



SPAEN Conference: Desmoid Tumors

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Update on systemic treatment options and clinical trials in desmoids

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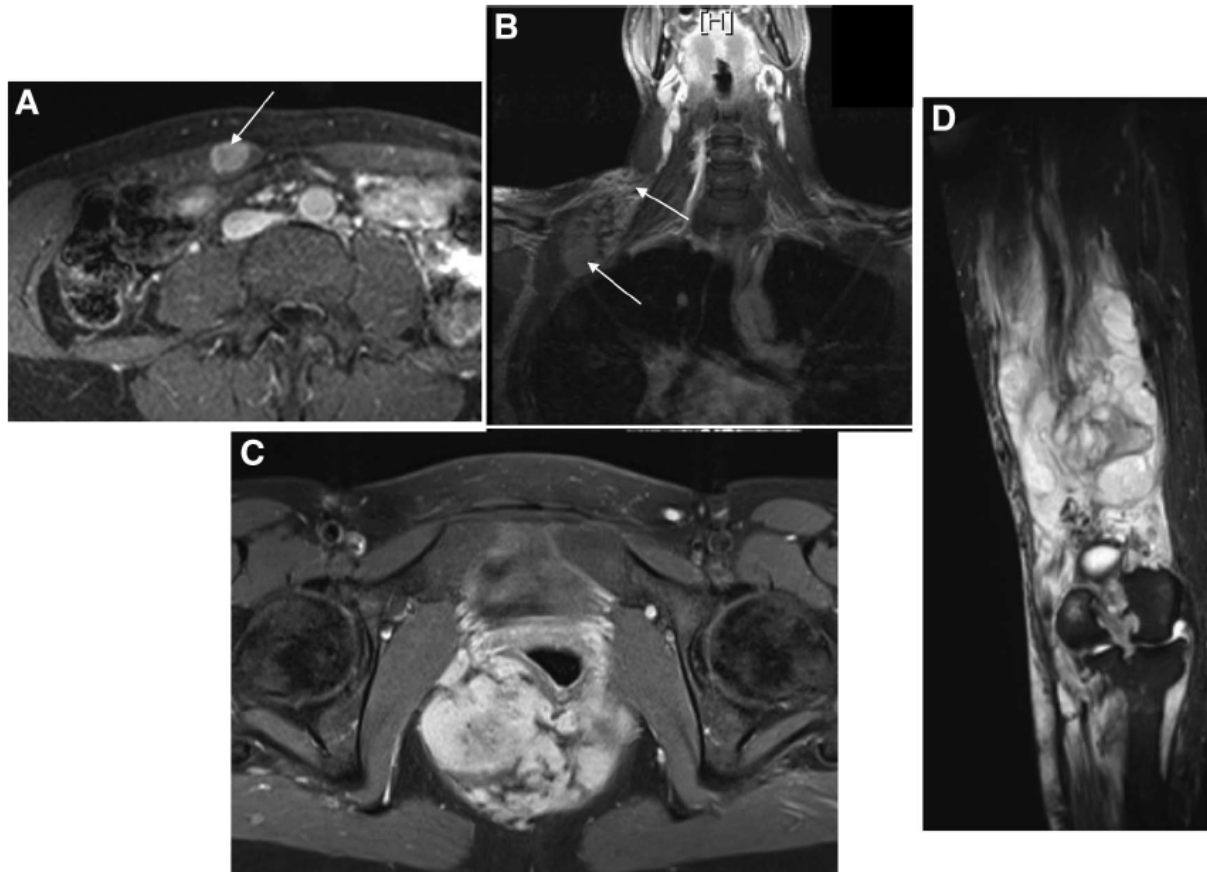
Educational: Desmoid Track

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. 200-300 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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Typical localizations of desmoid tumors including rectus abdominis muscle (A), head and neck (B), pelvis (C) and extremities (D):



Kasper B et al. Oncologist 2011; 16: 682-693

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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, may 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 and
 - tyrosine kinase inhibitors.
- **Watch & Wait Strategy** may be most appropriate in many clinical situations.

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Antihormonal and anti-inflammatory Drugs:

- Response rates for antihormonal or anti-inflammatory drugs vary up to 50 %.
- Main problem: 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 NSAID therapy may be considered as first-line medical treatment for unresectable disease without clinical symptoms (especially for FAP associated desmoids).²

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Antihormonal and anti-inflammatory Drugs:

Table 1. Antiestrogen therapy in patients with aggressive fibromatosis: single-arm trials and case reports

Author	No. of patients	Sex	Age, range (median)	History of FAP	Primary or recurrent	Location	Hormonal agent	NSAID	Response	Response duration
Kinzbrunner et al. 1983 [26]	1	F	29	Yes	Recurrent	Multifocal	Tamoxifen 80 mg/day	No	PR	NR
Rock et al. 1984 [27]	5	NR	NR	NR	Recurrent	NR	Tamoxifen	No	2 SD, 3 PD	NR
Procter et al. 1987 [28]	1	F	26	No	Recurrent	Multifocal	Tamoxifen 40 mg/day	No	SD	14 months
Eagel et al. 1989 [29]	1	F	29	Yes	Recurrent	Mesentery	Tamoxifen 20 mg/day, megace 300 mg/day	No	SD	7 months
Sportiello and Hoogerland 1991 [30]	1	F	40	No	Recurrent	Pelvic	Tamoxifen 80 mg/day	No	CR	27 months
Thomas et al. 1990 [31]	1	F	30	No	Recurrent	Shoulder girdle	Tamoxifen 20 mg/day	No	CR	12 months
Wilcken and Tattersall 1991 [32]	2	F	40	No	Recurrent	Calf	Tamoxifen 20 mg/day	No	1 PR	8 years
		F	40	No	Primary	Mesentery	Megace 500 mg/day	No	1 PR	10 months
Brooks et al. 1992 [33]	20	15 F, 5 M	18–70 (29)	NR	12 Primary, 8 recurrent	14 Abdominal and pelvic	Toremifene 200 mg/day	No	1 CR, 10 PR, 6 SD	NR
Benson et al. 1994 [34]	1	F	17	NR	Primary	Retroperitoneum	Toremifene 200 mg/day	No	PR	9 months
Mukherjee et al. 1995 [35]	1	M	16	NR	Primary	Pelvis	Tamoxifen 20 mg/day, prednisolone 60 mg/day	No	PR	2 years
Izes et al. 1996 [36]	1	M	54	NR	Primary	Pelvis	Tamoxifen 160 mg/day	Sulindac 300 mg/day	PR	54 months
Lackner et al. 1997 [37]	2	F	1	NR	Recurrent	Chest wall	Tamoxifen 2 mg/kg/day	Diclofenac 4 mg/kg/day	SD	4 years
		F	1.5	NR	Primary	Mandible	as above	as above	SD	1 year

55%

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.

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Antihormonal and anti-inflammatory Drugs:

Review

Annals of Oncology 14: 181–190, 2003
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The pharmacological treatment of aggressive fibromatosis: a systematic review

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Table 3. Anti-inflammatory therapy in aggressive fibromatosis: case reports

Author	No. of patients	Sex	Age (median)	History of FAP	Primary or recurrent	Location	Anti-inflammatory treatment	Other	Response	Response duration
Tsukada et al. 1992 [48]	14	NR	29	Yes	Recurrent	Abdominal	Sulindac 300 mg/day	No	1 CR, 7 PR, 4 SD	NR 57 %
Klein et al. 1987 [23]	3	2 M, 1 F	NR	Yes	Recurrent	Abdominal wall, mesentery	Indomethacin 100 mg/day	No	2 PD, 1 SD	NR
Waddell and Kirsch 1991 [41]	8	4 F, 4 M	22–76 (39)	4 Yes, 4 No	NR	4 Mesentery	Sulindac 300–400 mg/day or indomethacin 75–300 mg/day	Warfarin	3 PR, 3 SD, 2 PD	NR 38 %
Belliveau and Graham 1984 [49]	1	M	36	Yes	Primary	Mesentery	Sulindac 200 mg/day	No	1 PR	
Dominguez-Malagon et al. 1992 [50]	3	F	30	No	Primary	Extra-abdominal	Colchicine 3 mg/day	No	PR	NR
		F	21	No	Primary	as above	as above	No	PR	NR
		M	47	No	Primary	as above	as above	No	PR	NR

CR, complete response; F, female; FAP, familial adenomatous polyposis; M, male; NR, not reported; PD, progressive disease; PR, partial response; SD, stable disease.



Antihormonal and anti-inflammatory Drugs:

- Prospective phase II study of the Children's Oncology Group (COG): high-dose **tamoxifen + sulindac** for desmoid tumors in children.
- N = 59 (age < 19 years) were enrolled between 2004 and 2009.
- Treatment schedule: tamoxifen + sulindac (each 3 mg/kg/dose daily PO BID) for 12 months, until disease progression or intolerable toxicity
- 10 patients completed therapy without PD or withdrawal.
- Response: 4 PR + 1 CR = 5/59 = **8 %**
- Survival: 2-year PFS rate 36 % and OS rate 96 %
- Safety: 3 deaths due to PD, 12/30 females developed ovarian cysts
- **First and only prospective trial evaluating this combination, however, relatively low activity as measured by response and PFS rates.**

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Chemotherapy:

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

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Chemotherapy:

- Phase II trial of the Pediatric Oncology Group: **methotrexate + vinblastine**
- N = 28 (27 eligible and 26 evaluable for response)
- Inclusion criteria: recurrent disease or not amenable to radiation or surgery
- Treatment schedule: MTX 30 mg/m²/weekly + Vbl 5 mg/m²/weekly for 26 weeks and every other week for an additional 26 weeks (1 year therapy!)
- Response: 5 CR + PR (**19 %**) and 10 SD
- Survival: 18 pts. showed PD at a median time of 9.1 months
- Safety: neutropenia, 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 et al. (n = 68) anthracyclines in combination with hormonal therapy demonstrated the greatest RECIST response rates.¹
- **Pegylated liposomal doxorubicin** (50 mg/m²/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):

Reference	Chemotherapy regimen	Number of patients	Response	Follow-up [months]	
Patel	Doxorubicin 60-90 mg/m ² + dacarbazine 750-1000 mg/m ²	12	2 CR 4 PR 2 SD	28-235	50 %
Gega	Doxorubicin 20 mg/m ² d1-4 + dacarbazine 150 mg d1-4, d28	7	3 CR 4 PR	33-108	100 %
Constantinidou	Pegylated liposomal doxorubicin 50 mg/m ² , d28	12	4 PR 7 SD	7-39	33 %
Wehl	Pegylated liposomal doxorubicin 50 mg/m ² , d28	4	4 PR	NR	100 %
Azzarelli	Vinblastine 6 mg/m ² + methotrexate 30 mg/m ² , weekly	27	4 OR 19 SD	6-96	15 %
Weiss	Vinorelbine 20 mg/m ² + methotrexate 50 mg/m ² , weekly	13	NR	< 12	
Skapek	Vinblastine 5 mg/m ² + methotrexate 30 mg/m ² , weekly	27	8 PR 10 SD	5-37	30 %
Pilz	VAIA, VAC, cyclophosphamide + ifosfamide	19	4 CR 5 PR	NR	

No randomized trials!!



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Chemotherapy:

- Retrospective analysis from the French Sarcoma Group (FSG)
- N = 62 (12 pts. with Gardner syndrome)
- Previous treatments: 55 % previously received one or more lines of systemic treatment (44 % NSAID, 44 % antiestrogens, 31 % imatinib)
- Chemotherapy:
 - 71 % combination chemotherapy
 - 29 % single-agent
 - 21 % anthracycline-based
- Response: 2 % CR, 19 % PR, 60 % SD and 19 % PD
- Non-limb location was associated with improved PFS ($p = 0.03$).
- **Response rate was significantly higher for anthracycline-containing regimens (54 % vs. 12 %, $p = 0.0011$).**
- **If chemotherapy is administered, it should be anthracycline-based.**

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Chemotherapy:

Protocol	Drugs
Mesna, adriamycin, ifosfamide, dacarbazine	Doxorubicin 20 mg/m ² (day 1–day 3) Ifosfamide 2.5 g/m ² (day 1–day 3) Dacarbazine 300 mg/m ² (day 1–day 3) 21 days cycle
Adriamycin, dacarbazine	Doxorubicin 20 mg/m ² (day 1–day 3) Dacarbazine 300 mg/m ² (day 1–day 3) 21 days cycle
Metronomic etoposide	Oral etoposide 75 mg/day for 21 days of 28 days cycle
Metronomic cyclophosphamide	Oral cyclophosphamide 50 mg/day for 21 days of 28 days cycle
Doxorubicin	Doxorubicin 60–75 mg/m ² 21 days cycle
Methotrexate–vinblastine	Vinblastine 6 mg/m ² Methotrexate 30 mg/m ² (J1, J8, 15, 21) 28 days cycle
Methotrexate	Methotrexate 30 mg/m ² (J1, J8, 15, 21) 28 days cycle
Vinorelbine	Vinorelbine 20 mg/m ² (J1, J8) 21 days cycle

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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 (**response rate 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 %

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Tyrosine kinase inhibitors - Sorafenib:

- 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.
- Symptomatic improvement regarding pain and mobility was observed in 70 % of patients.
- Phase III study planned in the US.



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)

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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).



Interim analysis (06/2012):

- Primary endpoint: Non-progression rate at 6 months
- Interim analysis was performed at 17/37 evaluable patients.
- Accrual will continue if ≥ 4 patients are progression-free at 6 months.
- Interim analysis showed that **11 out of 17** evaluable patients had stable disease at 6 months indicating that imatinib had reached the primary endpoint.
- Accrual can be continued after the first step of the study.
- 6 “non-successors”: 3 PD, 1 toxicity, 1 withdrawal, 1 treatment change
- **Conclusion:** With a 65 % progression-free rate at the interim analysis, imatinib clearly exceeded its primary endpoint of the study and warrants further accrual and final analysis of the trial.

DESMOID Study GISG-01

Recrual Status:

- Cut-off-date 09/2013
- n = 39/39 in the following centers (since 07/2010):

Berlin	n = 8
Essen	n = 3
Hannover	n = 9
Heidelberg	n = 0
Mannheim	n = 19
- End of recruitment reached; final analysis expected in 2015.

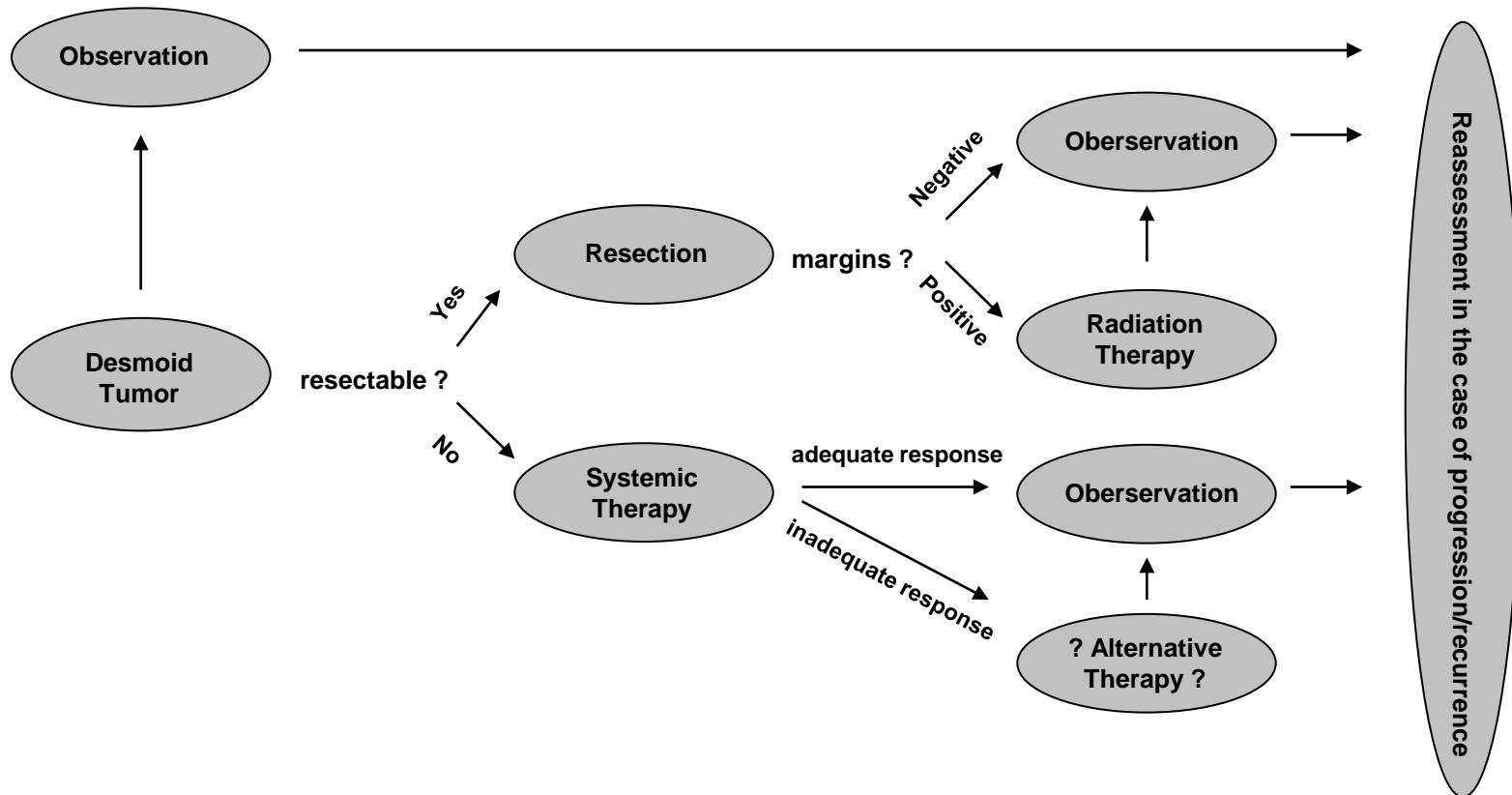
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Treatment Strategies:

- 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:



Educational: Desmoid Track



Treatment Strategies:

Ann Surg Oncol (2009) 16:2587–2593
DOI 10.1245/s10434-009-0586-2

Annals of

SURGICAL ONCOLOGY

OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

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

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Lack of randomized trials and evidence-based data:

EUROPEAN JOURNAL OF CANCER 45 (2009) 2928–2929



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Editorial Comment

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

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explored. 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.⁵ 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.



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Currently recruiting clinical trials:

- 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 = 94, age ≥ 18 years; Dr. Italiano, Institut Bergonié, Bordeaux). ONGOING
- A phase II study of **Imatinib** in patients with desmoid tumor and chondrosarcoma (BASKET 1):
The purpose of this study is to determine whether imatinib is active in diseases - such as desmoid tumor and chondrosarcoma - expressing the PDGFR both in its isoform alpha and beta (phase II, n = 35, age ≥ 18 years; Prof. Aglietta, Italian Sarcoma Group). ONGOING
- ???

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Take-Home-Messages:

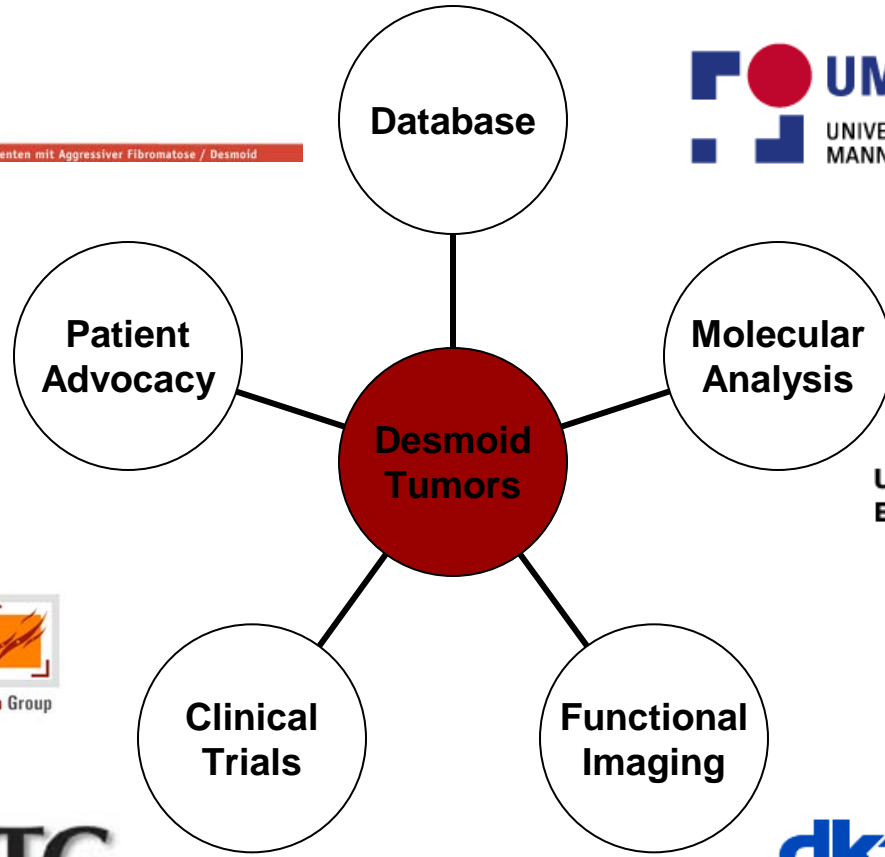
- Desmoid tumors represent an extremely heterogeneous disease with a natural biology varying between spontaneous regression and stabilization to rapid progression.
- Medical treatment is indicated when local surgery is infeasible or associated with severe function loss or morbidity.
- A strategy of observation 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.



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Questions?

