Management of Desmoid Tumors

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KEYWORDS

• Desmoid tumors • Desmoid-type fibromatosis • Aggressive fibromatosis
• Active surveillance • Outcomes

KEY POINTS

- Active surveillance, defined as serial MRI (ie, at 1–2 months after diagnosis and then every 3–6 months), is considered the first line of treatment for most patients with desmoid tumors (DT), according to international guidelines.
- Switching from active surveillance to treatment is considered in case of progressive symptoms and/or persistent interval growth.
- The choice of the first-line systemic therapy and the management of recurrence still represent a therapeutic challenge, for which well-defined and shared guidelines are lacking.
- Currently available treatments include tyrosine kinase inhibitors, liposomal doxorubicin, low-dose chemotherapy with IV methotrexate + vinblastine/vinorelbine, or oral vinorelbine alone. Some evidence exists concerning the efficacy and safety of pegylated liposomal doxorubicin, whereas studies are ongoing to test nirogacestat and tegavivint as new therapeutic agents.
- Function and structure preservation and attention to patients' quality of life are currently considered necessary in the management of patients with DT.

INTRODUCTION

Desmoid tumors (DT), also known as desmoid fibromatosis, are rare fibroblastic neoplasms that arise from the deep soft tissues and show a locally aggressive behavior in the absence of metastatic potential.[1] The incidence is 5 to 6 cases per million a year, with a peak in the third and fourth decades of life and a 2:1 female:male predominance.[2,3] Approximately 5% to 10% of cases are associated with familial adenomatous polyposis (FAP).[2]

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DT can arise from multiple abdominal and extra-abdominal locations, including the extremities, limb, girdles, thoracic wall, breast, and head and neck.[4] The occurrence of DT in the abdominal wall is more common in women, particularly during or after pregnancy,[5] whereas localizations in the abdominal wall and in the mesentery are more common in patients with FAP.[6]

DT require a multidisciplinary management in order to address symptoms while offering the best chances of care.[7]

A paradigm shift has occurred when upfront surgery has been replaced by active surveillance in most patients.[8] When active treatment is required, several systemic and local treatments are considered, including tyrosine kinase inhibitors (TKIs), conventional chemotherapy, and radiotherapy (RT).[9] Acknowledging the possible involvement of aberrancies in the Notch pathway in the development of DT, γ-secretase inhibitors have also been considered more recently as possible therapeutic agents for patients with nonresectable disease.[10]

In order to address the scarcity of prospective studies and meta-analyses, and in the effort of harmonizing treatment strategies worldwide, global consensus meetings were held in the recent years, leading to the release of evidence-based guidelines.[8,9]

The aim of the current article is to conduct a systematic review to summarize the recent literature on the management of DT, with a particular focus on the role of active surveillance and the most recent advances in systemic and local therapies.

MOLECULAR ASPECTS

The current guidelines recommend mutational analysis for the diagnosis of DT.[8,9] Approximately 90% of DT are characterized by point mutations on exon 3 of the *CTNNB1* gene, determining a disruption of the Wnt/Beta-catenin signaling.[11] Three specific amino-acid changes, T41A, S45F, and S45P, are responsible for the constitutive activation of the Wnt/Beta-catenin signaling cascade in most patients with DT. In a minority of patients, DT are associated with a mutation in the *APC* gene on chromosome 5, a negative regulator of beta-catenin stability, which is responsible for FAP.[2] Particularly, mutations happening between codons 543 to 713 and 1310 to 2011 of *APC* were associated with an increased risk to develop DT in FAP patients.[12] Because *CTNNB1* mutations and *APC* mutations are mutually exclusive, current guidelines strongly recommend that patients with DT with a *CTNNB1* wild-type status are investigated for FAP with a colonoscopy and/or a germline testing.[9]

The presence of different *CTNNB1* mutations has been found to affect the risk of recurrence of DT following active treatment. A recent meta-analysis showed that patients with DT with a *CTNNB1* S45F mutation had a higher risk of recurrence following surgery compared with T41A, S45P, and *CTNNB1* wild-type patients, even though this association appeared to be mediated by tumor size.[13] Patients with an S45F mutation were also found to have a poor response to meloxicam and imatinib.[14,15]

Timbergen and colleagues[16] stated the hypothesis that prognostic differences in *CTNNB1*-mutated patients could be determined by the presence of different methylation patterns. Nevertheless, a genome-wide analysis of 29 DT cases failed to demonstrate differences in DNA methylation patterns of patients harboring either an S45F or a T41A mutation. On the other hand, DNA methylation patterns seemed to correlate with tumor size, thus suggesting that methylation alterations in DT may develop with a stepwise modality.

Finally, Bräutigam and colleagues[17] aimed to evaluate the role of hormonal receptors and PARP-1 expression as risk factors for DT recurrence. Although the expression of hormonal receptors did not seem to affect recurrence risk, the expression of

PARP-1 in all 69 cases included in the analysis led to the hypothesis that there is a possible role of this gene in the pathogenesis of DT. Nevertheless, PARP-1 expression resulted in being extremely heterogeneous depending on the cutoff used, so caution is needed in interpreting these findings.

ACTIVE SURVEILLANCE

Active surveillance, defined as serial MRI (ie, at 1–2 months after diagnosis and then every 3–6 months), is considered the first approach to most patients with DT, according to international guidelines.[2,8,9] Treatment is currently reserved to patients presenting with complications or with large tumors located in potentially life-threatening sites. Special consideration concerning active surveillance as a first-line treatment should be given to specific conditions. Front-line therapies should be considered in particular situations, including patients with chronic pain, pregnancy, and FAP-associated DT. This indication is supported by the evidence that up to 60% of patients with DT do not progress, and up to 30% experience spontaneous tumor regression. Regression can also occur after initial progressions, as reported in some prospective observational studies.[18]

Although the behavior of DT is difficult to predict, tumor location seems to play a major role in the definition of prognosis, with abdominal wall tumors being more indolent than extra-abdominal ones. In a study by Bonvalot and colleagues[19] on 147 patients with abdominal wall DT, about one-third of patients managed with active surveillance did not show disease progression at 36 months, whereas another third experienced spontaneous regression.

Several studies supported the noninferiority of active surveillance compared with surgery in terms of disease-free survival (DFS) also in extra-abdominal DT. In 2009, Fiore and colleagues[20] analyzed the long-term outcomes of 142 patients treated at 2 major centers in France and Italy and found a 5-year progression-free survival (PFS) of approximately 50% in patients managed conservatively; the rate of progression was similar to those who received medical treatment as first line. Similar results were achieved by Penel and colleagues[21] on a series of 771 patients: slightly more than 50% of patients did not experience progression at 2 years, and long-term outcomes were comparable between patients treated conservatively and those who received upfront surgery. Interestingly, patients with tumors located in unfavorable sites seemed to benefit most from an initial management with active surveillance. Favorable long-term outcomes of active surveillance compared with upfront surgery were also confirmed by a recent study by Ruspi and colleagues[22] on 87 consecutive patients treated at Humanitas Clinical and Research Center in Milan. It should be noted that, although PFS represents an adequate end point to evaluate the efficacy of treatments, studies investigating the optimal management of DT should also take into account quality of life (QoL), functional impairment, use of narcotics, and impact on activities of daily living. A Dutch prospective trial is currently recruiting, evaluating these critical endpoints in adult patients with DT.[23]

According to a recent meta-analysis, including 25 studies and 3527 patients, most patients who are initially managed with active surveillance never progress, whereas only one-third needs to switch to another treatment, such as systemic treatment and surgery, after a period of time ranging from 6.5 to 19.7 months.[24] Of note, an initial conservative approach does not jeopardize the efficacy of following treatments, either surgical or medical, in the event of progression or recurrence,[8] as confirmed by several studies.[20,25] In an analysis of 216 patients managed with active surveillance, Colombo and colleagues[25] found a 5-year crude cumulative incidence of 5% (95%

confidence interval [CI]: 1.7%, 14%) of conversion to surgery and of 51% (95% CI: 41%, 65%) of conversion to other treatments. Moreover, no differences were found on overall survival at 5 and 10 years compared with patients who underwent front-line surgery.

These results, along with the consideration of surgery-related morbidity, including postoperative pain and loss of function, further confirm active surveillance as a good initial choice for the management of most patients with DT.

Patients who experience acute and/or chronic pain and functional impairment are frequently candidates to more aggressive first-line therapies. Nevertheless, the pathogenesis of pain could be multifactorial, and surgical resection could fail to achieve pain control. Thus, the indication to active surveillance as a first-line treatment should be maintained in this subset of patients, whenever possible.[8,26]

Similarly, although DT can appear or progress during pregnancy,[17] they usually tend to regress after delivery; thus, pregnancy per se does not constitute an indication for first-line aggressive treatment.[5,26]

In FAP-associated DT, resection of the primary tumor or early start of a pharmacologic treatment needs to be considered earlier, owing to a higher risk of complications, including intestinal obstruction, perforation, and mesenteric ischemia. Nevertheless, treatment should aim to preserve an adequate digestive function, so as to minimize the impact on patient's QoL. Thus, it is acceptable to treat complications without proceeding to resection of the primary tumor, in case this should result in an excessive sacrifice in terms of function.[26] On the other hand, upfront pharmacologic treatment with low-dose methotrexate and vinca alkaloids or TKIs can be considered in order to reduce morbidity and loss of function connected to surgical treatment.[27]

A recent study by Duhil de Bénazé and colleagues[28] analyzed the outcomes of 81 pediatric patients treated for DT in France. Overall, 52/80 participants (65%) answered the QoL questionnaires, of whom only 30 underwent active surveillance as a first-line treatment. Moreover, the study did not use a validated desmoid patient-reported outcomes (PRO) tool. Thus, despite that the study showed good results in terms of functional impairment, pain management, and social behavior in this population, the results should be interpreted with caution and need further confirmation from specifically designed studies.

Active surveillance should also be considered in patients undergoing incomplete surgery (ie, positive surgical margins). In 2003, Gronchi and colleagues[29] analyzed a series of 203 patients undergoing surgery for primary or recurrent extra-abdominal DT and found that microscopically positive margins did not affect DFS. Similarly, Crago and colleagues,[30] analyzing a cohort of 495 patients with DT who underwent surgery at Memorial Sloan Kettering Cancer Center between 1982 and 2011, did not find any significant association between the status of surgical margins (R0 vs R1) and the risk of recurrence. Based on these findings, active surveillance is currently recommended by international guidelines for the management of patients following R1 surgical resection.[9] At the 2021 ASCO Annual Meeting, Braggio and colleagues[31] presented the initial results of the natural history study from The Desmoid Tumor Research Foundation (DTRF), showing that approximately half of included patients had been managed with active surveillance at diagnosis. Active surveillance was also used as a first-line option in nearly 40% of 487 patients from the NetSARC and CONTICABASE French databases, with good results in terms of PFS, as reported by Bouttefroy and colleagues[32] at ESMO Virtual Congress 2020. A prospective trial is currently active in France, with the primary aim to assess the incidence of DT from 2016 on, and that will furnish data concerning the management of these patients and tumor response to treatments in terms of PFS. The initial results of the National

Clinical-biological Prospective Cohort of Incident Cases of Aggressive Fibromatosis trial are expected to be presented during ESMO 2021.[33]

INDICATIONS FOR TREATMENTS

According to a recent consensus statement,[26] active treatment of DT should be offered in case of intra-abdominal complications, particularly in patients with FAP-associated DT, and in patients with large tumors located in sites where progression could become life-threatening (ie, neck, mediastinum, and mesentery).

Switching from active surveillance to treatment is considered in the case of progressive symptoms and/or persistent interval growth.[2] The decision to undertake an active treatment should be shared with the patient, considering clinical and radiological findings, symptoms, and functional limitations. Recent guidelines suggest to consider switching from active surveillance to treatment after at least 3 consecutive reevaluations, and possibly after at least 1 year from the diagnosis.

In the case of disease progression, the first-line treatment is represented by either surgery or systemic therapies, based on tumor location. Surgery can be considered, taking into account some expected morbidities, for abdominal wall DT, whereas for all other locations, surgery represents a second-line therapy after failure of systemic treatments, such as chemotherapy and molecular targeted therapies.

SYSTEMIC TREATMENTS

Systemic treatments may represent the first line of treatment of intra-abdominal, retroperitoneal, and pelvic DT, along with tumors involving the extremities, girdles, thoracic wall, thoracic cavity, and head and neck region.[9] Systemic therapy should also be considered in patients who are at high risk of recurrence, such as young patients, those with an extremity location, and those with large tumors.[34]

Antihormonal therapies and nonsteroidal anti-inflammatory drugs showed limited efficacy in patients with DT and are not generally recommended.[35–38] Currently available treatments include TKI, liposomal doxorubicin, low-dose chemotherapy with IV methotrexate + vinblastine/vinorelbine, or oral vinorelbine alone.[8,9,21,39–45] TKI, such as sorafenib and pazopanib, were found to be safe and effective, with manageable side effects owing to their low dosage.[42,44–48] Recently, promising results in terms of disease control were achieved with apatinib and anlotinib in patients with DT located to the extremities, with an acceptable safety profile.[49,50]

Low-dose chemotherapy with methotrexate and vinblastine/vinorelbine also showed favorable results: in a randomized trial on 72 patients treated at 12 centers from the French Sarcoma Group, the investigators reported a PFS of 79% at 1 and 2 years.[45] Recently, a phase II trial showed that biweekly administration of methotrexate and vinblastine was well tolerated and more effective compared with weekly administration.[51] Weekly methotrexate + vinca alkaloids were also found to be active and tolerated in patients with FAP-associated DT allowing for disease control in 95% of patients.[52] Finally, oral vinorelbine was found to be effective, safe, and well tolerated in patients with progressive DT following active surveillance.[53] Nevertheless, chemotherapy regimens with methotrexate and vinca alkaloids are known to be associated with some relevant side effects, including myelosuppression with grade 3 or 4 neutropenia, which occurs in a significant rate of patients.[45]

Some studies also reported promising results using pegylated liposomal doxorubicin, which has been shown to be associated with a lower risk of neutropenia and cardiac toxic effects compared with parenteral doxorubicin.[54,55] Recently, a systematic review and meta-analysis conducted by the guideline committee for clinical care of

extra-abdominal desmoid-type fibromatosis in Japan reported a good efficacy of doxorubicin-based and liposomal doxorubicin chemotherapy, with a lower rate of G3 or G4 complications for liposomal doxorubicin chemotherapy regimens. These findings led to the committee formulating a weak recommendation favoring the use of doxorubicin-based chemotherapy regimens in patients with DT, despite a low evidence level.[56]

Recently, nirogacestat (PF-03084014), an orally available drug with effect on the Notch signaling, was also proved to be effective and safe in patients with DT.[10,57,58] The DeFi study, a randomized double-blind international clinical trial, is ongoing, comparing the efficacy of nirogacestat versus placebo in adult patients with progressing DT,[59] whereas the RINGSIDE trial, designed to evaluate the efficacy and safety of another inhibitor of the Notch pathway, AL102, is currently recruiting.[60]

Finally, tegavivint, an inhibitor of the Wnt and beta-catenin pathway, is currently being tested as a new therapeutic agent.

Because of the absence of comparative studies, the treatment plan should take into account the anticipated toxicity, switching from less toxic to more toxic agents in a stepwise fashion. In order to guide the treatment choice, The Desmoid Tumor Working Group, an international group of multidisciplinary clinicians and patient advocates, developed a model including the following variables: level of evidence, overall response rate, PFS rate, ease of administration, and expected toxicity.[9]

LOCAL TREATMENTS

RT is currently considered a treatment following surgery or systemic therapies, particularly when surgery carries a high risk of morbidity.[2] Definitive RT at moderate doses (ie, 50 Gy) can achieve local control in approximately 70% of patients, even though long-term side effects should be taken into account, particularly in young patients.[61] One issue with RT is the risk of radiation-associated sarcomas[62]; therefore, RT is not generally recommended, unless in refractory disease where other options have been exhausted.

Recently, cryotherapy, defined as the administration of repeated cycles of freezing or passive thawing of the tumor, has been proposed as an alternative to RT.[63,64] The phase II trial (CRYODESMO-O1) conducted on 50 patients with extra-abdominal progressive disease following at least 2 lines of systemic treatments, with functional symptoms or pain, and with inoperable tumors, showed favorable results in terms of efficacy, with an observed nonprogression rate at 12 months of 85.8%. The investigators also reported promising results in terms of safety, pain management, and QoL.[65]

ASSESSMENT OF TUMOR GROWTH DURING OBSERVATION AND RESPONSE TO TREATMENT

DT have an unpredictable behavior: some of them progress locally, whereas others remain stable or even spontaneously regress during time.[20,66,67]

Several studies were conducted in order to identify radiological signs of progression during active surveillance and to assess risk factors of a more aggressive behavior. Recently, Cassidy and colleagues[68] analyzed 37 patients managed with active surveillance at Memorial Sloan Kettering Cancer Center, finding that the presence of hyperintense T2 signal in $\geq$90% of baseline tumor volume was related to disease progression. Moreover, Murahashi and colleagues[69] found that the so-called black fiber sign (ie, the presence of low-signal-intensity bands) on T1- or T2-weighted images was a predictor of an indolent behavior. In a retrospective case series of 59 patients,

the absence of the black fiber sign was related to a higher risk of progression and need to switch to an active treatment.

Some investigators also proposed patient-tailored follow-up strategies depending on the predicted risk of progression, based on the presence of radiologic risk factors. Gondim Teixeira and colleagues[70] conducted a retrospective analysis of 48 patients with DT, finding that muscle/tumor T2 signal ratio was related with tumor growth. Based on the observation that tumors with T2 signal ratios lower than 1 tended to have an indolent behavior, the investigators proposed a 12-month interval for active surveillance of these patients.

Radiologic findings are also used to predict response to treatment in patients undergoing systemic therapies and recurrence following radical surgery. According to international guidelines, response evaluation should be defined according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).[9] Nevertheless, RECIST criteria can be difficult to apply in a clinical setting, partly because of the difficulties in assessing tissue cellularity.

During the last few years, radiomics has been used to identify prognostic factors of response to treatment. A multicentric study conducted by the French Sarcoma Group led to the development of a radiomics score that showed better performances in predicting PFS (CI 0.84; 95% CI, 0.71–0.96) compared with conventional radiologic criteria.[71] Radiomics was also proposed for the differential diagnosis of DT from soft tissue sarcomas. A radiomics model proposed by Timbergen and colleagues[72] showed good accuracy; nevertheless, radiomics is currently unable to predict the mutational status and cannot be considered an alternative to histology.

QUALITY OF LIFE

Because DT are locally aggressive tumors often arising in young patients, maintaining a good QoL is pivotal. Since the late 1990s, when Brennan and colleagues first compared the results of major amputation to observation in patients with recurrent desmoids of the extremity,[66] function and structure preservation have been considered necessary in the management of patients with DT.

In a recent work, Newman and colleagues[73] examined the associations between treatment modalities and Patient-reported Outcomes Measurement Information System function scores. Function scores were found to be lower in patients who underwent multiple surgical resections or RT. The investigators also reported that patients managed with local treatments had similar event-free survival rates compared with those receiving systemic treatment, thus further confirming the primary role of systemic therapies in the management of these patients.

Acknowledging the need for specific tools to assess QoL of patients with rare neoplastic conditions, Gounder and colleagues[74] also used PROs in order to develop a model to rate QoL of patients with DT. Their work resulted in an 11-item symptom scale and a 17-item impact scale, named the GODDESS (Gounder/DTRF Desmoid Symptom/Impact Scale), which is currently available in multiple languages and is being validated in the ongoing phase 3 trials.[74–77]

SUMMARY AND OPEN QUESTIONS

The management of DT is shifting more and more toward conservative and patient-tailored strategies, also thanks to the employment of radiologic and radiomics criteria, which are able to predict the risk of progression and the response to treatment. In order to offer better chances at PFS and an acceptable QoL, case discussion in the

context of a multidisciplinary tumor board at a center of excellence is highly recommended.

The assessment of tumor mutational status and the discovery of new mutations could provide enhanced prognostic tools to guide the choice of primary treatment, in the case of failure of active surveillance.

Surgery is still considered a first-line active treatment in only few selected cases and for the management of selected intra-abdominal complications.

The choice of the first-line systemic treatment continues to be a matter of debate; according to current guidelines, no specific criteria exist to select the appropriate treatment based on tumor location.

Finally, recurrence still represents a therapeutic challenge, for which well-defined and shared guidelines are still lacking, the next project for The Desmoid Tumor Working Group.

DISCLOSURE

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