SPAEN Meeting: Desmoid Tumors

23rd of November 2012, Firenze, Italy

Update on systemic treatment options and clinical trials in desmoids

Bernd Kasper
University of Heidelberg
Mannheim University Medical Center
ITM - Interdisciplinary Tumor Center Mannheim
Sarcoma Unit
German Interdisciplinary Sarcoma Group (GISG)
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 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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Examples: Typical localizations of desmoids including rectus abdominis muscle, head and neck, pelvis and extremities:
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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 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 or
  - tyrosine kinase inhibitors with highly variable results.
Antihormonal and anti-inflammatory Therapy:

- Response rates for antihormonal (e.g. tamoxifen) or anti-inflammatory drugs (e.g. sulindac, indomethacin) vary up to 50%.
- However, 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/or NSAID therapy is often considered first-line medical treatment for unresectable, advanced disease without clinical symptoms.²

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Antihormonal and anti-inflammatory Therapy:

<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>Egel et al. 1989 [29]</td>
<td>1</td>
<td>F</td>
<td>29</td>
<td>Yes</td>
<td>Recurrent</td>
<td>Mesentery</td>
<td>Tamoxifen 20 mg/day, mesencephal 300 mg/day</td>
<td>No</td>
<td>SD</td>
<td>7 months</td>
</tr>
<tr>
<td>Sportiello 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>Wilcken 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>F</td>
<td>40</td>
<td>No</td>
<td>Primary</td>
<td>Mesentery</td>
<td>Mabacec 500 mg/day</td>
<td>No</td>
<td>1 PR</td>
<td>10 months</td>
<td></td>
</tr>
<tr>
<td>Brooks et al. 1992 [33]</td>
<td>20</td>
<td>15 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>Retropertitoneum</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>PR</td>
<td>54 months</td>
<td></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>SD</td>
<td>4 years</td>
<td></td>
</tr>
<tr>
<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>
<td></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.

55%
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Antihormonal and anti-inflammatory Therapy:

Review

The pharmacological treatment of aggressive fibromatosis: a systematic review

J. Janinis1,2, M. Patriki1, L. Vini1, G. Aravantinos3 & J. S. Whelan1

1Social Security Organization Oncology Center, Athens Medical Center, Athens; 2Saint Andrew Cancer Center, Kifissia, Greece; 3The London Bone and Soft Tissue Tumor Service, Meyer Institute of Oncology, Midland Hospital, London, UK

Received 23 March 2002; revised 16 August 2002; accepted 16 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</td>
<td>4 SD</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</td>
<td>2 PD</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></td>
<td>F</td>
<td>21</td>
<td>No</td>
<td>Primary</td>
<td>as above</td>
<td>as above</td>
<td>No</td>
<td>PR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>47</td>
<td>No</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.

38%

57%
Antihormonal and anti-inflammatory Therapy:

- Children’s Oncology Group prospective phase II study: Evaluating high-dose tamoxifen + sulindac for desmoid-type aggressive fibromatosis in children\(^1\)
- N = 61 (age < 19 years)
- Treatment schedule: tamoxifen + sulindac (each 3 mg/kg/dose daily PO BID) for 12 months, until disease progression or intolerable toxicity
- Response rate: 13 patients completed therapy without PD or withdrawal (including 4 PR and 1 CR = 8 % RR)
- EFS at 1 year 44 %; OS at 2 years 96 %
- Safety: occasional grade 3 and three grade 4 toxicity (depression, hepatitis)
- First prospective trial: Response rate and EFS were similar to prior results with vinblastine + methotrexate in pediatric patients.

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Chemotherapy:

- **Indication:** Unresectable, rapidly growing and/or symptomatic and/or life threatening desmoid tumor.
- 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.
- However, the combination is toxic over time and adult patients generally cannot complete the recommended year of therapy.\(^1\)
- Alternatively, the combination of methotrexate / vinorelbine can be administered and is likely much less toxic.\(^2\)

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Chemotherapy:

- **Methotrexate/vinblastine** in a phase II trial of the Pediatric Oncology Group\(^1\)
- \(N = 28\) (27 eligible and 26 evaluable for response)
- Inclusion criteria: recurrent disease or not amenable to radiation or surgery
- CHT Schedule: MTX 30 mg/m\(^2\)/weekly + Vbl 5 mg/m\(^2\)/weekly for 26 weeks and every other week for an additional 26 weeks (1 year therapy!)
- Response rate: 5 (19%) CR + PR and 10 SD
- 18 pts. showed PD at a median time of 9.1 months
- Safety: neutropenia (22 pts.), anemia, nausea, vomiting
- **Combination of MTX / vinblastine can promote tumor regression or block tumor growth in most children.**

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Chemotherapy:

- There is greater benefit from anthracycline based therapy regarding response rates (*compare Table*).
- In the series of de Camargo (n = 68) anthracyclines in combination with hormonal therapy demonstrated the greatest RECIST response rates.\(^1\)
- Pegylated liposomal doxorubicin (50 mg/m\(^2\)/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.\(^2\)

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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>Follow-up [months] [%]</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>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>
Chemotherapy:

- Chemotherapy in desmoid tumor patients: a study from the FSG\textsuperscript{1}
- Retrospective analysis from desmoid tumor patients treated at FSG centers
- N = 62 (12 pts. with Gardner syndrome)
- Treatments: 37 pts. (55 \%) received previously one or more lines of systemic treatment (44 \% NSAID, 44 \% antiestrogens, 31 \% imatinib)
- CHT: 71 \% combination CHT, 29 \% single agent, 21 \% anthracycline-based
- Response: 1 (2 \%) CR, 12 (19 \%) PR, 37 (60 \%) SD and 12 (19 \%) PD
- Response rate was significantly higher for anthracycline-containing regimens: 54 \% vs. 12 \% (p = 0.0011)
- Nonlimb location associated with improved PFS (p = 0.03)

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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</td>
</tr>
<tr>
<td></td>
<td>of 28 days cycle</td>
</tr>
<tr>
<td>Metronomic cyclophosphamide</td>
<td>Oral cyclophosphamide 50 mg/day for 21 days</td>
</tr>
<tr>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>28 days cycle</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Methotrexate 30 mg/m² (J1, J8, 15, 21)</td>
</tr>
<tr>
<td></td>
<td>28 days cycle</td>
</tr>
<tr>
<td>Vinorelbin</td>
<td>Vinorelbin 20 mg/m² (J1, J8) 21 days cycle</td>
</tr>
</tbody>
</table>
# Educational: Desmoid Track

## Chemotherapy:

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy regimen</th>
<th>n of patients</th>
<th>Response</th>
<th>Follow-up (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al. [41]</td>
<td>Doxorubicin, 60–90 mg/m², + dacarbazine, 750–1,000 mg/m²</td>
<td>12</td>
<td>2 CR, 4 PR, 2 SD</td>
<td>28–235</td>
</tr>
<tr>
<td>Gega et al. [42]</td>
<td>Doxorubicin, 20 mg/m², days 1–4, + dacarbazine, 150 mg, days 1–4, day 28</td>
<td>7</td>
<td>3 CR, 4 PR</td>
<td>33–108</td>
</tr>
<tr>
<td>Constantioudou et al. [44]</td>
<td>Pegylated liposomal doxorubicin, 50 mg/m², day 28</td>
<td>12</td>
<td>4 PR, 7 SD</td>
<td>7–39</td>
</tr>
<tr>
<td>Wehl et al. [58]</td>
<td>Pegylated liposomal doxorubicin, 50 mg/m², day 28</td>
<td>4</td>
<td>4 PR</td>
<td>NR</td>
</tr>
<tr>
<td>Azzarelli et al. [59]</td>
<td>Vinblastine, 6 mg/m², + methotrexate, 30 mg/m², weekly</td>
<td>27</td>
<td>4 OR, 19 SD</td>
<td>6–96</td>
</tr>
<tr>
<td>Weiss et al. [60]</td>
<td>Vinorelbine, 20 mg/m², + methotrexate, 50 mg/m², weekly</td>
<td>13</td>
<td>NR</td>
<td>&lt;12</td>
</tr>
<tr>
<td>Skapek et al. [39]</td>
<td>Vinblastine, 5 mg/m², + methotrexate, 30 mg/m², weekly</td>
<td>27</td>
<td>8 PR, 10 SD</td>
<td>5–37</td>
</tr>
<tr>
<td>Pilz et al. [61]</td>
<td>VAIA, VAC, cyclophosphamide, + ifosfamide</td>
<td>19</td>
<td>4 CR, 5 PR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; NR, not reported; OR, objective response; PR, partial response; SD, stable disease; VAC, vincristine, actinomycin-D, and cyclophosphamide; VAIA, vincristine, doxorubicin, ifosfamide, and actinomycin-D.
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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 (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 %
Tyrosine kinase inhibitors - Sorafenib:

- Preliminary 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.¹
- Symptomatic improvement regarding pain and mobility was observed in 70 % of patients.

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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:

- Desmoid Tumor
  - resectable?
    - Yes → Resection
    - No → Systemic Therapy

Resection
- margins?
  - Negative → Observation
  - Positive → Radiation Therapy

Systemic Therapy
- adequate response
  - Yes → Observation
  - No → inadequate response
    - ? Alternative Therapy?

Reassessment in the case of progression/recurrence
Educational: Desmoid Track

Treatment Strategies:

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
Educational: Desmoid Track

Lack of randomized trials and evidence-based data:

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

*Stefan Sleijfer*

Department of Medical Oncology, Erasmus University Medical Cen 3075 EA Rotterdam, The Netherlands

...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.
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
ITM - Interdisciplinary Tumor Center Mannheim
Sarcoma Unit
German Interdisciplinary Sarcoma Group (GISG)
Desmoid Study GISG-01

Medication Intake:

- The target treatment consists of the oral intake of imatinib in a daily dose of **800 mg** (400 mg bid).
- To reach this dose level, it is permissible to initiate treatment with 400 mg imatinib daily, but the target dose of 800 mg should be reached within 4 weeks.
- For detailed information on the administration of imatinib please refer to the patient information leaflet of Novartis.
Desmoid Study GISG-01

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)
Recruitment Status:

- Cut-off date 01.11.2012
- $n = 25/39$ in the following centers (since 07/2010):
  - Mannheim $n = 11$
  - Berlin $n = 7$
  - Heidelberg $n = 0$
  - Hannover $n = 5$
  - Essen $n = 2$
Educational: Desmoid Track

Currently recruiting clinical trials:

- A pilot study evaluating the use of mTOR inhibitor Sirolimus in children and young adults with desmoid-type fibromatosis: The purpose of the study is to explore whether mTOR inhibition may be beneficial for children and young adults with desmoid tumor (neoadjuvant Sirolimus for 28 days before surgery, n = 15, age < 30 years; Prof. Skapek, University of Chicago). ONGOING

- 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 = …, age ≥ 18 years; Dr. Italiano, Institut Bergonié, Bordeaux). ONGOING
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Take-Home-Messages:

- Desmoid tumors represent an extremely heterogeneous disease with a natural biology varying between spontaneous regression and stabilization to rapid progression.
- The mutation status of the beta-catenin gene, CTNNB1, has prognostic significance and may be used to guide the therapeutic management.
- 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.
Educational: Desmoid Track

More to read …

Desmoid Tumors: Clinical Features and Treatment Options for Advanced Disease

BERND KASPER, a PHILIPP STRÖBEL, b PETER HOHENBERGER a

aITM-Interdisciplinary Tumor Center Mannheim, Sarcoma Unit, and bInstitute of Pathology, University of Heidelberg, Mannheim University Medical Center, Mannheim, Germany

Key Words. Aggressive fibromatosis • Desmoid tumor • Advanced disease • β-catenin • Individualized treatment
Questions?