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SARCOMAS (SR PATEL, SECTION EDITOR)

Desmoid Fibromatosis: Management in an Era of Increasing Options

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Abstract

Purpose of Review Desmoid fibromatosis (DF) is a locally aggressive clonal neoplasm with locally aggressive behavior and no metastatic potential. Historical treatment of DF has consisted primarily of up-front surgery when feasible. In recent years, recognition that DF can spontaneously stabilize or involute has allowed for many patients to be managed with watchful waiting rather than intervention. This review is intended to review recent developments in the treatment of DF.

Recent Findings Recent studies have demonstrated prospectively that patients with DF often have improvement in their lesions without intervention, enabling an initial period of surveillance as a standard option for patients with mild symptoms. Given the lengthening list of effective systemic treatments, including sorafenib, pazopanib, and experimental agents, there has been a less reliance on local therapies for those patients who require treatment.

Summary For patients with DF that require treatment, there is a growing list of options that includes radiation therapy (RT), percutaneous ablation, and a growing list of systemic agents with favorable toxicity profiles.

Keywords Aggressive fibromatosis · Systemic therapy · Sorafenib · Radiation therapy

Introduction

Desmoid tumors, also called desmoid fibromatosis (DF), are locally aggressive clonal proliferations of mesenchymal tissue. They lack metastatic potential but their locally aggressive behavior can be associated with pain, limitation of mobility, and impairment or organ function, most often mobility limitations, pain, bowel obstruction, or fistulization. The tumors are rare, with an incidence of 2–4 cases per million people per year [1], or approximate 1000 incident cases in the USA annually [2].

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There are two distinct categories of patients with DF. Those that have the tumor arise in the setting of the familial adenomatous polyposis (FAP) or gardener's syndrome, and those that arise sporadically in patients who do not have FAP. Sporadic, non-FAP associated DF accounts for approximately 85% of cases, with a 2:1 female predominance. The remaining 10–15% of DF are FAP associated and do not exhibit the same gender disparity [2].

The central biologic event in the formation of desmoid tumors is an alteration in the Wnt/β-catenin pathway which results in the nuclear accumulation of β-catenin. This protein then binds to *transducin beta-like protein 1 (TBL1/TBLR1),* and the complex activates downstream genes involved in proliferation [3]. In sporadic DF, the large majority of patients have somatic mutations in *CTNNB1*, the gene that encodes β-catenin, though mutations in *APC* and other Wnt/β-catenin-associated loci have been observed with very low frequency [2].

In FAP and Gardeners syndrome-associated desmoid fibromatosis, the germline *APC* mutation which underlies the FAP syndrome is implicated the pathogenesis of DF. The mutation creates a truncated APC protein which is unable to bind and facilitate the destruction of β-catenin. The resulting accumulation of nuclear β-catenin drives the proliferative process. The development of DF in APC seems primarily related to trauma, with as many as 72% of DFs in this

population occurring shortly after prophylactic colectomy either intrabdominally or in the abdominal wall [4].

Surveillance and Local Therapies

Watchful Waiting

Historical treatment of desmoid tumors involved up-front surgical resection for symptomatic and asymptomatic patients. As our understanding of the natural history and disease biology has evolved, the role of surgery has changed. Several retrospective studies in the early 2000s demonstrated progression-free survival rates of ~50% at 5 years for asymptomatic patients managed with active surveillance ("watchful waiting"), raising into question the role of upfront surgery [5–8]. A recent large, cohort study of 771 patients with DT in France treated with surgery or watchful waiting demonstrated no difference in event-free survival and similar long-term disease control between patients undergoing surgery and those managed with watchful waiting. Although 30.1% (117/388) of patients treated with watchful waiting developed progression, only 71 (18.2%) patients required a change in treatment (mainly systemic treatment). However, of the patients initially treated with surgical resection, 114 (31.7%) developed a local recurrence, of which the majority of patients were then successfully managed with watchful waiting [9]. These data, combined with the recognition that surgical resection of DT can result in significant long-term morbidity including abdominal wall weakness, short-gut syndrome, and chronic pain, have led to the current recommendation of watching waiting for patients with asymptomatic DF [10, 11].

It should be noted that anatomic site should be taken into consideration for a watchful waiting strategy. Specifically, although it is reasonable to consider watchful waiting for DT located in critical sites (i.e., mesentery), watchful waiting requires consistent and reliable follow-up for changes in imaging as well as symptom development, with a particularly low threshold for repeat imaging for patients with DT in critical sites as significant progression can be devastating.

Surgery

For patients that require treatment due to symptoms or risk of functional impairment, preservation of quality of life and function have become the priority. As discussed later in this article, there is increasing utilization of systemic therapy, radiation therapy, and other novel treatment modalities such as cryotherapy with excellent local control rates. However, surgery can be considered first line if surgical morbidity is limited. For patients that require surgical resection after multidisciplinary discussion, resection should aim at obtaining microscopic negative margins (R0) but microscopic-positive margins (R1) can be accepted to preserve function. However, even after margin negative resection, local recurrence remains an issue with up to 35% of patients developing a local recurrence after primary resection. In patients being undergoing surgery for previously resected disease, the recurrence rate is as high as 50% [10]. For patients that undergo R1 resection, observation or re-resection can be considered, after weighing the risks of re-resection vs. the morbidity of recurrence.

Radiation

When local therapy is recommended for desmoid tumors, radiation therapy (RT) is an effective, alternative option to surgery. Multiple considerations are factored in when determining which local therapy strategy to employ. In some clinical situations, RT may be the preferred local therapy when the tumor size or location has increased risk of causing functional consequences following wide local excision. However, when tumors are small and resection can be easily performed with low morbidity risk, surgery is often the preferred local treatment strategy unless the patient elects for a non-operative approach.

Desmoid tumor control is comparable when evaluating local control of patients receiving definitive RT compared to surgery alone. Long-term local control following definitive RT is achieved in approximately 65 to 80% of desmoid tumors [12–15], similar to large surgical series. One of the largest RT series was recently published evaluating 209 patients; the 5-year local control was 71% [14]. Another larger series evaluated 101 patients and reported a 10-year local control of 78% [15]. These data reveal favorable tumor control when radiation doses commonly between 56 and 60 Gy are delivered to gross tumor. Limited data are available to support the use of postoperative RT following a positive margin resection, and therefore, adjuvant therapy is not commonly recommended.

Despite overall durable tumor control with either RT or surgery, there is increasing recognition that not all tumors respond equally well. A study evaluating 412 patients observed that certain patient or tumor characteristics were associated with an increased risk of recurrence which included young patients stratified at ≤30 years old, extremity tumor locations, and larger tumor size [16]. Local control was noted to be ≤59% if any one of those factors was present. Previous studies have identified similar risk factors [15, 17, 18]. These studies reinforce that patient selection for local therapy, including RT, is critical.

Importantly, in addition to tumor control, toxicity risk needs to be considered when dispositioning local therapy. Radiation therapy can cause increased fibrosis and decreased range of motion depending on the location of the tumor.

Additionally, in these often young patients, the risk of secondary malignancies is an important consideration [16].

Following irradiation of the desmoid tumor, radiographic responses vary. Some tumors will regress while other remaining stable. The maximal response, however, whether measured by radiographic response or improved clinical symptoms, can take months to years.

Altnerative Local Control Methods

An additional treatment modality that has received some attention in recent years is percutaneous ablation. Cryoablation and/or radiofrequency ablation are of interest as a local procedures that may in select cases be less morbid than surgery, and can be performed even in locations that have been previously operated on or irradiated. There is limited long-term data available on the efficacy of this treatment, though early experiences suggest that the treatment can be effective in relieving pain and reducing tumor size. While techniques are evolving, the treatment is most straightforward in patients with smaller tumors and those not immediately adjacent to critical structures [19–22].

These therapies are considered minimally invasive, however depending on location, may still require general anesthesia to administer due to pain and need for immobilization. Also, when tumors are located in proximity to vital structures, ablation of the entire lesion may not be possible. The durability of symptom or dimensional benefit, particularly in partially treated tumors, is unclear. Our practice is generally to consider this option in patients in whom other therapies have failed or are felt to be unsuitable after multidisciplinary discussion.

Systemic Agents

Since the early 1980s, there has been interest in identifying systemic agents that may be of utility in treating patients with DF where local therapy is not feasible. In recent years, this has resulted a multitude of options (Table 1) which have facilitated increasing use of systemic therapy in the front line, including in patients who might otherwise be surgical candidates.

Hormonal Agents and NSAIDs

Given the increased incidence of sporadic DF in women and the observation that DF is often diagnosed or noted to progress rapidly during pregnancy [23], hormonal manipulation has been of interest as a treatment modality. A subset of patients with FAP-related desmoids have found to express estrogen receptors (ERs), and even ER-negative patients may have high level of anti-estrogen binding sites. The most commonly used hormonal agent in the literature is the selective estrogen receptor modulator (SERM) tamoxifen, with or without a non-steroidal inflammatory drug (NSAID) as an adjunct [24–26]. The largest available series investigating a hormonal approach was conducted by Fiore et al. reporting on the use of torimefene in 44 patients. The authors reported a 25% PR rate, with another 65% of patients with SD. Other studies have shown similar disease control rates [27–29], however are no controlled data that support the efficacy of these drugs above a watchful waiting approach, though case series and reports have been cited to support their use.

Similarly, there are limited data to support the efficacy of NSAIDs, either as single agents or as an adjunctive therapy, in patients with DF. After an initial case report of regression of DF in a patient treated for pericarditis with indomethacin [30], several small studies documented patients treated with NSAIDs, often in combination with other agents, with disease stabilization or shrinkage [26, 31, 32]. The largest of these, a series of FAP patients from the Cleveland Clinic, demonstrated 1 CR and 7 PRs out of 14 patients treated with sulindac [33].

Low-Dose Methotrexate and Vinblastine

In 1989, Weiss and Lackman described a series of 8 DF patients treated with the combination of methotrexate (MTX) and vinblastine with responses ranging from 10% reduction to complete remission [34]. A subsequent study of the combination was conducted by the Instituto Nazionale per lo Studio e la Cura dei Tumori in Italy which enrolled 30 patients with inoperable DF and demonstrated a response rate of 40%, with PFS of 65% at 10 years with a median follow-up of 72 months [35]. This analysis was updated in 2017 to include 75 patients with DF, treated with variable vinka alkaloid + MTX combinations over a 25-year period. They documented a RECIST 1.1 overall response rate of 48% with an additional 51% of patients achieving stable disease. Only 1 patient out 75 had progressive disease (PD) by RECIST, with a total of 4 treatment interruptions due to clinical PD. Median time to response was 6 months [36].

MTX and vinblastine is a well-tolerated regimen with clear efficacy. Noteably, as born out in the available case series, time to response can be long and lower response rates in some studies may be related to inadequate long-term follow-up, or courses of therapy that are not long enough to achieve an adequate dimensional response. While this therapy remains a part of the armamentarium for treatment of desmoid fibromatosis, newer novel agents have superseded it as the treatment of choice in most patients as they are often orally administered and have acceptable side effect profiles.

Doxorubicin and Pegylated Liposomal Doxorubicin

While larger prospective experiences of patients receiving doxorubicin for desmoid fibromatosis are lacking, several

Table 1 Selected studies of systemic agents and response rates

Drug	Authors and year	Number of patients	Response (criteria)
Toremifene	Fiore et al. 2015	44	0% CR, 25% PR, 65% SD, 10% PD (RECIST)
Methotrexate and vinblastine or vinorelbine	Palassini et al. 2017	70	1% CR, 47% PR, 51% SD, 1% PD (RECIST)
	Constantinidou et al. 2011	18	0% CR, 11% PR, 60% SD, 22% PD (WHO or RECIST)
	Garbay et al. 2011	27	0% CR, 15% PR, 52% SD, 33% PD (RECIST)
	Toulmonde et al. 2019	20	0% CR, 25% PR, 50% SD, 20% PD (RECIST)
Pegylated liposomal doxorubicin	Constantinidou et al. 2011	14	0% CR, 33% PR, 67% SD, 0% PD (WHO or RECIST)
Doxorubicin and dacarbazine	Gega et al. 2006	7	43% CR, 57 % PR, 0% SD, 0% PD (WHO)
	Patel et al. 1993	9	22% CR, 44% PR, 33% SD, 0% PD (not specified)
Imatinib	Chugh et al. 2010	51	0 % CR, 0% PR, 84% SD, 10% PD (RECIST)
	Kasper et al. 2017	38	0% CR, 18% PR, 29% SD, 42% PD (RECIST)
	Penel et al. 2010	40	3% CR, 5% PR, 75% SD, 5% PD (RECIST)
Sorafenib	Gounder et al. 2018	49	2% CR, 30% PR, 67% SD, 0% PD (RECIST)
Pazopanib	Toulmonde et al. 2019	46	0% CR, 37% PR, 59% SD, 4.4% PD (RECIST)

small retrospective series support the use of doxorubicin and doxorubicin-based combination treatments for patients with DF. These range from reports utilizing single agent, conventional doxorubicin [37, 38], or, more commonly in recent years, pegylated liposomal doxorubicin, with partial response rates ranging from 33 to 75% [37, 39–41]. In the combination therapy space, the most commonly studied combination is doxorubicin and dacarbazine, with response rates ranging from 54 to 100% in small series [37, 42, 43]. Responses to doxorubicin-based therapy are often durable and reported rates of CR are higher than with other therapies [37]. How doxorubicin and doxorubicin-based combination therapies compare to newer, novel agents including TKIs and investigational agents remains an open question. Given the possible long-term toxicities, including second malignancies and cardiac damage, we generally limit the use of anthracycline-based therapies to patients who require urgent responses for symptom relief, prevention of a pending anatomical complication, or those who have been refractory to other agents.

Tyrosine Kinase Inhibitors

Imatinib has been studied in several prospective trials as a treatment for desmoid fibromatosis. The first report of the drug's efficacy was by Mace et al. in 2002. This report demonstrated variable c-kit and PDGFR-α expression in several desmoid patient samples. The investigators went on to describe two patients with history of failure on other therapies who received the drug, one with stabilization of disease and another with dimensional response [44]. The role of KIT and PDGFRA expression was called into question in a subsequent analysis of 19 patient samples that demonstrated little to no KIT or PDGFRA expression but documented Wnt pathway alterations (in *APC or CTNNB1)* is 84%. This study confirmed that now commonly accepted role of the Wnt/β-catenin pathway, and suggested that PDGFRB may be the actual target of imatinib in desmoid fibromatosis rather than KIT or PDGFRA. In the accompanying clinical study, 16% of patients had a partial response to imatinib by Southwest Oncology Group (SWOG) criteria, and 37% of patients remained progression free at 1 year [45].

Larger clinical studies of imatinib in DF have subsequently been conducted. One such trial, conducted by the Sarcoma Alliance for Research through Collaboration (SARC), treated 51 patients with disease where surgery was not feasible with varying doses of imatinib ranging from 200 to 600 mg per day based on body surface area (BSA). The authors observed a 1-year PFS of 66% with a 6% objective response rate by RECIST, with a time to response ranging from 19 to 26 months [46]. Another series conducted by the French Sarcoma Group Other series of patients with desmoid fibromatosis treated with imatinib demonstrated a response rate (PR + CR) of 12%, and PFS at 2 years of 55% [47].

Additionally, the German Interdisciplinary Sarcoma Group conducted a study of imatinib 800 mg daily in 38 patients. In contrast to other uncontrolled studies done with imatinib in DF, this study required progressive disease by RECIST within 6 months prior to enrollment, likely selecting for a more refractory population and allowing for a more robust assessment of imatinib's potential to modify the clinical course of the disease. At 24 months, PFS was 45% with an overall response rate of 19% at 21 months.

In recent years, attention has shifted away from the relatively narrow spectrum TKI imatinib to the multitargeted TKIs pazopanib and sorafenib. The first retrospective series of patients treated with sorafenib was published by Gounder

et al. in 2011. In 26 patients with treated at a dose of 400 mg daily (half the labeled dose for patients with hepatocellular and renal carcinoma), 70% of patients had symptomatic improvement, 25% had a RECIST PRs, and an additional 70% had SD [48]. This report led prompted a double-blind, placebo-controlled, randomized phase II study of sorafenib in patients with DF. A landmark trial in this disease, the study is notable for its successful accrual of a placebo control arm, an acknowledgement that watchful waiting is an increasingly accepted initial strategy. Patients enrolled in the study had to have 10% unidimensional progression in the previous 6 months, inoperable disease, or symptoms. Forty-three percent of patients included in the study met the criterion of progressive disease within 6 months, suggesting a study population at moderately high risk for progression. The response rate by RECIST in the sorafenib arm was 33% in contrast to 20% in the placebo arm, with a median time to response of 9.6 months versus 13.3 months with placebo [49]. Given the clear efficacy and tolerable (though occasionally problematic) side effect profile, sorafenib has quickly become the most commonly utilized therapy in our practice for patients who have failed surveillance or have mild/moderate symptoms from their DF and require treatment.

Pazopanib is another multi-targeted TKI with increasing evidence for its role in DF. The drug's efficacy was initially suggested in a report of two patients with durable benefit [50]. A subsequent randomized, non-comparative phase II study of 72 patients treated with either MTX and vinblastine or pazopanib demonstrated that 83% of patients treated with pazopanib remained progression free at 6 months, in contrast to 45% with MTX and vinblastine. The pazopanib arm also seemed to demonstrate better improvement in pain [51]. In our practice, sorafenib is the most commonly utilized TKI in patients with DF, though there is no comparative data to support its efficacy over pazopanib. The toxicity profiles of the two drugs are distinct, allowing for selection of agents based on patient's priorities and lifestyle, and offering an alternative if one of the two is poorly tolerated.

Clinical Trials/Experimental Therapies

Given that the central event in the pathogenesis of desmoid fibromatosis is excess activity in the Wnt/β-catenin pathway, inhibition of β-catenin activity is of interest as a therapeutic strategy. Tegavivint is a small molecule which interferes with the complexing of β-catenin and TBL-1, and has shown growth inhibition in osteosarcoma, acute myeloid leukemia, and multiple myeloma preclinical models [52–54] The drug is currently being employed in a phase 2a clinical trial for patients with DF.

Another potentially efficacious agent under investigation for DF is nirogacestat, a gamma-secretase/notch inhibitor. While the precise mechanism of action is not fully understood, there is preliminary clinical evidence of activity. The initial phase I study of the compound demonstrated a partial response in 5 out of 7 evaluable DF patients, with the remaining 2 patients having stable disease. All of the patients who achieved a PR continued to respond in a subsequent long-term follow-up [55]. In a phase II study in DF patients, 5 out of 16 evaluable patients achieved a PR, and another 11 achieved stable disease by RECIST (with the 6 of the 11 having at least some tumor shrinkage). This drug is currently being evaluated in a phase III placebo-controlled randomized study in patients with DF.

Conclusions

Given the wide spectrum of treatments available for DF, ranging from local therapy with surgery, RT, percutaneous treatments, and a growing list of efficacious systemic therapies, there is now substantial ability to tailor treatments to the patient and their priorities. Nearly all patients with asymptomatic DF should receive a period of watchful waiting. For those with symptoms, progression on surveillance, or anatomical considerations warrant therapy, there is increasing ability to select treatment taking into account the patients risk factors for recurrence, location, and potential disease/treatment-related morbidity. Intrabdominal DF, particularly in patients with FAP, is rarely amenable to local methods like radiation and surgery, and patients with progressive disease are now most often managed with systemic therapies. Even in extremity and trunk sporadic DF, where surgery is often feasible with acceptable morbidity, our practice pattern has shifted towards systemic agents, particularly in young patients who are higher risk for relapse.

With respect to selection of systemic agents, the range of options available allows for tailoring of treatment. Less intensive therapies with questionable efficacy, including tamoxifen, NSAIDs, and imatinib, are less frequently used in our practice unless the patient is also a candidate for watchful waiting. The majority of patients requiring therapy receive sorafenib, with a subset that still elect to receive MTX and velban due to a generally favorable toxicity profile. Front-line use of doxorubicin-based therapies, including PLD, is more often reserved for patients who have either failed TKIs or urgently require a response, though data supporting better efficacy with anthracycline-based therapy are lacking, and the tolerability of PLD approaches that of the commonly used TKIs.

The outlook for the future of DF management continues to be hopeful, with investigational approaches and agents that may continue to decrease therapy-related morbidity while also maximizing efficacy and quality of life. The recent development of a patient-reported outcome instrument that measures the symptom burden of this disease and its treatment [56], and

its subsequent integration in prospective studies, will likely be important in rationally prioritizing the growing list of available therapies.

Compliance with ethical standards

Conflict of Interest Ravin Ratan currently oversees a clinical trial funded by Springworks Therapeutics, and has also received consulting fees from the same. He also has patients treated with Springworks' drug on a compassionate access protocol. Christina L. Roland has received research funding for clinical trials from Bristol-Myers Squibb paid to her institution. Andrew J. Bishop declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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