Overview in targeted therapy in advanced desmoid tumors

Amrallah A. Mohammed1, 2
Hani EL-Tanni2
Hani M. EL-Khatib2
Ahmad A. Mirza3
Emran H. Alsawaf4
Abdulrahim A. Mirza4

1 Department of Medical Oncology, Faculty of Medicine, Zagazig University, Zagazig, Egypt
2 Oncology Center, King Abdullah Medical City-Holy Capital, Makkah, Saudi Arabia
3 College of Medicine, Taif University, Taif, Saudi Arabia
4 Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia

Address for correspondence:
Amrallah A. Mohammed
Muzdallifa Street
P.O. Box 57657
21995 Makkah, Saudi Arabia
Tel.: + 966566979027
E-mail: amrallaabdelmoneem@yahoo.com

Abstract

Background: desmoid tumors/aggressive fibromatosis (DTs/AF) are cytological bland fibrous neoplasms originating from the musculoaponeurotic structures throughout the body. The exact cause still remains unknown, it may be a manifestation of familial adenomatous polyposis (FAP) or present sporadically. Although they lack the capacity to establish metastases, DTs/AF may be devastating and occasionally fatal. As a result of the heterogeneity of DTs/AF, treatment needs to be individualized to improve local tumor control and maintain patients’ quality of life. Therefore, after a multidisciplinary approach, all treatment options should be discussed with patients. Where systemic chemotherapy has been shown to be unsuccessful with marked side effects in case of advanced DTs/AF, new therapeutic options are needed. Methods: a Medline search was conducted and published articles from different studies from 2000 to present were reviewed. Conclusion: more research is needed to illustrate both the prognostic and predictive factors of target therapy and the value of their combinations with or without other treatment modalities to get the best result for the treatment of advanced DTs/AF.

KEY WORDS: desmoid tumors, aggressive fibromatosis, target therapy, molecular pathogenesis.

Introduction

Desmos, a Greek word referred as tendon was described by Muller in 1838. Desmoid tumors (DTs), also known as aggressive fibromatosis (AF), are benign fibrous growths that generally may occur in the root of the mesentery (intra abdominal desmoids), in the abdominal wall (abdominal desmoids), and outside the abdomen, mainly in the shoulder or pelvic girdles (extra abdominal desmoids) (1). DTs are among the rarest of tumors: the estimated incidence in the general population is 2-4 people per million per year. They are rare in the extremes of age; individuals between the ages of 15-60 are most commonly affected, slightly more common in women, without racial or ethnic prediction. Although they don’t exhibit the histological features to classify them as sarcomas, DTs are often considered as low- grade sarcoma because of high tendency for local recurrence after excision (2).

Since soon, it was not clear whether DTs should be considered a reactive proliferation or a malignant process. Just there were considered tumors; do we believe them as malignant or benign tumors? Based on patients outcomes; deformity, morbidity, and mortality resulting from local destruction and potential obstruction of vital structures and organs requiring frequent hospitalization, some researchers would consider them as malignant diseases. However, due to lacking of the main feature of malignancy metastasis, others consider them as benign (3).

DTs may infiltrate neighboring structures, stretching along the facial planes, and bones. Severe and even fatal complications are sometimes caused by these tumors, especially when destroying vital organs (4). Because of their heterogeneity, lesions can range from stable or spontaneously regressing to rapidly progressive with varying response to therapy.

To cover therapies designed to target the events that derive tumor initiation or progression, it is important to understanding molecular pathogenesis. Targeted therapy has changed the natural history of many cancers specially breast and colon cancers (5, 6). This section will discuss some aspects of targeted therapy used in DTs/AF.
Molecular pathogenesis

The molecular events that lead to DTs/AF formation are incompletely understood. However, growing evidence suggests the involvement of the adenomatous polyposis coli (APC) gene in familial adenomatous polyposis (FAP). On the contrary, APC mutations are usually arising from beta-catenin, CTNNB1 mutation (7). Gardner syndrome is defined as FAP with extra-abdominal tumors (osteomas, DTs, and other tumors), and was defined as a separate disease until the clarification of APC gene, as mutations were recognized as the underlying cause of both Gardner syndrome and FAP. Some Authors consider Gardner syndrome as a subset of the FAP and have been proposed to replace the term Gardner syndrome by FAP (8).

APC mutations in DTs

A normal APC protein prevents the accumulation of beta-catenin, by mediating its phosphorylation and resultant degradation. In APC mutation, either germline or sporadic, premature truncation will lead to loss of the beta-catenin regulatory domain, therefore, beta-catenin is accumulated and subsequently activates the transcription factor-4 (tcf-4), which in turn causes transcription of many genes such as CYCD1 and MYC, leading to proliferation and enhanced survival (9).

From 7.5 to 16% of patients with FAP have DTs, and the relative risk is much higher than the general population. Although they can occur with mutations in any APC gene location, in some reports the occurrence of DTs/AF in patients with FAP may be correlated with specific type and site of mutation (10). In one study of 36 patients from 20 families with FAP and mutations in codons 1445 to 1578, all developed DTs. In a meta-analysis of many studies of FAP patients, the independent predictors of increased risk of DTs were APC mutation 3’ to codon 1399, positive family history of DT and female sex (11). A study done by Wallis et al. revealed that the APC mutation in codons 1395-1493 was associated with 100% of DTs development (12). Another study of 953 FAP patients from 187 families revealed that mutations between codons 1310 and 2011 were associated with a six fold risk of DTs (13). The relationship between genotype and phenotype suggests specific roles of the APC protein in different tissues. For example, dental manifestations of Gardner syndrome have been suggested to be associated with mutations at or near codon 1556 (14).

Wnt/beta-catenin pathway in DTs

The Wnt/beta-catenin signaling pathway is thought to play a major key in the molecular pathogenesis of DTs, both those associated with FAP, and sporadic tumors. The basic features of the Wnt signaling pathway are illustrated in the Figure 1 (15).

Figure 1 A, B - The Wnt-signaling pathway. A) Illustrates the down-regulation of β-catenin transactivation activity in normal epithelial cell. B) Shows the role of mutations in the APC or β-catenin protein in the regulation of β-catenin level and its transactivation property in malignant cell. GSK3B: glycogen synthase kinas 3 beta; Lef: Lymphoid enhancer-binding factor; Tcf: Transcription factor. Adapted from Narayan S and Roy D (15).
As discussed before, the levels of beta-catenin in the cell is regulated by phosphorylation, which results in destruction of beta-catenin in the proteosome. Activation of the Wnt pathway was initiated by binding of an external ligand causing inhibition of the kinase activity of the APC complex resulting in greater levels of beta-catenin in the cell. Mutations in the beta-catenin gene have been found in sporadic DTs with variable prevalence (39 to 87%). In a retrospective study of patients with extra-abdominal DTs, Domont et al. reported CTNNB1 mutations in 87% of patients, and the 5-year RFS rate was significantly worse in patients with CTNNB1 mutation, regardless of the genotype, compared with wild-type tumors (49 vs 75%, respectively) (16).

Three distinct mutations, 41A, 45F, and 45P, were identified in 59, 33, and 8% of cases, respectively. Mutation 45F was associated with a high risk of recurrence; 5-year RFS rate was 23% for patients harboring 45F mutation compared to 57% with those 41A and 68% for those with no mutations (17), which are matched with study done by Columbo et al. (18).

In contrast to these findings, Mullen et al. reported that CTNNB1 mutation status was not associated with any statistically significant difference in recurrence risk in subset of 115 patients with DTs who underwent macroscopically complete surgical resection (19). At a median follow-up of 31 months, the 5-year RFS rates were 58 and 74%, for patients with CTNNB1 mutations and for those with wild-type tumors, respectively. In fact there is no an agreement on the prognostic significance of different beta-catenin mutations. The relation between the risk of recurrence and treatment selection with the genotyping of CTNNB1 are in need for more prospective studies.

**Receptor tyrosine kinases & signal transduction**

Although the activity of receptor tyrosine kinases (RTKs), epidermal growth factor receptor (EGFR), and receptor tyrosine- protein kinase erbB-2 (HER-2), had been proved in DTs/AF, no correlations between the expression or activation status of these RTKs and responses to their inhibitors (RTKI) (20, 21).

**Chromosomal anomalies**

Many chromosomal abnormalities have been described in DTs/AF, specially the occurrence of loss of 6q, 5q, trisomies 8, 20, and monosomy 20. Till now the clinical value of these genetic abnormalities is unclear, however, in some reports, their presence has been associated with a higher risk of local recurrence (22).

**Others**

There is no consensus on the importance of Ki-67, p53 and p53 in DTs/AF. However some reports have considered them markers of reduced disease-free survival (23). In trying to explain the lack of DTs/AF to metastasize, Bacac et al. revealed lower expression of osteopontin and secreted protein in relation to nodular fasciitis, which might help in understanding their inability to metastasize (24). The cyclooxygenase-2 gene, released in the wnt/beta-catenin pathway, plays an important role in carcinogenesis through inhibiting apoptosis, stimulating angiogenesis and invasion with increasing growth factors expressions (25). Many studies have proved that DTs/AF had high estrogen level (ER), but negative for progesterone receptor (PR). This information suggests that they may grow under hormonal control and can possibly be influenced by hormonal manipulations (26).

**Target therapy**

Systemic treatment should be thought when local treatment with curative intent is not achievable. Depending on ER over expression, hormone treatment is an accepted strategy in first-line setting in combination with non steroidal anti-inflammatory drugs (NSAIDs). Cytotoxic chemotherapy is a valid alternative when first line treatment fails. In a disease such as DTs/AF, where curative options are stingy, the main goal of treatment is to improve quality of life with relative fewer side effects. Several targeted agents have been recently assessed (27).

**Imatinib**

Imatinib is a small-molecule TKI that was primary developed for PDGFR. It was subsequently found to be a potent inhibitor of ABL kinases, and was also found to inhibit the RTK and KIT. Mace et al. revealed objective remissions and disease stabilization in two patients with unresectable and progressive DTs/AF when treated by imatinib (28). In phase II clinical study, 84% patients had mutations involving the Wnt pathway (APC or CTNNB1), imatinib was used in a dose 800mg/day to treat patients with advanced DTs/AF, resulted in partial response (PR) and stable disease (SD) in 15.7 and 21% of patients, respectively (29). Similar observations have been reported by Chugh et al. (30). Long term follow up results of phase II study done by the French Sarcoma Group also showed that at 3 months, 3% of patients achieved complete response (CR) and 9% PR in patients with recurrent or progressive DTs/AF. At a median follow up of 34 months, the non-progression rates at 3, 6 and 12 months were, respectively, 91, 80 and 67%. The 2-year progression free survival (PFS) and overall survival (OS) rates were 55 and 95%, respectively. Imatinib toxicity was similar to that previously reported in literature (31). However, there was not significant correlation between the expression/mutations in imatinib sensitive TK and the PFS, or OS.
Sorafenib
Sorafenib (BAY-43-9006) is a multitargeted oral TKI, inhibiting KIT, PDGFR, and VEGFR. In a retrospective cohort, Gounder et al. reviewed data for 26 patients with DTs treated with 400 mg oral daily sorafenib with dose adjustment. Sorafenib was the first-line therapy in 11 patients and a subsequent therapy in 15 patients.

Table 1 - Clinical trials in advanced desmoids tumors/Aggressive fibromatosis (DTs/AF).

<table>
<thead>
<tr>
<th>NCT ID</th>
<th>Trial description</th>
<th>Intervention</th>
<th>Trial phase</th>
<th>Last updated</th>
<th>Estimated Study Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01981551</td>
<td>To determine the response rate of PF-03084014 in patients with DT/AF progressed after receiving at least one line of standard treatment.</td>
<td>PF-03084014; small-molecule Gamma-secretase inhibitor</td>
<td>Phase 2</td>
<td>October 6, 2015</td>
<td>December 2016</td>
</tr>
<tr>
<td>NCT02495519</td>
<td>To define the activity of imatinib in the treatment of DT/AF, progression after local treatment and to determine the molecular basis for response.</td>
<td>Imatinib</td>
<td>Phase 2</td>
<td>July 10, 2015</td>
<td>December 2016</td>
</tr>
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</table>
| NCT02066181  | To compares the effects of sorafenib in patients with previously treated DT/AF.                                                                                                                                  | - Sorafenib  
- Laboratory Biomarker Analysis  
- Quality-of-Life Assessment  
- Placebo                                                     | Phase 3     | December 22, 2015 | March 2016                                 |
| NCT01137916  | To evaluate the activity and safety of imatinib in patients with DTs/AF who, after receiving the standard therapy.                                                                                                                                                 | Imatinib                                                                    | Phase 2     | December 1, 2015 | June 2016                               |
| NCT01265030  | To evaluate mTOR inhibitor, clinical and histological studies following a course of pre-operative Sirolimus.                                                                                                                                                     | Sirolimus                                                                    | Phase 1     | Last updated: September 22, 2015 | March 2017                        |
| NCT01876082  | To evaluate efficacy and safety of pazopanib versus a chemotherapy protocol combining methotrexate and vinblastine in progressive DTs.                                                                                                                                     | Drug: pazopanib  
Drug: Active Comparator: Vinblastine and Methotrexate                       | Phase 2     | November 25, 2015 | July 2019                                 |
| NCT01273168  | To test the safety and effectiveness of daily endoxifen in individuals with hormone receptor positive DTs after first line.                                                                                                                                               | Z-Endoxifen                                                                  | Phase 1     | July 30, 2015    | October 2016                   |
| NCT02354560  | To determine the lowest dose of erythromycin that can inhibit growth of in DT/AF.                                                                                                                                                                                     | Erythromycin                                                                | Phase 4     | January 29, 2015  | December 2017                   |
| NCT01608867  | To determine the safety of OMP-54F28 in subjects with previously treated DT/AF.                                                                                                                                                                                     | OMP-54F28                                                                   | Phase 1     | April 13, 2015    | July 2016                              |

Information based on clinical trials listing on clinicaltrials.gov. NCT ID National Clinical Trials Identifier* Biomarkers include; cadherin-associated protein, beta 1 (CTNNB1) genotype, platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor (VEGF).
after median of 2 prior lines of therapy. 88.5% patients had shown evidence of progressive disease, whereas 11.5% patients had achieved maximum benefit. At a median of 6 months of treatment, 25% of patients exhibited PR, 70% with SD, and 5% with progression and death (32).

**Sunitinib**

Sunitinib malate is a multitargeted TKI with activity against VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, KIT, and FLT3. In prospective multicenter phase II study included 19 patients with advanced DTS/AF showed that the OS rate was 26.3 %. With a median follow-up time of 20.3 months, the 2-year rates of PFS and OS were 74.7 and 94.4 %, respectively. According to this result, sunitinib is considered as option in advanced DTS/AF (33).

**Pazopanib**

Pazopanib is a multi-tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, (PDGFR)-α and KIT. Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) approved it in treatment of advanced renal cell carcinoma and soft-tissue sarcomas. It showed significant clinical improvement for more than 12 months with tolerable toxicity (34).

**Conclusion**

The lack of effective therapeutic options and its serious complications make DTS/AF a challenging disease. Although DTS/AF is not strictly considered a malignancy, the mechanisms that lead to local invasion, tissue destructions and survival are similar to those in cancer. Although there is an evidence support the activation of RTK in DTS/AF, still the therapeutic benefits of TKI therapy are unpredictable, which may be explained by the variability in signal transduction or cellular kinases. Because of poor response rate of imatinib, so it is recommended for use when other options have failed. In early studies, sunitinib showed potential antitumor activity in patients with advanced DTS/AF. Also, pazopanib is a promising drug with tolerable side effects. However, further investigations are necessary. As mentioned before, the use of sorafenib in first line or second line, both are equal as regard the radiological benefit. These findings suggest that the response of DTS/AF to sorafenib is a function of their biology. It is interesting that both sorafenib and pazopanib inhibit VEGFR and PDGFR. On the contrary, imatinib inhibits only PDGFR. These data suggest that the efficacy of these drugs in DTS/AF might be due to their antiangiogenic activity mediated by the inhibition of different key effectors. We hoped that the illustration of the main role of betacatenin and APC in the pathogenesis of DTS/AF will lead to developing promising molecular therapeutic targets. We summarized the most important clinical trials in advanced DTS/AF in Table 1.

**Conflict of interest**

The Authors certify that there is no actual or potential conflict of interest in relation to this article.

**References**

16. Dômont J, Salas S, et al. High frequency of betacatenin heterozygous mutations in extra-abdominal...