid liposarcoma may be influenced by the presence of the FUS/CHOP fusion gene, and large-scale clinical trials are expected to contribute to improving the prognosis of the patients with myxoid liposarcoma harboring FUS/CHOP chromosomal translocation in the future.

Conclusions

In the four cases of myxoid liposarcoma, we encountered, all were positive for the FUS/CHOP fusion gene products. All four patients were hospitalized during the administration of trabectedin to reduce the risk of subcutaneous extravasation, and no serious adverse events occurred. A relatively long period of response was achieved, and it was considered that the efficacy and safety could be expected, compared to other treatment methods. Prospective large-scale clinical trials for the patients with myxoid liposarcoma harboring FUS/CHOP fusion gene are expected to contribute to improving their prognosis in the future.

Data Sharing Statement

The datasets supporting the conclusions are included within this article.

Ethics Approval Consent to Participate

This study was approved by the Ethics Committee of the Kawaski Medical School and was conducted in accordance with the Declaration of Helsinki principles. All patients provided written informed consent.

Consent for Publication

Four patients provided written informed consent for their case details to be published and the institutional approval of the Kawasaki Medical School was obtained for this study. (No 6284-00)

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Author Contributions

Hirohito Kirishi and Hiromichi Yamane planned this study. Ayaka Mimura, Yoko Kosaka, Naruhiko Ichiyama, Tatsuyuki Kawahara, Yasunari Nagasaki, and Hidekazu Nakanishi were involved in collecting clinical data from medical records. Nobuaki Ochi, and Hiromichi Yamane analyzed the data. Hiromichi Yamane, Toshiyuki Kunisada and Nagio Takigawa wrote and revised the paper.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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