Desmoid Tumors: Clinical Features and Treatment Options for Advanced Disease

BERND KASPER,^a PHILIPP STRÖBEL,^b PETER HOHENBERGER^a

^aITM-Interdisciplinary Tumor Center Mannheim, Sarcoma Unit, and ^bInstitute of Pathology, University of Heidelberg, Mannheim University Medical Center, Mannheim, Germany

Key Words. Aggressive fibromatosis • Desmoid tumor • Advanced disease • β -catenin • Individualized treatment

Disclosures: Bernd Kasper: *Honoraria:* Merck Sharp & Dohme GMBH, PharmaMar; Philipp Ströbel: None; Peter Hohenberger: *Honoraria:* Novartis; *Research funding/contracted research:* Novartis.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

ABSTRACT

Desmoid tumors describe a rare monoclonal, fibroblastic proliferation characterized by a variable and often unpredictable clinical course. Although histologically benign, desmoids are locally invasive and associated with a high local recurrence rate, but lack metastatic potential. On the molecular level, desmoids are characterized by mutations in the β -catenin gene, *CTNNB1*, or the adenomatous polyposis coli gene, *APC*. Proof of a *CTNNB1* mutation may be useful when the pathological differential diagnosis is difficult and location might be predictive for disease recurrence.

Many issues regarding the optimal treatment of patients with desmoids remain controversial; however, surgery is the therapeutic mainstay, except if mutilating and associated with considerable function loss. Postoperative radiotherapy reduces the local recurrence rate,

in cases of involved surgical margins. Because of the heterogeneity of the biological behavior of desmoids, including long periods of stable disease or even spontaneous regression, treatment needs to be individualized to optimize local tumor control and preserve patients' quality of life. Therefore, the application of a multidisciplinary assessment with multimodality treatment forms the basis of care for these patients. Watchful waiting may be the most appropriate management in selected asymptomatic patients. Patients with desmoids located at the mesentery or in the head and neck region could present with life-threatening complications and often need more aggressive treatment. This review describes treatment options and management strategies for patients with desmoid tumors with a focus on advanced disease. *The Oncologist* 2011;16:682–693

INTRODUCTION

The term desmoid tumor describes a fibromatous proliferative disease that in its biological behavior is classified between benign fibrous tissue proliferation and fibrosarcoma. According

to the World Health Organization, desmoid tumors are defined as “clonal fibroblastic proliferations that arise in the deep soft tissues and are characterized by infiltrative growth and a tendency toward local recurrence but an inability to metastasize.”

Correspondence: Bernd Kasper, M.D., Ph.D., Sarcoma Unit, ITM - Interdisciplinary Tumor Center Mannheim, Mannheim University Medical Center, University of Heidelberg, Theodor-Kutzer-Ufer 1–3, D-68167 Mannheim, Germany. Telephone: 49-621-383-2447; Fax: 49-621-383-1479; e-mail: mail@berndkasper.de Received August 25, 2010; accepted for publication February 10, 2011; first published online in *The Oncologist Express* on April 8, 2011. ©AlphaMed Press 1083-7159/2011/\$30.00/0 doi: 10.1634/theoncologist.2010-0281

Figure 1. Typical localizations of desmoid tumors and treatment solutions. (A) Pregnancy-associated desmoid of the rectus abdominis muscle (38-year-old female, treated with resection, no evidence of disease 4 years later). (B) Recurrent, symptomatic desmoid of the head and neck area extending to the upper thoracic wall and brachial plexus (28-year-old male, treated with trans-cervical resection and adjuvant radiation therapy, free from recurrence at 34 months). (C) Desmoid of the lower pelvis, preventing vaginal delivery (34-year-old pregnant female, treated with imatinib, stable disease since March 2008). (D) Multiply recurrent desmoid reaching from the thigh to the popliteal fossa in a patient suffering from Recklinghausen's disease (37-year-old male, treated by isolated limb perfusion with rhTNF- α and melphalan, stable disease since August 2006).

Desmoid tumors may affect all sites, including the extremities, trunk, and abdomen [1]. For example, only 5% of sporadic desmoid tumors are intra-abdominal, but 80% of patients with familial adenomatous polyposis (FAP)-associated desmoid tumors develop intra-abdominal disease. The incidence is <3% of soft tissue sarcomas and about 0.03% of all malignancies [2]. Desmoids are therefore a distinct rare tumor entity and are seen in about three to four cases per 1 million of the U.S. population. Desmoids occur between the age of 15 and 60 years, but particularly during early adolescence, and with a peak age of about 30 years. Two different types of desmoid tumors are described: besides the sporadic desmoid tumor manifestation, there is a special relationship between desmoids and FAP (Gardner syndrome). An incidence of 3.5%–32% has been reported in these patients [3, 4].

The first-line therapy for patients with locally circumscribed desmoid tumors remains surgical resection. However, observation might be an option for a subgroup of patients. The growth pattern of these tumors is deep infiltrating, and there is no tumor capsule. Because the boundaries of the tumors are

difficult to distinguish intraoperatively from scars or connective tissue, R0 resection is not always possible and adjuvant radiotherapy is therefore often applied following sarcoma protocols. Desmoids, however, have a high local relapse rate after surgery and/or radiotherapy and exhibit locally aggressive growth, but can often take a multiply relapsing, multifocal course and therefore are not amenable to curative surgical treatment. In this situation, pharmacotherapy is often used to prevent disease progression [5]. The primary aim is to preserve the patient's quality of life, which is threatened by the loss of function and pain caused by proliferative disease. Therapeutic approaches to the treatment of recurrent or nonresectable desmoid tumors comprise antihormonal therapy (e.g., tamoxifen), nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., cyclooxygenase [COX]-2 inhibitors), and classic chemotherapy regimens, with highly variable results [6, 7]. It has not yet been possible to establish an optimal therapy protocol for this disease. However, multidisciplinary evaluation of patients with desmoid tumors is substantial, and treatment approaches may comprise surgical intervention and/or radiotherapy and/or an-

Figure 2. Case of a 66-year-old patient with a desmoid tumor of the right musculus deltoideus diagnosed in April 2009 (A); staging in October 2009 demonstrated a spontaneous tumor remission (B). The diagnosis was confirmed by β -catenin mutation analysis with a characteristic S45P mutation in exon 3 of the *CTNNB1* gene.

tiproliferative treatment [8]. The following review describes possible treatment options and management strategies for patients with desmoid tumors, with a focus on advanced disease.

CLINICAL FEATURES

The clinical course of desmoid tumors may be unusual and heterogeneous, characterized not only by tumor growth, proliferation, and disease progression but also by stabilization and even spontaneous remission. Figure 1 shows typical localizations of desmoid tumors, including the rectus abdominis muscle, head and neck, pelvis, and extremities, and options for therapeutic approaches. There are different factors associated with the development of desmoid tumors. Higher incidences during and after pregnancy and following exposure to oral contraceptives and reports of spontaneous tumor regression during menopause underline the potential influence of the female sex hormonal environment. These observations form the basis for hormonal therapy in desmoids, which is discussed later. Figure 2 shows the case of a 66-year-old female patient with a desmoid tumor of the right deltoid muscle diagnosed in April 2009 (Fig. 2A). The diagnosis was confirmed by β -catenin mutation analysis showing a characteristic S45P mutation in exon 3 of the *CTNNB1* gene. Surprisingly, restaging in October 2009 demonstrated spontaneous regression of the tumor (Fig. 2B). On the other hand, desmoid tumors show a remarkable propensity for local recurrence even after apparently complete surgical excision, but usually have no capacity for metastasis. There is little insight into the clinical and molecular determinants that govern this variable behavior and we currently cannot predict which desmoid tumors respond best to the various treatment options in our therapeutic armamentarium [9]. Therefore, watchful wait-

ing or conservative care is advocated by lots of specialists, especially for asymptomatic patients. All treatment algorithms and guidelines incorporate observation into the treatment plan at different time points; however, the ordering and sequence of patients to different treatment modalities before or after observation requires individualized assessment best delivered in a multidisciplinary setting [10].

DIFFERENTIAL DIAGNOSIS OF DESMOID TUMORS

The differential diagnosis of desmoid-type fibromatosis is broad, with fibroblastic sarcomas on the one extreme and reactive fibroblastic and myofibroblastic processes such as nodular fasciitis and even hypertrophic scars and keloids on the other. Different considerations apply for extra-abdominal and abdominal fibromatosis. Fortunately, nuclear staining for β -catenin greatly aids in the diagnosis and is a consistent finding (approximately 80% of cases), although it is not specific and is also seen in a rather large variety of other tumors. The diagnosis can be confirmed by screening for mutations (mainly in exon 3) of the β -catenin gene, which are found in ~85% of sporadic cases [11].

Extra-Abdominal Fibromatosis

One major concern is to rule out fibroblastic sarcoma and low-grade fibromyxoid sarcoma. Fibroblastic sarcoma can be positive in β -catenin staining [11], but is usually more cellular, has more atypia, and the spindle cells show a conspicuous herringbone pattern. Low-grade fibromyxoid sarcoma [12] usually shows more delicate nuclei and typically has a characteristic network of curvilinear blood vessels. β -catenin staining is positive in 30% of cases [11]. However, low-grade fibromyxoid sarcoma can be reliably ruled out by detection of characteristic translocations involving

Figure 3. (A) Classic fibroblastic, spindle cell morphology of a desmoid tumor (hematoxylin and eosin, x200); (B) desmoid tumor with the characteristic expression of β -catenin (endothelial cells as negative control, x200).

FUS–CREB3L2 gene fusion by fluorescence in situ hybridization analysis [13]. Gardner fibroma is a rare neoplasm in persons with abnormalities of the adenomatous polyposis coli gene, *APC*, on the long arm of chromosome 5 that occurs at similar sites and can in fact precede the development of fibromatosis [14]. Not surprisingly, both lesions show nuclear expression of β -catenin in a high percentage of specimens [11]. In contrast to desmoid-type fibromatosis, Gardner fibroma shows less cellularity and a greater abundance of collagen, and the spindle cells express CD34. Keloids and other reactive fibroblastic proliferations following trauma can also be difficult to distinguish from fibromatosis. These lesions usually show a more variable picture, with focal hemorrhage and inflammation, and are usually negative for β -catenin immunostains.

Intra-Abdominal Fibromatosis

The differential diagnosis of intra-abdominal fibromatosis includes gastrointestinal stromal tumor (GIST), solitary fibrous tumor (SFT), inflammatory myofibroblastic tumor (IMT), sclerosing mesenteritis, and retroperitoneal fibrosis (either idiopathic [Ormond's disease] or secondary to certain drugs or an underlying malignancy, such as a lymphoma). Recently the coexistence of abdominal desmoids with GISTs was described [15]. However, the differential diagnosis with GIST is usually straightforward, because GISTs usually express c-KIT (whereas fibromatosis is consistently negative), CD34, and discovered on GIST-1, and are virtually always β -catenin negative [11]. In addition, a high percentage of GISTs harbor mutations in the genes encoding KIT or platelet-derived growth factor receptor (PDGFR)-A. Solitary fibrous tumors can show striking hyalinization and may be difficult to differentiate from fibromatosis, especially in those cases with only a few vessels with a classical "staghorn pattern." However, SFTs typically express CD34, CD99, and Bcl-2. IMTs are more cel-

lular, have more pronounced atypia, and have a marked inflammatory background. Immunohistochemistry may aid in the differential diagnosis because IMTs can be activin-like kinase 1 positive [16] and are β -catenin negative [11]. Hyalinization in retroperitoneal fibrosis is more pronounced and often associated with marked lymphoblastic infiltrate [17].

THE ROLE OF *APC* AND β -CATENIN

β -catenin has dual roles in epithelial cells, acting as a cell adhesion molecule and also part of a transcription apparatus in the nucleus (Fig. 3). In mesenchymal cells, such as those in desmoid tumors, the transcriptional role of β -catenin is important. Phosphorylation of β -catenin is mediated by a portion of the protein encoded by exon 3 of *CTNNB1*, the gene encoding β -catenin. Mutations in *CTNNB1* lead to accumulation of β -catenin. Recent studies indicate that at least 85% of sporadic desmoid tumors show mutations in this gene, namely, three distinct mutations: T41A, S45F, and S45P. Interestingly, it was found, retrospectively, that the S45F mutation was the most important predictor of recurrence after surgery of the primary tumor, with a relative risk of 3.5 [18]. This finding represents the first documentation of a potentially clinically applicable molecular determinant of desmoid behavior. In another study, it was demonstrated that the 5-year recurrence-free survival rate was significantly worse for patients with desmoid tumors with mutations in the β -catenin gene than for patients with wild-type tumors (49% versus 93%; $p = .02$) [19]. The mutation status of *CTNNB1* apparently has prognostic relevance regarding the biological behavior of desmoid tumors, offering new possibilities for the therapeutic management of this disease.

In FAP patients, the coexistence of somatic and germline mutations of *APC* in desmoid tumors has been demonstrated. Mutations in *ras* genes or *p53* are usually not found

in desmoids, thus inactivation of both alleles of the *APC* gene is involved in the development of desmoid tumors [3, 20]. Several studies have established that specific phenotypic characteristics correlate with the position of the *APC* mutation in both intra- and extra-abdominal desmoid tumors. Mutations downstream of codon 1309 were associated with an approximately sixfold greater overall risk for desmoid tumors relative to the reference category (mutations between 159 and 495). In more detail, mutations after codon 1464 [21] or codon 1493 [22] were associated with a high risk for desmoid tumors, with a tenfold higher risk for intra-abdominal desmoids and a 20-fold higher risk for extra-abdominal desmoids [3]. *APC*-modifying genes or epigenetic and environmental factors may further influence the expression of the disease.

TREATMENT OPTIONS FOR LOCALIZED DISEASE

Surgery has traditionally been the therapeutic mainstay for primarily resectable, localized desmoid tumor patients. However, because of variability in the clinical course and the importance of site involvement, the application and use of surgical intervention have been extensively discussed [23, 24]. Variables associated with local recurrence include tumor site and age of the patient [25]. The role of the microscopic status of tumor margins is more complex. Some large retrospective studies demonstrated that microscopically positive margins were predictive of a higher local recurrence rate [10, 26]; other studies failed to demonstrate an effect of microscopic margins on recurrence [27, 28]. There are no data available from randomized controlled trials comparing “tumorectomy” with acceptable marginal resections with radical tumor removal aimed at an R0 resection. There is a significant correlation between tumor site and quality of surgery [29]. However, in a long-term follow-up of 89 patients, it turned out that patients with microscopically complete surgery had an event-free survival rate similar to that of patients undergoing nonsurgical strategies [29]. Thus, surgical therapy must be tailored to what is achievable in terms of margins while preserving functional status for the individual patient. Although margin status is of importance, operations that preserve function and structure should be the primary goal. Attempts to achieve negative margins may result in unnecessary morbidity and may not definitively prevent local recurrence. The consequences of radical excision may be worse than the disease itself. However, once surgery is finally thought necessary, it should be performed with the aim of achieving negative margins. Large intra-abdominal desmoid tumors in particular can often not be excised completely without sacrificing vital structures and without high perioperative mortality and major morbidity. In the past, procedures such as bowel

transplantation have been performed; however, the management of desmoid tumors has become substantially more conservative, including medical treatment options and even observation only [30].

THE CONTRIBUTION OF RADIATION THERAPY

Radiotherapy has been used both in the adjuvant setting after (incomplete) surgery and in the primary setting, and mainly for extra-abdominal tumors. In an international survey of 110 patients by the Rare Cancer Network, the addition of radiation therapy after surgery was an independent positive prognostic factor for local recurrence and overall survival [31]. Another study demonstrated that radiotherapy alone or in combination with surgery led to a significantly lower local recurrence rate [32]. A comparative review of 22 articles examined the results of surgery and radiotherapy for desmoid tumors. Seven hundred eighty patients were included and local recurrences were followed over a median period of 6 years. Radiotherapy alone (dose range, 10–72 Gy) and surgery combined with radiotherapy resulted in significantly better local control (78% and 75%) than with surgery alone (61%) [33]. In patients with positive margins after surgery, the relapse rate dropped from 59% to 25% when radiation therapy was added postoperatively. The effect was noted for both primary and recurrent desmoids tumors [33]. The complication rate from radiation therapy was 22.8%, with tissue fibrosis being the main problem. Aside from tissue fibrosis, the risk for radiation-induced neoplasms, which is of particular concern in this young patient population, has to be considered. In-field recurrence occurred mainly if the total irradiation dose was <50 Gy [33]. Another paper analyzed long-term outcomes of desmoid tumor patients treated with radiation therapy and concluded that desmoid tumors are effectively controlled with radiotherapy administered either as an adjuvant to surgery when resection margins are positive or alone for gross disease when surgical resection is not feasible. However, high rates of radiation-related complications were associated with doses >56 Gy [34]. Taken together, postoperative radiotherapy is indicated in cases with positive margins and significantly reduces the local recurrence rate. To evaluate the efficacy of radiotherapy for inoperable desmoid tumors, the Soft Tissue and Bone Sarcoma Group of the European Organization for Research and Treatment of Cancer (EORTC) performed a pilot study (EORTC 62991) assessing moderate-dose radiotherapy for aggressive fibromatosis in patients not amenable to resection without significant function loss. Patients received radiotherapy for a total of 56 Gy in 28 fractions. This nonrandomized, phase II study finalized recruitment with 44 patients in April 2008, and patients are still under follow-

up; the final analysis is awaited after 3 years of follow-up in the second quarter of 2011.

TREATMENT OPTIONS FOR ADVANCED DISEASE

For patients with advanced desmoid tumors that are not amenable to surgery or radiotherapy, or if surgery is potentially mutilating, various medical treatment options have been investigated, although generally not in a controlled clinical trial setting. These include antihormonal therapies, NSAIDs, targeted therapies, and traditional cytotoxic chemotherapies. Responses are seen only in a subset of patients, and there have been no markers yet identified being predictive for response. Furthermore, response evaluation according to the conventional Response Evaluation Criteria in Solid Tumors (RECIST) may be difficult in a tumor that can have spontaneous growth arrest and variable growth patterns.

The use of antihormonal therapy for the treatment of desmoid tumors is based on observations of the natural history of the disease. Certain observations, for example, higher incidences of desmoids during and after pregnancy and reports of spontaneous tumor regression after menopause, form the basis for antihormonal therapy. Studies have shown that virtually all desmoid tumors express nuclear estrogen receptor- β , but only a small subset of patients respond to antihormonal therapies [35]. One of the most commonly used antiestrogens in desmoid tumors is tamoxifen, with many citations in the literature excellently reviewed by Janinis et al. [5]. However, most of these reports were single case reports demonstrating some sort of response or disease stabilization. Larger series of patients are not available; therefore, no firm conclusion regarding the effectiveness of tamoxifen against desmoids can be reached. It was reported, in a nonrandomized setting, that high-dose tamoxifen (120–200 mg/day) may be more effective than lower doses of 10–40 mg/day [36]. However, there is no randomized data supporting the use of high doses of tamoxifen, and the risk for second cancers and deep venous thrombosis could be greater with its use.

The use of NSAIDs against aggressive fibromatosis initially was based on the surprising observation of total regression of a single desmoid tumor of the sternum in a patient taking indomethacin for radiation-induced pericarditis [37]. Because COX-2 seems to play a role in the pathogenesis of desmoid tumors, treatment with NSAIDs that inhibit COX may be effective. Moreover, NSAIDs demonstrate influence on the β -catenin pathway [38]. A variety of NSAIDs, such as indomethacin and sulindac, a long-acting analog of indomethacin, were tested in the treatment of desmoid tumor patients and were associated with partial and complete responses in several nonrandomized retrospective

studies, either alone or in combination with hormonal agents such as tamoxifen. These different studies are also excellently reviewed by Janinis et al. [5]. The overall response rate of patients treated with sulindac is ~50%, and the majority of responders experienced a delayed response with a mean time of 24 months. Therefore, administration of sulindac with or without tamoxifen seems to be an effective noncytotoxic drug treatment that has, however, not been proven through a randomized comparison [36, 37]. In a series of 25 patients, this combination was used as a first-line treatment, and all three patients with sporadic desmoids and 10 of 13 patients with FAP-associated disease developed stable disease, a partial response, or a complete response [36]. Because of its low toxicity, endocrine and/or NSAID therapy is usually considered first-line medical treatment for unresectable, advanced disease without clinical symptoms.

In contrast, in cases of an unresectable, rapidly growing and/or symptomatic and/or life-threatening desmoid tumor, traditional cytotoxic chemotherapy may be the treatment of choice. Table 1 gives an overview of selected chemotherapy regimens used for desmoid tumor patients with advanced disease. In summary, weekly administration of methotrexate and vinblastine has been evaluated mainly in the pediatric patient population and has reasonable activity with tolerable toxicity. The largest series showed at least stable disease in 18 of 27 patients, with eight of 27 patients being free from progression at a median of 43 months [39]. However, it has been questioned whether this regimen can also be applied safely in adults because the combination of vinblastine and methotrexate is quite toxic over time and patients generally cannot complete the recommended year of therapy [40]. Alternatively, the combination of vinorelbine and methotrexate can be administered and is likely much less toxic. There is greater benefit from anthracycline-based therapy [41–42] (compare Table 1), and anthracyclines and hormonal therapy appeared to be the most active agents in the series of de Camargo et al. [43]. More recently, pegylated liposomal doxorubicin at a dose of 50 mg/m² every 4 weeks was reported to have significant activity, with four of 12 objective responses and seven cases of stable disease according to the RECIST, and with acceptable toxicity. Nevertheless, six of 11 patients required dose reduction of liposomal doxorubicin because of toxicity [44]. Pegylated liposomal doxorubicin is therefore considered the treatment of choice by many investigators. However, the dose of 50 mg/m² every 4 weeks is too toxic for most patients, so dose reductions are appropriate for patients with toxicity, especially when the approach is to give therapy to a maximum response, which can take 12–18 months or even longer.

Table 1. Possible chemotherapy regimens for desmoid tumor patients with advanced disease

Study	Chemotherapy regimen	n of patients	Response	Follow-up (mos)
Patel et al. [41]	Doxorubicin, 60–90 mg/m ² , + dacarbazine, 750–1,000 mg/m ²	12	2 CR, 4 PR, 2 SD	28–235
Gega et al. [42]	Doxorubicin, 20 mg/m ² , days 1–4, + dacarbazine, 150 mg, days 1–4, day 28	7	3 CR, 4 PR	33–108
Constantinidou et al. [44]	Pegylated liposomal doxorubicin, 50 mg/m ² , day 28	12	4 PR, 7 SD	7–39
Wehl et al. [58]	Pegylated liposomal doxorubicin, 50 mg/m ² , day 28	4	4 PR	NR
Azzarelli et al. [59]	Vinblastine, 6 mg/m ² , + methotrexate, 30 mg/m ² , weekly	27	4 OR, 19 SD	6–96
Weiss et al. [60]	Vinorelbine, 20 mg/m ² , + methotrexate, 50 mg/m ² , weekly	13	NR	<12
Skapek et al. [39]	Vinblastine, 5 mg/m ² , + methotrexate, 30 mg/m ² , weekly	27	8 PR, 10 SD	5–37
Pilz et al. [61]	VAIA, VAC, cyclophosphamide, + ifosfamide	19	4 CR, 5 PR	NR

Abbreviations: CR, complete response; NR, not reported; OR, objective response; PR, partial response; SD, stable disease; VAC, vincristine, actinomycin-D, and cyclophosphamide; VAIA, vincristine, doxorubicin, ifosfamide, and actinomycin-D.

Locoregional chemotherapy in the form of isolated limb perfusion is another alternative to systemic chemotherapy in patients with limb desmoids, which is particularly interesting if one considers that desmoid tumors rarely form metastases. Melphalan and recombinant human tumor necrosis factor- α are used as therapeutic agents with overall response rates of up to 80%. Characteristically, intratumoral hypervascularity disappears after perfusion rather rapidly; however, it may take several weeks to months until a partial or complete response develops. This method seems to be especially useful for patients with locally advanced or recurrent tumors not amenable to function-preserving resections [45, 46].

Targeted therapies such as imatinib have also been investigated, and both objective remissions and disease stabilization have been reported. Initial data on the use of imatinib in patients with desmoid tumors showed a response in two patients with extra-abdominal fibromatosis [47]. In contrast to other imatinib-responsive tumors, for desmoids it is uncertain whether or not the response is a result of inhibition of known imatinib targets such as KIT, ABL, ARG, and PDGFR-A and PDGFR-B kinases. In chronic myeloid leukemia or GIST, specific genomic mutations and chromosomal translocations have been demonstrated. No such genomic changes have been observed for desmoids, showing that the response to imatinib is not attributable to Kit expression [48]. Heinrich et al. [49] treated 19 patients with desmoid tumors with 800 mg imatinib daily. Three partial responses and four

patients with disease stabilization were observed. Genomic analyses revealed no mutations in *KIT*, *PDGFR- α* , or *PDGFR- β* . The authors reported that a drop in serum values of PDGF- β was observed in patients responding to imatinib treatment. Two further reports showed promising results: Penel et al. [50] were able to demonstrate a 3% complete response rate, 9% partial response rate, and 83% stable disease rate in 40 patients with relapsed or refractory desmoid tumors. The 6-month progression-free survival rate was 74% and the 12-month progression-free survival rate was 69% [50]. These findings from the French Sarcoma Group were updated recently with a 2-year progression-free survival rate of 55% and a 2-year overall survival rate of 95%. Interestingly, none of the biological factors tested in that study, including PDGFR- α and PDGFR- β , β -catenin, KIT, and cyclin D1 were correlated with response, progression-free survival, or overall survival [51]. Chugh et al. [52] observed similar promising response rates and nonprogression rates in 51 patients. However, the objective response rate was low and disease progression at enrollment was not required.

Imatinib is not yet licensed for use for this indication, and this is still a matter of current research. The RECIST response rate for imatinib is <10% and therefore much lower than that of traditional chemotherapy or hormonal therapy. Given its expense and low response rate, it should be reserved for when other options have failed. Finally, the clinical impact of imatinib in the treatment of desmoid tu-

Figure 4. Case of a 19-year-old male with a desmoid of the thoracic/abdominal wall, diagnosed in 2007, treated preoperatively with imatinib 800 mg daily. FDG-PET showed a decrease of the average standardized uptake value (SUV) from 3.3 and of the SUV_{max} from 5.5 (A) to 1.7 and 3.1 (B), respectively. Corresponding conventional magnetic resonance imaging documented stable disease.

mors can only be evaluated prospectively. Currently, a trial of the German Interdisciplinary Sarcoma Group is studying the role of imatinib and nilotinib in a clinical phase II study to evaluate the induction of progression arrest in patients with aggressive fibromatosis/desmoid tumors with documented progression and not amenable to surgical R0 resection or accompanied by unacceptable function loss (EUDRACT: 2007–000624-40, ClinicalTrials.gov identifier, NCT01137916) [53].

Preliminary data on the use of sorafenib in 17 evaluable desmoid tumor patients have been presented, with six of 17 (35%) patients with a partial response, ten of 17 (58%) patients with stable disease, and one patient with progressive disease and death. Improvement in terms of pain and mobility was observed in 65% of patients [54].

To evaluate the efficacy of targeted therapies such as imatinib in desmoid tumors, 2-deoxy-2- ^{18}F fluoro-D-glucose positron emission tomography (PET) may be useful. In a pilot study, nine patients with progressive disease from a desmoid tumor receiving 800 mg of imatinib daily were studied [55]. Patients were examined with PET prior to the onset of therapy and during imatinib treatment. Seven of nine patients demonstrated stable disease and two patients showed progressive disease according to the RECIST. The 6-month progression-free survival rate for all patients was 67%. A 27% decrease in the median average standardized uptake value (SUV) of the sequential PET examinations was demonstrated, with three patients demonstrating a $\geq 48\%$ SUV decrease; no patient demonstrated a substantial increase in SUV. With further confirmation of these results, sequential PET imaging may serve as a surrogate marker allowing the de-

tection of SUV changes after imatinib induction, helping to decide whether treatment should be continued or not [55]. However, given the low response rate with imatinib in patients with desmoid tumors, it is also possible that imatinib merely decreases glucose transporters as a biomarker for drug absorption independent of drug activity. Other limitations of PET scanning in this patient population are the high cost and exposure to radiation. Figure 4 shows an example of PET imaging providing additional information over that with conventional computed tomography or magnetic resonance imaging. Imatinib apparently leads to a decrease in tumor cell activity and therefore stabilization of tumor growth. For desmoids, substantial benefit means progression arrest for most patients. PET imaging could therefore be used to monitor the efficacy of imatinib or other tyrosine kinase inhibitors in patients with desmoid tumors.

TREATMENT GUIDELINES

There are several guidelines published on diagnosis, treatment, and follow-up of patients with soft-tissue sarcomas, including desmoid-type aggressive fibromatosis. The clinical recommendations of the European Society for Medical Oncology (<http://www.esmo.org>) have already been mentioned [8]. They include a brief part on standard treatment and possible treatment options for patients with primary and recurrent desmoid tumors. Observation alone could be considered for patients with primary tumors in cases of diagnostic certitude (biopsy) or when the tumor is located such that progression would not cause significant morbidity. Another set of guidelines is published on the Website of the National Com-

prehensive Cancer Network (<http://www.nccn.org>). The National Cancer Institute (<http://www.cancer.gov>) summarizes possible treatment strategies for pediatric patients with desmoid tumors. The current state of the art can be summarized as follows:

- Patients with desmoids should be managed by a multidisciplinary team with expertise in sarcoma treatment.
- Shared decision making with the patient is of major importance.
- Treatment of desmoid tumors should be surgery whenever a complete resection with negative margins and preservation of function are possible.
- If surgery to completely remove the tumor is not possible or would be followed by unacceptable function loss, treatment may include the following:
 - External radiation therapy to shrink the tumor before surgery;
 - Postoperative brachytherapy or intraoperative radiation therapy to kill any remaining tumor cells after surgery;
 - An NSAID, antiestrogen therapy, or combination of the two;
 - Chemotherapy (a watchful waiting policy might be applied first to select only patients with tumor progression for treatment);
 - A clinical trial of targeted drug therapy with imatinib or other drugs under study.

DISCUSSION AND SUMMARY

Desmoid tumor is a rare and heterogeneous disease that definitely requires individualized treatment to reduce the chance for local tumor control failure. The aims of individualized therapy should include reducing morbidity and function loss and preserving patient quality of life. Many issues regarding the optimal treatment of patients with desmoid tumors remain controversial; however, adequate surgical resection with negative margins is the treatment of choice, except when surgery is mutilating and associated with considerable function loss or major morbidity. In cases with positive margins, postoperative radiotherapy is indicated and significantly reduces the local recurrence rate. Because of radiation-related morbidity and complications, radiotherapy should be avoided in cases with negative tumor margins, except for patients with large desmoids with difficulty intervening in cases of recurrence. With respect to the lack of randomized controlled clinical trials, there is much controversy regarding the optimal administration of systemic therapy for advanced disease. Medical treatment, including antihormonal therapy and NSAIDs, seems to be effective with acceptable toxicity. In 2004, the U.S. Food

and Drug Administration issued a public health advisory recommendation for COX-2 inhibitors (Paper No. T04–61). In cases of an aggressively growing desmoid tumor with significant clinical symptoms, chemotherapy, for example, with pegylated liposomal doxorubicin, can induce responses. However, the optimal choice, indication, and sequence of different medical treatment options, comprising antihormonal therapies, NSAIDs, and cytotoxic chemotherapy, can be elucidated only through prospective clinical trials. In patients with aggressive and disabling extremity desmoid tumors for whom resection without amputation or important functional sacrifice is impossible, isolated limb perfusion may be an effective treatment option, although there is limited experience published. Considering the significant morbidity from surgery and radiotherapy for desmoid tumors, in particular, mutilation and loss of function, and the natural history of desmoids, which is often characterized by prolonged periods of stability or even regression, a period of watchful waiting may be the most appropriate management in asymptomatic patients.

In many patients with desmoids, complete eradication of the disease may be worse than the disease itself. Even initial observation may be an adequate action to avoid overtreatment. Bonvalot et al. underline these findings, describing the possibility of a frontline conservative approach for patients with desmoid-type fibromatosis. They treated 142 desmoid tumor patients, of whom 83 received a “wait and see” approach and 59 were treated with medical therapy. Interestingly, there was no significant difference regarding the 5-year progression-free survival rate for the two groups (49.9% versus 58.6%; $p = .31$). Therefore, the authors concluded that “a conservative policy could be a safe approach to primary and recurrent desmoid-type fibromatosis, which could avoid unnecessary morbidity from surgery and/or radiation therapy” [56]. The primary aim is preservation of function. Neoadjuvant treatment strategies or a “wait and see” strategy could be performed instead of invasive surgery and/or radiation therapy. Figure 5 depicts a possible treatment algorithm for desmoid tumor patients, showing that all treatment pathways eventually end in an observation strategy. Even initial observation may be chosen for asymptomatic patients with a slowly growing tumor.

Considering their biological behavior, desmoid tumors represent a heterogeneous disease. The aim of individualized therapy is to identify methods to predict the biological behavior for each individual patient. Identification of tumors with a higher risk for local recurrence after excision will be the subject of further research. Specific β -catenin gene mutations have been found to correlate with local re-

Figure 5. Possible treatment algorithm for desmoid tumors. Adapted from Lev et al. [25] and Lazar et al. [57], University of Texas MD Anderson Cancer Center.

currence in sporadic desmoids. Agents that have β -catenin as a molecular target will be further evaluated. Functional imaging methods like PET could be used to predict the biological behavior of desmoid tumors as well as for the monitoring of therapeutic management.

Given the rarity of this disease, prospective trials and correlative laboratory investigations will require multi-center cooperation. The contribution of patient-based advocacy groups in different countries should be sought after (e.g., <http://www.dtrf.org>, <http://www.sos-desmoide.asso.fr>, <http://www.sos-desmoid.de>). Referral of desmoid tumor patients to expert teams is the only way to gain sufficiently large experience in a prospective way. Such efforts will be

able to identify clinical or molecular criteria by which patients can be selected for each single therapy, long-term observation, or intense multimodality approaches with the vision of keeping patients with this disease alive and preserving their quality of life [57].

AUTHOR CONTRIBUTIONS

Conception/Design: Bernd Kasper, Peter Hohenberger

Provision of study material or patients: Bernd Kasper, Peter Hohenberger, Philipp Ströbel

Collection and/or assembly of data: Bernd Kasper, Peter Hohenberger, Philipp Ströbel

Data analysis and interpretation: Bernd Kasper, Peter Hohenberger, Philipp Ströbel

Manuscript writing: Bernd Kasper, Peter Hohenberger, Philipp Ströbel

Final approval of manuscript: Peter Hohenberger

REFERENCES

- Biermann JS. Desmoid tumors. *Curr Treat Options Oncol* 2000;1:262–266.
- Micke O, Seegenschmiedt MH; German Cooperative Group on Radiotherapy for Benign Diseases. Radiation therapy for aggressive fibromatosis (desmoid tumors): Results of a national Patterns of Care Study. *Int J Radiat Oncol Biol Phys* 2005;61:882–891.
- Bertario L, Russo A, Sala P et al.; Hereditary Colorectal Tumor Registry. Multiple approaches to the exploration of genotype-phenotype correlations in familial adenomatous polyposis. *J Clin Oncol* 2003;21:1698–1707.
- Clark SK, Phillips RK. Desmoids in familial adenomatous polyposis. *Br J Surg* 1996;83:1494–1504.
- Janinis J, Patriki M, Vini L et al. The pharmacological treatment of aggressive fibromatosis: A systematic review. *Ann Oncol* 2003;14:181–190.
- Pignatti G, Barbanti-Bròdano G, Ferrari D et al. Extraabdominal desmoid tumor. A study of 83 cases. *Clin Orthop Relat Res* 2000;(375):207–213.
- Knudsen AL, Bülow S. Desmoid tumour in familial adenomatous polyposis. A review of literature. *Fam Cancer* 2001;1:111–119.
- Casali PG, Blay JY; ESMO/CONTICANET/EUROBONET Consensus Panel of Experts. Soft tissue sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(suppl 5):v198–v203.
- Okuno S. The enigma of desmoid tumors. *Curr Treat Options Oncol* 2006;7:438–443.
- Stoeckle E, Coindre JM, Longy M et al. A critical analysis of treatment strategies in desmoid tumours: A review of a series of 106 cases. *Eur J Surg Oncol* 2009;35:129–134.
- Carlson JW, Fletcher CD. Immunohistochemistry for beta-catenin in the differential diagnosis of spindle cell lesions: Analysis of a series and review of the literature. *Histopathology* 2007;51:509–514.
- Wu X, Petrovic V, Torode IP et al. Low grade fibromyxoid sarcoma: Problems in the diagnosis and management of a malignant tumour with bland histological appearance. *Pathology* 2009;41:155–160.
- Bartuma H, Möller E, Collin A et al. Fusion of the FUS and CREB3L2 genes in a supernumerary ring chromosome in low-grade fibromyxoid sarcoma. *Cancer Genet Cytogenet* 2010;199:143–146.
- Wehrli BM, Weiss SW, Yandow S et al. Gardner-associated fibromas (GAF) in young patients: A distinct fibrous lesion that identifies unus-

- pected Gardner syndrome and risk for fibromatosis. *Am J Surg Pathol* 2001;25:645–651.
- 15 Dumont AG, Rink L, Miettinen M et al. Coexistence of gastrointestinal stromal tumor (GIST) with desmoids tumor (DT): Case series of 22 patients [abstract 10052]. *J Clin Oncol* 2010;28(15 suppl):711s.
 - 16 Coffin CM, Hornick JL, Fletcher CD. Inflammatory myofibroblastic tumor: Comparison of clinicopathologic, histologic, and immunohistochemical features including ALK expression in atypical and aggressive cases. *Am J Surg Pathol* 2007;31:509–520.
 - 17 Swartz RD. Idiopathic retroperitoneal fibrosis: A review of the pathogenesis and approaches to treatment. *Am J Kidney Dis* 2009;54:546–553.
 - 18 Lazar AJ, Tuvin D, Hajibashi S et al. Specific mutations in the beta-catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoid tumors. *Am J Pathol* 2008;173:1518–1527.
 - 19 Dômont J, Salas S, Lacroix L et al. High frequency of beta-catenin heterozygous mutations in extra-abdominal fibromatosis: A potential molecular tool for disease management. *Br J Cancer* 2010;102:1032–1036.
 - 20 Miyaki M, Konishi M, Kikuchi-Yanoshita R et al. Coexistence of somatic and germ-line mutations of APC gene in desmoid tumors from patients with familial adenomatous polyposis. *Cancer Res* 1993;53:5079–5082.
 - 21 Vasen HF, van der Luijt RB, Slors JF et al. Molecular genetic tests as a guide to surgical management of familial adenomatous polyposis. *Lancet* 1996;348:433–435.
 - 22 Wallis YL, Morton DG, McKeown CM et al. Molecular analysis of the APC gene in 205 families: Extended genotype-phenotype correlations in FAP and evidence for the role of APC amino acid changes in colorectal cancer predisposition. *J Med Genet* 1999;36:14–20.
 - 23 Melis M, Zage JS, Sondak VK. Multimodality management of desmoid tumors: How important is a negative surgical margin? *J Surg Oncol* 2008;98:594–602.
 - 24 Nakayama T, Tsuboyama T, Toguchida J et al. Natural course of desmoid-type fibromatosis. *J Orthop Sci* 2008;13:51–55.
 - 25 Lev D, Kotilingam D, Wei C et al. Optimizing treatment of desmoid tumors. *J Clin Oncol* 2007;25:1785–1791.
 - 26 Spear MA, Jennings LC, Mankin HJ et al. Individualizing management of aggressive fibromatoses. *Int J Radiat Oncol Biol Phys* 1998;40:637–645.
 - 27 Merchant NB, Lewis JJ, Woodruff JM et al. Extremity and trunk desmoid tumors: A multifactorial analysis of outcome. *Cancer* 1999;86:2045–2052.
 - 28 Gronchi A, Casali PG, Mariani L et al. Quality of surgery and outcome in extra-abdominal aggressive fibromatosis: A series of patients surgically treated at a single institution. *J Clin Oncol* 2003;21:1390–1397.
 - 29 Bonvalot S, Eldweny H, Haddad V et al. Extra-abdominal primary fibromatosis: Aggressive management could be avoided in a subgroup of patients. *Eur J Surg Oncol* 2008;34:462–468.
 - 30 Bertagnolli MM, Morgan JA, Fletcher CD et al. Multimodality treatment of mesenteric desmoid tumors. *Eur J Cancer* 2008;44:2404–2410.
 - 31 Baumert BG, Spahr MO, von Hochstetter A et al. The impact of radiotherapy in the treatment of desmoid tumours. An international survey of 110 patients. A study of the Rare Cancer Network. *Radiat Oncol* 2007;2:1–12.
 - 32 Jelinek JA, Stelzer KJ, Conrad E et al. The efficacy of radiotherapy as post-operative treatment for desmoid tumors. *Int J Radiat Oncol Biol Phys* 2001;50:121–125.
 - 33 Nuytens JJ, Rust PF, Thomas CR Jr et al. Surgery versus radiation therapy for patients with aggressive fibromatosis or desmoid tumors: A comparative review of 22 articles. *Cancer* 2000;88:1517–1523.
 - 34 Guadagnolo BA, Zagars GK, Ballo MT. Long-term outcomes for desmoid tumors treated with radiation therapy. *Int J Radiat Oncol Biol Phys* 2008;71:441–447.
 - 35 Deyrup AT, Tretiakova M, Montag AG. Estrogen receptor-beta expression in extraabdominal fibromatosis: An analysis of 40 cases. *Cancer* 2006;106:208–213.
 - 36 Hansmann A, Adolph C, Vogel T et al. High-dose tamoxifen and sulindac as first-line treatment for desmoid tumors. *Cancer* 2004;100:612–620.
 - 37 Waddell WR, Gerner RE. Indomethacin and ascorbate inhibit desmoid tumours. *J Surg Oncol* 1980;15:85–90.
 - 38 Signorini S, Frattini M, Negri T et al. Cyclooxygenase-2 and platelet-derived growth factor receptors as potential targets in treating aggressive fibromatosis. *Clin Cancer Res* 2007;13:5034–5040.
 - 39 Skapek SX, Ferguson WS, Granowetter L et al. Vinblastine and methotrexate for desmoid fibromatosis in children: Results of a Pediatric Oncology Group phase II trial. *J Clin Oncol* 2007;25:501–506.
 - 40 Van der Hul RL, Seynaeve C, van Geel BN et al. Low dose methotrexate and vinblastine, given weekly to patients with desmoid tumours, is associated with major toxicity. *Sarcoma* 2003;7:153–157.
 - 41 Patel SR, Evans HL, Benjamin RS. Combination chemotherapy in adult desmoid tumors. *Cancer* 1993;72:3244–3247.
 - 42 Gega M, Yanagi H, Yoshikawa R et al. Successful chemotherapeutic modality of doxorubicin plus dacarbazine for the treatment of desmoid tumors in association with familial adenomatous polyposis. *J Clin Oncol* 2006;24:102–105.
 - 43 De Camargo VP, Keohan ML, D'Adamo DR et al. Clinical outcomes of systemic therapy for patients with deep fibromatosis (desmoid tumor). *Cancer* 2010;116:2258–2265.
 - 44 Constantinidou A, Jones RL, Scurr M et al. Pegylated liposomal doxorubicin, an effective, well-tolerated treatment for refractory aggressive fibromatosis. *Eur J Cancer* 2009;45:2930–2934.
 - 45 Lev-Chelouche D, Abu-Abeid S, Nakache R et al. Limb desmoid tumors: A possible role for isolated limb perfusion with tumor necrosis factor-alpha and melphalan. *Surgery* 1999;126:963–967.
 - 46 Grünhagen DJ, de Wilt JH, van Geel AN et al. Isolated limb perfusion with TNF-alpha and melphalan in locally advanced soft tissue sarcomas of the extremities. *Recent Results Cancer Res* 2009;179:257–270.
 - 47 Mace J, Sybill Biermann J, Sondak V et al. Response of extraabdominal desmoid tumors to therapy with imatinib mesylate. *Cancer* 2002;95:2373–2379.
 - 48 Leithner A, Gapp M, Radl R et al. Immunohistochemical analysis of desmoid tumours. *J Clin Pathol* 2005;58:1152–1156.
 - 49 Heinrich MC, McArthur GA, Demetri GD et al. Clinical and molecular studies of the effect of imatinib on advanced aggressive fibromatosis (desmoid tumour). *J Clin Oncol* 2006;24:1195–1203.
 - 50 Penel N, Le Cesne A, Bui B et al. Imatinib for the treatment of aggressive fibromatosis (desmoid tumors) failing local treatment. A phase II trial of the French Sarcoma Group. *J Clin Oncol* 2006;24(18 suppl):Abstract 9516.
 - 51 Penel N, Le Cesne A, Bui BN et al. Imatinib for progressive and recurrent aggressive fibromatosis (desmoid tumors): An FNCLCC/French Sarcoma Group phase II trial with a long-term follow-up. *Ann Oncol* 2010;22:452–457.
 - 52 Chugh R, Maki RG, Thomas DG et al. A SARC phase II multicenter trial of imatinib mesylate (IM) in patients with aggressive fibromatosis. *J Clin Oncol* 2006;24(18 suppl):Abstract 9515.
 - 53 ClinicalTrials.gov. Study to Evaluate Imatinib in Desmoid Tumors. Available at <http://www.clinicaltrials.gov/ct2/show/NCT01137916?term=NCT01137916&rank=1>, accessed June 4, 2010.

- 54 Gounder M, Lefkowitz R, Hameed M et al. Activity of sorafenib against desmoid tumor/deep fibromatosis (DT/DF) [abstract 894516]. Presented at the 16th CTOS Annual Meeting, Paris, France, November 11–13, 2010.
- 55 Kasper B, Dimitrakopoulou-Strauss A, Strauss LG et al. Positron emission tomography in patients with aggressive fibromatosis/desmoid tumors under therapy with imatinib. *Eur J Nucl Med Mol Imaging* 2010;37:1876–1882.
- 56 Fiore M, Rimareix F, Mariani L et al. Desmoid-type fibromatosis: A front-line conservative approach to select patients for surgical treatment. *Ann Surg Oncol* 2009;16:2587–2593.
- 57 Lazar AJF, Hajibashi S, Lev D. Desmoid tumor: From surgical extirpation to molecular dissection. *Curr Opin Oncol* 2009;21:352–359.
- 58 Wehl G, Rossler J, Otten JE et al. Response of progressive fibromatosis to therapy with liposomal doxorubicin. *Onkologie* 2004;27:552–556.
- 59 Azzarelli A, Casali P, Fissi S et al. Effective control of advanced aggressive fibromatosis with chemotherapy. Eight years experience with methotrexate and vinblastine in 27 patients. Proceedings of the Fourth Annual Meeting of the Connective Tissue Oncology Society, Milan, Italy, November 4–9, 1997.
- 60 Weiss AJ, Horowitz S, Lackman RD. Therapy of desmoid tumors and fibromatosis using vinorelbine. *Am J Clin Oncol* 1999;22:193–195.
- 61 Pilz T, Pilgrim TB, Bisogno G et al. [Chemotherapy in fibromatoses of childhood and adolescence: Results from the Cooperative soft tissue sarcoma study (CWS) and the Italian Cooperative study group (ICG-AIEOP)]. *Klin Padiatr* 1999;211:291–295. In German.