Update on systemic treatment options and clinical trials in desmoids

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Educational: Desmoid Track

Background:

- Desmoid tumors describe a rare monoclonal, fibroblastic proliferation characterized by a variable and often unpredictable clinical course.
- The incidence is less than 3 % of soft tissue sarcomas and about 0.03 % of all malignancies.
- Therefore, desmoid tumors represent a rare disease with 3-4 cases/1.000.000 US citizens (Germany: ca. 200-300 new cases each year).
- Desmoids occur between the age of 15 and 60 years, but particularly during early adolescence and with a peak age of about 30 years.
- There is a correlation of desmoid tumors and the Familial Adenomatous Polyposis (FAP, Gardner Syndrome) with an incidence of 3.5-32 %.
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Typical localizations of desmoid tumors including rectus abdominis muscle (A), head and neck (B), pelvis (C) and extremities (D):

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Treatment Options:

- The first-line therapy for locally circumscribed, resectable desmoid tumors remains surgical resection.
- However, desmoids can often take a multiply relapsing, multifocal course and, therefore, may not be amenable to curative surgical treatment.
- In many cases adjuvant radiotherapy or radiotherapy alone is performed. Cave: Radiation-related complications with doses above 56 Gy!
- **Systemic treatment approaches comprise:**
  - antihormonal therapy,
  - non-steroidal anti-inflammatory drugs,
  - chemotherapy and
  - tyrosine kinase inhibitors.
- **Watch & Wait Strategy** may be most appropriate in many clinical situations.

Kasper B et al. Oncologist 2011; 16: 682-693
Antihormonal and anti-inflammatory Drugs:

- Response rates for antihormonal or anti-inflammatory drugs vary up to 50%.
- **Main problem:** There is only data from single-case reports or small series.
- Larger series of patients or data from clinical trials are not available.¹

**Indication:** Endocrine and NSAID therapy may be considered as first-line medical treatment for unresectable disease without clinical symptoms (especially for FAP associated desmoids).²

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² Hansmann A et al. Cancer 2004; 100: 612-620
Antihormonal and anti-inflammatory Drugs:

Table 1. Antiestrogen therapy in patients with aggressive fibromatosis: single-arm trials and case reports

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Sex</th>
<th>Age, range (median)</th>
<th>History of FAP</th>
<th>Primary or recurrent</th>
<th>Location</th>
<th>Hormonal agent</th>
<th>NSAID</th>
<th>Response</th>
<th>Response duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinzbrunner et al. 1983 [26]</td>
<td>1</td>
<td>F</td>
<td>29</td>
<td>Yes</td>
<td>Recurrent</td>
<td>Multifocal</td>
<td>Tamoxifen 80 mg/day</td>
<td>No</td>
<td>PR</td>
<td>NR</td>
</tr>
<tr>
<td>Rock et al. 1984 [27]</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Recurrent</td>
<td>NR</td>
<td>Tamoxifen</td>
<td>No</td>
<td>2 SD, 3 PD</td>
<td>NR</td>
</tr>
<tr>
<td>Procter et al. 1987 [28]</td>
<td>1</td>
<td>F</td>
<td>26</td>
<td>No</td>
<td>Recurrent</td>
<td>Multifocal</td>
<td>Tamoxifen 40 mg/day</td>
<td>No</td>
<td>SD</td>
<td>14 months</td>
</tr>
<tr>
<td>Egele et al. 1989 [29]</td>
<td>1</td>
<td>F</td>
<td>29</td>
<td>Yes</td>
<td>Recurrent</td>
<td>Mesentry</td>
<td>Tamoxifen 20 mg/day, megestrol 300 mg/day</td>
<td>No</td>
<td>SD</td>
<td>7 months</td>
</tr>
<tr>
<td>Sportello and Hoogerland 1991 [30]</td>
<td>1</td>
<td>F</td>
<td>40</td>
<td>No</td>
<td>Recurrent</td>
<td>Pelvic</td>
<td>Tamoxifen 80 mg/day</td>
<td>No</td>
<td>CR</td>
<td>27 months</td>
</tr>
<tr>
<td>Thomas et al. 1990 [31]</td>
<td>1</td>
<td>F</td>
<td>30</td>
<td>No</td>
<td>Recurrent</td>
<td>Shoulder girdle</td>
<td>Tamoxifen 20 mg/day</td>
<td>No</td>
<td>CR</td>
<td>12 months</td>
</tr>
<tr>
<td>Wilckens and Tattersall 1991 [32]</td>
<td>2</td>
<td>F</td>
<td>40</td>
<td>No</td>
<td>Recurrent</td>
<td>Calf</td>
<td>Tamoxifen 20 mg/day</td>
<td>No</td>
<td>1 PR</td>
<td>8 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>40</td>
<td>No</td>
<td>Primary</td>
<td>Mesentry</td>
<td>Mecac 500 mg/day</td>
<td>No</td>
<td>1 PR</td>
<td>10 months</td>
</tr>
<tr>
<td>Brooks et al. 1992 [33]</td>
<td>20</td>
<td>15 F, 5 M</td>
<td>18–70 (29)</td>
<td>NR</td>
<td>12 Primary, 8 recurrent</td>
<td>14 Abdominal and pelvic</td>
<td>Toremifene 200 mg/day</td>
<td>No</td>
<td>1 CR, 10 PR, 6 SD</td>
<td>NR</td>
</tr>
<tr>
<td>Benson et al. 1994 [34]</td>
<td>1</td>
<td>F</td>
<td>17</td>
<td>NR</td>
<td>Primary</td>
<td>Retropertoneum</td>
<td>Toremifene 200 mg/day</td>
<td>No</td>
<td>PR</td>
<td>9 months</td>
</tr>
<tr>
<td>Mukherjee et al. 1995 [35]</td>
<td>1</td>
<td>M</td>
<td>16</td>
<td>NR</td>
<td>Primary</td>
<td>Pelvis</td>
<td>Tamoxifen 20 mg/day, prednisolone 60 mg/day</td>
<td>No</td>
<td>PR</td>
<td>2 years</td>
</tr>
<tr>
<td>Izes et al. 1996 [36]</td>
<td>1</td>
<td>M</td>
<td>54</td>
<td>NR</td>
<td>Primary</td>
<td>Pelvis</td>
<td>Tamoxifen 160 mg/day</td>
<td>Sulindac 300 mg/day</td>
<td>PR</td>
<td>54 months</td>
</tr>
<tr>
<td>Lackner et al. 1997 [37]</td>
<td>2</td>
<td>F</td>
<td>1</td>
<td>NR</td>
<td>Recurrent</td>
<td>Chest wall</td>
<td>Tamoxifen 2 mg/kg/day</td>
<td>Diacerein 4 mg/kg/day</td>
<td>SD</td>
<td>4 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>1.5</td>
<td>NR</td>
<td>Primary</td>
<td>Mandible</td>
<td>as above</td>
<td>as above</td>
<td>SD</td>
<td>1 year</td>
</tr>
</tbody>
</table>

CR, complete response; F, female; FAP, familial adenomatous polyposis; M, male; NR, not reported; NSAID, non-steroidal anti-inflammatory agent; PD, progressive disease; PR, partial response; SD, stable disease.

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Antihormonal and anti-inflammatory Drugs:

Review

The pharmacological treatment of aggressive fibromatosis: a systematic review

J. Janinis\textsuperscript{1,2}, M. Patraki\textsuperscript{1}, L. Vini\textsuperscript{2}, G. Aravantinos\textsuperscript{3} & J. S. Whelan\textsuperscript{4}

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Received 23 March 2002; revised 16 August 2002, accepted 10 September 2002

Table 3. Anti-inflammatory therapy in aggressive fibromatosis: case reports

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Sex</th>
<th>Age (median)</th>
<th>History of FAP</th>
<th>Primary or recurrent</th>
<th>Location</th>
<th>Anti-inflammatory treatment</th>
<th>Other</th>
<th>Response</th>
<th>Response duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsukada et al. 1992 [48]</td>
<td>14</td>
<td>NR</td>
<td>29</td>
<td>Yes</td>
<td>Recurrent</td>
<td>Abdominal</td>
<td>Sulindac 300 mg/day</td>
<td>No</td>
<td>1 CR, 7 PR, 4 SD</td>
<td>NR</td>
</tr>
<tr>
<td>Klein et al. 1987 [23]</td>
<td>3</td>
<td>2 M, 1 F</td>
<td>NR</td>
<td>Yes</td>
<td>Recurrent</td>
<td>Abdominal wall, mesentery</td>
<td>Indomethacin 100 mg/day</td>
<td>No</td>
<td>2 PD, 1 SD</td>
<td>NR</td>
</tr>
<tr>
<td>Waddell and Kirsch 1991 [41]</td>
<td>8</td>
<td>4 F, 4 M</td>
<td>22–76 (39)</td>
<td>4 Yes, 4 No</td>
<td>NR</td>
<td>4 Mesentery</td>
<td>Sulindac 300–400 mg/day or indomethacin 75–300 mg/day</td>
<td>Warfarin</td>
<td>3 PR, 3 SD, 2 PD</td>
<td>NR</td>
</tr>
<tr>
<td>Belliveau and Graham 1984 [49]</td>
<td>1</td>
<td>M</td>
<td>36</td>
<td>Yes</td>
<td>Primary</td>
<td>Mesentery</td>
<td>Sulindac 200 mg/day</td>
<td>No</td>
<td>1 PR</td>
<td>NR</td>
</tr>
<tr>
<td>Dominguez-Malagon et al. 1992 [50]</td>
<td>3</td>
<td>F</td>
<td>30</td>
<td>No</td>
<td>Primary</td>
<td>Extra-abdominal</td>
<td>Colchicine 3 mg/day</td>
<td>No</td>
<td>PR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>47</td>
<td></td>
<td></td>
<td>Primary</td>
<td>as above</td>
<td>as above</td>
<td>No</td>
<td>PR</td>
<td>NR</td>
</tr>
</tbody>
</table>

CR, complete response; F, female; FAP, familial adenomatous polyposis; M, male; NR, not reported; PD, progressive disease; PR, partial response; SD, stable disease.
Antihormonal and anti-inflammatory Drugs:

- Prospective phase II study of the Children’s Oncology Group (COG): high-dose tamoxifen + sulindac for desmoid tumors in children.
- N = 59 (age < 19 years) were enrolled between 2004 and 2009.
- Treatment schedule: tamoxifen + sulindac (each 3 mg/kg/dose daily PO BID) for 12 months, until disease progression or intolerable toxicity.
- 10 patients completed therapy without PD or withdrawal.
- Response: 4 PR + 1 CR = 5/59 = 8 %
- Survival: 2-year PFS rate 36 % and OS rate 96 %
- Safety: 3 deaths due to PD, 12/30 females developed ovarian cysts

First and only prospective trial evaluating this combination, however, relatively low activity as measured by response and PFS rates.

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Chemotherapy:

- There are different chemotherapy regimens with highly variable results.
- Methotrexate / vinblastine has been evaluated in the pediatric patient population with reasonable activity and tolerable toxicity.¹
- However, the combination is toxic over time and adult patients generally cannot complete the recommended year of therapy.
- Alternatively, the combination of methotrexate / vinorelbine can be administered and is much less toxic.²

Indication: Unresectable, rapidly growing and / or symptomatic and / or life threatening desmoid tumors can be treated with chemotherapy.

Chemotherapy:

- Phase II trial of the Pediatric Oncology Group: **methotrexate + vinblastine**
- N = 28 (27 eligible and 26 evaluable for response)
- Inclusion criteria: recurrent disease or not amenable to radiation or surgery
- Treatment schedule: MTX 30 mg/m²/weekly + Vbl 5 mg/m²/weekly for 26 weeks and every other week for an additional 26 weeks (1 year therapy!)
- Response: 5 CR + PR (19 %) and 10 SD
- Survival: 18 pts. showed PD at a median time of 9.1 months
- Safety: neutropenia, anemia, nausea, vomiting

> Combination of MTX + vinblastine can promote tumor regression or block tumor growth in most children.

Chemotherapy:

- There is greater benefit from anthracycline based therapy regarding response rates (compare Table).
- In the series of de Camargo et al. (n = 68) anthracyclines in combination with hormonal therapy demonstrated the greatest RECIST response rates.¹
- Pegylated liposomal doxorubicin (50 mg/m²/every 4 weeks) has been reported to have significant activity with 4/11 objective responses (RR = 36 %) and seven stable diseases and, therefore, is considered treatment of choice by many investigators for refractory disease.²

¹ De Camargo VP et al. Cancer 2010; 116: 2258-2265
² Constantinidou A et al. Eur J Cancer 2009; 45: 2930-2934
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Chemotherapy (selected regimens):

<table>
<thead>
<tr>
<th>Reference</th>
<th>Chemotherapy regimen</th>
<th>Number of patients</th>
<th>Response</th>
<th>Follow-up [months]</th>
<th>Rate [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel</td>
<td>Doxorubicin 60-90 mg/m² + dacarbazine 750-1000 mg/m²</td>
<td>12</td>
<td>2 CR</td>
<td>28-235</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gega</td>
<td>Doxorubicin 20 mg/m² d1-4 + dacarbazine 150 mg d1-4, d28</td>
<td>7</td>
<td>3 CR</td>
<td>33-108</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constantinidou</td>
<td>Pegylated liposomal doxorubicin 50 mg/m², d28</td>
<td>12</td>
<td>4 PR</td>
<td>7-39</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wehl</td>
<td>Pegylated liposomal doxorubicin 50 mg/m², d28</td>
<td>4</td>
<td>4 PR</td>
<td>NR</td>
<td>100</td>
</tr>
<tr>
<td>Azzarelli</td>
<td>Vinblastine 6 mg/m² + methotrexate 30 mg/m², weekly</td>
<td>27</td>
<td>4 OR</td>
<td>6-96</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19 SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weiss</td>
<td>Vinorelbine 20 mg/m² + methotrexate 50 mg/m², weekly</td>
<td>13</td>
<td>NR</td>
<td>&lt; 12</td>
<td></td>
</tr>
<tr>
<td>Skapek</td>
<td>Vinblastine 5 mg/m² + methotrexate 30 mg/m², weekly</td>
<td>27</td>
<td>8 PR</td>
<td>5-37</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilz</td>
<td>VAIA, VAC, cyclophosphamide + ifosfamide</td>
<td>19</td>
<td>4 CR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 PR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Chemotherapy:

- Retrospective analysis from the French Sarcoma Group (FSG)
- N = 62 (12 pts. with Gardner syndrome)
- Previous treatments: 55 % previously received one or more lines of systemic treatment (44 % NSAID, 44 % antiestrogens, 31 % imatinib)
- Chemotherapy: 71 % combination chemotherapy, 29 % single-agent, 21 % anthracycline-based
- Response: 2 % CR, 19 % PR, 60 % SD and 19 % PD
- Non-limb location was associated with improved PFS ($p = 0.03$).
  - Response rate was significantly higher for anthracycline-containing regimens (54 % vs. 12 %, $p = 0.0011$).
  - If chemotherapy is administered, it should be anthracycline-based.

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### Chemotherapy:

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesna, Adriamycin, Ifosfamide, Dacarbazine</td>
<td>Doxorubicin 20 mg/m² (day 1–day 3)</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide 2.5 g/m² (day 1–day 3)</td>
</tr>
<tr>
<td></td>
<td>Dacarbazine 300 mg/m² (day 1–day 3)</td>
</tr>
<tr>
<td></td>
<td>21 days cycle</td>
</tr>
<tr>
<td>Adriamycin, Dacarbazine</td>
<td>Doxorubicin 20 mg/m² (day 1–day 3)</td>
</tr>
<tr>
<td></td>
<td>Dacarbazine 300 mg/m² (day 1–day 3)</td>
</tr>
<tr>
<td></td>
<td>21 days cycle</td>
</tr>
<tr>
<td>Metronomic Etoposide</td>
<td>Oral etoposide 75 mg/day for 21 days of 28 days cycle</td>
</tr>
<tr>
<td>Metronomic Cyclophosphamide</td>
<td>Oral cyclophosphamide 50 mg/day for 21 days of 28 days cycle</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Doxorubicin 60–75 mg/m²</td>
</tr>
<tr>
<td></td>
<td>21 days cycle</td>
</tr>
<tr>
<td>Methotrexate–Vinblastine</td>
<td>Vinblastine 6 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Methotrexate 30 mg/m² (J1, J8, 15, 21) 28 days cycle</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Methotrexate 30 mg/m² (J1, J8, 15, 21) 28 days cycle</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Vinorelbine 20 mg/m² (J1, J8) 21 days cycle</td>
</tr>
</tbody>
</table>

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Tyrosine kinase inhibitors - Imatinib:

- Initial data by *Mace et al. 2002*: Response in two patients with extra-abdominal aggressive fibromatosis treated with imatinib.

- In contrast to CML or GIST, in desmoids no genomic changes have been observed showing that the response to imatinib is not attributable to KIT expression.

- *Heinrich et al. JCO 2006* treated 19 patients with desmoids with 800 mg imatinib daily:
  - 3 PR and 4 SD (response rate RR = 16 %)
  - No mutations of KIT, PDGFRA or PDGFRB were found

- *Penel et al. Ann Oncol 2010* presented the FNCLCC/French Sarcoma Group phase II study:
  - 3 % CR, 9 % PR and 83 % SD in 40 patients (RR = 12 %)
  - Non-progression rates at 3, 6, 12 months were 91, 80, 67 %
  - 2-years PFS and OS were 55 % and 95 %
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Tyrosine kinase inhibitors - Sorafenib:

- Data on the use of sorafenib have been published in 26 evaluable patients with desmoid tumors.
- The pilot non-randomized study demonstrated impressive response rates with 6/24 ($RR = 25\%$) partial responses and 17/24 (70\%) stable diseases and one patient with progressive disease and death.
- Symptomatic improvement regarding pain and mobility was observed in 70\% of patients.
- Phase III study planned in the US.

Phase II study to evaluate Glivec (imatinib mesylate) to induce progression arrest in aggressive fibromatosis / desmoid tumors not amenable to surgical resection with R0 intent or accompanied by unacceptable function loss (GISG-01)

Bernd Kasper
Mannheim University Medical Center
Interdisciplinary Tumor Center Mannheim
Sarcoma Unit
German Interdisciplinary Sarcoma Group (GISG)
Amendment:

- Administration of **Nilotinib 2 x 400 mg**, if PD or intolerance under therapy with imatinib.

**Translational Research:**

- Therapy monitoring using positron emission tomography (FDG PET) to determine early whether patients benefit from imatinib therapy or not.
- Analysis of mutations in the beta-catenin gene **CTNNB1** and correlation with patients’ survival (PFS).
Interim analysis (06/2012):

- **Primary endpoint:** Non-progression rate at 6 months
- Interim analysis was performed at 17/37 evaluable patients.
- Accrual will continue if ≥ 4 patients are progression-free at 6 months.
- Interim analysis showed that **11 out of 17** evaluable patients had stable disease at 6 months indicating that imatinib had reached the primary endpoint.
- Accrual can be continued after the first step of the study.
- 6 “non-successors”: 3 PD, 1 toxicity, 1 withdrawal, 1 treatment change

**Conclusion:** With a 65 % progression-free rate at the interim analysis, imatinib clearly exceeded its primary endpoint of the study and warrants further accrual and final analysis of the trial.
Desmoid Study GISG-01

Recruitment Status:

- Cut-off-date 09/2013
- $n = 39/39$ in the following centers (since 07/2010):
  - Berlin $n = 8$
  - Essen $n = 3$
  - Hannover $n = 9$
  - Heidelberg $n = 0$
  - Mannheim $n = 19$
- End of recruitment reached; final analysis expected in 2015.
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Treatment Strategies:

- However, it has not been possible to establish an optimal therapy protocol for this disease due to the lack of randomized data.

- Burning questions:  
  - Which patients should be treated?  
  - Which treatment should be selected?  
  - When is the right time to start treatment?

- Obviously, multimodality treatment including surgery, radiotherapy and systemic treatment forms the basis of care for these patients.

- Considering the natural history of desmoids, a period of watchful waiting may be the most appropriate management in asymptomatic patients.

- Due to the heterogeneity of the biological behavior of desmoids, treatment should be individualized to reduce local tumor control failure with preservation of patients’ quality of life.
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Treatment Strategies:

- Observation
- Desmoid Tumor
  - resectable?
    - Yes: Resection
    - No: Systemic Therapy
  - adequate response
  - inadequate response
  - Observation

- Observation

- Oberservation
- Radiation Therapy
  - Positive
  - Negative
  - margins?

- Observation

- Reassessment in the case of progression/recurrence

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Desmoid-Type Fibromatosis: A Front-Line Conservative Approach to Select Patients for Surgical Treatment

Marco Fiore, MD¹, Françoise Rimareix, MD², Luigi Mariani, MD³, Julien Domont, MD⁴, Paola Collini, MD⁵, Cecile Le Péchoux, MD⁶, Paolo G. Casali, MD⁷, Axel Le Cesne, MD⁴, Alessandro Gronchi, MD¹, and Sylvie Bonvalot, MD, PhD²

¹Department of Surgery, Istituto Nazionale Tumori, Milan, Italy; ²Department of Surgery, Institut Gustave Roussy, Villejuif, France; ³Department of Biostatistics, Istituto Nazionale Tumori, Milan, Italy; ⁴Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; ⁵Department of Pathology, Istituto Nazionale Tumori, Milan, Italy; ⁶Department of Radiotherapy, Institut Gustave Roussy, Villejuif, France; ⁷Department of Cancer Medicine, Istituto Nazionale Tumori, Milan, Italy
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Lack of randomized trials and evidence-based data:

Editorial Comment

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

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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. 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.
Educational: Desmoid Track

Currently recruiting clinical trials:

- A phase II randomized study evaluating **Pazopanib** versus Methotrexate / Vinblastine in adult patients with desmoid tumors (DESMOPAZ):
  The purpose of this study is to evaluate the efficacy of pazopanib in comparison to chemotherapy with methotrexate and vinblastine in adult patients with desmoid tumors (phase II, \( n = 94 \), age \( \geq 18 \) years; Dr. Italiano, Institut Bergonié, Bordeaux). ONGOING

- A phase II study of **Imatinib** in patients with desmoid tumor and chondrosarcoma (BASKET 1):
  The purpose of this study is to determine whether imatinib is active in diseases - such as desmoid tumor and chondrosarcoma - expressing the PDGFR both in its isoform alpha and beta (phase II, \( n = 35 \), age \( \geq 18 \) years; Prof. Aglietta, Italian Sarcoma Group). ONGOING

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Educational: Desmoid Track

Take-Home-Messages:

- Desmoid tumors represent an extremely heterogeneous disease with a natural biology varying between spontaneous regression and stabilization to rapid progression.
- Medical treatment is indicated when local surgery is infeasible or associated with severe function loss or morbidity.
- A strategy of observation may be the most appropriate management for asymptomatic patients with a non progressive desmoid tumor.
- There is an unmet medical need for prospective and / or randomized clinical trials to gain more evidence-based data.
- There are only a few interesting clinical trials on the way, however, designing and funding studies in this rare disease remains extremely difficult.
desmoid-type fibromatosis

While principles for the diagnosis of STS apply also to desmoids, beta catenin mutational analysis may be useful when the pathological differential diagnosis is difficult.

Given the unpredictable natural history of the disease (with the possibility of long-lasting stable disease and even occasional spontaneous regressions, along with a lack of metastatic potential), and functional problems implied by some tumor anatomical locations, an initial watchful waiting policy can be proposed [27] [III, B], after a shared decision-making with the patient, with the exclusion of potentially life-threatening extra-abdominal locations (e.g. head and neck region), and intra-abdominal desmoids (mesenteric fibromatosis). Under such a policy, treatment is reserved for progressing cases. The preferred imaging modality is MRI, taking into consideration that the tumor signal is not meaningful with regard to the disease evolution.

For progressing cases, optimal treatment needs to be individualized on a multidisciplinary basis and it may consist of surgery (without any adjuvant therapy), radiation therapy, observation, isolated limb perfusion (if the lesion is confined to an extremity) or systemic therapy (see below) [28, 29] [V, B]. Systemic therapies include: hormonal therapies (tamoxifen, toremifene, Gn-RH analogues), nonsteroidal anti-inflammatory drugs; low-dose chemotherapy, such as methotrexate + vinblastine or methotrexate + vinorelbine; low-dose interferon; imatinib; sorafenib; full-dose chemotherapy (using regimens active in sarcomas, including liposomal doxorubicin). It is reasonable to employ the less toxic therapies before the more toxic ones in a stepwise fashion.