I tumori miofibroblastici

Andrea Ferrari
**WHO Classification of Soft Tissue Tumours**

### Benign
- Nodular fasciitis
- Proliferative fasciitis
- Proliferative myositis
- Myositis ossificans
  - fibro-osseous pseudotumour of digits
- Ischaemic fasciitis
- Elastofibroma

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous hamartoma of infancy</td>
<td>8820/0</td>
</tr>
<tr>
<td>Myofibroma / Myofibromatosis</td>
<td>8824/0</td>
</tr>
<tr>
<td>Fibromatosis coli</td>
<td></td>
</tr>
<tr>
<td>Juvenile hyaline fibromatosis</td>
<td></td>
</tr>
<tr>
<td>Inclusion body fibromatosis</td>
<td></td>
</tr>
<tr>
<td>Fibroma of tendon sheath</td>
<td>8810/3</td>
</tr>
<tr>
<td>Desmoid-type fibromatosis</td>
<td>8812/3</td>
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<tr>
<td>Malignant fibroma</td>
<td>8812/3</td>
</tr>
<tr>
<td>Calcifying fibrous tumour</td>
<td></td>
</tr>
<tr>
<td>Giant cell angiofibroma</td>
<td>9160/0</td>
</tr>
</tbody>
</table>

### Intermediate (locally aggressive)
- Superficial fibromatosis (palmar / plantar)
- Desmoid-type fibromatosis
- Lipofibromatosis

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Code</th>
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<tbody>
<tr>
<td>Lipofibromatosis</td>
<td>8821/1</td>
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<tr>
<td>Superior palmar/plantar fibromatosis</td>
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<tr>
<td>Adult fibrosarcoma</td>
<td>8810/3</td>
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<tr>
<td>Myxofibrosarcoma</td>
<td>8811/3</td>
</tr>
<tr>
<td>Low grade fibromyxoid sarcoma</td>
<td>8811/3</td>
</tr>
<tr>
<td>Hyalinizing spindle cell tumour</td>
<td></td>
</tr>
<tr>
<td>Sclerosing epithelioid fibrosarcoma</td>
<td>8810/3</td>
</tr>
</tbody>
</table>

### Juvenile fibromatoses
- Benign
- Different clinicopathologic entities
  - solitary (fibrous hamartoma of infancy)
  - multicentric (myofibromatosis)
  - hereditary (juvenile hyaline fibromatosis)
<table>
<thead>
<tr>
<th>Differentiative lineage</th>
<th>Histotype</th>
<th>Site</th>
<th>Genetic alterations</th>
<th>Associated syndromes or malformations</th>
<th>Histologic key-features</th>
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</thead>
<tbody>
<tr>
<td>Fibroblastic myofibroblastic</td>
<td>Adult-type fibrosarcoma</td>
<td>Distal extremities, trunk, head, neck and lung</td>
<td>–</td>
<td>Previous radiotherapy</td>
<td>Spindle cells with tapered nuclei, in herringbone pattern</td>
</tr>
<tr>
<td></td>
<td>Myofibrosarcoma</td>
<td>Head and neck, rarely bone</td>
<td>Nonspecific alterations at 12p11, 12q13-12q22, 1p gain</td>
<td>–</td>
<td>Myofibroblastic differentiation (with EM or IHC)</td>
</tr>
<tr>
<td>Low-grade fibromyxoid sarcoma</td>
<td>Superficial, head and neck, lower extremities and trunk</td>
<td>t(7;16)(q32-34;p11)</td>
<td>t(11;16) (p11;p11)</td>
<td>–</td>
<td>Biphasic tumor with myxoid/fibrous areas and bland spindle cells in myxoid stroma with prominent arrector muscles (with EM or IHC)</td>
</tr>
<tr>
<td>Sclerosing epithelioid fibrosarcoma</td>
<td>Deep, limb, trunk, shoulder, neck</td>
<td>t(7;16)(q32-34;p11) in mixed tumors with LGFMS areas</td>
<td>–</td>
<td>Carcinoma-like nests, sheets or cords of epithelioid cells in a fibrous stroma</td>
<td></td>
</tr>
<tr>
<td>Myxofibrosarcoma</td>
<td>Trunk, distal extremities</td>
<td>–</td>
<td>–</td>
<td>Low-grade: scattered spindle/stellate cells with hyperchromatic nuclei in myxoid matrix</td>
<td>High grade: increase of cellularity and atypia</td>
</tr>
</tbody>
</table>

**Histology**:

- **Desmoid-type fibromatosis**
  - Abdominal, extra-abdominal
  - Mutations in APC gene in FAP, CTNNB1 (exon 3) in sporadic variants
  - FAP/Gardner syndrome
  - Uniform spindle cells in fascicle with thin-walled vessels running parallelly, scattered mast cells

- **Lipofibromatosis**
  - Distal extremities, trunk, head
  - t(4;6,9)
  - Mature adipose tissue traversed by fascicles of fibroblasts

- **Inflammatory myofibroblastic tumor**
  - Lung, mesentery, omentum, retroperitoneum, liver, head, neck
  - ALK rearrangements with different partner genes
  - Fasciitis-like, fibrohistiocytic-like desmoid-like

- **Infantile Fibrosarcoma**
  - Trunk, distal extremities
  - (12;15)(p13;q25)
  - Spindle cells with high nuclear/cytoplasmic ratio and nuclear hyperchromasia, in fascicles with herringbone pattern
### WHO Classification of Soft Tissue Tumours

#### FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
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<tbody>
<tr>
<td>Benign</td>
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<tr>
<td>Nodular fasciitis</td>
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<tr>
<td>Proliferative fasciitis</td>
<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Fibroma of tendon sheath</td>
<td>8815/1</td>
</tr>
<tr>
<td>Desmoplastic fibroblastoma</td>
<td>8825/0</td>
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<tr>
<td>Mammary-type myofibroblastoma</td>
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<tr>
<td>Calcifying aponeurotic fibroma</td>
<td></td>
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<tr>
<td>Angiomyofibroblastoma</td>
<td></td>
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<tr>
<td>Cellular angiofibroma</td>
<td>9160/0</td>
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<td>Nuchal-type fibroma</td>
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<tr>
<td>Gardner fibroma</td>
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<td>Calcifying fibrous tumour</td>
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<tr>
<td>Giant cell angiofibroma</td>
<td>9160/0</td>
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<td>Intermediate (locally aggressive)</td>
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<tr>
<td>Superficial fibromatoses (palmar / plantar)</td>
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<tr>
<td>Desmoid-type fibromatoses</td>
<td>8821/1</td>
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<tr>
<td>Lipofibromatosis</td>
<td></td>
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<tr>
<td>Intermediate (rarely metastasizing)</td>
<td></td>
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<tr>
<td>Solitary fibrous tumour</td>
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<tr>
<td>and haemangiopericytoma</td>
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<td>(incl. lipomatous haemangiopericytoma)</td>
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<tr>
<td>Inflammatory myofibroblastic tumour</td>
<td>8825/1</td>
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<tr>
<td>Low grade myofibroblastic sarcoma</td>
<td>8825/3</td>
</tr>
<tr>
<td>Myxoinflammatory fibroblastic sarcoma</td>
<td>8811/3</td>
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<td>Infantile fibrosarcoma</td>
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</table>
Fibroblastic **monoclonal** proliferation arising from musculo-aponeurotic structures, constituted by spindle cells in a collagen matrix, without atypical, pleomorphic or hypercromatic nuclei typical of malignancy.

Incidence: 0.2-0.4 / 100,000 / year

deep-seated
growth may be fairly slow, spreading over several years

growth diffusely along muscle bundles and fascial planes
lack of a pseudocapule, difficulties in defining the border of the tumour at resection

strong tendency for local recurrence… (24-77%)
but does not metastasize to other organs as truly malignant tumors do
(overall survival over 90-95% at 10 years)

**5%** Fibromatosis associated to FAP (Gardner syndrome)

**95%** Sporadic

*Quality of Surgery and Outcome in Extra-Abdominal Aggressive Fibromatosis: A Series of Patients Surgically Treated at a Single Institution*

By A. Gronchi, P.G. Casoli, L. Mariani, S. Lo Vullo, M. Calecchia, L. Lozza, R. Bertulli, M. Fiore, P. Olmi, M. Sentinelli, and J. Rossi

*Journal of Clinical Oncology, Vol 21, No 7 (April 1), 2003: pp 1390-1397*
Desmoid-type fibromatosis

### TABLE 10–1 CLASSIFICATION OF FIBROMATOSES

**Superficial (fascial) fibromatoses**
- Palmar fibromatosis (Dupuytren’s disease)
- Plantar fibromatosis (Ledderhose’s disease)
- Penile fibromatosis (Peyronie’s disease)
- Knuckle pads

**Deep (musculoaponeurotic) fibromatoses**
- Extraabdominal fibromatosis (extraabdominal desmoid)
- Abdominal fibromatosis (abdominal desmoid)
- Intraabdominal fibromatosis (intraabdominal desmoid)
  - Pelvic fibromatosis
  - Mesenteric fibromatosis
  - Mesenteric fibromatosis in Gardner syndrome
Desmoid-type fibromatosis in FAP

- 800 times more frequent in FAP than in healthy people
- intra-abdominal – abdominal wall (70-80%)
- **GERMLINE MUTATION** of *APC* gene located on chromosome 5 (5q21)
- first cause of death in the 10% of FAP patients who develop FA
- at least a 10-30% mortality

**Gardner syndrome**
- colonic polyps and gastrointestinal cancers,
- congenital hypertrophy of the retinal pigment epithelium
- desmoid tumours
- very specific osteomas of the face
- epidermoid cysts
- supernumerary teeth
- other tumours (< 5%): medulloblastoma, hepatoblastoma, thyroid cancer
Desmoid-type fibromatosis

Sporadic desmoid-type fibromatosis

- multifactorial pathogenesis: genetic predisposition, endocrine factors, trauma
- 85% of the cases harbor a somatic mutation CTNNB1 (encoding for β-Catenine protein, chromosome 3, exon 3) genes
- rarer APC (chromosome 5) deletion in CTNNB1 WT tumors may occur
- both are mediator of the wingless signaling pathway, which gives rise to an uncontrolled proliferation of fibroblasts
In FAP-related desmoids, germ-line mutations in APC gene inhibit phosphorylation of beta-catenin necessary for its proteosomal degradation and it accumulates in the cytoplasm and migrates to the nucleus with a permanent activation of genes involved in cell proliferation.

In sporadic desmoids, mutations more frequently involve codons 41 (41A) and 45 (45F and 45P) of beta-catenin gene CTNNB1 resulting in a non-phosphorylated active beta-catenin. The mutated form of beta-catenin shows a positive nuclear immunostaining.

APC and CTNNB1 are (always?) exclusive mutations.
Desmoid-type fibromatosis

Molecular analysis of CTNNB1

- for screening of FAP (if CTNNB1 mutated, no more investigation...)
- molecular biomarkers of recurrence

Specific Mutations in the \(\beta\)-Catenin Gene (CTNNB1) Correlate with Local Recurrence in Sporadic Desmoid Tumors

High frequency of \(\beta\)-catenin heterozygous mutations in extra-abdominal fibromatosis: a potential molecular tool for disease management
Desmoid-type fibromatosis

Molecular analysis of CTNNB1

- for screening of FAP
  (if CTNNB1 mutated, no more investigation…)
- molecular biomarkers of recurrence
- identification of possible therapeutic targets

Human Cancer Biology

Cyclooxygenase-2 and Platelet-Derived Growth Factor Receptors as Potential Targets in Treating Aggressive Fibromatosis

Stefano Signoroni,1,2 Milo Frattini,1,2 Tiziana Negri,1 Elisa Pastore,1 Elena Tamborini,1 Paola Casieri,1 Marta Orsenigo,1 Luca Da Riva,1 Paolo Radice,2,6 Paola Sala,3 Alessandro Gronchi,4 Lucio Bertario,3 Marco A. Pierotti,2,6 and Silvana Pilotti1
Desmoid-type fibromatosis

COX-2 expression

anti-inflammatory therapy

PDGFRA e PDGFRB expression

**Imatinib**  Chugh et al. Clin Cancer Res 2010;16:4884-91

**Sorafenib**  Gounder et al. Clin Cancer Res 2011; 17; 4082-90

**Sunitinib**  Skubitz et al. Cancer Chemother Pharmacol 2009; 64; 635-40

TGFβ1 pathway, collagene, MMP1 e MMP2, VEGFR2
toremifene

*Human Cancer Biology*  

**Cyclooxygenase-2 and Platelet-Derived Growth Factor Receptors as Potential Targets in Treating Aggressive Fibromatosis**

Stefano Signoroni,1,2 Milo Frattini,1,2 Tiziana Negri,1 Elisa Pastore,1 Elena Tamborini,1 Paola Casieri,1 Marta Orsenigo,1 Luca Da Riva,1 Paolo Radice,2,6 Paola Sala,3 Alessandro Gronchi,4 Lucio Bertario,3 Marco A. Pierotti,2,6 and Silvana Pilotti1
Sporadic desmoid-type fibromatosis

- female predominance (3:1)
- sites
- can be multifocal
  - foot – leg – thigh – pelvic girdle
  - hand - forearm – arm – scapular girdle
- can infiltrate the bone
Children

M:F = 1.1

extra-abdominal sites

60% of myofibroblastic tumors in childhood
(30% in the first year of life, peak incidence 4.5 yrs)
Pediatric Aggressive Fibromatosis
A Retrospective Analysis of 13 Patients and Review of the Literature

Saskia Buitendijk, M.D.¹
Cees P. van de Ven, M.D.²
Ton G. Dumans, M.D., D.O.S.³
Jan C. den Hollander, M.D.⁴
Peter J. Nowak, M.D., Ph.D.⁵
Wim J. Tissing, M.D.¹
Rob Pieters, M.D., Ph.D.¹
Marry M. van den Heuvel-Eibrink, M.D., Ph.D.¹

1 Department of Pediatric Oncology/Hematology, Erasmus MC-Sophia Children’s Hospital, Rotterdam, The Netherlands.
2 Department of Pediatric Surgery, Erasmus MC-Sophia Children’s Hospital, Rotterdam, The Netherlands.
3 Department of Oral and Maxillofacial Surgery, Erasmus MC-Sophia Children’s Hospital, Rotterdam, The Netherlands.
4 Department of Pathology, Erasmus MC-Sophia Children’s Hospital, Rotterdam, The Netherlands.
5 Department of Radiotherapy, Erasmus MC-Sophia Children’s Hospital, Rotterdam, The Netherlands.

BACKGROUND. Aggressive fibromatosis (AF) is a soft tissue tumor and is rare in childhood, with high potential for local invasiveness and recurrence. General recommendations for the clinical management of pediatric patients with AF remain undetermined.

METHODS. The authors retrospectively analyzed 13 children with AF who were diagnosed from 1987 until 2004 in the Erasmus MC-Sophia Children’s Hospital, and a review of the pediatric literature was conducted.

RESULTS. Two patients received preoperative chemotherapy with combined vincristine, actinomycin-D, and cyclophosphamide (VAC). All 13 patients underwent surgery. Three of six patients who underwent incomplete resection received adjuvant treatment, two patients received radiotherapy, and one patient received chemotherapy (VAC). The median follow-up was 3.9 years (range, 0.6–14.0 years). Three patients developed recurrent AF, including two recurrences after patients

TABLE 3
Overview of Reports Concerning Pediatric Aggressive Fibromatosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Median age (yrs) (range)</th>
<th>M:F ratio</th>
<th>Site of involvement (no)</th>
<th>MD (no.)</th>
<th>Primary tumor</th>
<th>Treatment (adjuvant)</th>
<th>Follow-up (range)</th>
<th>No. of recurrences (%)</th>
<th>No. of multiple recurrences</th>
<th>No. of deaths</th>
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</thead>
<tbody>
<tr>
<td>Ayala et al., 1980</td>
<td>25</td>
<td>7 (0-15)</td>
<td>15:10</td>
<td>4</td>
<td>13</td>
<td>8</td>
<td>2</td>
<td>4 (0-25)</td>
<td>6 (24)</td>
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<tr>
<td>Scougall et al., 1975</td>
<td>8</td>
<td>8 (1-14)</td>
<td>6:2</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>5 (0-15)</td>
<td>3 (38)</td>
<td>2</td>
<td>0</td>
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<td>Rao et al., 1979</td>
<td>20</td>
<td>9 (2-18)</td>
<td>12:8</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>6 (0-17)</td>
<td>9 (45)</td>
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<td>2</td>
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<tr>
<td>Faulkner et al., 1997</td>
<td>63</td>
<td>US (0-19)</td>
<td>30:33</td>
<td>8</td>
<td>41</td>
<td>11</td>
<td>5*</td>
<td>6 (US)</td>
<td>42 (67)</td>
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<td>Spiegel et al., 1999</td>
<td>18</td>
<td>7 (0-15)</td>
<td>12:6</td>
<td>1</td>
<td>12</td>
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<td>8 (1-22)</td>
<td>15 (83)</td>
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<td>Goddzinski et al., 2003</td>
<td>21</td>
<td>8 (0-17)</td>
<td>12:9</td>
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<td>0</td>
<td>4 (0-10)</td>
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<tr>
<td>Current study, 2015</td>
<td>13</td>
<td>4 (0-12)</td>
<td>6:7</td>
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<td>4</td>
<td>5</td>
<td>1</td>
<td>3 (0-14)</td>
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<td>Atahan et al., 1989</td>
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<td>10 (3-15)</td>
<td>3:1</td>
<td>3</td>
<td>1</td>
<td>0</td>
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<td>2 (0-6)</td>
<td>1 (20)</td>
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</table>

Total no. (%) 187 (100) 8 (0-18) 107:80 (57:43) 37 (20) 106 (57) 41 (22) 11 (6) 4 (0-25) 92 (49) 34 (19) 3 (2)
Vinblastine and Methotrexate for Desmoid Fibromatosis in Children: Results of a Pediatric Oncology Group

Phase II Trial


ABSTRACT

Purpose
To determine the efficacy and safety of using vinblastine (Vbl) and methotrexate (Mtx) in children with desmoid-type fibromatosis that is recurrent or not amenable to treatment with radiation or surgery.

Patients and Methods
A phase II study was conducted within the Pediatric Oncology Group. Patients were treated using Vbl (5 mg/m²/dose) and Mtx (30 mg/m²/dose), both administered by intravenous injection weekly for 26 weeks and every other week for an additional 26 weeks. Response was assessed by bidimensional measurements of tumor on axial imaging (magnetic resonance imaging or computed tomography).

Results
Over 35 months, 28 patients were enrolled; 27 were eligible, and 26 were assessable for response. A measurable response was documented in eight patients (31%), and 10 patients had stable disease documented as the best response to treatment. Eighteen patients had disease progression at a median time of 9.1 months. Eight patients remain free of disease progression at a median of 43.4 months from study entry. Nine patients reported no to moderate toxicity. Neutropenia was the most common toxicity (n = 22) and the most common grade 4 toxicity (n = 5). Anemia, nausea, vomiting, and elevations in hepatic transaminases were also common.

Table 2: Overall Best Response in Assessable Patients

<table>
<thead>
<tr>
<th>Response</th>
<th>Overall</th>
<th>Primary</th>
<th>By Stratum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Complete response</td>
<td>1</td>
<td>3.8</td>
<td>1</td>
</tr>
<tr>
<td>Partial response</td>
<td>4</td>
<td>15.4</td>
<td>0</td>
</tr>
<tr>
<td>Minor response</td>
<td>3</td>
<td>11.5</td>
<td>2</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10</td>
<td>38.5</td>
<td>3</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8</td>
<td>30.8</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>100</td>
<td>10</td>
</tr>
</tbody>
</table>

Fig. 1. Kaplan-Meier progression-free survival (PFS) for all patients enrolled onto the study. Three-year PFS rate (± SD) was 22.5% ± 10.1%.
Original Article

Aggressive Fibromatosis in Children and Adolescents

The Italian Experience

Cristina Meazza, MD; Gianni Bisogno, MD; Alessandro Gronchi, MD; Marco Fiore, MD; Giovanni Cecchetto, MD; Rita Alaggio, MD; Giuseppe M. Milano, MD; Michela Casanova, MD; Modesto Carli, MD; and Andrea Ferrari, MD

BACKGROUND: Aggressive fibromatosis (AF) is a rare tumor of intermediate malignancy that has a strong potential for local invasiveness and recurrence. To date, there are no general recommendations for the clinical management of pediatric AF. METHODS: The authors retrospectively analyzed 94 patients aged ≤21 years, including 23 patients who underwent complete surgery (Group I), 42 patients who underwent incomplete surgery with microscopic residual tumor (Group II), and 29 patients who underwent either biopsy or macroscopically incomplete surgery (Group III). RESULTS: The 5-year event-free survival (EFS) and overall survival rates were 44% and 99%, respectively. Local recurrences developed in 22% of patients in Group I, in 76% of patients in Group II, and in 76% of patients in Group III. Two of 7 patients with abdominal disease died of tumor progression, whereas none of the patients with extra-abdominal AF died of their disease. Systemic treatment was given to 15 patients as first-line treatment and to 34 patients at the time they developed recurrent disease: The response rate was 47% in the former patients and 50% in the latter patients. Objective responses were observed in 11 of 19 patients who received combined methotrexate plus vinblastine/vinorelbine, in 7 of 15 patients who received alkylating-agent chemotherapy, and in 4 of 11 patients who received other therapies (tamoxifen, sulindac, interferon alfa). CONCLUSIONS: The current analysis suggested that the clinical course of AF in children may resemble that of AF in adults. Local recurrences did not affect the chance of responding to systemic therapy or the survival rate. The completeness of initial resection was the main factor that influenced EFS, whereas disease control after marginal resection was much the same as that achieved after intralesional surgery/biopsy. Good responses to systemic treatments, and particularly to low-dose chemotherapy, were observed as reported previously in adults. Cancer 2010;116:233–40. © 2010 American Cancer Society.

KEYWORDS: aggressive fibromatosis, desmoid tumor, low-dose chemotherapy, methotrexate plus vinblastine/vinorelbine, prognostic factors, surgery.
5-yr survival rates: DFS 44%, OS 99%

**Desmoid-type fibromatosis**

### Table 3. Response to Systemic Treatments

<table>
<thead>
<tr>
<th>Variable</th>
<th>VNR/VBL and MTX</th>
<th>IVA-VAIA-VAC, Dacarbazine</th>
<th>Other Therapies</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatments</td>
<td>4 Patients: 1 PR, 1 MR, 2 SD</td>
<td>9 Patients: 3 PR, 5 SD, 1 PRO</td>
<td>2 Patients: Tamoxifen, 1 PR; diclofenac, 1 MR</td>
<td>15 Patients: 2 MR, 5 PR, 7 SD, 1 PRO</td>
</tr>
<tr>
<td>Second-line treatments</td>
<td>8 Patients: 6 PR, 2 SD</td>
<td>3 Patients: 1 CR, 1 PR, 1 PRO</td>
<td>6 Patients: Tamoxifen, 1 PR; tamoxifen and diclofenac, 1 PRO; sulindac, 1 SD; interferon alfa, 1 SD; imatinib, 1 PR; “alternative” therapies, 1 PRO</td>
<td>17 Patients: 1 CR, 7 PR, 4 SD, 5 PRO</td>
</tr>
<tr>
<td>Third-line treatments</td>
<td>7 Patients: 1 CR, 2 PR, 4 SD</td>
<td>3 Patients: 1 CR, 1 PR, 1 SD</td>
<td>3 Patients: Tamoxifen and diclofenac, 1 MR; tamoxifen and diclofenac, 1 SD; toremifene, 1 PR</td>
<td>13 Patients: 2 CR, 4 PR, 1 MR, 6 SD</td>
</tr>
<tr>
<td>Overall</td>
<td>19 Patients: 1 CR, 9 PR, 1 MR, 8 SD</td>
<td>15 Patients: 2 CR, 5 PR, 6 SD, 2 PRO</td>
<td>11 Patients: Hormone therapy, 2 PR, 1 PRO; anti-inflammatory therapy, 1 MR, 1 SD; hormone and anti-inflammatory therapy, 1 MR, 1 SD, 1 PRO; others, 1 SD, 2 PRO</td>
<td>45 Patients: 3 CR, 16 PR, 3 MR, 17 SD, 6 PRO</td>
</tr>
</tbody>
</table>

VNR indicates vinorelbine; VBL, vinblastine; MTX, methotrexate; IVA, ifosfamide, vincristine, and actinomycin D; VAIA, vincristine, actinomycin D, ifosfamide, and doxorubicin; VAC, vincristine, actinomycin D, and cyclophosphamide; PR, partial response; MR, minor response; SD, stable disease for >3 months; PRO, disease progression; CR, complete response.

CR/PR/MR- 49%
SD - 38%
minimal-morbidity systemic therapy

The goal of systemic therapy in desmoid fibromatosis should not be the tumor shrinkage to permit a subsequent resection (as for malignant mesenchymal tumors), but the induction of growth arrest and tumor stabilization.
Desmoid-type fibromatosis

**Chemotherapy**

- **Methotrexate** 30 mg/m²/week iv + **Vinblastine** 6 mg/m² (max 10 mg)/week iv
- **Methotrexate** 30 mg/m²/week iv + **Vinorelbine** 20 mg/m²/week iv
- **Vinorelbine** 25 mg/m²/iv (or alternatively, 60 mg/m² oral) day 1, 8, 15, + oral **Cyclophosphamide** 25 mg/m²/day (every day)
- **IVA regimen** (Vincristine 1.5 mg/m² day 1, Actinomycin 1.5 mg/m² day 1, Ifosfamide 3 g/m² day 1-2)
- **VAC regimen** (Vincristine 1.5 mg/m² day 1, Actinomycin 1.5 mg/m² day 1, Cyclophosphamide 1.2 g/m² day 1)
- **VA regimen** (Vincristine 1.5 mg/m² and Actinomycine 1.5 mg/m²) every 21 days
- **Pegylated liposomal doxorubicin** (20-50 mg/m² iv, every 3-4 weeks)
- **Hydroxyurea** (20 mg/kg/day to start and then 30 mg/kg/day)

**Target therapy**

- **Imatinib** (400 mg x 2/day)
- **Sorafenib** (400 mg day)

**Hormonal treatment**

- **Tamoxifene** 5 mg x 2/day if age < 10 years, 10 mg x 2/day if > 10 years
- **Toramifene** 60 mg x 3/day

**Non-steroidal anti-inflammatory drug**

- **Sundilac** (100-200 mg tablets) at the dose of 4 mg/kg x 2/day (100-200 mg twice daily) or 4 mg/kg twice daily
- **Celecoxib** (100-200 mg capsules), 100 mg twice daily

Remission of Rapidly Growing Desmoid Tumors
After Tamoxifen Therapy

BARRY KINZBRUNNER, MD, SEYMOUR RITTER, MD, JAVIER DOMINGO, MD, AND C. JULIAN ROSENTHAL, MD

A patient is described with Gardner's syndrome manifested initially by an extra-abdominal desmoid which was resected. The case was complicated by metastatic adenocarcinoma of the colon and recurrence of several large painful desmoid lesions. In view of the predilection of desmoids to occur in women in their childbearing years, it was decided to treat these painful lesions with an anti-estrogen, tamoxifen (20 mg orally, four times daily). This therapy led to a complete relief of pain within 1 week and a progressive decrease in the size of the desmoid tumors to less than 50% of their initial volume by the end of the second week. Unfortunately, the patient's metastatic adenocarcinoma progressed and was complicated by sepsis leading to her death. This case suggests that the growth of desmoid tumors is under hormonal influence, a suggestion which deserves further investigation.


Anti-oestrogen therapy in the treatment of desmoid tumours: a systematic review

D. Bocale*, M. T. Rotelli*, A. Cavallini† and D. F. Altomare*

*Department of Emergency and Organ Transplantation, General Surgery and Liver Transplantation Units, University ‘Aldo Moro’ of Bari, Bari, Italy and †Laboratory of Biochemistry, Scientific Institute for Digestive Diseases, IRCCS ‘Saverio de Bellis’, Castellaneta G., Bari, Italy

Colorect Dis 2011;13:e388
phase II study: toremifene in desmoid-type fibromatosis
Low-Dose Chemotherapy of Desmoid Tumors

ARTHUR J. WEISS, MD,* AND RICHARD D. LACKMAN, MD,†

Eight patients with desmoid tumors, symptomatic, and none a candidate for conservative surgery, were treated with weekly vinblastine, maximum dose 10 mg/week, and methotrexate, maximum dose 50 mg/week. Symptomatic relief was obtained in all patients. Using Eastern Cooperative Oncology Group (ECOG) criteria, two patients had a complete remission, one of which has lasted for 30 months, four patients have had partial remissions, one patient has had a mixed response, and one patient who has been treated for only 4 weeks, a minimal response. Toxicity has been minor and transient. Chemotherapy appears to be an acceptable alternative to radical surgery in selected patients with desmoid tumors.


Low-Dose Chemotherapy with Methotrexate and Vinblastine for Patients with Advanced Aggressive Fibromatosis

Alberto Azzarelli, M.D.¹
Alessandro Gronchi, M.D.¹
Rossella Bertulli, M.D.²
John D. Tesoro Tess, M.D.³
Dario Baratti, M.D.¹
Elisabetta Pennacchioli, M.D.¹
Paltia Dileo, M.D.²
Alessandro Rasponi, M.D.¹
Andrea Ferrari, M.D.³
Silvana Pioletti, M.B.⁴
Paolo G. Casali, M.D.²

Vinblastine and Methotrexate for Desmoid Fibromatosis in Children: Results of a Pediatric Oncology Group Phase II Trial

Chemotherapy in patients with desmoid tumors: a study from the French Sarcoma Group (FSG)

D. Garbay¹, A. Le Cesne², N. Penel³, C. Chevreau⁴, P. Marec-Berard⁵, J.-Y. Blay⁶, M. Debled¹, N. Isambert⁷, A. Thyss⁸, E. Bompas⁹, O. Collard¹⁰, S. Salas¹¹, J.-M. Coindre¹², B. Bui¹ & A. Italiano¹³

<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 etopooside</td>
<td>Oral etopooside 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</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>(J1, J8, 15, 21) 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>Vinorelbine</td>
<td>Vinorelbine 20 mg/m² (J1, J8) 21 days cycle</td>
</tr>
</tbody>
</table>

Pegylated liposomal doxorubicin, an effective, well-tolerated treatment for refractory aggressive fibromatosis

Anastasia Constantinidou ¹, Robin L. Jones, Michelle Scurr, Omar Al-Muderis, Ian Judson

Sarcoma Unit, Royal Marsden Hospital, Fulham Rd, London SW3 6JJ, UK
LETTER TO THE EDITOR

Objective Response to Hydroxyurea in a Patient With Heavily Pre-Treated Aggressive Fibromatosis

Fig. 1. Magnetic resonance imaging shows a volume reduction of the supraclavicular tumor from transverse and antero-posterior diameters of 4.5 cm × 7.5 cm (A) to 3 cm × 5.6 cm (B).

CLINICAL AND LABORATORY OBSERVATIONS

Hydroxyurea Treatment Can Avoid the Need for Aggressive Surgery in Pediatric Fibromatosis

Gianni Bisogno, MD, PhD, Arianna Togarelli, MD, Roberto Stramare, MD,† Valeria Beltrame, MD,† and Modesto Carli, MD*
Desmoid-type fibromatosis

Clinical and Molecular Studies of the Effect of Imatinib on Advanced Aggressive Fibromatosis (desmoid tumor)

Michael C. Heinrich, Grant A. McArthur, George D. Demetri, Heikki Joensuu, Perri Bono, Richard Herrmann, Hal Hove, Sara Crespi, D. Bradley Kodner, Christopher L. Corless, Stephan Denhardt, Allan T. van Oosterom, Zoriana Nikolaev, Seas Dimitrijevic, and Jonathan A. Fletcher

original article

Imatinib for progressive and recurrent aggressive fibromatosis (desmoid tumors): an FNCLCC/French Sarcoma Group phase II trial with a long-term follow-up


Cancer Therapy: Clinical

Activity of Sorafenib against Desmoid Tumor/Deep Fibromatosis

Mrinal M. Gounder, Robert A. Lefkowitz, Mary Louise Keohan, David R. D’Adamo, Meera Hameed, Cristina R. Antonescu, Samuel Singer, Katherine Stout, Linda Ahn, and Robert G. Maki

Response of imatinib-resistant extra-abdominal aggressive fibromatosis to sunitinib: case report and review of the literature on response to tyrosine kinase inhibitors

Keith M. Skabitz, J. Carlos Manivel, Denis M. Clohisy, Jerry W. Frolich
Next step: mTOR Inhibitor

- Nearly all desmoid tumors display histologic or molecular evidence of APC/β-catenin pathway activation
- New evidence suggests deregulation of mTOR cell proliferation/survival pathway plays important role in tumor biology when APC/β-catenin pathway disrupted
- Genetic Evidence from Murine Models of mTOR Pathway Activation in Desmoid Tumor
- Clinical Evidence of mTOR Pathway Activation in Desmoid Tumor
Desmoid-type fibromatosis

Commentary

The Desmoid Tumor: Still an Enigma

Optimizing Treatment of Desmoid Tumors

Desmoid tumor: from surgical extirpation to molecular dissection
Alexander J.F. Lazar\textsuperscript{a,c}, Shohrae Hajibashi\textsuperscript{b,c} and Dina Lev\textsuperscript{b,c}

\textsuperscript{a}Department of Pathology, \textsuperscript{b}Department of Cancer Biology and \textsuperscript{c}Sarcoma Research Center, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

Correspondence to Alexander Lazar, MD, PhD, The University of Texas M. D. Anderson Cancer Center, Sarcoma Research Center, 1515 Holcombe Blvd. – Unit 85, Houston, TX 77030-5009, USA
Tel: +1 713 563 1843; fax: +1 713 563 1843;
email: alazar@mdanderson.org

Current Opinion in Oncology 2009, 21:352–359
Desmoid-type fibromatosis
In sporadic patients’ survival is virtually unaffected by desmoid fibromatosis.

Desmoid tumors can remain stable for a long time, and sometimes may regress spontaneously.

Surgery - the mainstay of treatment for many years - is not resolutive in many cases (high rate of local relapse regardless of surgical margins, high rate of sequelae with multiple resections).

Some findings would suggest that surgery might be cause of fibromatosis growth and recurrence.

Local relapse did not affect survival neither the possibility of responding to systemic therapy.
Extra-abdominal primary fibromatosis: Aggressive management could be avoided in a subgroup of patients

S. Bonvalot a,*, H. Eldweny a, V. Haddad b, F. Rimareix a, G. Missenard a, O. Oberlin c, D. Vanel d, P. Terrier e, J.Y. Blay f, A. Le Cesne g, C. Le Pêchoux h
Desmoid-type fibromatosis

50% of untreated patients did not progress at 5 years…

3% of untreated patients did experience complete regression
Prognostic Factors Influencing Progression-Free Survival Determined From a Series of Sporadic Desmoid Tumors: A Wait-and-See Policy According to Tumor Presentation

Sébastien Salas, Armelle Dufresne, Binh Bui, Jean-Yves Blay, Philippe Terrier, Dominique Ranchere-Vince, Sylvie Bonvalot, Eberhard Stoekle, Louis Guillou, Axel Le Cesne, Odile Oberlin, Véronique Brouste, and Jean-Michel Coindre
Primary or recurring extra-abdominal desmoid fibromatosis: Assessment of treatment by observation only

O. Barbier, P. Anract, E. Pluot, F. Larouserie, F. Sailhan, A. Babinet, B. Tomeno

Figure 4 Normal curve of the length of evolution of primary extra-abdominal desmoid fibromatosis managed by surveillance.

Figure 5 Normal curve of the length of evolution of recurrent extra-abdominal desmoid fibromatosis managed by surveillance.
Optimal Approach to Sporadic Desmoid Tumors: From Radical Surgery to Observation. Time for a Consensus?

Alessandro Gronchi, MD¹ and Chandrajit P. Raut, MD, MSc²,³,⁴
Desmoid-type fibromatosis

Frontline observation
Avoid surgery as much as possible

“La chirurgia deve essere virtualmente abbandonata:
si opera se fallisce il wait & see,
se fallisce la terapia ormonale,
se fallisce le terapia medica,
se fallisce la terapia molecolare,
se il paziente è sintomatico”
Indolent AF
50%
No impact of margins
All treatments will be efficient
No treatment could be enough

Progressive AF
50%
Negative impact of positive margins
Need for adapted treatment

Site, size, age, beta-catenine mutation status be of help to identify these patients?
Patients **outcome** should be measured not in terms of EFS, but as a combination of survival rates, total burden of therapy and functional-cosmetic iatrogenic sequelae.

It is difficult to establish a risk-stratification or treatment flow-chart based on prognostic factors, because individual, less easily quantified variables may have a significant impact both on the risk of failure and on the functional fallout (including the patient’s age and the tumor’s location - not in terms of anatomic site, but of its interaction with adjacent anatomical structures)

**1. therapeutic strategy** → multidisciplinary approach, individualized decision

- **Stable disease**
  - No symptom
  - No threatening site
  - wait and see for 3 mos
  - Stable (< 25% progression)
  - Progression > 25% or symptoms

- **Tumor rapidly growing symptom threatening site**
  - TREATMENT
    - COMPLETELY resectable without damage
    - Yes
    - No
    - Resection
    - MTX+VBL
2. **first approach** → consider the *wait-and-see strategy* (clinical-radiological monitoring alone) might be suitable in cases of non-evolving disease, and therapies should be given only in the event of tumor growth.
3. **Treatment** should be proposed in case of threatening site, rapid tumor growth, symptoms

4. **First-line therapy:** minimal-morbidity systemic therapy (VBL-MTX? toremifene?)
   (or surgery if completely possible, without mutilation?)
Hyperthermic Isolated Limb Perfusion in Locally Advanced Soft Tissue Sarcoma and Progressive Desmoid-Type Fibromatosis with TNF 1 mg and Melphalan (T1-M HILP) Is Safe and Efficient

Sylvie Bonvalot, MD, PhD¹, Françoise Rimareix, MD¹, Sylvain Causeret, MD¹, Cécile Le Péchoux, MD², Bérénice Boulet, MD³, Philippe Terrier, MD⁴, Axel Le Cesne, MD⁵, and Jane Muret, MD⁶
CLINICAL INVESTIGATION

LONG-TERM OUTCOMES FOR DESMOID TUMORS TREATED WITH RADIATION THERAPY

B. ASHLEIGH GUADAGNOLO, M.D., M.P.H., GUNAR K. ZAGARS, M.D., AND MATTHEW T. BALLO, M.D.

Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX
Desmoid-type fibromatosis
Desmoid-type fibromatosis

- **Complete S**
  - Biopsy → Chemotherapy → Delayed Complete S

- **Incomplete S**
  - Relapse → Incomplete S → Relapse

- **Incomplete S**
  - Radiotherapy → Relapse

- **Complete S**
  - Chemotherapy → Relapse

- **Biopsy** → Chemotherapy → PR → Chemotherapy → SS → Wait-and-see

- **Incomplete S**
  - Chemotherapy → MR → Wait-and-see

- **Biopsy** → Wait-and-see → Wait-and-see → Wait-and-see → Progression → Chemotherapy → PR → Wait-and-see
WHO Classification of Soft Tissue Tumours

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Benign
Nodular fasciitis
Proliferative fasciitis
Proliferative myositis
Myositis ossificans
  fibro-osseous pseudotumour of digits
Ischaemic fasciitis
Elastofibroma 8820/0
Fibrous hamartoma of infancy
Myofibroma / Myofibromatosis 8824/0
Fibromatosis colli
Juvenile hyaline fibromatosis
Inclusion body fibromatosis
Fibroma of tendon sheath 8810/0
Desmoplastic fibroblastoma 8810/0
Mammary-type myofibroblastoma 8825/0
Calcifying aponeurotic fibroma 8810/0
Angiomyofibroblastoma 8826/0
Cellular angiofibroma 9160/0
Nuchal-type fibroma 8810/0
Gardner fibroma 8810/0
Calcifying fibrous tumour
Giant cell angiofibroma 9160/0

Intermediate (locally aggressive)
Superficial fibromatoses (palmar / plantar)
Desmoid-type fibromatoses 8821/1
Lipofibromatosis

Intermediate (rarely metastasizing)
Solitary fibrous tumour 8815/1
and haemangiopericytoma 9150/1
(incl. lipomatous haemangiopericytoma)
Inflammatory myofibroblastic tumour 8825/1

Inflammatory myofibroblastic sarcoma 8825/3

Malignant
Adult fibrosarcoma 8810/3
Myxofibrosarcoma 8811/3
Low grade fibromyxoid sarcoma 8811/3
  hyalinizing spindle cell tumour
Sclerosing epithelioid fibrosarcoma 8810/3
Original Article

Inflammatory Myofibroblastic Tumors in Childhood

A Report From the Italian Cooperative Group Studies

Rita Alaggio, MD; Giovanni Cecchetto, MD; Gianni Bisogno, MD; Claudio Gambini, MD; Maria Luisa Calabrò, PhD; Alessandro Inserra, MD; Renata Boldrini, MD; Gian Luca De Salvo, MD; Emanuele S. G. d’Amore, MD; and Patrizia Dall’Igna, MD

BACKGROUND: Inflammatory myofibroblastic tumors (IMTs) are myofibroblastic lesions with unpredictable biologic behavior that occur at a young age. For this report, the authors investigated clinicopathologic features in a series of pediatric IMTs. The objective of the study was to identify morphologic or immunohistochemical prognostic markers and the possible pathogenic role of human herpes virus 8 (HHV-8). METHODS: Twenty-six patients were observed over a period of 18 years. Clinical/histologic data were reviewed, and immunohistochemical/molecular studies were performed. RESULTS: Patients ages 8-216 months (median age, 60 months) presented with tumors of the lung-bronchus (8 patients), abdomen (17 patients), and thoracic wall (1 patient). Twenty-one patients underwent complete excision, and microscopic or macroscopic residual disease was present in 5 of those patients. Chemotherapy was received by 5 patients. After a median follow-up of 6.6 years, 24 patients were in complete remission, and 2 patients had died of disease. Local recurrences were observed in 6 patients (including 4 recurrences that occurred after a complete excision). Cytologic atypia, low inflammatory infiltrate, and a rich myxoid pattern were detected in patients who had recurrent disease or a poor prognosis. Anaplastic lymphoma kinase (ALK) was positive in 7 patients (including 2 patients with recurrent disease). No correlation between clusterin expression and prognosis was demonstrated. HHV-8 was identified in 1 pulmonary IMT. CONCLUSIONS: IMTs are locally aggressive lesions. In this series, the local recurrence rate was 23%, and the 5-year and 10-year event-free survival rates were 87.4% and 72.8%, respectively. The results indicated that the treatment of choice is a complete, nonmutilating excision; chemotherapy may be given to patients who have microscopic or macroscopic residual disease, although the results are controversial; cytologic atypia and positive ALK status are more frequent in aggressive tumors, whereas metastatic tumors are negative for ALK; and HHV8 is not involved in the pathogenesis of IMT. Cancer 2010;116:216-26. © 2010 American Cancer Society.

KEYWORDS: inflammatory myofibroblastic tumors, anaplastic lymphoma kinase, clusterin, pseudotumor, children.
Inflammatory myofibroblastic tumors

- children and young adults
- lung, but also mesentery, omentum, retroperitoneum, soft tissues, liver, head and neck
- a palpable mass may be the clinical presentation, sometimes accompanied by an inflammatory syndrome, microcytic hypochromic anemia, thrombocytosis, polyclonal hyperglobulinemia
- 35-60% of cases – specific chromosomal rearrangements involving the anaplastic lymphoma kinase (ALK) gene locus in the chromosome 2p23 with other partner genes (TPM3, CLTC, RANBP2 and others)
- the recurrence rate varies according to the anatomical site extra-pulmonary IMT lesions tend recur more frequently, with a relapse rate of 25%
- distant metastases occur in less than 5% of cases, mostly in lung and brain.
- wide resection is the mainstay of treatment radiotherapy and systemic treatments (corticosteroids, chemotherapy) have been variously used in high-risk situations, but their role remains to be established yet

Fig. 2. The proliferation of neoplastic spindle cells showed a cytoplasmic positive immunoreaction for ALK.
Inflammatory myofibroblastic tumors

Successful Treatment of Inflammatory Myofibroblastic Tumor With Malignant Transformation by Surgical Resection and Chemotherapy

Megan K. Disho, M.D., Brad W. Warner, M.D., Louis P. Delnies, M.D., Vesta M. Kriss, M.D., Martha F. Greenwood, M.D., John D. Gell, M.D., and Jeffrey A. Moscow, M.D.

**TABLE 1.** Chemotherapy for inflammatory myofibroblastic tumors in children

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Histology</th>
<th>Clinical course</th>
<th>Outcome and survival</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 m</td>
<td>M</td>
<td>Mesenteric, peritoneum</td>
<td>IMT with sarcornal transformation</td>
<td>Excision (April 1990); chemotherapy (VCR, DACT, CPM); Recurrence (Feb. 1992).</td>
<td>DOD 43 mo after dx</td>
<td>1</td>
</tr>
<tr>
<td>12 y</td>
<td>F</td>
<td>Mesenteric, peritoneum</td>
<td>IMT</td>
<td>Excision with multiple reexcisions and excisions</td>
<td>AWD 75 mo. after dx</td>
<td>1</td>
</tr>
<tr>
<td>8 y</td>
<td>M</td>
<td>Mesentery</td>
<td>IMT</td>
<td>Initial biopsy (Feb. 1989). Local recurrence superior mesenteric artery (July 1989)</td>
<td>ADF 62 mo. after dx</td>
<td>1</td>
</tr>
<tr>
<td>14 y</td>
<td>F</td>
<td>Omentum, mesenterial</td>
<td>IMT</td>
<td>Excision (May 1980); chemotherapy (VCR, CPM, DACT, ADM, 5FU)</td>
<td>ADF 10 yrs after dx</td>
<td>1</td>
</tr>
<tr>
<td>16 y</td>
<td>F</td>
<td>Thigh</td>
<td>IMT</td>
<td>Biopsy (Dec 1978); Chemotherapy (Including ADM) x 3 mo</td>
<td>Died 8 mo. after dx due to infection</td>
<td></td>
</tr>
<tr>
<td>5 y</td>
<td>M</td>
<td>Mesenterity</td>
<td>IMT</td>
<td>Reexcision, abdomin and pelvis (July 1972); Chemotherapy (VCR, DACT, CPM)</td>
<td>Died 5 mo. after dx</td>
<td></td>
</tr>
<tr>
<td>3 y</td>
<td>F</td>
<td>Omentum, peritoneum</td>
<td>IMT</td>
<td>Excision, pelvic recurrence (feb 1971); Multifocal abdominal disease</td>
<td>AWD, terminal state 14 mo after dx</td>
<td>21</td>
</tr>
</tbody>
</table>

Pediatric Blood Cancer

**BRIEF REPORT**

Inflammatory Myofibroblastic Tumor of the Conjunctiva: Response to Chemotherapy With Low-Dose Methotrexate and Vinorelbine

Francesca Favi, MD,1 Antonio Giordano Resti, MD,2 Paola Collini, MD,3 Michela Casanova, MD,3 Cristina Mezza, MD,4 Giovanna Trecate, MD,5 and Andrea Ferrari, MD1

Inflammatory myofibroblastic tumor (IMT) is an unusual entity that mainly affects children and young adults, and for which standardized therapies for inoperable cases are still lacking. We report on a 12-year-old patient with an extremely rare and inoperable conjunctival location that was treated with chemotherapy using low-dose methotrexate plus vinorelbine, achieving complete tumor remission. This regimen is usually well-tolerated and may be considered as the treatment of choice for cases of unresectable advanced IMT. Pediatr Blood Cancer © 2009 Wiley-Liss, Inc.

**Key words:** conjunctiva; inflammatory myofibroblastic tumor; low-dose methotrexate; response to chemotherapy; vinorelbine

Fig. 1. Magnetic resonance imaging: notice the conjunctival thickening on the medial side of the ocular globe (A—pre-treatment image). After 3 months of therapy (B), a partial regression of the conjunctival mass was demonstrated on the same sequence.

**BRIEF REPORT**

Crizotinib in ALK-Rearranged Inflammatory Myofibroblastic Tumor

James E. Butynski, M.D., David R. D’Adamo, M.D., Ph.D., Jason L. Hornick, M.D., Ph.D., Paola Dal Cin, Ph.D., Cristina R. Antonescu, M.D., Suresh C. Jhanwar, Ph.D., Marc Ladanyi, M.D., Marzia Capelletti, Ph.D., Scott J. Rodig, M.D., Ph.D., Nikhil Ramaiya, M.D., Eunice L. Kwak, M.D., Jeffrey W. Clark, M.D., Keith D. Wilner, Ph.D., James G. Christensen, Ph.D., Pasi A. Jänne, M.D., Ph.D., Robert G. Maki, M.D., Ph.D., George D. Demetri, M.D., and Geoffrey I. Shapiro, M.D., Ph.D.
Infantile Fibrosarcoma: Management Based on the European Experience

Daniel Orbach, Annie Rey, Giovanni Cecchetto, Odile Oberlin, Michela Casanova, Estelle Thebaud, Marcelo Scopinaro, Gianni Bisogno, Modesto Carli, and Andrea Ferrari

Abstract

Purpose
To retrospectively analyze the clinical features of infants with fibrosarcoma enrolled on cooperative European trials with a combination of surgery and chemotherapy.

Patients and Methods
We performed a retrospective case review of infants treated between 1979 and 2005 in six European Intergroup Rhabdomyosarcoma Staging System (IRSS) trials and analyzed survival data using the Kaplan-Meier method.

Results
Primary tumor site was the limbs in 66% of patients; and postoperative staging III, 47%; and group IV, 4%. Response rate to vincristine-dactinomycin was 71%. Local control was achieved in 46% of patients treated with surgery and chemotherapy, and 2-year overall survival (OS) rate was 89%. The 5-year OS rate was 89% and 81%, respectively.

Conclusion
Although complete resection is rarely feasible, these results show that for infants with localized fibrosarcoma, surgical treatment is usually effective and should be considered. Overall prognosis is good, but progress needs to be made in improving treatment outcomes.

Fig 1. Overall survival and event-free survival of patients with localized infantile fibrosarcoma. Vertical bars indicate standard deviation.
Infantile fibrosarcoma

- the most common sarcoma under 1 year of age
  it occurs in the first two years of life, and near 50% of cases are diagnosed at birth (or, occasionally, in utero)

- specific translocation t(12;15)(p13;q25) with the transcript ETV6-NTRK3, that is shared by cellular mesoblastic nephroma

- deep soft tissues of distal extremities (and less frequently trunk or head-neck)

- rapid growth and huge size
distant metastases are rare but can occur

- the prognosis is favourable in the majority of cases, with a survival rates between 80-100%
Infantile fibrosarcoma

Surgery is the mainstay of treatment...

...but chemotherapy is effective, also utilizing mild alkylating/anthracyclines-free regimens: the VA regimen (vincristine and actinomycin) is the chemotherapy of choice, and more intensive regimen should be considered only in the event of no response to VA chemotherapy.
Neonatal soft tissue sarcomas
Andrea Ferrari a,*, Daniel Orbach b, Iyad Sultan c, Michela Casanova d, Gianni Bisogno d

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c Department of Pediatric Oncology, King Hussein Cancer Center, Amman, Jordan
d Pediatric Hematology and Oncology Division, Padova University, Padova, Italy

Fig. 4. Localized groin congenital fibrosarcoma, with ETV-NTRK3 fusion transcript, at diagnosis in a 1.5-month-old girl (clinical and computed tomography aspect) revealed by a growing painless right mass. Tumor showed a very good partial response (>95% of tumor reduction) after 4 months of neoadjuvant vincristine and actinomycin chemotherapy. No histological residual viable cells were found after surgical exploration. Child is still in persistent complete remission 4 years after without sequelae.
The widespread use of molecular characterization has allowed the identification of a group of lesions previously classified as infantile FS because of their occurrence in infants and their morphologic overlap.

These tumors, now identified as **Primitive Myxoid Mesenchymal Tumor of Infancy** (PMMTI), are characterized by a diffuse growth of primitive spindle, polygonal, and round cells embedded in a myxoid stroma with a characteristic prominent vascular network. The few cases studied by RT-PCR lack the ETV6-NTRK3 transcript. PMMTI may have an aggressive behaviour: in the published cases, 2 out of 5 newborns with available follow-up died of disease and two experienced either distant metastases or local aggressive growth, not responding to chemotherapy (Alaggio et al. 2006).
Neonatal soft tissue sarcomas

Andrea Ferrari a,*, Daniel Orbach b, Iyad Sultan c, Michela Casanova a, Gianni Bisogno d

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**Fig. 3.** Highly vascularized congenital fibrosarcoma of the parotid region, initially misdiagnosed as a vascular benign tumor and treated accordingly.
Benign lesion may mimic malignant disease and vice versa. The appropriate diagnosis depends upon clinical, radiological and pathological features, but also on the expertise of clinicians, radiologists and pathologists. A **multidisciplinary approach** is essential to establish a correct diagnosis and define accordingly the appropriate treatment.

An infant presenting an atypical soft tissue mass require prompt attention and should be managed in a tertiary pediatric center even before the precise diagnosis is established.

A critical point is to define **when the physician who first see the patient (e.g. neonatologist, pediatric dermatologist, vascular surgeon) should have the suspect of an aggressive disease and refer the patient for a pediatric oncologists consultation or for a biopsy.**

A high index of suspicion must be present among the providers who encounter the infant with a soft tissue lesion: but doctors must be aware of malignant tumors masquerading as vascular tumors.

Vascular tumors are often diagnosed through clinical and imaging findings and histology is sometimes not pursued. Radiologic investigations may fail to distinguish benign from malignant tumors (no well-defined criteria).

**Biopsy** is recommended to rule out malignant tumors, when the lesion simply has a non-specific appearance or when it has potentially aggressive features (i.e. size larger than 3-5 cm, increase in size, depth beneath the deep fascia).
Figure 15.6: Pediatric Oncology Team
### Table 6: All patients registered by country

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>PATIENTS REGISTERED</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>571</td>
<td>29.07</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>550</td>
<td>28.00</td>
<td></td>
</tr>
<tr>
<td>UK &amp; EIRE</td>
<td>343</td>
<td>17.46</td>
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<tr>
<td>Spain</td>
<td>140</td>
<td>7.13</td>
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<tr>
<td>The Netherlands</td>
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<td>Belgium</td>
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</tr>
<tr>
<td>Israel</td>
<td>77</td>
<td>3.92</td>
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</tr>
<tr>
<td>Czech Rep.</td>
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<td>Norway</td>
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</tr>
<tr>
<td>Brazil</td>
<td>19</td>
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<td></td>
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<tr>
<td>Slovakia</td>
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<tr>
<td>Switzerland</td>
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<tr>
<td>Argentina</td>
<td>7</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>2</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1964</strong></td>
<td><strong>100.00</strong></td>
<td></td>
</tr>
</tbody>
</table>

#### Histology
- Alveolar soft part sarcoma: 9 (1.6%)
- Angiosarcoma of soft tissue: 4 (0.7%)
- Clear Cell Sarcoma of soft tissue: 7 (1.3%)
- Dermatofibrosarcoma protuberans: 25 (4.5%)
- **Desmoid-type fibromatosis**: 53 (9.6%)
- Desmoplastic small round cell tumour: 4 (0.7%)
- Ectomesenchymoma: 1 (0.2%)
- Epithelioid haemangioendothelioma: 7 (1.3%)
- Epithelioid sarcoma: 14 (2.5%)
- Ewing tumour pPNET (extraskeletal): 46 (8.3%)
- Fibrosarcoma – adult type: 9 (1.6%)
- **Fibrosarcoma – infantile type**: 46 (8.3%)
- Hemangiopericytoma: 2 (0.4%)
- **Inflammatory myofibroblastic tumour**: 25 (4.5%)
- Leiomyosarcoma: 12 (2.2%)
- Liposarcoma: 13 (2.4%)
- Malignant Fibrous Histiocytoma: 5 (0.9%)
- Malignant Peripheral Nerve Sheath Tumour (Malignant Schwannoma): 27 (4.9%)
- Mesenchymal Chondrosarcoma: 5 (0.9%)
- Myxoid Chondrosarcoma (“chordoid” type) (extraskeletal): 1 (0.2%)
- Other: 40 (7.3%)
- Rhabdoid tumour: 47 (8.3%)
- Sarcoma N.O.S.: 21 (3.8%)
- Synovial Sarcoma: 96 (17.4%)
- Undifferentiated Soft Tissue Sarcoma: 32 (5.8%)
the LYONMYOSARCOMA!

Picture by Andrea Ferrari