The Present and Future of Medical Therapy - Desmoid

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Disclosures:

Advisory Role:
EMD Serono
Plexxikon
Novartis

IDMC Chair: Morphotek
Desmoid Tumor

-- Fibroblastic origin, excess collagen and fibrous stroma
-- 2-4 individuals per million
-- Occur at any age (median 30 years)
-- Sporadic – 85% have Beta-catenin mutations
-- FAP/Gardner’s syndrome - mutations in APC

Both cause aberrant signaling WNT pathway
Desmoid Tumor

- Occur at any location
  - extra abdominal (60%), abdominal wall (25%), Intra Abdominal (15%)
  - (extremity > trunk > intra-abdominal)
Clinical Behavior

- Develop deep soft tissues
- Characterized by an infiltrative growth pattern
- Locally aggressive: pain, loss of ROM, hydro, SBO etc.
- **No metastatic potential** (can be multi-focal)
- Long clinical history: waxing and waning
  - Long periods of quiescence
- Spontaneous regressions (rare)
Goals of Care!!

- Surgery
  - high local recurrence (20 – 40%)
  - associated with significant deformity (amputations) and morbidity (short gut)
  - Adjuvant XRT (Controversial – positive margins)

- Definitive Radiation???

- Limb Perfusion

- Systemic therapy
  - Anti-inflammatory
  - Hormonal Blockade
  - Chemotherapy
  - Tyrosine Kinase Inhibitors
  - Experimental/Future
NOT ALL DESMOIDS NEED TO BE TREATED: OBSERVED (NCCN 2011)

Primum Non Nocera

First, Do No Harm
TRIGGER TO INITIATE THERAPY REMAINS UNDEFINED

- **Low Risk:**
  - <5 cm, primary, asymptomatic, abdominal wall, older age.
  - Observation
  - Surgery: **HIGH cure rates.**

- **High Risk:**
  - >5 cm primary, any size recurrent, extremity, non-abdominal wall, younger age, symptomatic.

- **Growth Phase**

Responses can be slow, length of tx - several months to a few years?
Changes for toxicity
Stable disease – victory
  - Affecting inflammatory mediators
  - Changing cellularity (quiescent stage) stable years

Timing of discontinuation requires clinical judgment.
Sporadic desmoid-type fibromatosis: a stepwise approach to a non-metastasising neoplasm—a position paper from the Italian and the French Sarcoma Group

A. Gronchi1*, C. Colombo1, C. Le Péchoux2, A. P. Dei Tos3, A. Le Cesne4, A. Marrari5, N. Penel6, G. Grignani7, J. Y. Blay8, P. G. Casali9, E. Stoeckle9, F. Gherlinzoni10, P. Meeus11, C. Musi12, F. Gouin13, F. Duffaud14, M. Fiore1, S. Bonvalot15 & on behalf of ISG and FSG

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Diagram showing a stepwise approach to managing sporadic desmoid-type fibromatosis, with decision points for diagnosis, treatment options, and follow-up strategies.
No Standard of Care

- NSAID – case reports, unknown efficacy
  (COX2 + HD Vitamin C)

- Anti-Hormonal - binding sites for estrogens and antiestrogens
  - small case series, responses of ~ 15%
  - ARST0321 (COG) Phase II Sulindac + Tamoxifen
    Interim results: ORR 8%; 2yr PFS 36%
  - Toremifene: Fiore et al., ASCO 2011: RR 22%, PFS 76% 6 mths
  - NCI with zendoxifen (active metabolite tamoxifen)
Cytotoxic Chemotherapy:

-- Methotrexate + (VINCA) Alkaloids

-- Phase II study: 30 patients with weekly therapy.
-- 40% PR and 60% SD.
-- 10 year actuarial PFS: 67%

-- COG trial – 28 pts
-- ORR 19%
-- 3yr PFS 32%

HYDROXYUREA???
Doxorubicin or liposomal doxorubicin

- case series with 2 – 35 patients
- Response rates of 20 – 36%
- Durable response rates of 7 - 40 months

**Doxorubicin + DTIC**

- 20mg/m2 x 4 days; 150 mg/m2 x 4 days
  - Followed by meloxicam
- 7 pts with FAP
- 3 CRs, 4 PRs
- Average PFS 74 months
- cardiac toxicities, myelosuppression, mucositis and nausea

Patel SR; Cancer 1993 Dec 1;72(11):3244-7
Imatinib

-- 19 patients with desmoid (imatinib): **3 PR (15%) AND 4 SD**
-- Correlative biomarkers: KIT, PDGFRA/B, CTNNB1 and plasma PDGF AA/BB.
-- No biomarker correlation to response

-- Large exploratory Phase II (imatinib): DT/DF = 20 pts. **2 PR (10%), 8 SD (40%)**

-- Chugh et al. Phase II study (imatinib) (SARC):
  **51 patients. 3 PR (6%). 1 year PFS: 66%**
-- Extensive correlative studies: PDGFR, AKT, PTEN, FKHR, APC and CTNNBI
-- No biomarker to correlate for response

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
Clin Cancer Res; 17(12) June 15, 2011

-- 26 patients with progressive disease
-- sorafenib: expanded access program from Bayer
-- single institution, retrospective review

<table>
<thead>
<tr>
<th>Patient Characteristics: 26 patients</th>
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<tbody>
<tr>
<td>Location:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-Abdominal/Retroperitoneal</td>
<td>12</td>
<td>(46%)</td>
</tr>
<tr>
<td>Trunk/Chest wall</td>
<td>6</td>
<td>(24%)</td>
</tr>
<tr>
<td>Extremity</td>
<td>6</td>
<td>(24%)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>2</td>
<td>(8%)</td>
</tr>
</tbody>
</table>

- Intra-Abdominal/Retroperitoneal: 7%
- Trunk/Chest wall: 20%
- Extremity: 70%

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Overall Response Rates: RECIST

- Partial Response: 25%
- Stable Disease: 70% at 6 mos
### MRI T2 Signal

<table>
<thead>
<tr>
<th>BRIGHT ON T2</th>
<th>DARK ON T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td>Fibrous tissue/Scar</td>
</tr>
<tr>
<td>Edema</td>
<td>Protein rich fluid</td>
</tr>
<tr>
<td>Inflammiation</td>
<td>Calcification</td>
</tr>
<tr>
<td>Infarction</td>
<td>Anti-VEGF therapy ???</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td>Meth-hemoglobin (extracellular)</td>
<td>Iron, ferritin, melanin, deoxyhemoglobin, methemoglobin (intracellular),</td>
</tr>
</tbody>
</table>
A 30% decrease in T2 signal seen in 90% of patients
A multicenter, Phase III, double blind, randomized, placebo-controlled trial of sorafenib in desmoid tumors or aggressive fibromatosis.

Study Chair/PI: Mrinal Gounder
Co-PI: William Tap
(Maki and Schwartz)
ALLIANCE chair: Monica Bertagnolli
Desmoid tumor

R
2:1

Sorafenib 400 mg daily
Placebo

CT or MRI scans every 2 months

Decrease in size or stable
Stay on sorafenib or placebo

Increase in size
If progression
If on placebo, then switch to sorafenib. If on sorafenib, then off study

Voluntary Biopsies

UNBLIND
Proposed Endpoints

Primary Endpoints: **Response rates**

Secondary Endpoints:
- Progression Free Survival
- Pain Palliation

Exploratory Endpoints:
- Pre and Post tumor biopsy for response. Focus on Wnt pathway and major/minor targets of sorafenib (12 paired biopsies will give a 93% power to detect a 1 SD deviation in change)

- Novel imaging biomarker: MRI T2 signal. What degree of decrease is significant? Can MRI T2 signal be a new criteria for response in DT and replace RECIST.
Clinical Outcomes of Systemic Therapy for Patients With Deep Fibromatosis (Desmoid Tumor)

Veridiana Pires de Camargo, MD; Mary L. Keohan, MD; David R. D'Adamo, MD; Cristina R. Antonescu, MD; Murray F. Brennan, MD; Samuel Singer, MD; Linda S. Ahn, MD; and Robert G. Maki, MD

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- 68 patients
- Median follow up of 63 months.
- Median of 2 prior notherapies.
- Highest response rates with anthracycline containing regimens and hormonal therapy.
Future Considerations

- Gamma Secretase Inhibitor
- GSI/Hedgehog inhibitor
- Selective WNT inhibitors
WNT/B-Catenin

Moon et al. 2004 Nat Rev Gen 5, 691-701
Gamma Secretase Inhibitors
Thank You

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