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The treatment of desmoid tumors: a stepwise clinical approach

S. Bonvalot1*, A. Desai1, S. Coppola1, C. Le Péchoux2, P. Terrier3, J. Dômont4 & A. Le Cesne4

1 Departments of Surgery; 2 Radiotherapy; 3 Pathology; 4 Medical Oncology, Institut Gustave Roussy, Villejuif, France

Aggressive fibromatosis (AF) is a monoclonal proliferative disease but does not metastasize and does not dedifferentiate to a high-grade malignancy in case of recurrence. Biopsy is usually necessary to confirm the diagnosis. A hallmark is its apparent unpredictable clinical course producing a large heterogeneity even with an indistinguishable morphology. Additional studies of the molecular determinants of desmoid behavior are needed to guide selection of the various therapeutic modalities. During the last 10 years, the treatment of AF has evolved and the role of routine, aggressive first-line treatment (radiotherapy and surgery) is now debated. If a wait-and-see policy is used at initial presentation, it is observed that >50% of patients will have relatively indolent disease. Aggressive treatments that take their indications from retrospective studies should be re-evaluated in the light of new data. The objective of this article is to propose an algorithm that commences with more conservative approaches before treatments that have associated long-term morbidity, the more aggressive therapies being reserved only for those who really need it.

Key words: desmoid, fibromatosis

A hallmark of aggressive fibromatosis (AF or desmoid tumors) is its unpredictable clinical course producing a large heterogeneity in clinical behavior despite the absence of histological or biological markers of aggressiveness. Although some AF has an aggressive course with a high tendency for local recurrence even after apparently adequate resection, other cases present with an initial growth phase followed by disease stabilization, in the absence of treatment. Intrinsic biological characteristics of the tumor cells and the host microenvironment could be critical and account for the diversity in outcomes. In the near future, it will be essential to find biological or radiological methods that discriminate between these forms of the disease and thereby allow treatments to be tailored to the individual.

Clinical properties

Fibroproliferative processes are a group of disorders characterized by excessive proliferation of spindle-shaped mesenchymal fibroblast-like cells. They range from hypertrophic scars to keloids and superficial fibromatoses (including Dupuytren’s and Peyronie’s diseases). The deep type, exhibiting infiltrative growth (Figure 1) into adjacent structures is known as AF (also called desmoid tumors) [1]. AF is a monoclonal proliferative disease but does not metastasize [2] and, unlike sarcomas, does not dedifferentiate into a high-grade malignancy in cases of recurrence. It is considered a benign disease, although large tumors at anatomically critical sites cause significant morbidity and mortality.

Until now, spontaneous tumor regression has been reported in ~5% of cases [3]. However, most examples of regression in desmoids have been described in patients with recurrent rather than primary disease because, traditionally, the treatment of these lesions has been excision. Regression in desmoids is likely to have been underestimated as it has been calculated in a group of patients with recurrences where surgical options have been exhausted and with a poor prognosis from the outset. If a wait-and-see policy is used at initial presentation, it is observed that >50% of patients will have relatively indolent disease. Aggressive treatments that take their indications from retrospective studies should be re-evaluated in the light of new data.

The incidence of this tumor is low: 2.4–4.3 new cases per 1 000 000 per year. It accounts for 0.03% of all neoplasms and 3% of all soft-tissue tumors [4]. The median age at diagnosis is ~30 years, with a female-to-male sex ratio of 2:1. The clinical course of AF in children may resemble that of AF in adults [5].

AF occurs mainly in two groups: sporadically (usually harboring somatic β-catenin-activating mutations) and within the context of familial adenomatous polyposis (FAP; exhibiting germline inactivating mutations of APC gene). Nevertheless, ~8% of patients with sporadic AF had cases of colorectal cancer in their family [6], which is far higher than expected in the general population, suggesting a genetic predisposition to both conditions.

Deep AF may be observed in any soft-tissue location, although patients with FAP tend to present with tumors in the intestinal mesentry [7], whereas sporadic AF occurs most
commonly on the extremities and limb girdles [8]. A third group represented by young females who develop deep AF during or after pregnancy is also described. The involvement of abdominal wall is common and, in this context, the influence of estrogen appears to be important [9].

Diagnosis is based on clinical, radiological, and histological parameters. The main characteristic of AF is the infiltration of muscles, deep tissue, and along muscle planes as opposed to the majority of sarcomas, which push the adjacent tissue. Computed tomography is valuable for assessing intra-abdominal lesions, and magnetic resonance imaging (MRI) is preferred for the extremities, head and neck, and the abdominal or thoracic walls. On MRI, most lesions are infiltrative with an irregular or lobulated contour. The lesions cross major fascial boundaries in around one-third of cases. Homogeneous isointensity or mild hyperintensity on T1-weighted images and heterogenous high signal on T2-weighted or short tau inversion recovery images is seen. It is not possible to predict clinical behavior based on the MRI signal [10]. Biopsy is usually necessary to confirm the diagnosis [11]. The differential diagnosis includes low-grade fibromyxoid sarcoma and fibrosarcoma and distinguishing these may be difficult. Determining β-catenin mutational status on formalin-fixed tissues may help with diagnosis [12].

available treatments

surgery

During the last 10 years, the treatment of AF has evolved and the role of routine, aggressive first-line treatment (radiotherapy and surgery) is now debated. Local control remains a significant problem, with local failure rates ranging from 25% to 60% at 5 years in institutional retrospective studies, regardless of the therapeutic modality used [13]. However, retrospective studies from major centers often select patients with the worst outcomes.

Before 2000, radical surgical resection was the standard treatment, with the primary goal always being complete excision with negative margins as indicated for sarcomas [14]. AF is a star-shaped tumor with infiltrative growth, so the resection that is needed to achieve clear margins is often larger than for a sarcoma of similar dimensions. The surgeon’s ‘zeal’ to cure this potentially malignant lesion has led to many patients being subjected to radical surgery [15]. Unlike soft-tissue sarcomas, where positive margins are consistently a predictive factor for local failure [16], the effects of involved surgical margins after excision of AF remains unclear. A positive surgical margin was found to be an adverse parameter for local control in some series [17, 18], but not in others [19, 20]. These contrasting data can be explained by a number of factors: the retrospective nature of these studies, the lack of statistical power, the varying techniques used by the pathologist to determine margin involvement and varying treatment protocols including patients who have received postoperative radiotherapy to try to offset the deleterious effect of positive margins. Most reported series include a heterogeneous group of patients with indolent and progressive disease who were formerly routinely treated with surgery where feasible. In these studies, patients with progressive disease are in a minority and it is therefore difficult to demonstrate the impact of involved surgical margins on outcome. Indolent tumors will not recur regardless of margin positivity due to their natural tendency to regress. It seems likely that, if analysed independently, patients with poor prognosis tumors would benefit most from clear surgical resection margins.

In addition, growth factors released after surgery, during the initial phase of wound healing, could transmit signals that promote the activation of β-catenin [21]. R1 resections leave behind genetically altered cells that are exposed to these repair mechanisms; surgery could act as a tumor enhancer in subgroups of AF and not in others, depending on biology [18]. The management of patients who have microscopic residual disease after surgery is not established; observation may be the most appropriate course of action [5].

In sarcomas, the extent of surgery is dependent on grade, with some surgeons suggesting less aggressive intervention for low-grade, well-differentiated liposarcomas. On the contrary in AF, the results of surgery are evaluated and presented independently of its nature. Clinical experience shows that local recurrence may occur after adequate R0 resection and yet some patients with R1 resection and without adjuvant treatment will never experience a recurrence. This suggests that the biology of AF is an important variable with as yet unidentified differing subtypes with varying biological behaviors. Some authors [3, 20] advocate operations that try to spare function, and conclude that attempting to achieve negative margins in all patients’ results in unnecessary...
morbidity. Thus, function-sparing surgery that does not leave macroscopic residual disease has become a reasonable choice where feasible.

There is a conflict between the fact that some patients undergo multiple operations for recurrent disease on one hand and yet amputations for desmoid tumors are reported only occasionally in the literature on the other [22]. This suggests that in many cases after the surgeon or the patient has given up the tumor becomes stable. Observation alone was first described for recurrent but stable lesions [3, 15, 23]. Rock [15] reports a series of 68 patients with residual or recurrent disease where the decision was made (often by the patient) to wait and see; stable disease (with a median follow-up of 6.3 years) was observed in 60 of the 68 patients. Lewis et al. [23] reported 15 patients harboring recurrences without surgical resection, including six without any medical treatment. During follow-up, no patient required amputation and no patient died from disease.

Following these reports, a period of expectant observation was proposed in cases where the primary was deemed unresectable (instead of routinely delivering radiotherapy). Philipp et al. [3] reported on 23 patients (including those with unresectable primary tumors) whose disease remained stable with a median follow-up of 35 months. Clearly, amputation should not be the initial treatment in cases of locally advanced AF, and the consequences of radical excision can be worse than the disease itself [8].

Many authors now question whether surgery and other aggressive treatments should routinely be part of first-line treatment, even in patients with resectable tumors [6, 13, 18]. In a French study [18], a subset of patients with resectable extra-abdominal primary fibromatosis was managed using a systematic, conservative protocol (Figure 2). Based on clinical observation, more than 50% of patients did not show disease progression after the initial growth of the tumor. This conservative approach was applied to a larger multi-institutional cohort of patients [6, 24], and its implementation avoided aggressive surgery in two-thirds of patients with primary tumors. Half of these patients were able to avoid any treatment at all, and all patients are still being followed up [6]. A ‘wait-and-see’ strategy selects patients who have a progressive AF, justifying aggressive multimodality treatments.

Moreover, the fact that some tumors recurred after surgery, but then remained stable without treatment, suggested that growth factors released following surgery may have promoted recurrence in tumors that would otherwise have been indolent. This has been suggested by some authors [1]. Approximately 50% of desmoids demonstrate an aggressive biology, continuing to grow or becoming symptomatic. The vast majority of progressions (89%) occurred within the first 2 years of observation, and almost all of them within the first 5 years. The patients who remained stable for the first 2 years were then much less likely to experience a progression later on [6].

It is vital to properly identify cases that need and benefit from an aggressive approach. Operations that preserve function and structures should be the primary goal [8].

The patients who have Gardner’s syndrome should be considered separately from patients who have extra-abdominal AF due to the threat to vital structures. Owing to the infiltrative pattern of mesenteric desmoids, extensive surgery results in major morbidity without a survival advantage [25]; decision making must take into account the proximity of the superior mesenteric vessels (i.e. vessels involved or not, location of the tumor with regard to the proximal superior mesenteric artery and the length of small bowel requiring resection). In a recent study of 62 patients with intra-abdominal desmoids and FAP, with a median follow-up of 8 years, progression-free survival at 10 years was comparable between the patients who had surgical and nonsurgical treatments (33% and 49%, respectively, $P = 0.163$) [26]. Finally, it must be emphasized that surgical recommendations were traditionally based on retrospective studies on over long periods where surgery was routinely proposed where feasible. More conservative approaches were therefore ignored.

### Radiotherapy

Radiotherapy has been incorporated into the management of extra-abdominal fibromatosis, either as an adjuvant treatment to surgical resection in cases of positive surgical margins or as a primary treatment when surgical resection is not feasible or may result in significant loss of function. Many studies support its efficacy. However, direct tissue toxicity and potential late radiation effects, including second malignancies, are important considerations in the treatment of otherwise healthy, often, young patients [27]. The use of radiotherapy in children with AF should therefore be highly limited.

Nuyttens et al. [28] conducted a comparative review of 22 articles evaluating the treatment of AF in 780 patients. Patients were treated from 1983 to 1998 with surgery alone, radiotherapy alone or surgery plus radiotherapy. Local control rates after surgery were dependent on the status of margins: 72% in cases with negative margins against 41% in cases with positive margins, and 61% overall after surgery. For the patients who underwent surgery and radiotherapy, the local control results with reference to margin status were 94%, 75%, and 75%, respectively. For the radiotherapy group, the local control was 78%, significantly superior to that of the surgery group (61%). Radiotherapy alone or surgery and radiotherapy resulted in better local control than surgery alone. Even after dividing the groups into cases with clear and positive margins, and cases with primary and recurrent tumors, the best local control was achieved with radiotherapy alone or surgery and radiotherapy.

In a multicenter study, Baumert et al. [22] confirmed that postoperative radiotherapy significantly improved progression-free survival compared with surgery alone. In the study reported by Guadagnolo et al. [29], there was no significant difference in local control for patients treated with radiotherapy alone for gross disease compared with a combination of surgery and radiotherapy. Radiation doses over 56 Gy did not significantly improve local control but were associated with an increased risk of radiation-induced complications especially in patients ≤30 years [29]. The median time to radiation-related complications was 33 months and included localized fibrosis, soft-tissue necrosis, paresthesia, pathological fractures, edema, and rarely vascular complications requiring amputation or secondary malignancies [28, 29]. Based on the published literature, the recommended dose of radiotherapy is 50–56 Gy in 2-Fy fractions.
systemic medical treatment
In a recent analysis, Lev et al. [30] compared a series of 189 desmoid patients treated at the University of Texas M. D. Anderson Cancer Center (1995–2005) with a previously published series from the same institution (1965 and 1994). Significantly increased systemic therapy was used in the more recent time period with a decreased reliance on surgery alone. Although patients treated between 1995 and 2005 had higher rates of macroscopic residual disease and equivalent rates of positive microscopic margins after definitive surgery, the estimated 5-year local recurrence rate of 20% was improved with the 30% rate observed in the earlier series. The authors suggested that the increased use of neoadjuvant treatments may be associated with improved outcomes in patients with desmoids. De Camargo et al. [31] examined the outcomes of patients with desmoids tumors who received systemic therapy at Memorial Sloan-Kettering Cancer Center. The greatest Response Evaluation Criteria in Solid Tumors (RECIST) response rate was observed with anthracyclines and hormone therapy, and the lowest response was noted with single-agent dacarbazine (DTIC)/temozolomide or tyrosine kinase inhibitors, principally imatinib. Antiestrogen and anthracycline-containing regimes appear to be associated with higher radiological response rates against desmoid tumors, when compared with other agents.

hormone therapy
Tamoxifen is the most commonly used drug, with some suggesting that higher doses (up to 120 mg/day) in combination with anti-inflammatories are more effective than tamoxifen alone [32]. Recent data suggest that antiestrogen treatment could be mediated by estrogen receptor beta (ER-β) [30]. Deyrup et al. [33] demonstrated that extra-abdominal fibromatosis does not express ER-α, but there appears to be nearly uniform expression of ER-β. This finding clarifies discrepancies in the literature regarding estrogen expression in fibromatosis, and provides a receptor-mediated mechanism for the action of antiestrogenic compounds in the treatment of fibromatosis.

anti-inflammatory drugs
The most commonly used nonsteroidal anti-inflammatory drugs in the treatment of AF are sulindac and indomethacin. AF is characterized by Wnt/oncogene pathway alterations triggering cyclooxygenase-2 (COX-2)-mediated constitutive coactivation of platelet-derived growth factor receptor A (PDGFRα) and PDGFRB, and may therefore benefit from combined nonsteroidal anti-inflammatory drug with tyrosine kinase inhibitor treatment [34]. COX-2 is an enzyme involved in prostaglandin synthesis and is involved in the development of colonic neoplasia, particularly in cases where mutations result in β-catenin stabilization. Human aggressive fibromatoses demonstrate elevated COX-2 levels and partially regulates proliferation because of β-catenin stabilization in AF. COX-2 blockade either by the selective agent 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl-2(5H)-furanone (DFU) or by nonselective COX-blocking agents results in reduced proliferation in human tumor cell cultures [35]. Cytotoxic drug combinations were initially described by Patel et al. [36]. Eleven patients received doxorubicin (DOX; 60–90 mg/m²) and DTIC (750–1000 mg/m²)-based regimens for a median of five cycles (2–10 cycles). Six of the nine patients who could be evaluated had an objective response. Gega et al. [37] investigated the efficacy of a chemotherapeutic regime involving four or five cycles of DOX (20 mg/m² daily) and DTIC (150 mg/m² daily). Symptomatic patients with desmoids were given chemotherapy continuously for 4 days by intravenous infusion (days 1–4) and the cycle repeated every 28 days, followed by the COX-2 inhibitor meloxicam (10 mg/m²). Significant tumor regression was observed clinically and radiologically in all seven patients. Other investigators have also reported activity with other DOX-based regimens, a combination of methotrexate and vinblastine, vinorelbine, and other agents. In all cases, durable responses have been reported, establishing the efficacy of systemic chemotherapy in this disease.

tyrosine kinase inhibitors
Tyrosine kinase inhibitors have also been used [38–40]. Heinrich et al. [38] reported a series of 19 patients with AF, treated with imatinib (800 mg/day) as part of a phase II clinical study. Three (15.7%) of 19 patients had a partial response to treatment, with four additional patients having stable disease that lasted >1 year (overall 1-year tumor control rate of 36.8%). No mutations of cKIT, PDGFRα or PDGFRB were found. Sixteen (84%) of 19 patients had mutations involving the Wnt pathway (APC or CTNNB1). However, there was no correlation between Wnt pathway mutations and clinical response to imatinib. Similar observations have been reported more recently in a larger phase II trial (400 mg daily for 1 year), with one complete response and three partial responses of 40 patients and a nonprogression rate at 1 year of 67% [40]. Imatinib may be considered as an option in the treatment of recurrent AF but further clinical trials with translational studies are required to clearly identify the molecular target and better characterize the position of this drug in the order of treatment [41]. More impressively, sorafenib (nexavar®, Bayer), a multityrosine kinase inhibitor, inhibiting KIT, PDGFR, and VEGFR has been successfully tested (400 mg daily) in 14 patients progressing at inclusion (the majority with FAP) with a 65% objective response rate according to RECIST after a median of 14 months of treatment [42].

isolated limb perfusion
In patients with extensive and locally advanced extremity AF, where resection would result in important functional sacrifice, isolated limb perfusion (ILP) with tumor necrosis factor-α and melphalan is an option and seems to be a very effective treatment. In our experience, most patients become stable or experience at least a partial response after ILP [43].

cryoablation
Cryoablation appears to be an effective alternative treatment of the achievement of local control of small and moderately sized extra-abdominal desmoid tumors. It is likely of limited use in patients with larger tumors that can only be partially treated due to the involvement of vital structures. Continued research evaluating cryoablation for the treatment of extra-abdominal desmoid tumors is needed [44].
molecular insights

Clearly, further research is required to understand the molecular mechanisms behind tumorigenesis and progression in desmoid tumors, and to identify which mutations are at particularly relevant to recurrence or progression. The ultimate objective is to use the genetic alterations in tumors to individualize the selection of management protocols. This application of personalized medicine in fibromatosis could lead to the right treatment at the right time for the optimal outcome.

Lazar et al. [45] has evaluated the prevalence of CTNNB1 mutations in a large cohort of sporadic desmoids and examined whether mutation type was relevant to outcome. CTNNB1 mutations were observed in 117 (85%) of 138 desmoids. Three discrete mutations in two codons of CTNNB1 exon 3 were identified: 41A (59%), 45F (33%), and 45P (8%, excluded from further analysis because of rarity). Five-year recurrence-free survival was significantly poorer in 45F-mutated desmoids (23%) compared with either 41A (57%) or nonmutated tumors (65%). Nuclear β-catenin expression was observed in 98% of specimens and intensity was inversely correlated with incidence of desmoid recurrence ($P < 0.01$).

Conversely, Domont et al. [12] found that 5-year recurrence-free survival was significantly worse in β-catenin-mutated tumors, regardless of specific genotype, when compared with wild-type tumors (49 versus 75%, respectively). More recently, analysis of data from three centers seems to confirm the prognostic value of the 45F mutation [46]. However, it is probably not the only biological factor responsible for outcome, as >85% of sporadic desmoids tumors harbor the CTNNB1 mutation and yet 50% of patients do not display aggressive disease. The 45F mutation is now widely used routinely to confirm the histological diagnosis. In contrast, when analysed by comparative genomic hybridization on frozen samples in a series of 194 patients, Salas et al. [47] observed a high frequency of genomically normal tumors (76%). Samples were screened for APC mutations in patients without CNNTB1 mutation. Four relevant and recurrent alterations (loss of 6q, loss of 5q, gain of 20q, and gain of chromosome 8) were found in 40 of 46 tumors with chromosomal changes. Gain of chromosomes 8 and 20 was not associated with an increased risk of recurrence. Cases with loss of 5q had a minimal common region in 5q22.5 including the APC locus. Alterations of APC, including loss of the entire locus, and CTNNB1 mutation could explain the tumorigenesis in 89% of sporadic desmoids tumors and desmoids tumors occurring in the context of Gardner’s syndrome. Assessment and treatment of individual patients in a multidisciplinary setting is critical in order to achieve the most favorable outcomes. Additional studies of the molecular determinants of desmoid behavior are needed to guide selection of the various therapeutic modalities.

treatment algorithm

It is now clear that desmoid tumors exhibit a wide range of biological behaviors and a significant proportion will remain...
stable or regress (‘indolent’) while others demonstrate continued and unrelenting growth although this may be relatively slow (‘progressive’). Up to 50% of patients with desmoids benefit from a front-line nonaggressive policy, because growth arrest is not an uncommon feature of this disease [6, 18, 24, 25]. Conversely, an aggressive policy (surgery and/or radiotherapy) as a primary modality for all patients might over treat 50% of them and is associated with significant sequelae given that these tumors have a diameter of ∼5 cm at presentation. Surgical intervention can be disfiguring and often requires reconstruction. Patients may complain of pain from these lesions but this must be put into the context of an operation that is in itself painful and the surgeon must not be persuaded to offer surgery as an analgesic. On the other hand, patients with an evolutive presentation would benefit from an aggressive multimodal treatment.

Of course, the majority of patients exhibiting indolent disease will respond well to aggressive treatments; however, it is likely that their natural history is such that they would have had an equally good outcome without any intervention. At present, there are no clear histological discriminators between the ‘indolent’ and ‘progressive’ groups, and we therefore advocate an initial watch-and-wait policy in all but a few selected cases such as tumors at anatomical locations close to critical structures or that are progressing rapidly (Head and neck, limb girdles).

Our treatment algorithm commences with more conservative approaches before treatments that have associated long-term morbidity (Figures 2 and 3). This is achieved through a strategy of careful clinical assessment and a period of observation for 2 months after which an MRI is performed. This has the advantage of allowing discrimination between the two clinical groups and avoiding surgical morbidity and late radiation-associated complications, the more aggressive therapies being reserved only for those who really need it. Progression, if it is to occur, will be evident in the first 2 years after presentation and surveillance must be an active and intensive process particularly in the first few months, in order to treat promptly those patients who are ‘progressive’.

In cases of documented progression on MRI, treatments are increasingly more aggressive but moderated by the age, comorbidity, and wishes of the patient (Figure 4). Patients may pass through various treatment modalities in succession but it is important to recognize that the lesion may continue to grow, as seen on serial imaging, when compared with the first scan. The clinician must take a pragmatic, common sense approach, and be prepared to intervene at any stage depending on the initial size of the tumor, the rate of growth, and the failure of medical treatment. For example, it is possible to take a conservative approach with a 2-cm tumor of the abdominal

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Figure 3. Initial treatment algorithm for primary desmoids.

Figure 4. Treatment algorithm in cases of documented progression on MRI (part 1).

Figure 5. Thirty-four-year-old female: post-partum tumor of obturator internus. Percutaneous biopsy: desmoid. Treatment with tamoxifen and LHRH agonist for 18 months. The surgery would have been mutilating and radiation the source of morbidity. (A) MRI 2007 and (B) MRI 2010.
wall, waiting until it has doubled in size because the consequences of surgery are not significantly different. Conversely, a 10-cm tumor of the thigh requires definitive intervention much earlier in line with RECIST progression.

In patients that appear to progress after a period of initial stability, a careful search will often reveal an extrinsic cause for this. Surgery or trauma, causing the release of factors responsible for wound healing can promote desmoid growth at a distant site. Similarly, pregnancy will promote these tumors not only secondary to hormonal influences, but also due to the systemic release of growth factors. Tumor growth in these patients should not necessarily deter the clinician from persisting with a watch-and-wait policy, as once the event that initiated the growth has subsided, so too will rate of progression. However, abdominal wall desmoids associated with pregnancy are a difficult problem with no large series published to date, and indications for treatment are debated [9].

In cases of documented progression, treatment is tailored according to the age, gender, and location. Our proposal is to start with medical treatments that offer the advantage that they have no major long-term sequelae when they are discontinued. A young female patient without any significant medical history of deep venous thrombosis that has progressed after 2 months is offered antihormonal therapy as first-line treatment (Figure 5). This is given regardless of the hormone receptor status of the tumor because these lesions express a wide range of ERs which are not sought routinely in the laboratory.

In men and postmenopausal females, where hormonal manipulation is not feasible, tumors that continue to grow after a period of observation can be started on chemotherapy such as a vinca alkaloid and methotrexate. Desmoids have long been considered to be largely composed of benign cells without the tendency to metastasize although having a propensity to recur locally. Therefore, chemotherapy is a controversial treatment and administration of systemic therapy must be appropriate to the symptoms that the desmoid is causing. However, it is clear that, although data are scarce, agents such as doxorubicin and vincristine are active against these lesions. In young, premenopausal women who continue to progress despite hormonal manipulation, cytotoxic chemotherapy can be used as second-line treatment. Another option offered to our patients is to participate in ongoing trials comparing these cytotoxic drugs to the newer tyrosine kinase inhibitors.

Treatment failure after chemotherapy (~20%) should prompt more aggressive treatments to be commenced (surgery, radiotherapy or both) (Figure 6).

In our treatment algorithm, we would favor surgical intervention only in those patients where an R0 resection is not possible, or where there is a high risk of recurrence. Treatment is individualized, taking into account the age, gender, and location of the tumor as well as the patient's preferences.

Figure 6. Treatment algorithm in cases of documented progression on MRI (part 2).

Figure 7. (A) 2005: Twenty-year-old female, desmoid after a plastic surgery for breast reduction; (B) MRI 2005; (C) appearance after radical thoracic wall resection with reconstruction with two pedicled flaps and postoperative radiotherapy (56 Gy); (D) MRI 2011.
feasible without major sequelae (e.g. the abdominal/thoracic wall) (Figure 7). We reserve surgery for patients with aggressive disease, but it is likely that, in this group, impact of margins is more important that in desmoid tumors as a whole. In the abdomen or abdominal wall, surgery is the mainstay of treatment. Excision of the tumor and a margin normal tissue with reconstruction using a biological or coated mesh will usually allow extirpation of large tumors of the parietes. Intra-abdominal tumors can be more problematic and careful consideration must be given to the tumor’s relationship with the superior mesenteric artery and the amount of small bowel that will need to be sacrificed in any potential resection. The aim must be to achieve an R0 resection; however a proportion of these lesions will be inoperable due to anatomical location.

Otherwise radiotherapy should be given consideration as primary treatment when balanced against the age of the patient and anatomical location. For example, lesions at anatomically critical sites such as the head and neck or limb girdles, in which chemotherapy has failed, can be treated with radiotherapy. Surgery at these locations can be technically very challenging or indeed impossible.

Desmoids of the limbs that is resistant to all other treatments can be subjected to ILP. Various studies (in addition to our own experience) show overall response rates of 80% in patients whose only other option may be radical surgery with major functional consequences or amputation. Following ILP we do not propose surgery but occasionally use radiotherapy as an adjuvant treatment.

A group of patients should be treated aggressively from the outset and be excluded from the watch-and-wait policy that has been proposed. For example, the patients who present with a desmoid that is clearly enlarging very quickly from the outset and/or is approaching a critical size, as dictated by anatomical site.

conclusion

Desmoids are tumors that must be treated by a multidisciplinary team in a high-volume center familiar with this challenging disease. ‘Wait and see’ strategies versus treatment decisions must be balanced against the clinical presentation. These centers should collaborate in further translational research.

disclosure

The authors have declared no conflicts of interest.

references


