The Management of Desmoid Tumors: A joint global evidence-based consensus approach for adult and pediatric patients

2018 Desmoid Tumor Research Foundation (DTRF) International Desmoid Tumor Research Workshop, Philadelphia, PA, USA

Peter Hohenberger & Bernd Kasper
Mannheim University Medical Center
on behalf of The Desmoid Tumor Working Group
Background

- Desmoid tumor (DT) is a monoclonal, fibroblastic proliferation characterized by a variable and often unpredictable clinical course.
- The incidence is ~5-6 cases per 1 million of the population per annum.

- There has been no level I/II evidence for DT treatment approach available; there were only few prospectively conducted studies/meta-analysis.


Joint SPAEN & EORTC/STBSG Initiative

What can Patients and Patient Advocates provide?

• Are a helpful voice in really understanding patients’ problems and needs and avoid some misunderstanding (e.g. “watchful waiting”).
• May focus on issues of DT patients which experts hardly see (e.g. pain).
• Help to identify experienced experts, centers or networks of excellence.
• Play a fundamental role in connecting contributors & resources and in disseminating information.
• Can jointly develop together with the medical experts a consented treatment approach and therapeutic algorithm.
An update on the management of sporadic desmoid-type fibromatosis: a European Consensus Initiative between Sarcoma PaItients EuroNet (SPAEN) and European Organization for Research and Treatment of Cancer (EORTC)/Soft Tissue and Bone Sarcoma Group (STBSG)

B. Kasper1*, C. Baumgarten2, J. Garcia2, S. Bonvalot3, R. Haas4,5, F. Haller6, P. Hohenberger1, N. Penel7, C. Messiou8, W. T. van der Graaf9 & A. Gronchi10*, on behalf of the Desmoid Working Group1

1Sarcoma Unit, Interdisciplinary Tumor Center, Mannheim University Medical Center, University of Heidelberg, Mannheim; 2SPAEN Sarcoma Patients EuroNet eV, Wöllenstein, Germany; 3Department of Surgical Oncology, Institut Curie, PSL University, Paris, France; 4Department of Radiotherapy, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam; 5Department of Radiotherapy, Leiden University Medical Center, Leiden, The Netherlands; Institute of Pathology, Friedrich Alexander University Erlangen, Erlangen, Germany; 6Department of Medical Oncology, Centre Oscar Lambret, Lille, France; 7Department of Radiology, The Royal Marsden Hospital, London; 8Division of Clinical Studies, The Institute of Cancer Research, London, UK; 9Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

*Correspondence to: Prof. Bernd Kasper, Sarcoma Unit, Interdisciplinary Tumor Center, Mannheim University Medical Center, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. Tel: +49-621-383-2588; E-mail: bernd.kasper@umm.de

Dr. Alessandro Gronchi, Department of Surgery, Sarcoma Service, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy. Tel: +39-02-29-00-12-34; E-mail: alessandro.gronchi@istitutotumori.mi.it

Additional Members of the Desmoid Working Group are listed in the Acknowledgements.

2017

2017
Consensus Algorithm

Diagnosis (core needle biopsy)

Front-line approach: watch & wait (1-2 years)

In case of stabilization or regression: watch & wait

In case of progression (consider-if clinically possible-to wait until 3 subsequent progression)

- Abdominal wall
  - S
  - MT (or RT)

- Intra-abdominal
  - HT
  - S*

- Retroperitoneal/pelvic
  - MT

- Extremity/girdles/chest wall
  - S*
  - MT

- Head & neck/intrathoracic
  - MT

Investigational treatments...

Abbreviations: HT: hormonal therapy; S: surgery; S*: surgery is an option if morbidity is limited; MT: medical therapy; RT: radiotherapy; ILP: isolated limb perfusion
Desmoid Meeting 2018 - Methodology & Workflow

Kick-off @ CTOS
Nov 10, 2017

IFOM Literature Search
1-4/2018

Draft Paper
4-5/2018

Milan Meeting
6/2018

Publication
Q4/2018

Workflow
Desmoid Milan Meeting 2018 - Topics Covered

• Pathology & Molecular Genetics
• Indications for an Active Treatment
• Available Medical Therapies in Different Indications
• Assessment of Treatment Effects
• Pain, Quality of Life, Fertility & Pregnancy
• Radiation therapy
• Which Endpoints, Study Designs & Regulatory Requirements do we need for Desmoids?
Desmoid Meeting 2018 - Funding

- Initial Meeting & Idea 10th November 2017, CTOS, Maui, Hawaii

- Kick-off/seeding Grant: SOS-Desmoid, Germany 10,000 €
  10th December 2017!

- Desmoid Tumor Research Foundation (DTRF) 30,000 $

- Sarcoma Patients EuroNet (SPAEN) 6,000 €
Desmoid Meeting 2018 - Methodology

PubMed
January 2018
2265 Citation(s)

Embase
January 2018
441 Citation(s)

2489 Non-Duplicate Citations Screened

Inclusion/Exclusion Criteria Applied

2390 Articles Excluded After Title/Abstract Screen

99 Articles Retrieved

Inclusion/Exclusion Criteria Applied

59 Articles Excluded After Full Text Screen
P: 3
I: 11
C: 25
O: 3
S: 17

0 Articles Excluded During Data Extraction

40 Articles Included
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<thead>
<tr>
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<tr>
<td><strong>Patients</strong></td>
<td>Patients with sporadic desmoids</td>
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<tr>
<td><strong>Exposure</strong></td>
<td>Beta-catenin mutated desmoids (T41A, S45F, S45P, S45N)</td>
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<tr>
<td><strong>Comparison/Control</strong></td>
<td>Wildtype desmoids</td>
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<tr>
<td><strong>Outcomes/Endpoints</strong></td>
<td>RFS, PFS</td>
<td></td>
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<tr>
<td><strong>Study types</strong></td>
<td>Comparative studies with at least two arms (at least 20 patients)</td>
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<tr>
<th>Indication for an active treatment</th>
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<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Patients with sporadic (beta-catenin mutated vs wildtype) and FAP-associated desmoids</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Active treatment (surgery, radiotherapy, medical therapy)</td>
<td></td>
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<tr>
<td><strong>Comparison/Control</strong></td>
<td>No intervention/watchful waiting</td>
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<tr>
<td><strong>Outcomes/Endpoints</strong></td>
<td>RFS, PFS, side effects, QoL</td>
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<tr>
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<thead>
<tr>
<th>Hierarchy of medical therapies</th>
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<tr>
<td><strong>Patients</strong></td>
<td>Patients with sporadic and FAP-associated desmoids</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Medical therapies (antihormonal therapies, NSAIDs, interferon, imatinib, nilotinib, sorafenib, pazopanib, PF-03084014, chemotherapy: methotrexate, vinblastine, vinorelbine, doxorubicin, dacarbazine, cyclophosphamide, pegylated liposomal doxorubicin)</td>
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<tr>
<td><strong>Comparison/Control</strong></td>
<td>No intervention</td>
<td></td>
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<tr>
<td><strong>Outcomes/Endpoints</strong></td>
<td>RFS, PFS, side effects, quality of life</td>
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<tr>
<td><strong>Study types</strong></td>
<td>Comparative studies with at least two arms (at least 20 patients)</td>
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### Pain control and physical therapy

<table>
<thead>
<tr>
<th><strong>Patients</strong></th>
<th>Patients with sporadic and FAP-associated desmoids</th>
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</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Pain medication, physical therapy</td>
</tr>
<tr>
<td><strong>Comparison/Control</strong></td>
<td>No intervention</td>
</tr>
<tr>
<td><strong>Outcomes/Endpoints</strong></td>
<td>RFS, PFS, side effects, QoL</td>
</tr>
<tr>
<td><strong>Study types</strong></td>
<td>Comparative studies with at least two arms (at least 20 patients)</td>
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### Radiation therapy

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<tr>
<th><strong>Patients</strong></th>
<th>Patients with sporadic and FAP-associated desmoids</th>
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</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Radiotherapy</td>
</tr>
<tr>
<td><strong>Comparison/Control</strong></td>
<td>No intervention/Surgery only</td>
</tr>
<tr>
<td><strong>Outcomes/Endpoints</strong></td>
<td>RFS, PFS, side effects, QoL</td>
</tr>
<tr>
<td><strong>Study types</strong></td>
<td>Comparative studies with at least two arms (at least 20 patients)</td>
</tr>
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**Abbreviations:** RFS, recurrence-free survival; PFS, progression-free survival; QoL, quality of life.
Desmoid Global Consensus – Our Claim:

The management of desmoid tumors:

A joint, global, evidence-based, consensus approach for adult and pediatric patients

The Desmoid Tumor Working Group
Diagnosis of DT has to be confirmed by an expert soft tissue pathologist.

β-catenin mutations and APC mutations are mutually exclusive in DT, thus, detection of a somatic β-catenin mutation may help to exclude a syndromic condition.

Vice versa, β-catenin wild-type status in DT should raise suspicion for FAP, with more extensive diagnostic clinical work-up (e.g. colonoscopy).

Therefore, our group gives a strong recommendation to perform a mutational analysis in DT to confirm diagnosis and guide the work-up.
Desmoid Global Consensus – Results: **Active treatment**

- When active management for DT is required, surgery as 1st line therapy can be considered, provided expected surgical morbidity is limited and radical resections are pursued.

- **If R1 resection** is obtained in first line management, there is not enough evidence to justify perioperative radiotherapy.

- The risk of a local recurrence seems to be lower after combined modality, the difference between surgery alone and surgery + perioperative RT is not statistically significant.

- When surgery is not an option and active management is required, **RT alone** has also been shown to provide adequate local control in a majority of progressive patients.
Desmoid Global Consensus – Results: Effects of wait & see

- An initial W&S approach does not influence the efficacy of further treatments when needed.
  - Thus being safe and not harmful, this approach is now considered the first step after diagnosis in the majority of patients.
- Neither surgery nor other forms of active treatments are proposed as primary therapy at diagnosis.
  - Considering the biology and unpredictable course of the disease, active treatments should be considered only in the case of persistent progression.
- Progression at a single assessment, especially in the absence of specific symptoms and in non-critical anatomic sites, should not per se be considered as an indication to start an active treatment immediately.
- Patients need to be continuously monitored with a 1st MRI within 1-2 mos., then in 3-6 mos.intervals.
  - A decision towards an active treatment should be postponed until the occurrence of subsequent PD, assessed with at least two further assessments and possibly not before one year from diagnosis.
  - This policy avoids overtreatment in patients who could spontaneously regress and discourages treatment for stable and pauci-symptomatic patients.
- When the DT is located close to a critical structure that may pose significant problems to the patient’s life (mesenteric or head & neck DT) an earlier decision towards an active therapy may be taken.
The treatment algorithm shows, that the type of further treatment is guided according to the anatomical site and the decision should be shared with the patients in a stepwise approach:

- For abdominal wall DT, surgery is still the first option in case of progression.
- For intraabdominal / retroperitoneal / pelvic DT, surgery may not be considered as the first treatment option; medical therapy should be preferred.
- For extremity / girdles / chest wall DT, again surgery should not be the first treatment option unless the location is easy and the expected morbidity is nil and in any case not before MDT discussion; medical therapy should be administered preferably.
- For head & neck / intrathoracic DT, medical therapy is generally considered the first line option.
- In selected conditions (age, patient intolerance / preference, comorbidities, lesion growing rapidly and threatening vital organs, etc.) RT is a reasonable and effective 1st line alternative.
Diagnosis (core needle biopsy)

Front-line approach: Watch & Wait (1–2 years)

In case of Progression
(consider if clinically possible to wait until 3 subsequent progression)

- Abdominal wall
- Intraabdominal / Retroperitoneal / pelvic
- Extremity / girdle / chest wall
- Head & neck / intrathoracic

- S
- MT
- MT
- Head & neck / intrathoracic

- MT (or RT)
- MT
- S* / RT or both
- S* or ILP
- RT
- MT
- RT or S* + RT

Investigational treatments, ...

Abbreviations: S: Surgery; S*: Surgery is an option if morbidity is limited; MT: Medical therapy; RT: Radiotherapy; ILP: Isolated limb perfusion.
FAP DT seems to be more aggressive and multifocal and, therefore, tends to be treated more aggressively in terms of medical treatment.

Act with caution regarding biopsy.

In the setting of a confirmed FAP mutation, a mesenteric mass may likely be a DT, particularly if the patient had prior surgery.

However, data are not enough to absolutely discourage biopsy at this point. FAP patients should be jointly managed by sarcoma specialists and experts in gastrointestinal cancer.

Surgery should stay in the hands of experienced surgeons; small bowel transplantation should be discouraged.

There is a lack of evidence that pediatric patients need to be treated differently than adult ones.

Thus, the treatment approach is very similar to that of adult patients and should follow the same treatment algorithm.
Desmoid Global Consensus – Results: Systemic therapy

- Due to the lack of comparative studies we are still not in the situation to propose a definitive sequence of the existing systemic treatment options.
- Randomized data only exists for sorafenib, pazopanib and MTX/Vin.
- Prospective phase II studies do exist for the administration of low-dose chemotherapy with methotrexate plus vinblastine and for the use of imatinib.
- It is reasonable to employ the less toxic before the more toxic therapy in a stepwise fashion.
- Out of the variety of possible systemic treatment options, one can be chosen taking into account the (1) level of evidence, the (2) overall response rate, the (3) PFS rate, the (4) ease of administration, and the (5) expected toxicity of the drug.
- As an example, in a worst case scenario with a mesenteric, potentially life-threatening DT there is consensus to administer more aggressive therapies.
Desmoid Global Consensus – Results: Systemic therapy

Tyrosine kinase inhibitors

ORR (CR + PR)

Level of evidence (Credits 0-5)

Ease of administration.

G3/4 Toxicity %

PFS @ 12 months

- imatinib [48]
- imatinib [49]
- imatinib [50]
- sorafenib [52]
- pazopanib [54]
### Desmoid Global Consensus – Results: **Systemic therapy**

<table>
<thead>
<tr>
<th>Treatment class</th>
<th>Tyrosine kinase inhibitors</th>
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<tr>
<td>Drugs</td>
<td>Imatinib</td>
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<tr>
<td>ORR (CR + PR) [%]</td>
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<tr>
<td>PFS @ 12 months [%]</td>
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<tr>
<td>G3/4 toxicity [%]</td>
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<tr>
<td>Ease of administration</td>
<td>Oral</td>
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<tr>
<td>Level of evidence / credits (0-5)</td>
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Desmoid Global Consensus – Results: **Systemic therapy**
## Desmoid Global Consensus – Results: **Systemic therapy**

<table>
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<th>Treatment class</th>
<th>Chemotherapy</th>
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<tr>
<td>Drugs</td>
<td>MTX + VBN</td>
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<td>ORR (CR + PR) [%]</td>
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<tr>
<td>PFS @ 12 months [%]</td>
<td>79</td>
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<tr>
<td>G3/4 toxicity [%]</td>
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<tr>
<td>Ease of administration</td>
<td>IV weekly</td>
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<tr>
<td>Level of evidence / credits (0-5)</td>
<td>5</td>
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<tr>
<td>Reference</td>
<td>Toulmonde [66] Azzarelli [70] Skapek [71]</td>
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Desmoid Global Consensus – Conclusions

- Assessment of treatment effects in DT remains an unresolved issue and no standard validated response criteria are available as of today.
- RECIST criteria are not sufficiently sensible to catch all clinically relevant responses, though the majority of prospective trials forcibly reported data by RECIST.
- Integration of “tissue response” is probably needed, mainly based on MRI signal changes.
- There is no role for FDG-PET.
- Circulating tumor DNA is presently under evaluation and may become a valid biomarker of response/progression.
- Symptomatic relief evaluation has to be included into the response assessment, though a specific validated tool for DT patients is not (yet) available.
- A comprehensive definition of clinical benefit from treatment in DT patients needs to be agreed upon.
- Validation of dedicated response criteria should be included in the design of future clinical studies.
Typically for guidelines:

- **Long/full version:**
  - to be put on websites of PAGs, institutions involved, ..... 
  - printed version (booklet?, 49 pages)

- **Short version:** publication in a scientific, peer-reviewed, high-ranked journal
The Desmoid Tumor Working Group goes global!

18th of June 2018, Istituto Nazionale dei Tumori, Milan, Italy