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Effect of Tranilast on the Frequency of Invasive Treatment for Extra-Abdominal Desmoid Fibromatosis

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Background: Active surveillance (AS) has been suggested for managing extra-abdominal desmoid fibromatosis (EADF), but a substantial percentage of such patients transitioned to invasive secondary treatments. The anti-keloid medication tranilast is frequently used in Japan but its effectiveness for EADF is not well understood.

Methods: We retrospectively analyzed the medical records of EADF patients treated with tranilast between January 2009 and March 2021. EADF has been reported to shrink spontaneously, so the effects of all drugs must be compared with AS. To assess the effect of tranilast, we compared the clinical courses of patients receiving tranilast with those managed by AS (as identified in a systematic review). A systematic review of AS outcomes was conducted on July 22, 2021, in accordance with PRISMA guidelines. The primary endpoint was rate of conversion to secondary treatment. Secondary endpoints were progression-free survival, objective response rate (ORR), disease control rate (DCR), and adverse events. The rates of conversion to secondary treatment, ORRs, and DCRs were compared between the two groups by using the Fisher exact test.

Results: Eighteen patients who received tranilast as initial treatment for EADF were included. Two patients (11.1%) underwent surgical resection for treatment of tumor growth and persistent pain. The rate of conversion to secondary treatment was significantly lower for tranilast than for a pure AS approach (40.1%; $p = 0.01$). ORR and DCR did not differ between groups.

Conclusions: Tranilast was better than AS for initial management of EADF.

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Key words: desmoid fibromatosis, extra-abdominal desmoid fibromatosis, tranilast, active surveillance

Introduction

Soft tissue tumors are classified as benign or malignant on the basis of their ability to invade surrounding tissues and form distant metastases. Intermediate-malignant tumors include those that recur frequently after resection or present with local symptoms such as pain due to tumor growth. Desmoid fibromatosis (DF) is a soft tissue tumor mainly comprising myofibroblasts and is classified as an intermediate-malignant tumor according to the World Health Organization classification[1]. DF does not cause distant metastases but has a strong tendency for local invasion and local recurrence. Lesions are often tender and may limit patient mobility, especially when located near a joint. The tumor may invade or compress local nerves,

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resulting in neurological symptoms such as numbness, pain, and loss of mobility[2]. Aggressive treatment may be required when clinical symptoms such as localized pain are severe or affect appearance[3,4].

Although surgical resection has long been the first choice for treating DF, 20% to 64% of patients experience recurrence[5,6]. Conversely, even when untreated, tumors may stop growing or even shrink during the natural course of the disease[7–9]. Therefore, in recent years, follow-up by active surveillance (AS) has been recommended for initial management[10,11]. Because of the possibility of natural resolution of the tumor, the efficacy of any drug therapy for DF should be compared with that of AS. During follow-up, secondary intervention is required (1) when the tumor develops and affects surrounding organs, (2) when it begins to cause clinical symptoms, or (3) when it adversely affects the patient's appearance. Secondary treatments are more invasive and include surgical resection, radiotherapy, multi-drug chemotherapy, and molecular targeted therapy. Although this disease has a good prognosis, local invasion is a concern. Because of the high rate of recurrence and associated functional deficits, tumors must be treated as noninvasively as possible. In addition, intra-abdominal desmoid fibromatosis (IADF) associated with familial adenomatous polyposis, a familial disease caused by adenomatous polyposis coli gene mutations, have a poor prognosis[12,13]. Our group defines IADF as tumors arising from connective tissue of the mesentery and retroperitoneum, and extra-abdominal desmoid fibromatosis (EADF) as tumors arising from superficial structures of the trunk, such as the muscular and myoneural structures of the abdominal wall.

Tranilast (N-[3,4-dimethoxycinnamoyl]-anthranilic acid) inhibits fibroblast proliferation and limits transforming growth factor-β-induced collagen synthesis by keloid-derived fibroblasts[14]. In addition, tranilast was found to inhibit fibrosis-promoting growth factors, such as transforming growth factor-β, platelet-derived growth factor, and connective tissue growth factor, and inhibited fibrosis and extracellular matrix hyperplasia[14]. DF and keloids share histological features, such as abnormal growth of fibroblasts and local deposition of abundant collagen fibers. Goto et al. reported that tranilast seemed to be an effective treatment for DF[15]. Tranilast is covered by insurance as a treatment for keloids/hypertrophic scars in Japan, and studies have investigated its general use as a treatment for DF[16,17]; however, no study has examined its use in other countries, perhaps because of the absence of evidence from prospective studies. Furthermore, no study has compared the efficacy of drugs for DF with that of AS, and the evidence is thus insufficient. We investigated the usefulness of tranilast in a large number of patients and describe the limitations of evaluating the results of a retrospective study.

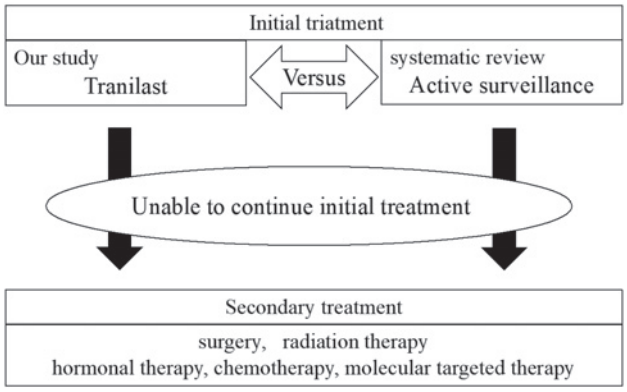

Fig. 1 Overview of the study design.

To evaluate the effectiveness of tranilast as initial treatment, we retrospectively analyzed data from patients with EADF who received tranilast as initial treatment at two centers and compared the findings with data derived from studies of AS.

Materials and Methods

Study Design

This retrospective study evaluated the efficacy of tranilast for initial management of patients with EADF. DF often spontaneously shrinks, and the effect of tranilast should thus be compared with that of AS. However, there were almost no AS cases at our center, so we were unable to compare these two groups. Therefore, a systematic review was performed to compare the clinical efficacy of tranilast with the efficacy of AS to assess the extent to which an actual tumor response and invasive secondary treatment were avoided (**Fig. 1**). Secondary treatment was defined as surgical resection, radiation therapy, or invasive drug therapy (hormonal therapy, chemotherapy, molecular targeted therapy), which have a high incidence of adverse events.

Patient Enrollment

This retrospective study was performed in two centers dealing with bone and soft tissue tumors. We reviewed the records of 34 patients diagnosed as having DF between January 2009 and March 2021. This study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of Yokohama City Univer-

sity Hospital (IRB No. F211200005). Informed consent for treatment was provided orally, but not in written form, by all patients. The selection criteria were as follows: (1) pathologically confirmed DF, (2) tranilast used as initial drug therapy for primary tumor or grossly remaining lesion after the first resection, and (3) at least one follow-up examination within 3 months of treatment initiation. The exclusion criteria were (1) presence of intra-abdominal lesions, (2) initial treatment with anticancer drugs, molecular targeted therapy, antihormonal therapy, or radiotherapy, (3) recurrent tumors, (4) incomplete medical records, and (5) discontinuation of tranilast therapy within 3 months or duration of follow-up less than 3 months. IADF occurring from the mesentery or retroperitoneum was excluded because the clinical course significantly differs because of gastrointestinal symptoms and complications after resection. Therefore, superficial trunk lesions were treated as EADF. The data collected included age, sex, tumor location, tumor size, treatment history, dose of tranilast administered, presence of pain, and combined use of cyclooxygenase (COX) 2 inhibitor therapy.

Treatment and Evaluation

Tranilast was administered orally at an initial dose of 300 mg per day. Routine surveillance was performed via clinical examination and magnetic resonance imaging. Tumor size was assessed at the time of diagnosis and monitored every 3 to 6 months after the start of tranilast treatment, using the same imaging techniques. Tumor size was defined as the longest diameter of the mass that could be measured on any plane. Tumor response was defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[18]. Follow-up was continued at the same intervals after the tumor stopped increasing or began to decrease in size. Measurements were taken by two orthopedic oncologists and all disagreements were resolved through a discussion between these two authors. During follow-up, dates, pain, side effects of medical treatment, and longest tumor diameter were recorded. The primary endpoint was rate of conversion to secondary treatment after starting tranilast. Secondary treatment was defined as invasive treatment such as surgical resection, radiotherapy, and drug therapy, including anticancer drugs, molecular targeted drugs, and hormonal agents. Secondary treatment was selected when tranilast did not resolve tumor growth, when clinical symptoms such as pain worsened, or when the patient had cosmetic concerns. Treatment timing and methods were determined on the basis of the patient's wishes and the recommendations of the attending doctor. The secondary endpoints were progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and drug-related adverse events. ORR was defined as the proportion of patients who achieved CR and PR. DCR was defined as the percentage of patients with no documented disease progression, ie, as the percentage of patients who achieved CR, PR, or SD, excluding PD. Drug-related adverse events were assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0 (CTCAE).

Information Sources and Data Extraction

A literature search was conducted by the authors on July 22, 2021, using PubMed, the Web of Science, and the Cochrane Library. There were no limitations on publication date. The search strategy is shown in **Supplementary Table 1** (https://doi.org/10.1272/jnms.JNMS.2023_90-113). Articles that reported the number of patients who were transitioned to secondary treatment or RECIST evaluation as the outcome of AS for DF were selected and included in this systematic literature review, in accordance with the PRISMA guidelines. The authors cross-referenced studies for which the full text was available to ensure that all relevant articles were included. A flowchart showing the procedure for selecting studies is shown in **Supplementary Table 2** (https://doi.org/10.1272/jnms.JNMS.2023_90-113). For reports that differed from the RECIST assessment but used similar terms, tumor response was categorized according to the RECIST categories. Inability to maintain AS was defined as secondary treatment intervention. Secondary treatment was defined as systemic therapy (hormonal therapy, chemotherapy, and molecular targeted therapy), surgery, or radiation therapy. Use of analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) must be considered separately from basic AS; however, their use was not included as secondary treatment.

Statistical Analysis

All statistical analyses were performed using EZR (R version 2.7.1.; Saitama Medical Center, Jichi Medical University, Saitama, Japan)[19], a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of R commander and is designed to add statistical functions frequently used in biostatistics. The last date for the evaluation of clinical outcomes was March 31, 2021. Estimates of PFS were calculated using the Kaplan-Meier method. Factors that

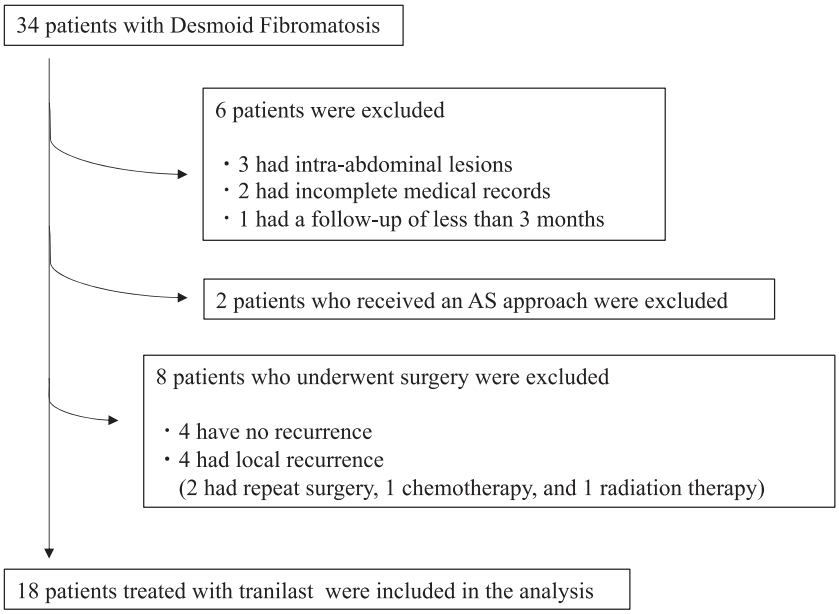

Fig. 2 Flowchart of patient selection.

may be associated with disease progression in DF were analyzed with the log-rank test for univariate analysis. Two-sided p-values of less than 0.05 were considered statistically significant. Using variables that showed significant differences in the univariate analysis, a multivariate analysis was performed with the Cox proportional hazards model. The Fisher exact test was used to compare rates of transition to secondary treatment, ORR, and DCR outcomes between tranilast treatment and AS.

Results

Patient Characteristics

Of the 34 patients diagnosed with DF, 16 were excluded and data from the remaining 18 patients who received tranilast as initial therapy were analyzed (**Fig. 2**, **Table 1**). Histological diagnosis was made in all cases. The time until pathological diagnosis was confirmed and the time until a treatment decision was made varied in each case; thus, the time to start of treatment varied. Nevertheless, the median interval from the date of the first visit to the start of tranilast was 1 month (range, 0-6 months), and treatment was started soon after diagnosis in all patients. In two patients who chose surgical resection as initial treatment, tranilast was started immediately after surgery because they had gross residual lesions that were impossible to resect (**Table 1**; cases 12 and 18). These cases were classified as having received initial treatment because the treatment was not for recurrent lesions but for residual tissue from primary lesions.

Tranilast Treatment Did Not Affect Tumor Shrinkage in EADF

The clinical features and treatment outcomes of each patient are summarized in **Table 1**. The median observation period was 47 months (range, 9-131 months). Regarding the tranilast treatment response at the final evaluation, no patients (0%) and four (22.2%), eight (44.4%), and six (33.3%) patients had a CR, PR, SD, and PD, respectively. The ORR and DCR for tranilast were 22.2% and 66.7%, respectively. Because DF often spontaneously shrinks, we compared our results for tumor size and local controls to AS outcomes obtained from the systematic review to determine whether tranilast had the potential for local control. There were no statistically significant differences in ORR or DCR between our study and prior studies (**Tables 2, 3**).

Tranilast Treatment Reduced the Rate of Invasive Secondary Treatment

Two patients had progressive tumors and worsening clinical symptoms and surgical resection was chosen as secondary treatment; tranilast treatment was discontinued at 4 months in one patient and at 16 months in the other, and surgical resection was performed (**Table 1**; cases #8 and #15). In addition to the results for the present tranilast treatment, the patient number, tumor response, and rate of transition to secondary treatment in all 18 articles on AS (identified in the review) are shown in **Table 2**. Three reports[4,20,21] included use of analgesics such as NSAIDs, morphine, and corticosteroids and were separated from the pure AS cases. The outcomes of AS

Table 1 The clinical features and treatment outcomes of patients treated with Tranilast

Case	Gender/ Age	Tumor Location	Duration of tranilast treatment (mo)	Recurrence after surgery	Initial pain	COX2 inhibitor therapy	PFS (mo)	Change in tumor size (%)	RECIST 1.1 Response	Secondary treatment	FU (mo)
1	F/35	Abdominal wall	101	primary lesion	–	–	NS	–50.5	PR	–	101
2	F/35	Abdominal wall	25	primary lesion	–	–	NS	–18.9	SD	–	25
3	F/71	Trunk	39	primary lesion	+	+	8	36.3	PD	–	39
4	M/46	Neck	43	primary lesion	+	+	4	5.1	SD	–	43
5	M/41	Neck	122	primary lesion	+	–	NS	–32.2	PR	–	131
6	M/52	Trunk	78	primary lesion	–	–	8	–36	PR	–	78
7	F/18	Trunk	31	primary lesion	+	+	10	87.3	PD	–	31
8	F/47	Trunk	4	primary lesion	+	+	4	30	PD	+	9
9	F/19	Trunk	19	primary lesion	+	+	8	43.6	PD	–	19
10	F/79	Trunk	12	primary lesion	+	+	NS	–8.8	SD	–	12
11	F/35	Trunk	17	primary lesion	–	–	NS	–40	PR	–	20
12	M/43	Extremities	58	Residual lesions after SG	–	+	38	89	PD	–	58
13	M/45	Abdominal wall	55	primary lesion	–	+	NS	–4	SD	–	55
14	F/25	Extremities	51	primary lesion	–	–	NS	–1	SD	–	51
15	F/35	Extremities	16	primary lesion	+	+	14	40	PD	+	76
16	F/40	Extremities	65	primary lesion	+	–	NS	–4	SD	–	65
17	F/30	Neck	40	primary lesion	–	–	NS	10.6	SD	–	40
18	F/18	Trunk	11	Residual lesions after SG	+	+	NS	15	SD	–	62

Abbreviations: COX, cyclooxygenase; mo, Months; NS, not specified; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, surgery.

reported in the systematic review are summarized and described in **Table 3**. The rates of transition to secondary treatment—40.1% for pure AS and 11.1% for the present tranilast treatmentd—significantly differed (**Tables 2, 3**, **Fig. 3A**). However, a comparison with all previous studies, ie, including those that used analgesics, did not yield significant results for tranilast (**Table 3**).

There Was No Difference in PFS between Tranilast and AS

The present PFS rates were 66.7%, 60.6%, and 53.0% after 1, 3, and 5 years, respectively (**Table 4**). Although no significant difference was found, our PFS and event-free survival (EFS) data were comparable to or slightly better than those in some AS studies. Use of COX2 inhibitors was significantly associated with EADF progression (**Table 5**). COX2 inhibitors (celecoxib 200 mg per day or meloxicam 10 mg per day) were used in 10 patients with pain. These drugs were used intermittently and briefly in all patients, without consistent timing of initiation or continuous duration. Although the effects of these drugs could not be analyzed with precision, we cannot exclude the possibility that the analgesic effects of these drugs during tranilast treatment in this study affected the results.

Table 2 Patient data, tumor response, and outcomes for present study and each AS study

References	patients	CR	PR	SD	PD	NS	Shift to ST (ST%)	ST	ORR (%)	DCR (%)	median F/u of AS
Present study	18	0	4	8	6	0	2 (11.1)	2SG	22.2	66.7	47 mo (r: 9-131)
Studies of a pure AS approach											
Bonvalot S, 2008 [6]	11	NS	NS	NS	3	8	3 (27.3)	2MT+SG, 1MT	NS	72.7	NS
Nakayama T, 2008 [32]	11	0	3	7	1	0	3 (27.3)	2SG, 1MT	27.3	90.9	56 mo (r: 16-132)
Fiore M, 2009 [33]	54[a]	0	0	35	19	0	16 (29.6)	6SG, 10MT	0*	64.8	NS
Barbier O, 2010 [10]	11[b]	1	0	10	0	0	0 (0)	NA	9	100*	8 mo (r: 2-127)
Bonvalot S, 2013 [34]	102	NS	29	NS	NS	102	37 (36.2)	15SG, 22MT	NS	NS	NS
Fiore M, 2014 [35]	15[c]	NS	NS	NS	12	3	8 (53.3)*	4SG, 4MT	NS	20*	NS
Roussin S, 2015 [36]	11	NS	NS	NS	2	9	3 (27.3)	1SG, 2HT	NS	9	23 mo (r: 3-144)
Colombo C, 2015 [37]	70	NS	15	24	28	3	28 (40)*	3SG, 22MT, 3RT	74.3*	60	39 mo (r: 15-62)
Burtenshaw SM, 2016 [38]	109[d]	NS	NS	NS	NS	109	51 (46.8)*	16SG, 4CT, 29HT, 2RT	NS	NS	54 (1-346)
Park JS, 2016 [39]	20	1	5	13	1	0	1 (5)	1SG	30	95*	NS
Van Broekhoven, 2018 [40]	37	2	4	21	5	5	15 (40.5)*	15NS	18.9[e]	84.4[e]	16 mo (IQR: 7-31)
Andreas HK, 2019 [41]	15	0	3	9	3	0	3 (20)	1SG+RT, 2NS	20	80	4.1 yr (r: 2.0-11.5)
Duazo-Cassin L, 2019 [42]	17	0	6	9	2	0	2 (11.8)	2SG	35.3	88.2	42.2 mo (r: 0-214)
Van Houdt WJ, 2019 [3]	168	12	33	60	60	3	78 (46.4)*	40SG, 36MT, 2RT	27.3[f]	63.6[f]	40.5 mo
Cassidy, 2020 [43]	72	NS	NS	NS	10	62	42 (58.3)*	42NS	NS	NS	25.1 mo (r: 1.8-177)
Reports including analgesics during AS approach											
Briand S, 2014 [20]	31[g]	3	NS	23	5	0	4 (12.9)	3SG, 1CT	9.7	83.9	73 mo
Penel N, 2017 [4]	388	NS	NS	NS	117	271	71 (18.3)	2SG, 61MT, 4RT, 3CrT, 1RF	NS	69.8	NS
Sobczuk P, 2021 [21]	139	NS	NS	NS	60	7	43 (30.9)	22SG, 6CT, 2HT, 13RT	NS	56.8	NS

: In comparison with the results of the present study, the difference was significant (: P<0.05).
Abbreviations: AS, active surveillance; CT, chemotherapy; CrT, cryotherapy; DCR, disease control rate; HT, hormone treatment; IQR, interquartile range; MT, Medical treatment; NA, not applicable; NS, not specified; ORR, objective response rate; RF, radio-frequency; RT, radiotherapy; SG, surgery; ST, secondary treatment; mo, months; r, range; yr, years.
a) This value excludes the 20 patients who used any medical treatment from the primary tumor group.
b) This value is for the primary tumor group only, and the watchful waiting group for recurrent tumors was removed.
c) This value is only for watchful waiting cases limited to Group A. Group B also had treated primary tumors, but some of the patients who did not undergo resection were treated medically and were excluded because the outcome of only the watchful waiting group could not be evaluated.
d) This value is for the Observation group, which excluded the 67 patients in Group A of Primary tumor who received active treatment.
e) This value was derived by excluding the five unspecified cases from the total and then calculated.
f) This value was derived by excluding the three unspecified cases from the total and then calculated.
g) This value excludes 13 cases of recurrent tumors in which a conservative approach was used as the first-line treatment.

Table 3 Summary of outcomes of reports of AS identified in the systematic review

Number of references	AS patients	Shift to ST (%)	ORR (%)	DCR (%)
Reports for the pure AS approach				
15	723	290 (40.1)*	30.9	68.5
Reports including analgesics during AS approach				
3	558	118 (21.5)	9.7	67.4
All AS approach data				
18	1,281	408 (31.9)	29.3	67.9

: As compared with the present results, the difference was significant (: P<0.05).
Abbreviations: AS, active surveillance; DCR, disease control rate; ORR, objective response rate; ST, secondary treatment.

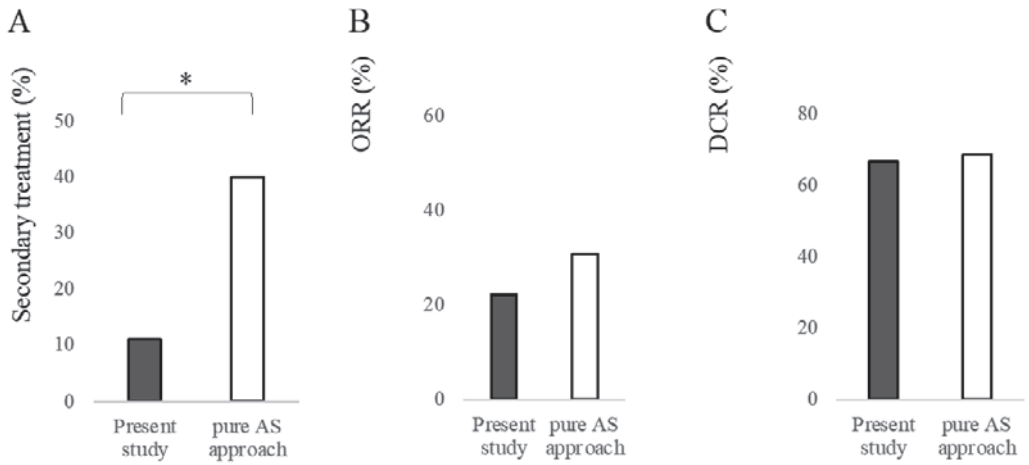

Fig. 3

A. The rate of secondary treatment was compared between tranilast treatment in the present study and a pure AS approach.
B. ORR was compared between tranilast treatment in the present study and a pure AS approach.
C. DCR was compared between tranilast treatment in the present study and a pure AS approach.

Table 4 Comparison of PFS or EFS between the present study and the AS approach articles

Present study	
	1y PFS; 66.7% (95% CI; 40.4-83.4) 3y PFS; 60.6% (95% CI; 34.6-79.0) 5y PFS; 53.0% (95% CI; 27.1-73.5)
References included in Systematic Review	outcome
Penel N, 2017 [4]	2y EFS; 57.9%
Park, 2016 [39]	3y PFS: 92%
Fiore, 2009 [33]	5y PFS; 49.9% (47% primary tumors)
Sobczuk P, 2021 [21]	1,3,5y EFS; 70%, 56%, 55%
References not included in Systematic Review	
de Bruyns A, 2020 [44]	2y PFS; 71% (95% CI; 60-84)
Turner, 2019 [45]	3y PFS; 38%
Huang, 2014 [46]	5y EFS; 71.2%
Orbach D, 2017 [47]	5y PFS; 26.7% (95% CI; 14.2–41.0)

Abbreviations: AS, active surveillance; CI, confidence interval; EFS, event-free survival; PFS, progression-free survival; y, year.

Long-Term Tranilast Administration Resulted in Few Adverse Events

All patients received an initial tranilast dose of 300 mg per day; this dose was not reduced until the final evaluation. The median duration of medication was 39.5 months (range, 4-122 months). No patient required discontinuation of medication because of adverse events. Five patients discontinued treatment before the final evaluation for reasons other than side effects. In three of five, tumor shrinkage was observed or the clinical symptoms stabilized without progression, and the drug was withdrawn (**Table 1**; cases #5, #11, and #18). The remaining two patients received surgical interventions because of persistent pain and growing tumors. We identified only one adverse event: a grade-1 increase in alanine aminotransferase level (**Table 1**; case #9). The patient had no subjective symptoms, and values improved spontaneously without tranilast withdrawal. In this case of elevated alanine aminotransferase, and in all other cases, tranilast did not result in a peripheral blood eosinophil count higher than 500/μL. COX2 inhibitors (200 mg of celecoxib or 10 mg of meloxicam per day) were administered to 10 patients with pain; however, there was no uniformity in the criteria for the initiation or duration of this treatment.

Table 5 Univariate analysis of progression-free survival (PFS) DF according to initial characteristics

Initial characteristics		p-value (log-rank)
Age, years		
	<40 (n = 9)	0.3
	≥40 (n = 9)	
Gender		
	Female (n = 13)	0.48
	Male (n = 5)	
COX2 inhibitor therapy		
	No (n = 8)	0.02
	Yes (n = 10)	
Pain		
	No (n = 8)	0.11
	Yes (n = 10)	
Tumor size, mm		
	>71 (n = 8)	0.13
	≤71 (n = 10)	
Tumor location		
	Abdominal wall (n = 3)	0.28
	Extremities (n = 4)	
	Neck (n = 3)	
	Trunk (n=8)	

Discussion

This study retrospectively reviewed the clinical outcomes of 18 EADF patients treated with tranilast as initial therapy for EADF. This is the first report to describe the efficacy and safety of tranilast treatment for DF. Because DF sometimes shrinks spontaneously, the treatment effect of drugs must be compared with the outcome of AS. However, the rarity of this disease makes such trials difficult. Therefore, we performed a systematic review to obtain data on clinical outcomes of AS as initial treatment and compared them with outcomes of tranilast treatment. Tranilast reduced the rate of transition to secondary treatment, as compared with pure AS. Furthermore, since tranilast has less side effects and can be used for a long period, it is better for initial management than wasting time with AS alone after a DF diagnosis. Although some reports permitted analgesic use during AS, these effects could explain the lower number of patients transitioning to secondary treatment. Nevertheless, at least in our study, use of COX2 inhibitors was limited and short-term and was thus unlikely to have affected our results. To address this problem, the duration and start time of analgesic therapy should be fixed. However, the side effects of these drugs make long-term use difficult in clinical practice. In actual clinical use, analgesics should be used temporarily for episodes of severe pain. Furthermore, PFS was slightly better for tranilast treatment than for EFS, as reported by Penel et al. for the AS approach with NSAIDs. That study included the largest number of cases and is the only prospective study of this topic (**Table 4**). In conclusion, tranilast is a better initial treatment option than AS, because it also improves PFS and decreases the need for secondary therapy.

Tranilast has fewer adverse events than other drugs used for secondary treatment. Antihormonal drugs such as tamoxifen were found to be effective, with an estimated 2-year PFS rate of 36%; however, adverse events such as sporadic vomiting and ovarian cysts were reported in 40% of patients[22]. Chemotherapy drugs such as doxorubicin, liposomal doxorubicin, and low-dose methotrexate combined with vinblastine were reported for treatment of DF[23,24]. The mean response rates were 44%, 33.3%, and 36%, respectively. However, the corresponding rates of adverse events of CTCAE grade 3 or higher (mainly neutropenia and cardiac dysfunction) were 28%, 13%, and 31%, respectively, and not negligible[23,24]. Finally, molecular targeted agents such as sorafenib, imatinib, and pazopanib have also been tested, and the response rates were 33%[25] for sorafenib and 6%[26] or 19%[27] for imatinib. Furthermore, the 2-year PFS rate for imatinib was 55%[28] and the 1-year PFS rate for pazopanib was 85.6%[29]. Adverse events of CTCAE grade 3 or higher were reported in 29%[28], 11%, and 45% of patients treated with sorafenib[28], imatinib[27], and pazopanib[28], respectively.

Among reported adverse events, hypertension and diarrhea are frequent and should not be ignored[29]. Because of the high frequency of such serious adverse events, their use for DF may lead to undesirable effects.

For surgery, the risks of recurrence and functional impairment must be considered, and resection may lead to excessive recurrence[30]. Some studies of radiotherapy reported that a local control rate of 70-93% could be achieved with a dose of 50-60 Gy as monotherapy[31]. However, because survival is usually long after EADF, the long-term effects of radiation should be considered. Soft tissue fibrosis may affect function, and radiation-induced malignancies are a concern. Thus, routine use of radiation therapy is not recommended.

In EADF, there is a clinical need for a noninvasive treatment that suppresses disease and has minimal adverse events. In our study, we showed that long-term use of tranilast resulted in few or no side effects and reduced the rate of transition to secondary therapy.

This study had several limitations. Unlike malignant tumors, which continue to grow, DF can shrink spontaneously, which complicates the study of the effects of drugs. A randomized controlled trial with an AS group would be ideal, but the rarity of this tumor makes it impossible to plan such a trial. Furthermore, the need for secondary treatment and its timing should be determined by considering not only simple tumor growth, but also clinical symptoms such as pain and the impact on neighboring organs. Because this is based on patients' desires and informed consent, comparisons with reports from other countries or centers may not be informative.

Conclusion

Our findings indicate that tranilast treatment for EADF is a safer and more effective approach to reduce the number of patients who choose to undergo additional, more invasive treatments. Tranilast may be a first choice for use in DF because it has fewer adverse effect and is better suited for long-term use.

Conflict of Interest: None.

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