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Efficacy of Imatinib on Advanced and Refractory Desmoid Tumors: A Retrospective Study

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ABSTRACT Objective: Our study aimed to analyze imatinib's efficacy, tolerability, and safety in treating naive patients with unresectable and progressive desmoid tumors. **Material and Methods:** The data of patients who were ≥18 years old diagnosed with desmoid tumors treated with imatinib were evaluated retrospectively regarding their demographic features, comorbidities, disease stage, pathological features of the tumor, response rates and progression-free survival (PFS). **Results:** In our study, 36 patients with advanced desmoid tumors receiving imatinib with a median age of 28 [interquartile range (IQR): 21-40] years-old of whom 58.3% were female were included. The patient's complete response, partial response, stable disease, and progressive disease with imatinib 800 mg/day were 13.9%, 44.4%, 27.7%, and 13.9%, respectively. The Grade-3 adverse events, including neutropenia (n=3, 8.3%) and rash (n=3, 8.3%), were relieved after dose reduction. The median PFS was 29 months (95% confidence interval, 16-42 months) with imatinib, and only 3 (8.3%) patients were exitus due to disease progression during the follow-up (median: 43 months, IQR: 24.3-70.8). **Conclusion:** Our study provided clinical evidence of the efficacy and safety of imatinib in patients with desmoid tumors with real-world experience. However, appropriately designed randomized-controlled clinical trials are needed to explore the effectiveness of imatinib in desmoid tumors to provide an alternative management approach.

Keywords: Desmoid tumors; imatinib; efficacy

Desmoid tumors (aggressive fibromatosis) are scarce benign monoclonal fibroblastic proliferation derived from musculoaponeurotic tissues.[1] Despite a histologically benign nature and lack of metastatic potential, desmoid tumors can recur in the same area and invade surrounding tissues.[2] It is a rare disease, with an incidence of about 2-5 per million per year.[3] Although desmoid tumors occur sporadically, they may be found in 5-10% of familial adenomatous polyposis (FAP), and younger age, female, and pregnancy were commonly linked with sporadic tumors.[4-6] Desmoid tumors are observed in the extremities, the trunk, the head-neck region, and the pelvic area.[7] Locoregional approaches, including surgery and radiotherapy, have traditionally been the mainstay of management due to their lack of metastasis ability. The two main problems during the follow-up were unpredictable disease course and frequent local relapses, even in cases with re-resections.

A multidisciplinary approach to management has been used frequently, particularly with intraabdominal desmoids.[8] Effective disease control up to 96% can be achieved with interdisciplinary treatment, even if it occurs at difficult locations, such as the intestinal mesentery.[9] In addition, desmoid tumors may have an unpredictable clinical course. An initial observation period was an acceptable strategy for well-selected patients with an asymptomatic or minimally symptomatic, radiologically non-progressive tumor, particularly an intraabdominal/mesenteric tumor in

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patients with FAP.[10] There are no evidence-based or widely accepted guidelines for managing unresectable desmoids. Current treatment options are antiestrogens, chemotherapy, interferon-alfa, tyrosine kinase inhibitors (TKIs), and nonsteroidal anti-inflammatory drugs (NSAIDs).[11] In a randomized trial, initial therapy with a TKI is preferred over hormone therapy with or without an NSAID due to the higher response rates in patients with minimally symptomatic, slowly progressive desmoids. However, TKI therapy or cytotoxic chemotherapy was preferred for moderately symptomatic or faster-growing tumors because of the greater likelihood of an objective response. They concluded that if a TKI was chosen for initial treatment, sorafenib, pazopanib, or sunitinib rather than imatinib was suggested, given the greater degree of activity with this broader-spectrum, albeit more toxic, TKIs.[12,13]

Mace et al. reported the utilization of imatinib in two patients with extra-abdominal desmoid tumors for the first time.[14] In desmoids, KIT genomic changes are seen rarely; therefore, imatinib response in desmoids may not be related to KIT mutations.[15] Imatinib is a protein-TKI that inhibits the BCR-ABL tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). It inhibits proliferation and induces apoptosis in BCR-ABL positive cell lines and fresh leukemic cells from Philadelphia chromosome-positive CML. It also inhibits the receptor tyrosine kinases of a platelet-derived growth factor (PDGF) and stem cell factor.[16] Despite a low response rate (5-15%), three prospective, non-randomized trials found high disease stabilization rates (60-80%) with a favorable toxicity profile; however, the data with the real-life setting is limited.[1-3,7-11,14] This study retrospectively analyzed imatinib's efficacy, tolerability, and safety in treating naive patients with unresectable and progressive desmoid tumors.

MATERIAL AND METHODS

The data of unresectable, recurrent and progressive desmoid tumor patients treated with imatinib between 2012 and 2020 were reviewed retrospectively. The patients <18 years old, without imatinib treatment, having missing data, and previous systemic treatment or radiotherapy were excluded. Survival data, demographic features, Eastern Cooperative Group (ECOG) performance status, stage, pathological tumor features, and comorbidities were also noted.

The overall survival (OS) was described as the time from treatment initiation to the last follow-up and/or death. Progression-free survival (PFS) was defined as the period between imatinib onset to disease progression.

Although there is no commonly used or agreed upon staging system for desmoids, the staging system used in this study was the eighth edition of the American Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system for soft tissue sarcomas.[17]

Treatment response was assessed using magnetic resonance imaging and/or contrast-enhanced computed tomography according to Response Evaluation And Criteria in Solid Tumors 1.1 (RECIST 1.1).[18]

All patients were treated with an initial dose of 800 mg/day imatinib.[19] All adverse drug reactions and toxicities in the study group were recorded to the Common Terminology Criteria for Adverse Events v 4.0 (CTCAE).[20]

Descriptive data were presented as median, interquartile range (IQR; 25^{th}-75^{th} percentile), standard errors for continuous variables, and frequency and percentages for categorical variables. Baseline groups were compared using independent t-tests and Chi-square tests for continuous and categorical variables, while survival analyses were conducted using Kaplan-Meier analysis. All statistical analyses were performed in SPSS (IBM Inc, Armonk, NY, USA) and $p<0.05$ was considered statistically significant.

The primary endpoints of our study were response rates and PFS, while the co-primary endpoint was the evaluation of tolerability and safety.

ETHICS

The study was conducted according to the Declaration of Helsinki and approved by the Ethics Review Committee of İstanbul, Prof. Dr. Cemil Taşcıoğlu City Hospital (date: 28.01.2021 no: 48670771-514.10/11).

RESULTS

In our study, 36 patients with advanced desmoid tumors treated with imatinib were included. The demographical and clinical features of our cohort are tabulated in Table 1. The median age of the patients was 28 (IQR 21-40) years-old, 58.3% were female, and the ECOG performance status of most patients (83.3%) was 0. The R0 resection was present in 69.4% of the patients (Table 1). All surgical margins were obtained from the patients' data before the recurrence and progression of the disease resulting with the initiation of imatinib. The primary tumor locations were upper extremity in 10 (27.8%) patients, lower extremity in 6 (16.7%) patients, abdominal/retroperitoneal in 16 (44.4%) patients, and trunk in 2 (5.5%) patients.

The complete response, partial response, stable disease, and progressive disease rates were 13.9%, 44.4%, 27.7%, and 13.9%, respectively. The median PFS was 29 [95% confidence interval (CI), 16-42 months] months, and the median follow-up interval was 43 (IQR: 24.3-70.8) months (Figure 1). Only 3 (8.3%) patients died during the follow-up due to disease progression. A limited number of patients were concerned with median follow-up time, and the OS data was immature.

The initial dose of 800 mg imatinib was administered daily to all patients.[19] The imatinib-related adverse events are summarized in Table 2. Only 6 (16.7%) patients decreased the dosage due to intolerable drug-related toxicity. However, none of the patients discontinued treatment due to uncontrolled adverse events. The most common adverse events were: neutropenia (n=9, 25%), rash (n=7, 19.4%), fatigue (n=6, 16.7%) and peripheral edema (n=6, 16.7%). Most adverse events were Graded 1 or 2 and managed by symptomatic treatment. The Grade-3 adverse events, neutropenia (n=3, 8.3%), and rash (n=3, 8.3%), showed satisfactory improvement after dose reduction, and no treatment-associated death or Grade-4 adverse event was observed.

DISCUSSION

This study analyzed 36 patients with advanced desmoid tumors treated with imatinib. The World Health Organization describes a desmoid tumor as a type of soft-tissue tumor with distinct features, and the clinical disease differs among patients.[21] Because of the variable disease course, the treatment of unresectable or recurrent desmoid tumors remains debatable.[22] For desmoid patients whose tumors are not located in a life-threatening region, watchful waiting is a good option. Although radiotherapy is still underutilized, systemic treatments, including NSAIDs,

TABLE 1: The demographical and clinical features of our study cohort.

Variables		Patient number (n)	Percentage (%)
Age (years), median (IQR)	28 (21-40)		
Sex	Male	15	41.7
	Female	21	58.3
Type 2 diabetes mellitus	Absent	35	97.2
	Present	1	2.8
Hypertension	Absent	34	94.4
	Present	2	5.6
Smoking	Absent	34	94.4
	Present	2	5.6
Alcohol	Absent	35	97.2
	Present	1	2.8
ECOG performance status	0	30	83.3
	1	5	13.9
	2	1	2.8
Stage	1	9	25
	2	5	13.9
	3	22	61.1
Grade	1	9	25
	2	2	61.1
	3	5	13.9
Capsule invasion	Absent	29	80.6
	Present	7	19.4
Surgical margin	R0	25	69.4
	R1	5	13.9
	R2	6	16.7
Surrounding tissue infiltration	Absent	31	86.1
	Present	5	13.9
Localization of tumor	Upper extremity	10	27.8
	Lower extremity	6	16.7
	Abdominal/ retroperitoneal	16	44.4
	Trunk	2	5.5
	Head or neck	2	5.5

IQR: Interquartile range; ECOG: Eastern Cooperative Oncology Group.

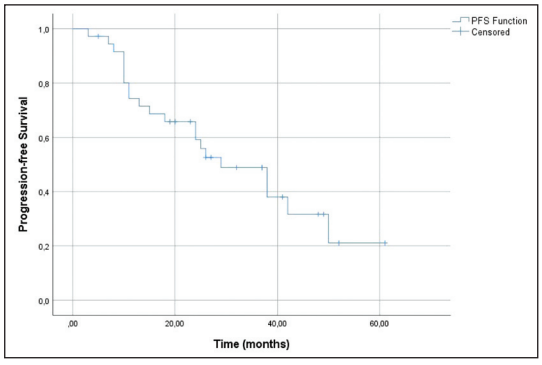

FIGURE 1: Progression-free survival of the study cohort. PFS: Progression-free survival.

TABLE 2: Adverse events of imatinib treatment in our study cohort.

Adverse events	Total, n (%)	Grade 1 (n)	Grade 2 (n)	Grade 3 (n)
Rash	7 (19.4)	2	2	3
Abdominal pain	3 (8.3)	2	1	-
Vomiting	4 (11.1)	3	1	-
Nausea	3 (8.3)	3	-	-
Diarrhea	3 (8.3)	3	-	-
Myalgia	4 (11.1)	4	-	-
Neutropenia	9 (25)	4	2	3
Fatigue	6 (16.7)	5	1	-
Peripheral edema	6 (16.7)	4	2	-

tamoxifen, and chemotherapy, are often used with variable outcomes.[23]

Modern systemic treatment options include TKIs like pazopanib, sorafenib, and imatinib. Heinrich et al. analyzed tumor specimens for mutations of KIT, PDGFRA, PDGFRB, and CTNNB1 (beta-catenin) and found that imatinib response in patients with desmoid tumors may be mediated by inhibition of PDGFRB kinase activity.[24] Both sorafenib and pazopanib inhibit angiogenesis effectors, which are vascular endothelial growth factor (VEGFR), the PDGF, and receptor (PDGFR).[25] Conversely, imatinib affected PDGFR but not VEGFR.[26]

Desmoid tumors commonly develop between 15 and 60 (average: 30 years) years-old and are found to be slightly more common in women than men.[27] Similarly, the mean age in our population was 28 years-old, with a slight female predominance. Imatinib has been used in unresectable, progressive, and recurrent desmoid tumors. In a Phase II trial, Chugh et al. reported a 6% objective response rate (ORR) and a 1-year PFS rate of 66% with imatinib.[28] Another French Sarcoma Group also conducted a Phase II study of patients with desmoid tumors and reported that the median PFS was 25 months, while the 2-year PFS and OS rates were 55% (95 CI 36-69) and 95% (95% CI 82-99), respectively. Two patients died because of a progressive mesenteric desmoid tumor in that study.[29] In our study, more than half of the patients (58.3%) showed complete or partial response to imatinib, and the median PFS was 29 (95% CI, 16-42 months) months in a median follow up time of 43 (IQR: 24.3-70.8) months.

Our study found the ORR as 58% (13.9% of CR, 44.4% PR), which can be related to the initial use of the maximum dose of imatinib (800 mg/day), and all patients were treatment-naive. On the other hand, despite the high (800 mg/day) dosage, the ORR in the prospective study conducted by the German group was 19% in a group of primarily treatment-naive patients (29% of all patients who had previously received medical therapy).[19] We think that the retrospective nature of our study, patient selection bias, non-standardization of radiological evaluation and reporting, and polarizing patients with regression as PR or patients with PR as CR was the main weakness of our study and may be related to the higher ORR.

Penel et al. reported that approximately 45% of patients interrupted or discontinued imatinib administration due to severe drug-related toxicities in terms of side effects.[29] In our study, the most common toxicities of imatinib were neutropenia, fatigue, peripheral edema, and rash, similar to those reported in previous literature.[30] No Grade-4 adverse events were observed. However, 3 (8.3%) patients suffered from Grade-3 neutropenia, and 3 (8.3%) patients had a Grade-3 rash that resolved with dose reduction.

Kasper et al. used 800 mg/day imatinib in a Phase II study of the German Interdisciplinary Sarcoma Group (GISG) and reported Grade-4 toxicities in one patient, and Grade-3 toxicities were reported in 4 (11%) patients including neutropenia, leucopenia, nausea/vomiting, gastritis, rash, and contracture.[19]

The main limitations of our study were as follows; the retrospective nature of the study, a small sample size without a control group, short mean follow-up time, and imatinib not being comparable with new TKIs such as pazopanib, sunitinib due to the reimbursement statements. In addition, molecular analysis of catenin beta-1, PDGF receptor, and adenomatous polyposis coli mutations could not be carried out.

CONCLUSION

In conclusion, our study showed a good disease course with imatinib treatment. Imatinib (800 mg/day) was more effective and tolerable in treatment-naive patients with desmoid tumors. More randomized controlled trials are need to be done to see the effectiveness of imatinib in desmoid tumors, which could provide an alternative management approach.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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