Doxorubicin eluting intra-arterial therapy for extra-abdominal desmoid fibromatoses – a promising approach for a perplexing disease

Eldad Elnekave, MD
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Desmoid Tumors
A Comprehensive Review of the Evolving Biology, Unpredictable Behavior, and Myriad of Management Options

Husson et al., “Desmoid fibromatosis through the patients’ eyes: time to change the focus and organisation of care?” Supportive Care in Cancer, 2018
Sporadic extra abdominal wall desmoid-type fibromatosis: Surgical resection can be safely limited to a minority of patients

C. Colombo\textsuperscript{a}, R. Miceli\textsuperscript{b}, C. Le Péchoux\textsuperscript{c}, E. Palassini\textsuperscript{d}, C. Honoré\textsuperscript{e}, S. Stacchiotti\textsuperscript{d}, O. Mir\textsuperscript{f}, P.G. Casali\textsuperscript{d}, J. Dômont\textsuperscript{f}, M. Fiore\textsuperscript{a}, A. Le Cesne\textsuperscript{f}, A. Gronchi\textsuperscript{a,\ast}, S. Bonvalot\textsuperscript{e}
Successful Treatment of a Desmoid Tumor with Doxorubicin

K. Seiter, M.D.,* and N. Kemeny, M.D.

Cancer, 1993

Figure 1. (Left) Computed tomographic scan of the pelvis, January 1985, shows a large abdominal wall desmoid and extensive mesenteric fibromatosis. (Right) Computed tomographic scan, October 1985, after 10 months of doxorubicin therapy. There is almost complete resolution of the abdominal wall mass and a lesser degree of shrinkage in the mesenteric tumor.

- 17 year retrospective study of 62 patients

- The objective response rate was significantly higher in the anthracycline group than in the nonanthracycline group: **54% versus 12% (P = 0.0011)**
- Concerning the anthracyline-containing regimens, seven patients (54%) had partial response and six patients (46%) had stable disease.
- Toxicity = at least grade 3 or 4 hematological adverse events was higher in the anthracycline group: **31% versus 10% P = 0.06.**
• 7 patients
• 320-360 mg/m² DOX
• 3 CR, 4 PR
• 3 patients grade 3 adverse events
• “This modality should be considered for use as first-line chemotherapy in symptomatic desmoid tumors”
Prognostic factors

- Age <37 years (P .005)
- Size > 7 cm (P .004)
- Extra-abdominal localization (P .001)
  - Among extra-abdominal tumors, the worst outcome was observed in limb and buttocks tumors.
  - Among limb tumors, distal tumors were those with the worst prognosis.
- Three prognostic groups for PFS were defined on the basis of the number of unfavorable prognostic factors.

Cardiotoxicity After Childhood Cancer: Beginning With the End in Mind

Steven E. Lipshultz, Department of Pediatrics, University of Miami Leonard M. Miller School of Medicine, the University of
Liposomal doxorubicin: Effective treatment for pediatric desmoid fibromatosis  
Ananth et al., Pediatric Blood & Cancer 2017

• Median cumulative dose of LD was 240 mg/m²
• Toxicity: 1 grade II/III mucositis, 1 grade 3 cardiotoxicity and 4 grade 1 mucositis.
• All stable disease, overall reduction of 5% in tumor size

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (%)</th>
<th>Median (range)</th>
<th>Average percentage change in tumor size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal doxorubicin</td>
<td>5 (100%)</td>
<td>29 (7–48)</td>
<td>-4.5</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>4 (80%)</td>
<td>18.5 (1–49)</td>
<td>-12.4</td>
</tr>
<tr>
<td>Vinblastine/methotrexate</td>
<td>5 (100%)</td>
<td>9.5 (3.5–10)</td>
<td>+1.1</td>
</tr>
<tr>
<td>Tamoxifen/sulindac</td>
<td>2 (40%)</td>
<td>4.3 (2.5–6)</td>
<td>+25.8</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>1 (20%)</td>
<td>-</td>
<td>+7.0</td>
</tr>
</tbody>
</table>
Can we improve doxorubicin efficacy and minimize its toxicity by selective anatomic delivery via arterial distribution to the target tissue?
6 yr old girl, pt 1 (2014)
1. right axillary
2. superior thoracic
3. thoraco-acromial
4. thoraco-dorsal
5. lateral thoracic
6. internal mammary
Gluteal Desmoid Fibroma in a 16 year old - Doxorubicin eluting 75uM Beads
1. lateral thoracic
2. internal thoracic (anterior intercostal branches)
3. thoraco-acromial
### Results

**Table 2. Intra-arterial Doxorubicin Eluting Embolization Treatment and Results**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Vessels Treated</th>
<th>Total Treatments</th>
<th>Posttreatment Size; Volume</th>
<th>Volume Reduction</th>
<th>Total Dose</th>
<th>Post-treatment Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right axillary, superior thoracic, thoracoacromial, thoracodorsal, lateral thoracic, internal mammary</td>
<td>3 (times = 4, 8, 15)</td>
<td>5.3 x 4.0 x 4.2 cm; 44 mL (time = 35)</td>
<td>97%</td>
<td>125 mg (133 mg/m²)</td>
<td>32 months</td>
</tr>
<tr>
<td>2</td>
<td>Right superior gluteal artery</td>
<td>2 (times = 2, 6)</td>
<td>5.6 x 4.6 x 3 cm; 40 mL (time = 24)</td>
<td>90%</td>
<td>75 mg (45 mg/m²)</td>
<td>16 months</td>
</tr>
<tr>
<td>3</td>
<td>Lateral thoracic, internal mammary (anterior intercostal branches), thoracoacromial</td>
<td>3 (times = 3, 6, 11)</td>
<td>8.4 x 5.5 x 2.2 cm; 53 mL (time = 23)</td>
<td>76%</td>
<td>75 mg (45 mg/m²)</td>
<td>24 months</td>
</tr>
<tr>
<td>4</td>
<td>Right T8 intercostal, right T9 intercostal</td>
<td>1 (time = 2)</td>
<td>2.4 x 3.4 x 3.0 cm; 13 mL (time = 3)</td>
<td>52%</td>
<td>40 mg (27 mg/m²)</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Note—All times refer to months from MR imaging performed before treatment.

Elnekave et al., “Doxorubicin eluting intra-arterial therapy for pediatric extra-abdominal desmoid fibromatosis: a promising approach for a perplexing disease,” J Vasc Int Rad 2018
What’s next?

- We have become the referral center for Pediatric DF in Israel → treating 8 more children since presenting our work at ISPHO.
- Expanded protocol for treating Adult Extra-abdominal & Intra-abdominal DF.
- Further localized delivery of combined therapeutics for DF.
Thank you!

Eli Atar
Shirah Amar
Elchanan Bruckheimer
Isaac Yaniv
Tal Dujovny
Meora Feinmesser
Shifra Ash
Doxorubicin-Eluting Intra-arterial Therapy for Pediatric Extra-Abdominal Desmoid Fibromatoses: A Promising Approach for a Perplexing Disease

Eldad Elnekave, MD, Eli Atar, MD, Shirah Amar, MD, Elchanan Bruckheimer, MBBS, Michael Knizhnik, MD, Isaac Yaniv, MD, Tal Dujovny, MD, Meora Feinmesser, MD, and Shifra Ash, MD

ABSTRACT
Systemic doxorubicin is effective for desmoid fibromatosis (DF), but its use is limited by dose-dependent cardiotoxicity. A protocol of selective intra-arterial doxorubicin drug-eluting embolization (DIE) was designed to maximize tissue efficacy of doxorubicin, while minimizing systemic exposure. Four children with recurrent or refractory DF were treated between 2014 and 2017. Tumor volumes were reduced by 54%–97% over a follow-up interval of 6–32 months. A single patient experienced transient lower extremity paresthesia (Common Terminology Criteria for Adverse Events grade 1). Further investigation is needed to better establish these promising results for doxorubicin DIE in DF treatment.

ABBREVIATIONS
DIE – drug-eluting embolization, DF – desmoid fibromatosis
• Rx options:
  • Surgery (40-80% recurrence)
  • Radiation* (morbidity & 2nd CA)
  • Chemotherapy*
  • Hormornal therapy *
  • NSAIDs*
  • TKI’s*
• *Marginal benefit
Desmoid fibromatosis through the patients’ eyes: time to change the focus and organisation of care?

Olga Husson¹,² • Eugenie Younger¹ • Alison Dunlop¹ • Lucy Dean¹ • Dirk C. Strauss¹ • Charlotte Benson¹ • Andy J. Hayes¹ • Aisha Miah¹ • Winan van Houdt¹ • Shane Zaidi¹ • Myles Smith¹ • John Williams³ • Robin L. Jones¹,² • Winette T. A. van der Graaf¹,²