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Desmoid with biweekly methotrexate and vinblastine shows similar effects to weekly administration: A phase II clinical trial

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Abstract

Low-dose methotrexate (MTX) plus vinblastine (VBL) chemotherapy is an effective treatment for desmoid-type fibromatosis (DF). However, previous reports have described a weekly regimen, with no reports available on a biweekly one. The aim of this study was to determine the clinical outcomes of a biweekly regimen in a cohort prospectively treated in our single institution. Since 2010, we have prospectively treated refractory DF patients with biweekly MTX (30 mg/m^2) + VBL (6 mg/m^2). Efficacy, progression-free survival (PFS), and correlating factors were analyzed. Adverse events (AEs) were recorded. In total, 38 patients received low-dose MTX + VBL therapy, and its efficacy was assessed in 37 of them. Nineteen (51%) patients showed partial response (PR). Clinical benefit rate was 95%. PFS at 5 y was 80.8%. In PR cases, median time to response was 10 mo. Longer duration of therapy was significantly associated with the response of PR (P = .007) by univariate analysis. There was no clear association between various clinicopathological factors, including tumor size, location, catenin beta-1 (*CTNNB1*) mutation status with effect. Only 3 AEs of grade 3/4 were observed. Tumor regrowth after MTX + VBL discontinuation was observed in 5 (20%) of 25 patients. Biweekly administration of MTX + VBL chemotherapy was well tolerated compared with weekly administration, and its efficacy was anticipated in DF patents, although the time needed to achieve a response may be relatively long. The treatment interval should be determined taking into account both the condition of the tumor and the patient's preference.

KEYWORDS

biweekly, clinical benefit rate, desmoid, methotrexate, vinblastine

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; APC, adenomatous polyposis coli; AST, aspartate aminotransferase; CBR, clinical benefit rate; CR, complete response; CT, computed tomography; DF, desmoid-type fibromatosis; ECOG, Eastern Cooperative Oncology Group; FAP, familial adenomatous polyposis; HR, hazard ratio; MRI, magnetic resonance imaging; MTX, methotrexate; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID, nonsteroidal anti-inflammatory drug; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; ROM, range of motion; SD, stable disease; VBL, vinblastine; WHO, World Health Organization.

UMIN Clinical Trials Registration Number: UMIN000019337

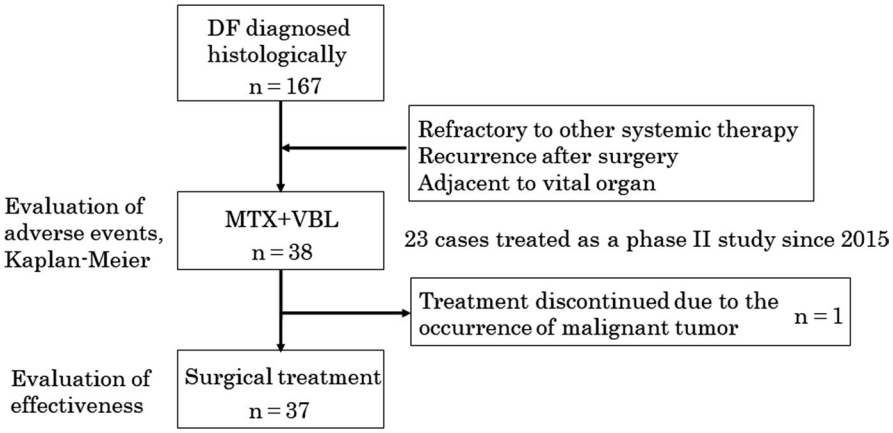

FIGURE 1 Flowchart for the inclusion of patients with methotrexate plus vinblastine (MTX + VBL) chemotherapy in the present study

1 | INTRODUCTION

DF is a slowly growing, proliferation of monoclonal fibroblast-like cells. It is defined by the WHO as a locally aggressive, intermediate soft tissue tumor, but does not metastasize. The incidence of DF is low, ranging from 2 to 4 per million people annually, mainly in the age group of 15-60 y.[1,2] The treatment modality for DF has shifted from extensive resection with wide surgical margin to conservative treatment based on a wait-and-see policy.[3-5] An initial "active surveillance" approach was recommended also by the management guideline for DF based on a global consensus meeting held by experts from Europe, North America, and Japan regarding DF practice.[6]

DF is not controlled in all patients for whom the wait-and-see policy has been selected. Recent reports have reported a control rate of 60%-90% with wait and see,[7,8] but it was poorer at 27% in the young cohort.[9] Such patients require effective systemic treatment. Methotrexate (MTX) and vinblastine (VBL) chemotherapy is an effective treatment for DF. Most of the past studies using MTX + VBL for DF have adopted a weekly regimen, and major side effects have been reported.[10-13]

The treatment modality in our institution has been shifted since 2003 from surgery with wide operative margin to conservative treatment, with meloxicam, which is a nonsteroidal anti-inflammatory drug (NSAID) and a selective COX-2 inhibitor.[5] Patients with abdominal wall lesions, those with non-S45F mutations and non-limb locations, and those with paralysis or limited ROM unable to wait for the effects of drug treatment to be obtained, are considered for surgery with marginal resection.[14] Treatment results with meloxicam were initially favorable[15], however the number of patients with PD gradually increased, necessitating a switch to a more effective subsequent treatment. Since March 2010 we have prospectively treated patients refractory to meloxicam treatment with low-dose MTX + VBL chemotherapy.[16] Initially, MTX + VBL was administered weekly in accordance with the overseas regimen.[10,12,17] However, the first 2 patients had intolerable side effects (grade 4 neutropenia, grade 2 anemia, or grade 2 alanine/aspartate aminotransferase (ALT/AST) increase), and so we decided to treat subsequent patients with a regimen of MTX + VBL biweekly. We previously reported the efficacy and side effects of MTX plus VBL chemotherapy as a pilot study.[16] The cohort was composed of only 15 patients, and factors correlated with efficacy were not analyzed with statistically sophisticated methods. Subsequently we have been prospectively administering MTX + VBL to DF at 2-wk intervals to reduce the incidence/severity of side effects and increase tolerability as a phase II clinical study.

In this study, we reported the results of this phase II, non-randomized, single arm study in combination with the results of a previous cohort. The primary endpoint was to report the response rate, and the secondary endpoint was safety of the initial biweekly regimen of MTX + VBL, as compared with the weekly regimen documented in previous studies. In the past, analysis of factors related to the clinical outcomes of MTX + VBL treatment has been scarcely performed. Therefore, the secondary endpoints of this study were to analyze factors, including catenin beta-1 (*CTNNB1*) mutation status, correlating with efficacy (responders), and factors correlating with PFS.

2 | MATERIALS AND METHODS

Since 2003, 167 patients have been diagnosed histologically with DF in our institution. Among them, low-dose MTX + VBL chemotherapy was considered for patients experiencing tumor growth during the wait-and-see period, while being refractory to other medical treatment or with recurrent tumors after surgery in the pre-referral hospital or at our institution. Together, the main 3 reasons for administering low-dose MTX + VBL chemotherapy were: (i) increased DF size, (ii) worsened pain, paralysis, limited ROM, and (iii) proximity to or surrounding vital organs. Radiation therapy has been considered as a treatment option for refractory DF only if it does not respond to various medical treatments. Excluding operative cases[14] and patients who did not consent to low-dose chemotherapy, we administered low-dose MTX + VBL chemotherapy to 38 patients (Figure 1) including 23 patients enrolled in a phase II, non-randomized, single arm study. Azzarelli and colleagues[10] reported, based on the analysis of 30 patients, a 12-mo PFS of approximately 95%. Another report analyzing 26 cases of children

indicated a 12-mo PFS of <60%.[12] Threshold PFS at 12 mo was set at 70%, expected PFS with MTX + VBL at 90%. With a single arm design for MTX + VBL treatment, one-sided alpha level 10%, power of 80%, it was necessary to accumulate at least 21 cases. This sample size was considered an achievable number compared with those (5-30, mean: 21) of previous studies reporting the results of MTX + VBL treatment.[11-13,17-20]

Patient eligibility was as follows: histologically confirmed to have DF, which was not controlled with a wait-and-see policy or meloxicam treatment; aged from 6 (initially) to 75; having a PS of 0 or 1 according to the ECOG, and who had never received MTX and/or VBL. Patients who were intolerant to chemotherapy, did not give informed consent to this therapy were excluded.

Chemotherapy was administered at biweekly intervals at starting doses of MTX 30 mg/m^2 and VBL 6 mg/m^2. If the patient was unable to tolerate the side effects, the interval was extended to once every 3 wk or once every 4 wk instead of reducing the dose. If PR or SD was obtained according to RECIST, version 1.1.[21] We recommended to the patients that their MTX + VBL treatment be discontinued. However, if patients wished to continue chemotherapy, they continued treatment biweekly or once every 3-4 wk. Each once every 2-4 wk administration was considered as 1 cycle of chemotherapy. If the tumor showed PD on MTX + VBL treatment, we discontinued it and considered other options. Parental consent was especially obtained to administer this treatment in the case of a 4-y-old girl younger than the age specified in the initial inclusion criteria. This phase II non-randomized, uncontrolled trial was registered in the UMIN Clinical Trials Registration as UMIN000019337.

In all cases, frozen or formalin fixed paraffin embedded specimens obtained during biopsy or surgery were collected, and stored, and then subjected to DNA isolation and *CTNNB1* mutation analyses by direct sequencing (Sanger method) as previously reported by our institution.[22] Mutational analysis of the *APC* gene was performed in patients suspected of having FAP based on clinical signs.

Basically, tumors were followed-up by MRI without enhancement before and every 3 mo after the start of MTX + VBL chemotherapy. Patients who could not tolerate MRI were evaluated by CT without enhancement. Radiological response was evaluated according to RECIST. CBR was defined as the percentage of patients evaluated as showing CR, PR, or SD. Best response is defined as the best response across all the time points assessed.[21] Response rate was evaluated as a primary endpoint based on best response.

Progression-free survival (PFS), which is one of the most crucial endpoints of MTX + VBL chemotherapy, was defined from the date of treatment start to the time of disease progression with censoring at the last date of follow-up. Patients achieving PR or SD, and discontinuing MTX + VBL chemotherapy, but showing tumor growth and PD during the discontinuation of chemotherapy, were counted as having experienced an event. Safety was assessed in all patients who received at least 1 MTX + VBL chemotherapy session. Severity of AEs was categorized on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.0).

2.1 | Statistical analysis

First, the best obtained response was categorized as CR or PR and SD or PD, and any factors significantly related to the CR or PR groups were analyzed by univariate logistic regression analysis. The factors to be analyzed were limited through a preliminary analysis of multicollinearity to remove strongly correlated factors. Multivariate logistic regression analysis with Firth's penalization was performed to obtain stable estimates of regression coefficients under small sample sizes.

PFS was estimated with the Kaplan-Meier method. Factors for adjustment were gender (male vs female), age in years (<36 y, ≥36), tumor size (<11 cm vs ≥11), location (abdominal wall vs trunk vs neck vs extremity), tumor status (primary vs recurrent), treatment duration (<18 vs >18 mo), or treatment cycles (<28 cycles vs ≥28 cycles). Cox proportional hazards models with these factors as covariates were used to estimate HRs to analyze for significance of the timing of events.

We focused on cases showing PR, and analyzed whether various clinicopathological factors were related to the period until showing PR as the best response. A survival analysis was performed with PR as the event, and subjected to univariate and multivariate Cox regression analyses. All statistical analyses were performed using R version 3.5.1 software.

3 | RESULTS

3.1 | Patient characteristics

Some demographic features of the patients receiving MTX + VBL chemotherapy are listed in Table 1. Thirteen patients are male and 25 are female. In 33 of 38 patients, PD was confirmed before MTX + VBL treatment. In the other 5 patients, treatment was started in 3 patients for severe pain, and in 2 patients with tumors close to the critical organ (spinal cord and brachial plexus). One female patient was excluded from the analysis of efficacy because a new malignancy was found shortly after MTX + VBL treatment was started. AEs were evaluated in 38 patients, and the efficacy of MTX + VBL was evaluated in 37 of them (Figure 1). The median age at the start of MTX + VBL was 34 y (mean: 36 y, range: 4-74), and the median maximum diameter of the tumor was 10.5 cm (mean: 11.0 cm, range: 4.2-33.7). Tumors occurred in the head and neck in 8 patients, trunk in 12 patients (2 patients with abdominal cavity were included), abdominal wall in 5 patients, and limbs and limb girdles in 12 patients. There were 28 primary tumors and 9 postoperative recurrent tumors. CTNNB1 analyses revealed that activating mutations were T41A was 17 patients, S45F was 9 patients, S45P was 1 patient, T41I was 1 patient, and wild type (WT) was 6 patients. An APC mutation was observed in 3 patients. Of the 37 patients, 31 (84%) had a gene mutation in the Wnt/β-catenin pathway. Three patients with APC mutation had a family history and/or clinical symptoms of FAP. NSAIDs were used in 32 patients, tranilast in 8

TABLE 1 Characteristics of patients received MTX + VBL chemotherapy

Variables	Category	Total number
Gender	Male	13 (35%)
	Female	24 (65%)
Age	Median (range)	34 (4-74) y
Location	Neck	8 (22%)
	Trunk	10 (27%)
	Abdominal wall	5 (14%)
	Extremity	12 (32%)
	Mesentery	2 (5%)
Primary	Primary	28 (76%)
	Recurrence	9 (24%)
Tumor size	Median (range)	10.5 (4.2-33.7) cm
CTNNB1	T41A	17 (46%)
	T41I	1 (3%)
	S45F	9 (24%)
	S45P	1 (3%)
	APC	3 (8%)
	WT	6 (16%)
Prior medical treatment[a]	NSAID	32
	Tranilast	8
	Tamoxifen	2
Prior chemotherapy		0
Prior targeted therapy		0
Radiotherapy		0

Abbreviation: APC, adenomatous polyposis coli; CTNNB1, catenin beta-1; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; VBL, vinblastine; WT, wild type.

[a]Duplicate use of NSAID, tranilast, and tamoxifen in some cases.

patients, and tamoxifen in 2 patients as prior medical treatment to MTX + VBL. None of the patients received doxorubicin-based chemotherapy, molecular targeted therapies or radiation therapy before MTX + VBL treatment. No radiotherapy was performed, even after MTX + VBL treatment.

3.2 | Treatment and efficacy

The mean duration of low-dose MTX + VBL chemotherapy was 19 mo (range: 3-64), and the median was 14 mo. The mean number of chemotherapy cycles was 29 (range: 5-111), and the median was 26. The mean and median duration between the start of low-dose MTX + VBL chemotherapy and the last follow-up was 50 and 44 mo, respectively (range: 6-116). Based on the evaluation of 37 patients with RECIST, there were no CR, 19 (51%) patients achieved PR, 16 (43%) patients showed SD, and 2 (5%) had PD. CBR; CR+PR+SD was 95%. Among 19 PR patients, it took a mean of 13 mo and a median of 10 mo to obtain the best response (PR) according to RECIST. Treatment was continued on a biweekly basis, however the interval was extended to every 4 wk after SD was obtained in 10 patients. Clinical data including efficacy of low-dose chemotherapy of MTX and VBL are provided as in Table S1. There was no difference in patient background between the former cohort (n = 15) and the phase II cohort (n = 23) including gender, age, tumor location and size, primary or recurrent tumor, prior medical treatment, and *CTNNB1* mutation status. There was also no statistical difference in the intervention of MTX + VBL treatment and its efficacy between the 2 cohorts (Table S2). The reasons for extending the interval included patient preference in 4 cases, because they lived far away from our institution. Ten patients decided to extend the interval after discussion between the physician and patient after SD/ PR was obtained, and 3 patients because of adverse effects, mainly grade 2 nausea. The dose was reduced to 80% due to nausea in only 2 patients.

In the univariate logistic regression analysis, the sole factor associated with PR group was long treatment duration ($P = .007$). Other factors including *CTNNB1* mutation status, age, tumor size, and location, had no significant association (Table 2). As treatment duration and cycles were shown to be highly correlated (multicollinearity), either of these 2 factors was included in the multivariate models. A multivariate logistic regression analysis with Firth's penalization excluding the factor of cycles showed that treatment duration was the only factor significantly associated with PR with multivariate analysis ($P = .003$, Table S3).

Next, we analyzed the factors related to the time to obtain PR with 19 patients obtaining PR evaluation. Survival analysis was performed with the objective variable as the time until the best response is obtained. In the univariate analysis, location in extremity

TABLE 2 Analysis of the relationship between PR and various factors in the whole population (37 patients) with univariate logistic regression analysis

Variable	OR	Lower CL	Upper CL	*P*-value
Gender (female)	0.86	0.22	3.31	.823
Age[a]	1.02	0.98	1.05	.406
Tumor size[a]	1.00	0.23	4.34	.997
Location[b]				
Trunk	0.67	0.08	5.54	.707
Neck	1.11	0.11	10.9	.928
Extremity	0.48	0.06	3.99	.494
Tumor (recurrent)	0.69	0.15	3.14	.635
CTNNB1 (S45F)	0.93	0.22	3.96	.920
Treatment duration (<18 mo)	0.09	0.02	0.51	.007
Cycles (<28 cycles)	0.32	0.08	1.33	.116

Abbreviations: CL, confidence limits; CTNNB1, catenin beta-1; OR, odds ratio; PR, partial response.

[a]Effect when 1 unit is increased.

[b]Reference category is abdominal wall.

was significantly related to a longer time until PR (P = .013), and there was a tendency for recurrent tumor (P = .059; Table 3).

3.3 | Progression-free survival

Kaplan-Meier survival analysis of all 38 patients showed PFS at 5 y to be 80.8% (Figure 2). The median PFS duration could not be estimated because PFS was approximately 80% at the end, and so did not fall below 50%. No factors were significantly associated with PFS in the univariate Cox regression analysis (Table 4). A multivariate analysis was performed, but results of stable estimation were not obtained, mainly due to the small number of events.

3.4 | Follow-up after treatment discontinuation

MTX + VBL treatment was discontinued in 25 of 37 patients. Twenty patients discontinued treatment because of the evaluation of PR or SD. Four patients preferred not to continue treatment due to side effects, while 1 patient discontinued treatment for pneumonia, which was considered as drug-related one. The pneumonia resolved without major problems, after which the tumor continued to shrink without restarting MTX + VBL. In 25 patients with discontinuation, the median period with MTX + VBL treatment before discontinuation was 14 mo (range: 3-84). The median follow-up period from treatment discontinuation was 21 mo (range; 3-82). During this follow-up, 5 patients (20%) experienced regrowth on RECIST criteria. Two patients had a S45F mutation, 1 patient had an APC mutation, and the other 2 patients had a T41A mutation. In 5 cases of regrowth, 2 received MTX + VBL re-challenge, and both achieved SD status. Two other patients had pazopanib treatment, and the other a wait-and-see modality. Details of 5 cases of regrowth are provided in Table 5.

TABLE 3 Univariate analysis of the time until PR and various factors in 19 patients with PR with Cox regression analysis

Variable	HR[c]	Lower CL	Upper CL	*P*-value
Gender (female)	1.01	0.38	2.66	.987
Age[a]	0.99	0.97	1.01	.386
Tumor size[a]	0.98	0.91	1.04	.462
Location[b]				
Trunk	0.13	0.02	0.74	.022
Neck	0.48	0.11	2.15	.335
Extremity	0.10	0.02	0.62	.013
Tumor (recurrent)	0.30	0.08	1.04	.059
CTNNB1 (S45F)	1.16	0.41	3.33	.779

Abbreviations: CL, confidence limits; CTNNB1, catenin beta-1; HR, Hazard ratio; PR, partial response.

[a]Effect when 1 unit is increased.

[b]Reference category is abdominal wall.

[c]Hazard reaching PR compared with a reference category.

3.5 | Symptomatic relief

Prior to treatment, 29 (78%) of 37 patients had desmoid-derived pain. MTX + VBL treatment reduced or eliminated the pain in 22 of them (76%). Two patients had brachial plexus palsy before MTX + VBL treatment, and in 1 patient the paralysis improved with tumor shrinkage, whereas in the other the tumor size increased and the paralysis worsened. The paralysis was completely resolved with doxorubicin-based chemotherapy. Limitation of the ROM due to DF was found in 15 of 37 patients (41%) at the start of MTX + VBL treatment. MTX + VBL treatment improved the ROM in 5 of 15 patients (33%).

3.6 | Toxicity

Three grade 3 or 4 AEs were observed, including neutropenia, anemia, ALT, and AST elevation. One of them occurred in an initial case with weekly administration. Grade 2 adverse reactions were observed in 10 patients with nausea, anemia and ALT/ AST elevation in 3 patients each (Table S4). Except for pneumonia in 1 patient, none of the adverse effects necessitated the interruption of MTX + VBL chemotherapy.

4 | DISCUSSION

Several studies have reported the results of treatments combining MTX and vinca alkaloids for DF.[10-13,16-18,23-25] The present study, which analyzed the results of 38 patients, is the largest ever using VBL as a vinca alkaloid. In addition, it is important to note that this study used a biweekly regimen, whereas previous reports have been limited to a weekly regimen for basically 6 mo from the start of treatment. It was surmised that the response rate, time to obtain the best response, rate of AEs, durability of response after discontinuation of chemotherapy, and regrowth rate, would differ between the weekly and biweekly dosing regimens.

Response rate and CBR, the primary endpoints of this study, were 51% and 95%, respectively. Palassini et al[18] reported based on 30 patients receiving MTX + VBL therapy that response rate was 50% and CBR 97%. A multi-institutional study in Europe for DF patients with FAP noted a response rate of 54% and CBR of 95%.[25] Efficacy as the best response was almost identical between the weekly and biweekly regimens. It took a median of 10 mo to achieve PR according to RECIST in the present study. Few reports have clearly analyzed the time to response in responders, however Palassini[18] described that median time to response was 6 mo in responders, which is 4 mo shorter than that found in the present study. The biweekly regimen might take longer to obtain a measurable response than the weekly one. However, the important point is that, unlike malignant tumors, even with biweekly regimen, long-term administration might increase the number of patients with PR. In the present study, treatment interval was initially once every 2 wk, but extended to once every 4 wk in not a few cases. The initial biweekly regimen was non-inferior to the weekly one, even if the dosing interval was extended to once every 4 wk.

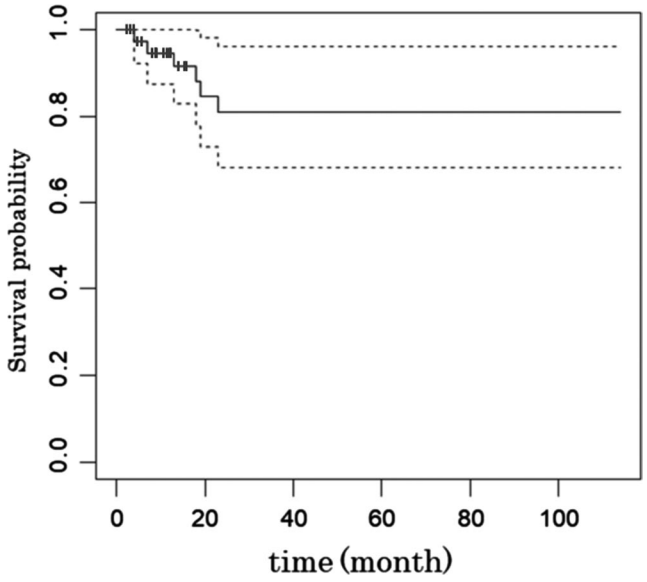

FIGURE 2 Kaplan-Meier survival curve of PFS in all cases (n = 38). Dotted lines represent 95% confidence intervals. In cases with interval extension of methotrexate plus vinblastine (MTX + VBL) chemotherapy, the time points of interval extension are plotted in the graph

TABLE 4 Univariate Cox regression analysis for progression-free survival

Variable	HR	Lower CL	Upper CL	*P*-value
Gender (female)	3.79	0.44	32.8	.226
Age (<36)	4.23	0.49	36.22	.188
Size (<11)	1.26	0.25	6.26	.775
Location[a]				
Trunk	0.48	0.03	7.63	.601
Neck	1.90	0.17	21.07	.603
Extremity	1.10	0.10	12.18	.940
Tumor (recurrent)	0.47	0.05	4.01	.487
CTNNB1 (S45F)	0.44	0.28	8.47	.614

Abbreviations: CL, confidence limits; CTNNB1, catenin beta-1; HR, hazard ratio.

[a]Reference category is abdominal wall.

Further studies are needed on the regimen of MTX + VBL once every 4 wk from the beginning.

A major concern was whether tumors would regrow after MTX + VBL treatment was stopped. Analysis of children reported that 50% had regrowth.[12] In a study of 48 patients (median age: 33 y) with MTX + VNL treatment, 75% had no regrowth at a median follow-up of 38 mo after discontinuation.[23] In another report, 12 (46%) of 26 patients did not experience regrowth.[18] In the present study, during the median follow-up of 21 mo, 20% of discontinuing patients experienced regrowth thereafter. The biweekly regimen had no negative effects on the durability of the response or regrowth rate compared with the weekly regimen.

Our facility used VBL among vinca alkaloids in combination with MTX. The use of VBL, in terms of side effects, did not seem to be as well tolerated as VNL,[23] which is partly attributable to the frequent re-scheduling of MTX + VBL described in previous reports.[10-12,26,27] Palassini et al[18] reported that with a weekly regimen the mean time interval between cycles was prolonged in the large majority of patients. In a recent report, a non-comparative, randomized, phase 2 study also revealed a low rate of tolerability of weekly MTX + VBL treatment. Only 23% of patients completed the planned schedule, and unacceptable AEs were observed in 23%.[13] Especially with weekly administration of MTX + VBL in an Asian cohort, neutropenia of grade 3 or higher was 33.3%, and liver transaminase elevations of all grades were 90.4%, necessitating reduction of the dose intensity.[11] Biweekly administration of MTX + VBL in the present study was associated with few grade 3/4 AEs, and elevated transaminases (all grades) in only 16%, indicating the relative paucity of AEs as compared with a weekly MTX + VBL regimen,[11,13] and an outcome of AEs similar to that with MTX + VNL.[23,25]

The outcome of MTX + VBL treatment in children was reported to be not as good as that in adults. In the phase II trial, the response rate was 19%, which was reported to be worse than that of adults. With weekly administration for children in this study, treatment was discontinued in 12%, mainly for nausea and vomiting.[12] In the present study with biweekly administration, none of the 4 patients under the age of 15 y discontinued the therapy due to side effects.

Previous reports have not described symptomatic relief in detail other than that concerning pain. Three previous studies described that pain was reduced in almost all cases.[11,18,25] In the present study, pain was also reduced or disappeared in 76%, whereas ROM of the involved joint improved in only 33%. This suggests that it is better to start MTX + VBL treatment early in cases with limitation of ROM because this impairment may become irreversible with time.

Due to the small number of cases, there have been few reports on factors that effectively predict the effects of MTX + VBL chemotherapy. Clinical factors including age, gender, tumor size, and location, had no impact on the prediction of efficacy.[24,25] In the present study, we analyzed the clinicopathological factors including CTNNB1 status related to PR as a best response in univariate and multivariate models, despite the inadequate number of cases. In addition, factors correlating with PFS were also examined. Results demonstrated that background factors already determined before treatment (age, gender, tumor size, location, primary/recurrent, *CTNNB1* mutation status) did not predict prognosis of MTX + VBL treatment significantly. Intriguingly, we found that extending the duration of the treatment may enhance the efficacy of this chemotherapy to obtain PR status. These findings suggested that MTX + VBL chemotherapy can be expected to be effective to some extent in any patient, regardless of differences in the background of the tumor, if the duration of treatment was sufficiently long.

Several reports have analyzed the relationship between *CTNNB1* mutation status and surgical outcome, and indicated that patients with S45F mutation had worse outcomes compared with

TABLE 5 Clinical data for patients with regrowth after discontinuation

Case	Sex	Age[a]	Site	CTNNB1 Mutational status	Treatment duration[b] (months)	No. of cycles[c]	Time to recurrence[d] (months)	Treatment after regrowth	Response after regrowth
2	M	43	Chest wall	45F	28[e]	45[e]	7	MTX + VBL	SD
21	F	17	Knee	41A	3	7	10	Pazopanib	PR
27	F	47	Neck	41A	14[e]	27[e]	10	MTX + VBL	SD
32	F	36	Neck (FAP)	APC	12	20	6	Pazopanib	SD
33	F	32	Abdominal wall	45F	13	28	6	Wait and see	PD

Abbreviations: APC, adenomatous polyposis coli; CTNNB1, catenin beta-1; F, female; FAP, familial adenomatous polyposis; M, male; MTX, methotrexate; P/rec, primary/recurrence; PD, progressive disease; PR, partial response; SD, stable disease; VBL, vinblastine.

[a]Age at discontinuation of MTX + VBL.

[b]Treatment duration of initial treatment with MTX + VBL.

[c]Cycle number of MTX and VBL before discontinuation.

[d]Duration from discontinuation of MTX + VBL to recurrence.

[e]Cycle number of MTX + VBL after regrowth not included.

patients with other *CTNNB1* mutation status.[28-31] Conversely, very few studies have reported an association between outcomes of drug treatment and *CTNNB1* mutation status. Hamada et al showed that patients with S45F type were more resistant to meloxicam treatment.[22] In an analysis of patients treated with imatinib, there was a statistically significant difference when comparing patients with S45F mutations vs WT ($P = .05$).[32] A pilot study based on 15 patients receiving MTX + VBL treatment found no apparent relationship between efficacy and *CTNNB1* mutation status, although detailed examination was not possible at that time.[16] The present study proved S45F not to be of prognostic value for MTX + VBL therapy in contrast to that with meloxicam. This is good information to have in advance of MTX + VBL treatment for patients with S45F .

There are several limitations in the present study with a biweekly regimen. Although this report enrolled the largest number of cases so far treated with MTX + VBL, this number is still small. It is not clarified whether dose reduction or interval extension should be selected when patients have SD/PR or have AEs. Considering that patients are mostly in their thirties to forties, interval extension is considered preferable from the viewpoint of their work once SD/PR is obtained. When AEs occur, either should be selected depending on the content and grade. We did not explicitly decide when to discontinue treatment, such as incorporating patient preferences. Improvement of symptoms with MTX + VBL treatment was analyzed, but no quality of life assessment was performed.

In conclusion, the biweekly regimen of MTX + VBL is effective, with fewer side effects, and is reasonably well tolerated. Even considering the prolonged period needed to obtain a response, it is a good regimen to recommend to patients with refractory DF. However, consider a weekly regimen for patients requiring an effect as early as possible.

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ETHICAL CONSIDERATIONS

This study was approved by the ethics committee of Nagoya University Graduate School and School of Medicine (registration number: 2014-0217), and undertaken under the provisions of the Declaration of Helsinki. All of the participating patients or their parents signed informed consent forms.

DATA AVAILABILITY STATEMENT

All relevant data are within the manuscript and its Supporting Information file.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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