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Editorial Comment

Management of aggressive fibromatosis: Can we unravel the maze of treatment options?

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The complexity and heterogeneity of aggressive fibromatosis (AF) is already reflected in its nomenclature. In addition to AF, desmoid tumour, desmoids, and desmoid-type fibromatosis are other names for the same entity. AF is a rare disease with an annual incidence of 2–4 per 1×10^6 people, and consists of a monoclonal proliferation of fibroblasts exhibiting infiltrative growth into adjacent structures, but without the ability to metastasise. Consequently, AF is classified as a benign disorder.[1]

Increased activity of β-catenin is the hallmark and driving force of AF. Besides a role in cell–cell adhesion, β-catenin regulates the expression of numerous genes involved in proliferation and survival. Activation of β-catenin leading to AF occurs in two distinct settings; sporadically or within familial adenomatous polyposis (FAP). FAP is a hereditary disease characterised by a germ-line mutation in the adenomatous polyposis coli (*APC*) gene. In physiological conditions, APC forms with other proteins the APC complex, which phosphorylates β-catenin leading to the degradation of β-catenin. In case of *APC* mutations, β-catenin remains unphosphorylated finally resulting in upregulation of β-catenin's target genes. FAP patients are not only prone to develop colorectal polyps, eventually resulting in cancer, but also have a 800–1000-fold higher risk to develop AF compared to the general population. FAP-associated AF occurs mainly intra-abdominally and although only being locally infiltrative, approximately 10% of the FAP patients die from the consequences of AF. In contrast, sporadic AF is rarely fatal, but frequently causes pain and functional impairment. Sporadic AF occurs predominantly in the extremities and girdles, but also in the thoracic and abdominal wall, intra-abdominally, and other locations. In at least 85% of the sporadic AF cases, a gain-of-function mutation in the gene encoding β-catenin, *CTNNB1*, is found.[1]

Another hallmark of AF is its highly unpredictable natural course. Evidence is mounting that after a growth stimulus, there is an expansion phase lasting about 3 years followed by stabilisation and sometimes even regression.[2] Suggested growth triggers include surgery, trauma and hormonal factors.

Key questions in managing AF are when and how to treat. Importantly, expected benefits from therapy should be well-balanced against potential treatment-induced untoward effects. Unfortunately, randomised studies or even large prospective studies on which treatment strategies can be based are currently lacking. As a consequence, no evidence-based guide-lines exist. Despite the lack of evidence, it is highly likely that numerous factors such as symptoms, the site of disease, tumour size, and of course, the preferences of physician and patient determine whether and if so, how AF should be managed in individual cases. For asymptomatic patients, a

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wait-and-see policy is increasingly applied. And indeed, the rationale for watchful waiting was recently underlined given a median progression-free survival (PFS) of 5 years in a retrospectively analysed group.[2] For symptomatic patients, surgery is the mainstay of therapy. Although tumour-positive margins are likely associated with local recurrences, striving for radical surgery may cause morbidity outweighing the symptoms from AF itself. Radiotherapy as primary therapy can be considered in AF not amendable for surgery. But outcomes from radiotherapy are currently only available from retrospective series and therefore, the results from a recently completed prospective study are eagerly awaited. As holds true for all strategies in AF, radiotherapy-induced toxicities, both in the short and long-term, should be considered thoroughly.

For patients with symptomatic disease, in particular disease that is not, or not anymore, amendable for local treatment options, systemic agents can be considered. Over the recent decades, a broad spectrum of different systemic agents has been explored, but mostly only retrospectively and in small series. Potential active agents include interferon, corticosteroids, non-steroidal anti-inflammatory (NSAIDs), specific COX-2 inhibitors, hormonal agents such as tamoxifen, and cytotoxic combinations such as methotrexate/vinblastine and dacarbazine/doxorubicin.[3,4] Another interesting agent is imatinib, which in general has a more favourable toxicity profile than conventional cytotoxics. Only reported in abstract form yet, imatinib demonstrated a RR in 4/35 patients and a PFS at 2 years of 55%.[5] However, despite these interesting outcomes, the lack of randomised studies and the great differences in patients' and disease characteristics between the diverse studies render it impossible to determine which systemic therapy should be preferred. Because of the relatively mild toxicity profile, primary systemic treatment of choice is mostly a NSAID or an anti-oestrogen, but obviously, there is a high need for more robust data and novel active drugs.

In today's issue of the *European Journal of Cancer*, Constantinidou and colleagues report on the effects of pegylated liposomal doxorubicin (PLD) in 12 heavily pretreated AF patients.[6] PLD deserved to be studied in AF since anthracyclines as monotherapy were not thoroughly explored yet. Furthermore, PLD lacks the cardiotoxicity which is so characteristic for other anthracyclines and which is a major disadvantage given the long-term survival of AF patients. PLD induced a partial response (PR) in 4/12 patients, while another PR was observed long after treatment completion. Four patients progressed 9–14 months after treatment initiation; the other patients had ongoing disease control ranging from 7 to 39 months. Importantly, 11/12 patients experienced pain relief or functional improvement. Toxicities were deemed acceptable, though in 6/12 patients a dose reduction was applied. This study strongly suggests that PLD exerts activity in AF. But to put its activity into context is impossible given the non-randomised study design.

Collectively, there are now numerous approaches to manage AF, but in the maze of multiple treatment options physicians and patients are still puzzled about the best way to go. The most obvious way to move the field forward is by performing randomised studies exploring the different strategies. Importantly, study populations should be as homogeneous as possible, including in terms of molecular characteristics. As it becomes increasingly clear, the genetic background of a disease greatly influences the outcome to treatment and this applies to AF as well. There are indications that AF patients with a S45F *CTNNB1* mutation have a higher risk to recur after surgery[7] thereby likely to impact outcome to any therapy. Furthermore, treatment-induced adverse events and quality-of-life should be main endpoints in randomised studies in AF. Additionally, research is needed on how to specifically inhibit β-catenin activity in AF and on the identification of factors predicting disease behaviour. The latter will hopefully enable the establishment of different prognostic groups for which different strategies can be explored. Obviously, because of its rarity and heterogeneity, performing large studies in AF will be a major challenge. Nevertheless, it took the French Sarcoma Group one year to recruit 40 patients.[5] This clearly shows that by close collaboration in international networks it must be feasible to conduct large trials in AF. Only on the basis of such studies, it will be possible to make more evidence-based choices for AF patients.

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