Desmoid-type fibromatosis: What works best?

Chiara Colombo, Alessandro Gronchi

Department of Surgery, Istituto Nazionale Tumori, Milan, Italy

Desmoid-type fibromatosis (DF) is a rare monoclonal proliferative disease of fibroblastic origin. It accounts for 0.03% of all malignancies and 3% of all soft tissue sarcomas [1]. It usually occurs sporadically but it can also be associated to Gardner's syndrome.

DF is considered a benign disease, since it does not have the capacity to metastasise. Nevertheless, it may harbour some features distinctive of malignant behaviour that may be the cause of its local aggressive course. Cytogenetic studies revealed that chromosome abnormalities are present in some cases, including trisomy 8, trisomy 20 or absence of 5q [1]. The loco-regional course, especially when the disease is located at critical sites, may seldom lead to death.

DF occurs more frequently in patients affected by Gardner's syndrome than in the general population: in these patients the germline mutation of the adenomatous polyposis coli (APC) gene predisposes to develop hundreds of colonic polyps and several other neoplastic diseases. The APC protein regulates the level of β-catenin in the cell; β-catenin is a mediator in the Wingless/Wnt signalling pathway related to cell proliferation and is also involved in cell adhesion. The majority of APC mutations result in a truncated protein that lacks normal regulatory function resulting in β-catenin accumulation that mimics activation of Wnt signalling [1].

Familial adenomatous polyposis (FAP) patients are characterised by germline inactivating mutations of the APC gene whereas patients with sporadic DF usually harbour somatic β-catenin activating mutations.

Some authors demonstrated an overexpression of COX-2 in DF. This over-expression was hypothesised to conduct the inhibition of apoptosis, and stimulation of angiogenesis and cell proliferation mediated by platelet-derived growth factor (PDGF) [1].

The role of trauma and surgery in the development of DF is not completely understood. Some authors presented a correlation beetween abdominal surgery and the development of desmoid tumors in the vicinity of surgical scars.

There is a higher incidence of DF in females but the role of oestrogen receptors is not yet well established. Some authors showed that 17βE2 induced both cell proliferation and matrix synthesis by desmoid cells in primary culture, while tamoxifen counteracted 17βE2 effects in these cells [1].

The main pathologic characteristic of this tumour is the growth pattern: infiltration of deep tissues along muscle planes is the main cause of the frequent recurrences.

Surgery with wide microscopic resection margins has been the treatment mainstay so far, especially if function and cosmesis can be preserved. Local failure rates have been reported to be as high as 25–60% at 5 years. Interestingly, many authors have claimed that the outcome of primary disease is quite unpredictable and not influenced by surgical margins [2–4]. The explanation provided has been that DFs are made by different diseases. There seems to be a subset with an aggressive behaviour and a worse local outcome. This subset maybe constituted by tumours characterised by a different molecular profile, even if with an undistinguishable morphology [5]. This hypothesis has recently been supported by the finding that a particular beta-catenin gene mutation subtype could correlate with the outcome. The results of this study, though needing to be prospectively validated, look very attractive.

This issue, along with the natural history of the disease, the lack of metastatic potential, and the possible implication of inflammatory agents in further tumour re-growth, have all become arguments in favour of a less aggressive primary approach. Pursuing wide margin resection in primary surgery should always be weighted with function preservation and cosmesis.

At recurrence, repeated surgical excisions are usually not the first choice, and again, preservations of function and cosmesis are always to be carefully taken into account.

Some authors advanced the hypothesis that a group of patients could be managed with a front-line non aggressive approach [6]. The wait and see policy or medical therapy could select patients who will most benefit from a surgical approach. As a matter of fact,

it could be an indirect way to understand the biology of each single disease.

Adjuvant radiotherapy following surgery seems to improve local control compared to surgery alone [1]. Radiation therapy may offer some benefits in patients with positive margins, as well as a unique modality when repeated surgery is not indicated for functional impairment or not feasible at all. The optimal dose of radiation is between 50 and 60 Gy. Many collateral effects are especially seen for doses greater than 60 Gy. Possible complications of external beam radiation include growth arrest in children and adolescents, pathologic fracture especially in cases involving periosteal stripping, fibrosis, oedema secondary cancers, skin ulceration, cellulitis, paraesthesias and paresis [1].

A number of clinical observations suggest that the natural history of DF is hormonally related and in particular to oestrogenic stimulation, even if the mechanisms are poorly understood. Tamoxifen is the drug mostly used and the action is probably mediated by the interaction with oestrogen receptor beta.

Other available medical treatments include non-cytotoxic and cytotoxic chemotherapy, including non-steroidal antiinflammatory drugs (NSAIDs). Many NSAIDs are used to treat DF even if the mechanism of action is not completely known, although probably, the alterations of the Wnt/oncogene pathway trigger the COX-2-mediated constitutive coactivation of PDGFRA and PDGFRB.

Medical treatments seem particularly attractive in FAP-associated DF, given the poor results of surgery and the typically difficult locations of the tumours (mesenteric) limiting the value of radiation. Conventional chemotherapy has been used in FAP-associated life-threatening lesions including those characterised by diffuse infiltration of the mesentery and its vasculature, which, therefore, renders the process unresectable [1].

Conventional chemotherapy has also been employed in inoperable or locally advanced sporadic DF. Many regimens have been used including doxorubicin, dacarbazine, methotrexate, vinblastine and vinorelbine in different combinations and doses. In the literature, there is limited information about the action of single agents, but combination chemotherapy regimens are used more frequently [1]. The rate of response varies broadly, ranging from 17–100% in different single arm studies. Isolated limb perfusion is an alternative regional use of chemotherapy for extremity located lesions. In two reported series, limb salvage could be obtained in all patients.

Finally, new target therapies, such as imatinib mesylate, have also been recently tried, but only a few, non convincing responses have so far been documented in phase II studies: it has been hypothesised that they are mediated by the inhibition of PDGF receptor β (PDGFRB) kinase activity rather than KIT [1].

In brief, it is becoming evident that up to 50% of patients with desmoids benefit from a front-line non aggressive policy, because growth arrest is not an uncommon feature of this disease. This strategy could avoid surgical function-loss and late radiation-associated complications, the aggressive therapy being selected only for those who really need it. Indeed, a surgical policy for all patients might overtreat 50% of them. For the future, a stepwise strategy may be tested, encompassing an initial wait and see approach, then medical therapy if needed, then surgery and/or radiation therapy. Otherwise, some prognostic factors could be picked up as criteria for the treatment choice, promptly selecting some patients for surgery or for medical therapy from the beginning. These factors may well include the molecular profile, as long as new insights into this rare disease are collected and validated in the clinic.

Conflict of interest statement

None declared.

References

1 De Bree E, Keus R, Melissas J, et al. Desmoid tumors: need for an individual approach. *Exp Rev Antican Ther* 2009;**9**(4):525–35.
2 Lev D, Dhanasekaran K, Wei Caimiao, et al. Optimizing treatment of desmoid tumors. *J Clin Oncol* 2007;**25**(13):1785–91.
3 Gronchi A, Casali PG, Mariani L, et al. Quality of surgery and out come in extra-abdominal aggressive fibromatosis: a series of patients treated at a single institution. *J Clin Oncol* 2003;**21**(7): 1390–7.
4 Merchant NB, Lewis JJ, Woodruff JM, et al. Extremity and trunk desmoid tumors: A multifactorial analysis of outcome. *Cancer* 1999;**86**:2045–52.
5 Lazar AJ, Tuvin D, Lev D, et al. Specific mutations in the beta-catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoids tumors. *Am J Path* 2008;**173**(5):1518–27.
6 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* [in press].