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Research Article

Efficacy of Sorafenib in Symptomatic Patients with Pretreated Progressive Desmoid Tumors

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Abstract

Objectives: Desmoid tumors (DTs) are rare benign neoplasms characterized by histologically monoclonal fibroblastic proliferation. Although current treatment guidelines recommend active surveillance as the initial approach, systemic therapy should be considered in rapidly progressive or symptomatic patients. In this study, we aimed to evaluate the efficacy of the kinase inhibitor, sorafenib, as a treatment for patients with progressive or symptomatic DTs.

Methods: The clinical, pathological, and demographic data of a sample of patients treated for DTs with sorafenib were retrospectively evaluated.

Results: Seventeen patients were included in the study. The ratio of female to male patients was 2.4, and the median age was 32 (range: 14-65). Four (23.5%) patients had Gardner syndrome. The rates of extra-abdominal and ıntraintra-abdominal tumors were 64.7% and 35.3%, respectively. The median follow-up duration before sorafenib treatment began was 6 years. Before sorafenib, 15 patients had undergone surgical resection. All patients had received a median of two lines of systemic therapy, and four (23.5%) patients had received chemotherapy. The median sorafenib treatment duration was 23.4 months. The 1 and 2 year progression-free survival rates were 94.1% and 80.7%, respectively. Grade 3–4 toxicities were observed in six (35.2%) of the patients.

Conclusion: Sorafenib was deemed an effective treatment for previously treated advanced DTs.

Keywords: Aggressive fibromatosis, desmoid tumors, gardner syndome, sorafenib,TKİ

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Desmoid tumors (DTs), also known as aggressive fibromatosis (AF), are rare monoclonal infiltrative fibroblastic proliferations that derive from fascial or musculoaponeurotic soft tissue structures.[1] Although benign and unable to metastasize, they can be locally aggressive. They occur in a variety of anatomical locations including the abdominal cavity or wall, the mesenteric root, and the extremities.[2] The peak age of diagnosis is between 30 and 40 years, with female predominance.[2] The incidence in the general population is estimated to be 5–6 per million each year.[3] The manifestation of DTs can vary considerably, from asymptomatic to severe pain, intestinal obstruction or ischemia, and neurological deficits because of compression of the neural plexuses. However, the tumor itself usually presents as a painless mass.[4] Generally, survival rates are high, but local recurrence and

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progressive disease can cause various morbidities and impair quality of life.[4]

The etiology of DM is not well understood, but there are two major types, sporadic and a familial adenomatous polyposis-associated form, known as Gardner syndrome. Possible causes of sporadic DTs may be estrogen exposure, trauma, or abdominal surgery , connective tissue, or mutation of the CTNNB1 gene, which encodes for β-catenin. This proto-oncogene regulates cell-to-cell adhesion and functions in the Wnt signaling pathway.[2,3,4]

Surgery was historically considered the standard treatment for DM, but improved understanding of the natural course of the disease and clinical reports describing spontaneous tumor regression have altered the treatment strategy in favor of a more conservative approach.[5,6] Recent global consensus-based guidelines by The Desmoid Tumor Working Group recommend active surveillance as the frontline approach. Surgery remains an option for the treatment of DTs when tumors are progressive or symptomatic.[7] Multiple retrospective studies have found local control rates 5 years after complete surgical resection in the range of 70%–80%.[8,9] Postoperative radiotherapy can further reduce the risk of local recurrence.[10] When DTs are rapidly progressive or symptomatic, systemic therapy should be considered for cases not amenable to surgery or radiotherapy.[7,11] Established treatment agents include NSAIDs, antiestrogens, and cytotoxic chemotherapeutics.[7] In recent years, tyrosine kinase inhibitors (TKI) have also emerged as promising DT treatments. In 2002, imatinib was the first of these to be tested.[12] Subsequently, various clinical trials have been conducted investigating the effects of imatinib and other TKI (e.g., sorafenib and pazopanib) on DTs.[5,6,7] Sorafenib is an orally administered, multitarget drug that interferes with both serine/threonine kinases (c-RAF, BRAF, and mutant BRAF) and receptor tyrosine kinases, including platelet-derived growth factor receptors, VEGF (vascular endothelial growth factor) receptors 2 and 3, c-Kit, RET, and FLT3.[13] Among the TKI, sorafenib has received the most research attention for use as a DT treatment.[5-7] The effects of sorafenib on DTs were initially observed in 2011 in a retrospective trial of 26 patients treated with 400 mg sorafenib/day.[14] In 2018, a phase III randomized trial of sorafenib demonstrated a 2 year progression-free survival (PFS) rate of 81% in DT patients treated with sorafenib, compared with a PFS of 36% in a placebo group with DTs, with objective response rates of 33% and 20%, respectively.[15] To the best of our knowledge, no prior real life study has the efficacy of the sorafenib therapy with progressive or symptomatic DTs. In this real-life study, we aimed to evaluate the efficacy and safety of sorafenib in patients with progressive or symptomatic DT treated at our sarcoma center.

Methods

After receiving approval for this study from the ethics committee of our institution, we retrieved the medical records of 17 patients with unresectable symptomatic or recurrent DTs treated with sorafenib at Istanbul University Institute of Oncology between January 01, 2015, and January 01, 2021. These were analyzed retrospectively.

We collected the following data: age at diagnosis, sex, Eastern Cooperative Oncology Group (ECOG) performance status, presence of Gardner syndrome, tumor extension, status before sorafenib (primary or recurrent disease), previous treatments (surgery, radiotherapy, and/or systemic treatments such as chemotherapy, NSAIDs, hormone therapy, or TKI), duration and dose of sorafenib treatment, toxicities, best responses (complete response, partial response, stable disease, or progression), time to progression, and overall survival (OS) and status.

Sorafenib treatment was administered to all patients once a day at a dose of 400 mg/day. In instances of intolerable toxic effects, dose modification to 200 mg/day was implemented following the recommendations of the responsible physician. The development of comorbidities during treatment was also addressed with dose modifications or delays recommended by the responsible physician. Radiological evaluations were conducted using computed tomography or magnetic resonance imaging once every 3 months in the first year and then once every 3–6 months.

The Response Evaluation Criteria in Solid Tumors v. 1.1 were used to measure patient treatment responses. Adverse events (AEs) were reported using the Common Terminology Criteria for Adverse Events v. 4.0.

All statistical analyses were conducted using SPSS 25.0 (SPSS Inc, Chicago, IL, USA) software. PFS was defined as the time from diagnosis to either the time of recurrence at any site or death from any cause. OS was defined as the time from diagnosis to death from any cause or last known contact.

Results

Patient Characteristics

The median age of the study participants was 32 years (range: 14–65 years), and 12 (70.6%) of the 17 were female. Table 1 presents the patients' demographic and clinical characteristics. Eleven patients (65%) had an ECOG performance score of 0, and six (35%) had an ECOG score of 1. Tumors were intra-abdominal in six (35%) and extra-abdominal in 11 (65%) patients. The mean tumor size was 12.7 cm (diameter). Gardner syndrome was present in four (23.5%) patients. Before the initiation of sorafenib treatment, two

(11.8%) patients were unresectable, seven (41%) patients had undergone one operation, and eight (47%) had undergone two operations. Four (23.5%) of the patients had received adjuvant radiotherapy. All 17 (100%) patients had been treated with NSAIDs before they began sorafenib treatment. Previously, six (35%) patients had received hormone therapy, four (23.5%) had received chemotherapy, six (35%) had received imatinib, and one (5.9%) had received pazopanib. The median sorafenib treatment duration was 23.4 months.

Table 1. Demographic and Clinicopathological Characteristics of Patients in this Study

Variables	Sorafenib (n=17) n/% or mean + SD (range)
Sex	
Male	5/29.4%
Female	12/70.6%
Age at diagnosis	
Mean*	32±3 (14–65)
Age at start of sorafenib treatment	
Mean*	35±2 (18–67)
ECOG performance status	
0	11/64.7%
1	6/35.3%
Primary tumor site	
Intra-abdominal	6/35.3%
Extra-abdominal	11/64.7%
Tumor extension	
Mean (cm)	12.7±1.1 (4–21)
Gardner syndrome	
Present	4/23.5%
Absent	13/76.5%
Status before sorafenib	
Unresectable	2/11.8%
Recurrence after the first surgery	7/41.2%
Recurrence after the second surgery	8/47.1%
Adjuvant radiotherapy	
Yes	5/29.4%
No	12/70.6%
Previous systemic therapy	
NSAIDs	17/100.0%
Hormones	6/35.3%
Chemotherapy	2/11.8%
Imatinib	6/35.3%
Pazopanib	1/5.9%
Duration of sorafenib treatment	
Mean (month)*	23.4±2.2 (8.5–46.3)
Cumulative proportion of surviving patients	
One year	94.1%
Two years	81.4%
Three years	55.9%

ECOG: Eastern Cooperative Oncology Group; NSAİDs: Non-steroidal anti-inflammatory drugs.

Treatment Outcomes

Table 2 summarizes treatment details for the patients in this study. The median follow-up duration was 6 years. One patient had a complete response to the treatment, and eight had partial responses. The overall response rate (ORR) was 52.9%. The cumulative PFS was 94.1% at the end of the first year, which declined to 80.7% and 60.5% at the end of the second and third years, respectively. Median PFS was not calculated since most cases did not progress (Fig. 1). All of the 17 patients are still alive at the time of writing. Our log-rank test results found maleness (p=0.012), higher ECOG performance status (p=0.032), and the presence of Gardner syndrome (p=0.021) to have significant negative effects on PFS.

Safety and Toxicity

Table 3 summarizes the AEs experienced by our patients. The median sorafenib treatment duration was 23.4 months. The most frequently observed AEs were grade 1 or 2 events of fatigue (70%), rash (47%), diarrhea (47%), and hypertension (35%). Grade 3 and 4 AEs were observed in 35.2% of the group, as follows: one case of cardiac toxicity (QT prolongation), one case of alopecia, one case of malaise, one case of hypertension and diarrhea, one case of diarrhea, and two cases of skin rashes. These AEs were addressed with dose reduction or a respite from treatment. None of the patients required treatment cessation due to side effects.

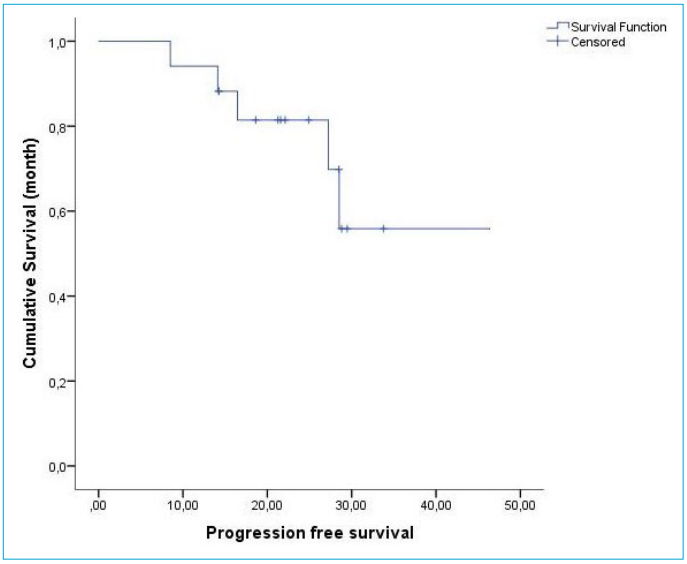

Figure 1. The 1 and 2 year progression-free survival (PFS) rates were 94.1% and 80.7%, respectively. Median PFS was not calculated since most cases did not progress.

Table 2. Clinical Characteristics of Patients with Desmoid Tumors Treated with Sorafenib.

Patient	Age and gender	Location and risk factors	Tumor size	Surgery status	Previous therapies response	Best	Time between diagnosis and sorafenib	Duration of sorafenib treatment (Months) initiation (Months)	Sorafenib toxicities (Grades 3–4)
1	29/female	Lower extremity	8 cm	Recurrence after two surgeries	NSAIDs, tamoxifen, imatinib RT	PR	90.12	21.26	0
2	28/male	Lower extremity	12 cm	Recurrence after one surgery	NSAIDs	PD	11.99	8.51	Long QT
3	20/male	Intra-abdominal Gardner	15 cm	Recurrence after one surgery	NSAIDs, tamoxifen, imatinib, CT	SD	52.4	16.46	0
4	35/female	Lower extremity	15 cm	Recurrence after one surgery	NSAID, tamoxifen, imatinib	PR	31.77	33.77	0
5	16/female	Intra-abdominal	6 cm	Recurrence after two surgeries	NSAIDs	PR	25.46	29.47	Alopecia
6	14/female	Lower extremity	21 cm	Recurrence after two surgeries	NSAIDs, imatinib, CT, RT	PR	153.3	28.81	Skin rash
7	39/female	Upper extremity	7 cm	Recurrence after two surgeries	NSAIDs, RT	SD	65.08	14.23	0
8	40/female	Lower extremity Trauma	12 cm	Recurrence after two surgeries	NSAIDs, tamoxifen, imatinib	PR	48.76	24.9	0
9	38/female	Upper extremity	3.5 cm	Recurrence after two surgeries	NSAIDs, imatinib	CR	68.47	21.59	Malaise
10	43/male	Intra-abdominal Gardner	11 cm	Recurrence after one surgery	NSAIDs	SD	21.49	28.48	0
11	38/female	Lower extremity	14 cm	Recurrence after one surgery	NSAIDs, pazopanib, RT	PR	49.31	46.36	Skin rash
12	18/female	Lower extremity	11 cm	Unresectable	NSAIDs	SD	0.23	14.26	0
13	41/female	Upper extremity	14 cm	Recurrence after one surgery	NSAIDs, tamoxifen	SD	14.75	22.11	Diarrhea, hypertension
14	27/female	Intra-abdominal	13 cm	Unresectable	NSAIDs	PR	0.59	18.63	0
15	65/male	Lower extremity	21 cm	Recurrence after one surgery	NSAIDs, tamoxifen	PR	29.5	28.52	0
16	33/male	Intra-abdominal Gardner	18 cm	Recurrence after one surgery	NSAIDs, tamoxifen, CT	SD	49.25	27.24	0
17	23/female	Intra-abdominal Gardner	15 cm	Recurrence after three surgeries	NSAIDs, tamoxifen, imatinib, CT	SD	89.43	14.13	0

CR: Complete response; CT: Chemotherapy; NSAİDs: Non-steroidal anti-inflammatory drugs; PR: Partail response; PD: Progressive disease; RT: Radiotherapy; SD: Stable disease.

Discussion

In this study, we aimed to evaluate the efficacy and safety of sorafenib treatment in patients with DTs. We evaluated previous findings regarding effectiveness and adverse effects for comparison with our own data. This report is the first real-life data of sorefenib, there is only phase trials of the drug which are evaluating more fit and strictly seleted patient population. We have found the drug is effective and tolerable in real-world setting; even better response results have been reached with sorefenib compered to previous studies.

In recent years, there has been a shift toward more conservative DT management. Surgery was previously considered the standard treatment; however, unpredictable prognoses and frequent recurrence of AF after surgery led to a search for novel treatment methods. In this regard, TKI such as imatinib, pazopanib, and sorafenib have emerged as promising therapeutic options.[5,6,16] Imatinib, the first TKI used against DTs, has shown low response rates (6%–19%) and an acceptable toxicity profile.[17,18] In a retrospective study of eight DT patients treated with pazopanib, three

Table 3. Adverse Events of the patients

Adverse Event	Total n/%	Grade 1-2	Grade 3-4
Rash	9/52,9	8	2
Fatigue/malaise	12/70,5	11	1
Hypertension	6/35,2	6	0
Diarrhea	10/58,8	8	2
Nausea/vomitting	8/47	8	0
Abdominal Pain	5/29,4	5	0
Oral mucosit	3/17,6	3	0
Myalgia	3/17,6	3	0
Long qt interval	1/5,8	0	1
Alopecia	3/17,6	2	1

patients achieved PR, and durable disease stabilization was obtained in five. The median PFS was 13.5 (range: 5–36) months.[19]

Sorafenib is currently the most studied TKI treatment for DTs.[14,15] In 2011, a retrospective trial of 26 patients treated with 400 mg sorafenib a day reported a promising ORR of 25%, with disease stabilization and improved quality of life.[14] In 2018, Gounder et al. presented the initial results of their randomized phase III trial of sorafenib treatment of DTs. The 1 year PFS rates were 89% (95% CI, range: 80–99) with sorafenib compared with 46% (95% CI, range: 32–67) with the placebo. The 2 year PFS rates were 81% (95% CI, range: 69–96) in the sorafenib-treated group and 36% (95% CI, range: 22–57) in the placebo group. A median PFS was not reached (NR) with sorafenib but was 9.4 months (95% CI: 5.7, NR) in the placebo group, with a hazard ratio of 0.14 (95% CI: 0.06, 0.33) ($p<0.0001$). The objective response rate was 33% in the sorafenib arm and 20% in the placebo group.[15]

İn the present study, progression occurred in six of the 17 patients. The median PFS duration was NR with sorafenib. However, the PFS rates at 1 year, 2 years, and 3 years were 94.1%, 80.7%, and 60.5%, respectively. The complete response rate was 5%. These results are consistent with those seen in the phase 3 trial;[15] however, our ORR was 52.9%, slightly higher than that seen in the phase 3 trial.[15]

Current treatment guidelines recommend active surveillance as the initial response to DTs and systemic treatment in cases with rapid progression, symptomatic disease, or morbidity.[7,11] İn our study, the median time from diagnosis to initiation of sorafenib treatment was 6 years. Fifteen patients had been heavily pretreated (with a median of two surgeries and two lines of systemic therapy), whereas the remaining two had unresectable DTs.

An interesting point of note in our study was that the PFS rate was poor in patients with Gardner syndrome. The literature indicates a rate of Gardner syndrome in patients with DTs of 5%–15%, whereas the rate in our sample was 25%.[7,16] In contrast to the CTNNB1 mutation in sporadic DTs, Gardner syndrome is characterized by a mutation in the adenomatous polyposis coli (APC) protein. As Gardner syndrome has a more aggressive clinical course than sporadic DTs, it is often treated with more aggressive systemic treatments.[16] Braggio et al. evaluated in vitro activity of sorafenib on DTs and found that the response to sorafenib differed between DTs with the CTNNB1 S45F mutation and those with T41A or wild-type CTNNB1.[20] However, as yet, there is insufficient clinical evidence that sorafenib is more effective in the treatment of DTs in which genetic mutation is present.[21]

In a phase 3 trial by Gounder et al., the most common AEs were grade 1–2 rash (73%), fatigue (67%), hypertension (55%), and diarrhea (51%), in addition to grade 3–4 AEs in 47% of the sorafenib patients and 25% of the placebo group patients.[15] The most frequently observed AEs in our study were grade 1 or 2 events, including fatigue (70%), rash (47%), and diarrhea (47%). Similar phase 2-3 trials have noted hypertension (35%) and grade 3–4 AEs in 35.2% of patients.[14,15] One of the most important concerns in the treatment of DTs with this drug is the increased risk of toxicity with long-term use. However, although the sorafenib dose is 800 mg/day for the treatment of other solid tumors, only 400 mg/day is necessary for the treatment of DTs, and no significant decrease in effect was observed when the dose was halved to 200 mg/day. The median sorafenib treatment duration was 23.4 months. The drug was generally well-tolerated.

Our study had several limitations. This was a retrospective, single-center study with a small sample of patients and no control group. We were also limited to clinical assessment as we did not have the data for detailed analysis of the relevant genetic mutations (CTNNB1, PDGFR-β, c-KIT, and APC) since the detailed genetic analyses are not covered by insurences for our patients.

Conclusion

We concluded that sorafenib is an effective treatment for previously treated advanced DTs. Despite the small number of patients in our sample, we found male gender, poor ECOG performance status, and the presence of Gardner syndrome to be negative prognostic indicators of PFS.

Disclosures

Ethics Committee Approval: This study was conducted in accordance with the tenets of the Declaration of Helsinki 1964. The study was approved by ethics Committee of Isranbul University (673675) signed statements of informed content to participation and publication were obtained from participants.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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