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REVIEW

Clinical trials in desmoid-type fibromatosis in children and adults: A systematic review

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Abstract

Desmoid-type fibromatosis (DTF) is a rare locally aggressive soft tissue neoplasm, which occurs in children and adults, with a peak incidence in young adults. For the majority of the patients, DTF is a chronic and symptomatic disease, which affects health-related quality of life. Systemic treatment regimens tend to differ for patients treated by pediatric oncologists compared to medical oncologists. This systematic review identified 14 clinical trials in children and adults with DTF. Tumor response and progression-free survival rates varied widely between studies and study populations. Treatment choices for patients with DTF are based on a paucity of (randomized) trials. Treatment principles of DTF are similar in pediatric and adult oncology, but the treatment itself is different. This seems mostly driven by a lack of tyrosine kinase inhibitor (TKI) accessibility in pediatric oncology. An insufficient number of studies examined patient-reported outcomes, which are extremely important for patients with a chronic disease like DTF.

KEYWORDS
clinical trials, medical oncology, pediatric cancer, quality of life, desmoid

1 | INTRODUCTION

Desmoid-type fibromatosis (DTF) is a locally aggressive soft tissue tumor without metastatic tendency but with a high relapse rate and episodes of progression.[1] DTF mainly arises in the extremities, head and neck, and abdomen and accounts for approximately 0.03% of all neoplasms and <3% of all soft tissue tumors.[2,3] DTF occurs mostly in young adults (YAs) and has two relative peaks among 6–15-year olds and between puberty and the age of 40 in women.[4]

A wait-and-see strategy is the recommended first-line approach for both adult and pediatric patients with DTF without symptoms.[5–8] Systemic treatment options for symptomatic patients and/or unresectable tumor vary between chemotherapy approaches and targeted treatments.[9] The goal for treatment is to render the disease

Abbreviations: BPI, Brief Pain Inventory; CONSORT, Consolidated Standards of Reporting Trials; CR, complete response; DTF, desmoid-type fibromatosis; EORTC, European Organization for Research and Treatment for Cancer; EORTC QLQ, European Organization for Research and Treatment for Cancer Quality of Life Questionnaire; HRQoL, health-related quality of life; MTX–VBL, methotrexate–vinblastine; ORR, objective response rate; PFS, progression-free survival; PR, partial response; PRO, patient-related outcome; RCT, randomized controlled trial; SD, stable disease; TKI, tyrosine kinase inhibitor; YA, young adult.

asymptomatic or induce stable disease (SD) or a partial response (PR). Complete remissions are rare and not the primary aim of treatment. DTF frequently relapses with symptomatic disease and/or tumor growth, which has an enormous impact on health-related quality of life (HRQoL), especially in YAs.[10] There is no consensus in the field for standard drug combinations for first and relapsed disease, and many patients experience multiple treatments for subsequent relapses. The varying treatment results and lack of randomized controlled trials (RCTs) for comparing treatment strategies, precludes the establishment of a standard treatment protocol.[6,11]

Defining the treatment trajectory in the management of DTF is challenging, especially for YAs (15–39 years[12]) divided between the pediatric (<18 years) and adult protocols.[11] In addition, the (systemic) treatment options seem different between patients under the care of a pediatric oncologist compared to a medical oncologist.[5,6] In highly symptomatic pediatric patients or incidental cases with rapid tumor growth coinciding with life-threatening disease, (low-dose) chemotherapy can be recommended as first-line treatment. In abdominal wall locations, primary resection may be considered.[5] For adults, systemic treatment if indicated, consists mainly of chemotherapy or targeted agents, also depending on national reimbursement of novel, targeted treatment options.[6] The aim of this study is to conduct a systematic review of current clinical studies and outcomes in children up to 18 years and (young) adults with DTF.

2 | METHODS

2.1 | Search strategy

A computerized search of the literature through the search engine PubMed and Embase was performed on July 1, 2020. For trials in progress, Clinicaltrials.gov was searched. A search string was composed combining terms related to "aggressive fibromatosis," "abdominal fibromatosis," "desmoid tumor," "therapy," "treatment outcome," and "clinical trial" (Table S1). It included relevant subject headings per database and all synonyms in title, abstract, and keywords. The reference lists of all identified publications were checked to retrieve other relevant publications.

2.2 | Selection criteria

Studies were included according to the following criteria: (i) diagnosis of DTF for all study participants; (ii) RCT study design or a non-RCT phase 2; (iii) study objective to assess an anticancer therapy; (iv) full-text articles only, containing results on survival rate and/or tumor response; and (v) studies from 2000 to July 2020. The studies were analyzed based on information regarding outcome: tumor responses, survival rates, adverse events, and patient-related outcomes (PROs).

Initial screening of the retrieved citations was conducted by two independent reviewers (Simone A. van Maren and Milou Reuvers) based on the title and abstract. The full-text publications of all citations of potential interest regarding treatment of DTF were subsequently screened for inclusion criteria by two independent reviewers (Simone A. van Maren and Max M. van Noesel). When the two reviewers disagreed on selection of studies, a third reviewer (Olga Husson) resolved this and made a final decision. The PRISMA flowchart of this selection procedure is shown in Figure 1.

2.3 | Data abstraction

The author, year, continent/country, number of participants, study design, duration of follow-up, patient characteristics, tumor responses, survival rates, PROs, and adverse events were extracted from included studies. The data endpoints extracted included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), complete response (CR), PR, minor response (MR), SD, progressive disease (PD), median progression-free survival (mPFS), median time to progression (mTTP), median time to response (mTTR), and time to treatment failure (TTF). The heterogeneity of inclusion criteria and methods precluded a meta-analysis, and the results are reported descriptively.

2.4 | Quality assessment

Quality assessment of the included studies was performed using the Consolidated Standards of Reporting Trials (CONSORT) 2010 checklist to improve the quality of reports of RCTs. The checklist contains 37 (sub)items and each fulfilled item scores 1 point. In a consensus meeting with the four authors, the following data-driven cutoff points were selected: low-quality score <20 points, medium-quality score 20–28 points, and high-quality score <28 points. Two reviewers independently assessed all 14 studies. Discrepancies between the two reviewers (Simone A. van Maren and Milou Reuvers) were resolved through a mutual decision after discussion or involvement of a third reviewer (Olga Husson).

3 | RESULTS

3.1 | Overview studies

The search yielded a total of 1226 articles. After application of a title and abstract screen, 40 articles were identified, and finally 14 articles[13-26] met the inclusion criteria after full-text screen (Figure 1). Of the articles, one was a randomized phase 3 clinical trial, one was a randomized phase 2 clinical trial, and 12 were nonrandomized phase 2 clinical trials. To compare the treatments of children and adults, three different study groups were created based on the age-related eligibility criteria of the articles. Eight studies (57%) were addressed as adult studies (age range of study protocol: ≥18 years), two studies (14%) were addressed as pediatric studies (age range of study protocol: ≤18 years), and four studies (29%) were addressed as mixed studies (i.e., crossed the 18-year-old inclusion frontier) (Table 1).

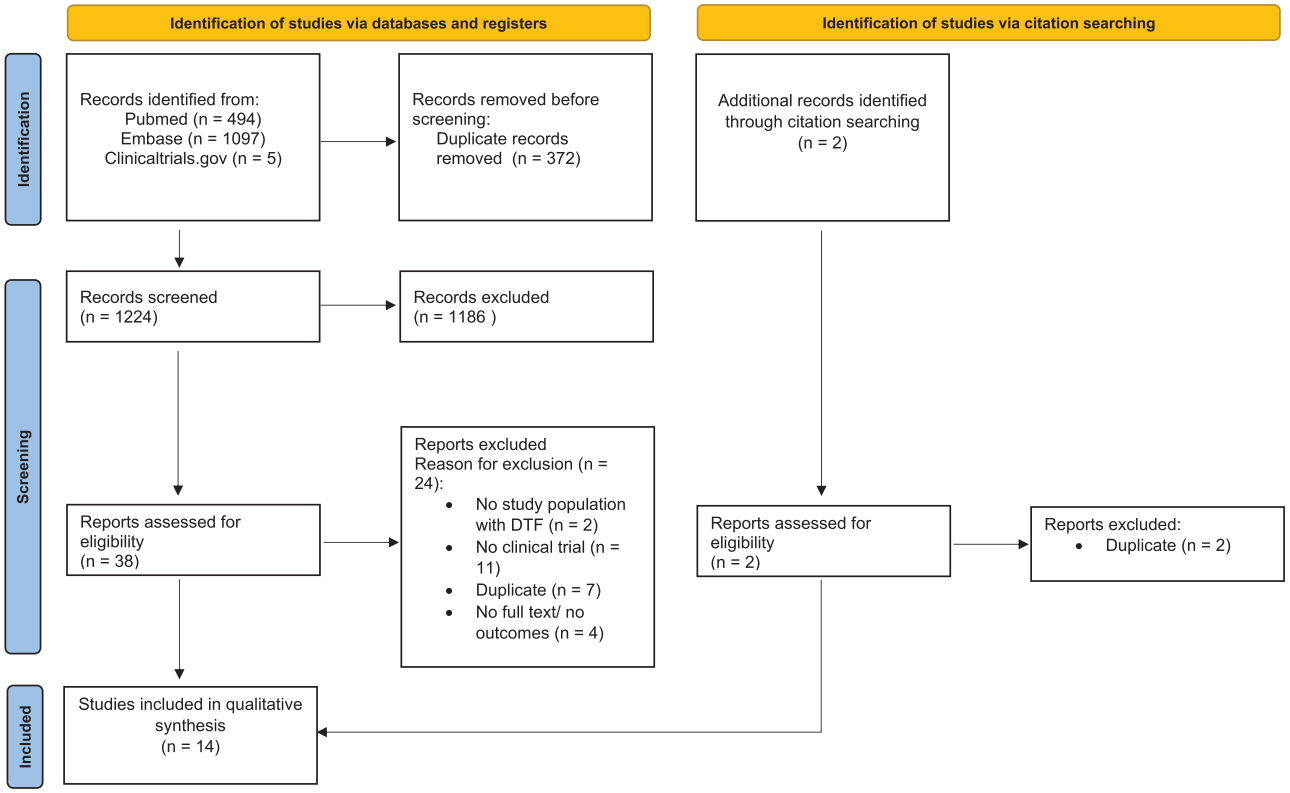

FIGURE 1 PRISMA flow diagram of selection procedure

TABLE 1 Study characteristics of clinical trials on treatment of desmoid patients ($n = 529$)

Author, publication year	Continent/ country	Number of participants	Study design	Follow-up in months (interquartile range)	Age range of study protocol (years)	Median age + age range published in article (years)
Adult studies						
Gounder, 2018	America	87	Randomized phase 3 trial	27.2 (22.0–31.7)	≥18	37 (18–72)
Toulmonde, 2019	France	66	Randomized phase 2 trial	23.4 (17.1–25.5)	≥18	40 (18–79)
Anter, 2019	Egypt	25	Phase 2 trial	15 (3–36)	≥18	32 (18–60)
Jo, 2014	Korea	19	Phase 2 trial	20.3 (1.8–50.7)	≥18	30 (22–67)
Kasper, 2017	Germany	38	Phase 2 trial	17	≥18	44 (19–80)
Kummar, 2017	America	17	Phase 2 trial	25 (3–30)	≥18	34 (19–69)
Penel, 2011	France	35	Phase 2 trial	34	≥18	41 (20–72)
Liu, 2017	China	15	Phase 2 trial	26.1	18–75	41 (24–63)
Pediatric studies						
Skapek, 2007	America	26	Phase 2 trial	43.2 (12–70.8)	–	11.5 (0.6–20.5)
Skapek, 2013	America	59	Phase 2 trial	39.6 (0–73.2)	<19	At diagnosis: 13 (<1–18)
Mixed studies						
Azzarelli, 2001	Italy	30	Phase 2 trial	75 (14–125)	–	27 (4–68)
Chugh, 2010	America	49	Phase 2 trial	–	≥10	34 (12–67)
Heinrich, 2006	America	19	Phase 2 trial	–	–	25 (17–63)
Keus, 2013	Europe	44	Phase 2 trial	57.6	≥16	39.5 (17.7–73.7)

The trials were scored and categorized as low (eight studies), medium (five studies), and high quality (one study) (Table S1). The CONSORT 2010 checklist was developed especially for RCTs, which resulted in low scores for certain checklist items, randomization and comparing two groups (items: 1a, 3a, 8a–11a, 12a, and 18). None of the studies reported all 37 (sub)items (Table S2). The mean score of the 14 studies was 19.9 points (range: 13.5–20). Main improvements can be made in the reporting of specific information about the methods (items: 3b, 4b, 6b, 14b), binary outcomes (item: 17b), and in the reporting of the trial number and protocol (items: 23, 24) (Figure S1).

3.2 | Adult studies

The anticancer therapies of the eight adult studies (Table 2) included tyrosine kinase inhibitor (TKI) therapies (five studies of low to high quality),[13–17] γ-secretase inhibitor therapy (one study of medium quality),[26] chemotherapy combined with targeted therapy (one study of low quality),[19] and hormonal therapy combined with a nonsteroidal anti-inflammatory drug (NSAID) (one study of low quality).[20] ORRs ranged from 11% to 60% and the 2-year PFS from 36% to 81%. The most favorable responses were seen in the sorafenib group in Gounder et al. (sorafenib group: ORR: 33% [95% CI: 20–48], 2-year PFS: 81% [95% CI: 69–96] vs. placebo group: ORR: 20% [95% CI: 8–37], 2-year PFS: 36% [95% CI: 22–57]) and in Anter et al. (ORR: 60%, 2-year PFS: 55%).

3.3 | Pediatric studies

Two clinical trials with a pediatric study population were conducted by the Pediatric Oncology Group/Children's Oncology Group (Table 3). The tolerability and efficacy of methotrexate–vinblastine (MTX–VBL) was evaluated in the study by Skapek et al. (2007, medium quality).[21] The other pediatric study (low quality) was a phase 2 study of 59 patients, less than 19 years of age, in which patients with measurable DTF (recurrent or not amenable to surgery or radiation) were treated with sulindac and tamoxifen.[22] Of these two pediatric studies, the study of Skapek et al. (2007) showed the most favorable outcomes (ORR: 19.2%, 2-year PFS: 46%).

3.4 | Mixed studies

Four mixed studies were identified with the search (Table 4). The anticancer therapies of these studies included TKI therapy (two studies of low quality),[24,25] chemotherapy (one study of low quality),[23] and radiotherapy (one study of medium quality).[26] ORRs ranged from 16% to 50%. Two studies reported individual outcome data.[23,25] Both studies reported a wide age range in their study protocol, the mean age was 34.6[23] and 27.3 years.[25] The effect of age on outcome could not be evaluated due to the low numbers of pediatric patients. Of the four studies, the most favorable outcomes (ORR: 50%, 3-year PFS: 81.5%) were seen in the European Organization for Research and Treatment for Cancer (EORTC) radiotherapy study.[26]

3.5 | Description of adult and pediatric studies

When comparing the response and PFS outcomes between pediatric and adult studies, the outcomes in the pediatric studies were less favorable. The ORRs (8%–19.2%) reported in the pediatric studies were relatively low compared to the ORRs in adult studies (11%–60%). Both ORRs were lower than the ORR of the placebo group (20% [95% CI: 8–37]) in Gounder et al. However, one should be careful with comparing these studies, as they were executed in different settings.

Sulindac and tamoxifen were given in one pediatric and one adult study. In the pediatric study, high doses of sulindac and tamoxifen (both dosed at 3 mg/kg BID) were given. In the phase 2 adult study, sulindac (100 mg TID) and tamoxifen (20 mg OD) were given. Tumor response rates, survival rates, and adverse events were more favorable for the adult population (Table 5).[20,22]

Chemotherapy was used in one pediatric study and in a randomized study arm of an adult study. In both studies, the same dosages of MTX–VBL were administered. The results in the adult study were more satisfactory (Table 5).[14,20–22]

3.6 | Patient-reported outcomes

Three adult studies reported on the impact of symptoms that interfered with the patients' day-to-day HRQoL. Toulmonde et al. described HRQoL with the European Organization for Research and Treatment for Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and pain intensity with the Brief Pain Inventory (BPI).[14] The EORTC QLQ-C30 reported five domains (global health status, physical functioning, emotional functioning, pain, and fatigue) that were scored at baseline and during or at the end of a treatment on a 100-point scale. In the pazopanib group, the pain intensity between baseline and cycle 6 decreased from 33 to 17 points, which was considered as a clinically meaningful[27] and positive effect. This improvement was associated with a stabilization in global health status (stable score 67). In the MTX–VBL group, no change was observed in pain intensity. The global health status decreased between baseline and cycle 6 (score from 67 to 50). Patients with available data at cycle 6 scored worse on emotional functioning (score from 100 to 67), which was considered a clinically meaningful decrease and a negative effect.

In the trial of Gounder et al. with sorafenib versus placebo, 11 side effects were assessed with the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE, version 1.0) across eight cycles, and the severity of pain was assessed with the BPI (only at randomization).[13] Limited results were available because PRO completion was not mandatory. Significantly more patients in the sorafenib group reported nausea, diarrhea, rash, and hand–foot syndrome compared to the placebo group. However, in case of hand–foot syndrome, this did not translate to a statistically significant increased interference in activities of daily living in the sorafenib group. For the other symptoms, interference in activities of daily living was not reported.

TABLE 2 Details of the adult studies

Author, publication year	Patient population	Therapy	Number of patients	Tumor response outcomes and response criteria	Survival rates	Adverse events (grade 3 or 4)
Gounder, 2018	Patients with measurable, progressive, recurrent, or primary disease that was deemed inoperable or as requiring extensive surgery, or symptomatic disease	TKI: sorafenib at a starting dose of 400 mg once daily	50	Sorafenib: 1 CR, 15 PRs, ORR 33% [95% CI: 20–48] (RECIST v1.1)	1-year PFS: 89% [95% CI: 80–99] 2-year PFS: 81% [95% CI: 69–96] mPFS: 15 months	Total grade 3/4 AE: 31 Most common grade 3: rash (14), fatigue (3), hypertension (4) Grade 4: thrombocytopenia (1), anemia (1) (CTCAE, version 4.03)
		Placebo	37	Placebo: 7 PRs, ORR 20% [95% CI: 8–37] (RECIST v1.1)	1-year PFS: 46% [32–67] 2-year PFS: 36% [95% CI: 22–57] mPFS: 6 months	Total grade 3/4 AE: 13 Most common grade 3/4: abdominal pain (4), vomiting (2) (CTCAE, version 4.03)
Toulmonde, 2019	Patients with progressive, histologically confirmed DTF	TKI: pazopanib 800 mg daily orally for up to 1 year	46	Pazopanib: 17 PRs, 27 SD, 2 PD, ORR 37%[a] (RECIST v1.1)	1-year PFS: 85.6% [95% CI: 70.7–93.2], 2-year PFS: 67.2% [95% CI: 49.0–81.9]	Total grade 3/4 AE: 34 Most common grade 3: hypertension (9), diarrhea (7) Grade 4: neutropenia (1), hypertension (1) (NCI-CTCAE version 4.0)
		Chemotherapy: intravenous methotrexate 30 mg/m^2 plus vinblastine 5 mg/m^2, once a week for 6 months and then every 2 weeks for 6 months	20	Intravenous methotrexate: 5 PRs, 10 SD, 4 PD, ORR 25%[1] (RECIST v1.1)	1-year PFS: 79.0% [95% CI: 53.2–91.5], 2-year PFS: 79.0% [95% CI: 53.2–91.5]	Total grade 3/4 AE: 20 Most common grade 3/4: neutropenia (9), liver transaminitis (6) Grade 4: neutropenia (1), liver transaminitis (1) (NCI-CTCAE version 4.0)
Jo, 2014	Patients with advanced DTF	TKI: sunitinib 37.5 mg daily for 4 weeks	19	5 PRs, 8 SD, 3 PD, ORR 26.3% [95% CI: 6.3–45.7] (RECIST v1.0)	2-year PFS: 74.7%, OS: 94.4%	Total grade 3/4 AE: 16 Most common grade 3: neutropenia (5) Grade 4: neutropenia (1)
Kasper, 2017	Patients with DTF being RECIST progressive, not amenable to surgical resection with R0 intent or accompanied by unacceptable function loss	TKI: imatinib 800 mg daily planned over 2 years	38	7 PRs, ORR 19% (RECIST v1.0)	1-year PFS: 59%, 2-year PFS: 45%, OS: 100% mTTR: 11 months [95% CI: 6–19]	Total grade 3 AE: 4 patients (11%) (neutropenia, leukopenia, nausea/vomiting, gastritis, rash, and contracture) Grade 4 AE: neutropenia (1)
		TKI: nilotinib 800 mg daily (for patients showing disease progression under imatinib)	8 of 38	No disease progression occurred until end of study (PR at 3 months of 88%)		

(Continues)

TABLE 2 (Continued)

Author, publication year	Patient population	Therapy	Number of patients	Tumor response outcomes and response criteria	Survival rates	Adverse events (grade 3 or 4)
Penel, 2011	Patients with radiological evidence for progressive DTF	TKI: imatinib 400 mg daily for 1 year	35	1 CR, 3 PRs, 28 SD, 3 PD, ORR 11%[1] (RECIST)	2-year PFS: 55% [95% CI: 39–69] OS: 95% [95%: CI 82–99] mPFS: 25 months	Total grade 3 AE: 18 Most common: rash (4), abdominal pain (4), vomiting (3) No grade 4 AE (NCI-NCTCAE version 3.0)
Kummar, 2017	Patients with histologically confirmed DTF not amenable to surgical resection or definitive radiation therapy, and who experienced actively progressing disease following at least one line of standard therapy	ɣ-secretase inhibitor: PF-03084014 orally 150 mg twice a day throughout a 21-day cycle	17	5 PRs, 11 SD, ORR 29% (RECIST v1.1)		Total grade 3 AE: 8 (47%) (reversible hypophosphatemia) (NCI-CTCAE version 4.0)
Liu, 2017	Patients with refractory DTF	Chemotherapy + targeted therapy: doxorubicin 30 mg/m^2 on days 1–2 and thalidomide 200 mg at night on days 1–21 every 3 weeks for a maximum of six cycles	15	5 PR, 8 SD, 2 PD, ORR 33% (RECIST v1.0)	mPFS: 20.6 months [95% CI: 14.5–26.7]	Total grade 3/4 AE: 17 Most common grade 3: neutropenia (5), leukopenia (3) Grade 4 AE: neutropenia (4), leukopenia (2) (NCI-NCTCAE version 3.0)
Anter, 2019	Patients with measurable histologically confirmed recurrent or newly diagnosed tumors, not amenable to R0 resection, or those who underwent tumor excision with gross residual DTF	NSAID and hormonal therapy: tamoxifen 20 mg and sulindac 300 mg daily for 12 months	25	2 CRs, 13 PRs, 7 SD, 3 PD, ORR 60% (RECIST v1.0)	2-year PFS: 55%, mPFS: 25 months [95% CI: 21.6–28.3]	No grade 3/4 AE (NCI-CTCAE version 3) During the course of therapy, 2 out of 13 females developed 1–4 ovarian cysts

Abbreviations: AE, adverse events; CI, confidence interval; CR, complete response; DTF, desmoid-type fibromatosis; mPFS, median progression-free survival; mTTR, median time to response; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.0/1.1, Response Evaluation Criteria in Solid Tumors version 1.0/1.1; SD, stable disease.

[a]Analyzed results: (ORR = CRs + PRs)/number of patients.

TABLE 3 Details of the pediatric studies

Author, publication year	Patient population	Therapy	Number of patients	Tumor response outcomes and response criteria	Survival rates	Adverse events (grade 3 or 4)
Skapek, 2007	Children with recurrent DTF, or with newly diagnosed disease not amenable to surgery or radiation	Chemotherapy: vinblastine 5 mg/m^2 and methotrexate 30 mg/m^2, both administered by intravenous injection weekly for 26 weeks and every other week for an additional 26 weeks	26	1 CR, 4 PRs, 3 MRs, 10 SD, 8 PD, ORR[a] 19.2% [95% CI: 6.6–43.7] (>50% decrease in product of maximum perpendicular dimensions)	2-year PFS: 46% [95% CI: 25–65][1] mTTP: 9.1 months (n = 18) [range: 2.1–47.3 months]	Total grade 3/4 AE: 31 Most common grade 3: neutropenia (9), anemia (2), nausea (2), vomiting (2), and elevated hepatic transaminases (2) Grade 4: neutropenia (5), cortical (1), mood (1) (NCI-CTCAE)
Skapek, 2013	Children who had measurable DTF that was recurrent or not amenable to surgery or radiation	NSAID and hormonal therapy: sulindac and tamoxifen, 3 mg/kg daily with the maximum daily dose of 300 mg for each agent for 12 months	59	1 CR, 4 PR, ORR[a] 8% (>50% decrease in product of maximum perpendicular dimensions)	2-year PFS: 36% [95% CI: 0.23–0.48]	Total number of grade 3 AE: 5 Most common grade 3: abdominal pain (3) (NCI-CTCAE v.3.0) 12 (40%) of 30 females developed ovarian cysts, which were asymptomatic in 11 cases

Abbreviations: AE, adverse events; CI, confidence interval; CR, complete response; DTF, desmoid-type fibromatosis; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.0/1.1, Response Evaluation Criteria in Solid Tumors version 1.0/1.1; SD, stable disease.
[a]Analyzed results: (ORR = CRs + PRs)/number of patients.

In the study of Kummar et al., with γ-secretase inhibitor PF-03084014, the MD Anderson Symptom Inventory was used to assess the severity of 13 treatment-related symptoms at baseline and at restaging visits over the previous 24 hours on a 0–10 numerical scale.[18] Small improvements were seen in mean symptom severity scores in patients with SD or a PR. A 1.65-point improvement in mean symptom severity was found in partial responders (p = .008). None of the five PRs experienced worsening of symptoms. Improvements were seen in pain, numbness/tingling, fatigue, and distress. A 0.8-point improvement in mean symptom severity was seen in five patients with SD as their best tumor response rate (p = .08).

4 | DISCUSSION

This systematic review examined the current (systemic) treatment regimens available to children, YAs, and adults with DTF. We identified 14 studies: eight adult studies, two pediatric studies, and four mixed studies. The majority were YA and adult studies. The overall quality of the studies was low to medium, of which included were two RCTs and 12 phase 2 clinical trials. Notably, the majority of the adult studies concerned targeted agents, mainly TKIs. The pediatric studies mostly included chemotherapeutic drugs. In studies in which adult and pediatric patients were treated with similar agents, the outcome in the pediatric population was inferior to the outcome in the adults.

The treatment and drug combinations in this systematic analysis were variable with little overlap. Chemotherapy was reported in two adult studies, one pediatric study, and one mixed study. Chemotherapeutic combinations consisted of MTX in combination with VBL or vinorelbine, and in one study thalidomide was combined with doxorubicin. Response rates were 19.2%–40%, with relatively long progression-free periods. Given the serious side effects related to thalidomide in fertile young females, this drug should not be prescribed for DTF.

TKIs were reported in five adult studies and in two mixed studies. Numerous different TKIs were evaluated, either as single agent, or in randomized studies, and all contained either sorafenib, pazopanib, sunitinib, and imatinib. Response rates were 6%–33%, with varying progression-free periods. Overall, treatment with TKIs seemed to be as effective or more favorable in symptomatic patients compared to chemotherapy. Especially, pazopanib and sorafenib show encouraging response and PFS outcomes (Table 2). Imatinib appeared to be the least

TABLE 4 Study details of mixed studies

Author, publication year	Patient population	Therapy	Number of patients	Tumor response outcomes and response criteria	Survival rates	Adverse events (grade 3 or 4)
Azzarelli, 2001	Patients with primary or recurrent, advanced, inoperable DTF	Chemotherapy: methotrexate at a dose of 30 mg/m^2 plus vinblastine at a dose of 6 mg/m^2 for a median interval of 1 year	30	12 PRs, 18 SD, ORR[a] 40% (WHO criteria)	Overall actuarial progression-free interval at 5 years: 67%	Most common grade 3: leukopenia (94%)
Chugh, 2010	Patients with DTF not curable by surgical management or in whom curative surgery would lead to undesirable functional impairment	TKI: imatinib 300/200/100 mg twice daily	49	3 PRs, 43 SD, 5 PD, ORR 6%	1-year PFS: 66%	Grade 3/4 AE occurring with a frequency of >5% Neutropenia (5), rash (5), fatigue (4)
Heinrich, 2006	Patients with advanced DTF	TKI: imatinib 800 mg daily	19	3 PRs, 13 SD, 3 PD, ORR[a] 16%[1] (SWOG response criteria)	mTTF: 10.7 months	Most common grade 3/4: gastro-intestinal (9), dermatologic (3), hematologic (2)
Keus, 2013	Patients with inoperable progressive disease of primary, recurrent, or incompletely resected lesions (DTF)	Radiotherapy: dose of 56 Gy in 28 fractions, 2 Gy per fraction, 5 fractions per week	44	6 CRs, 16 PRs, 18 SD, 3 PR, ORR[a] 50%[1] (RECIST v1.0)	3-year PFS: 81.5%	Acute grade 3 AE: skin, mucosal membranes, and pain Late toxic effects (RTOG-EORTC scale) Total number of grade 3/4: skin (2)

Abbreviations: AE, adverse events; CI, confidence interval; CR, complete response; DTF, desmoid-type fibromatosis; mTTF, median time to treatment failure; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.0/1.1, Response Evaluation Criteria in Solid Tumors version 1.0/1.1; SD, stable disease; SWOG, Southwest Oncology Group; WHO, World Health Organization.

[a]Analyzed results: (ORR = CRs + PRs)/number of patients.

effective TKI for DTF, with ORRs ranging from 11% to 19%. Imatinib was not compared directly to a placebo; however, it did not exceed the ORR (20% [95% CI: 8–37]) in the placebo group of Gounder et al.

Adverse events were variable and in general, grade 3–4 adverse events were comparable between TKIs and chemotherapy. Treatment with sorafenib led to a significantly higher rate of discontinuation of the trial regimen than in the placebo group (20% vs. no patients). The most common reason for dose reduction in the sorafenib group was skin disorders (grade 1–2 toxicity). In the other studies, grade 1–2 toxicity was hardly collected but is relevant given the often long-lasting treatment in DTF.

The PRO studies were limited, which is surprising given the chronic character of symptoms in DTF. Overall, only one study reported on HRQoL[14] and two on PROs that interfere with daily living.[13,26] It is therefore important to note that pazopanib increased the HRQoL score according to the EORTC QLQ-C30 compared to MTX–VBL. The global health status stabilized in the pazopanib group, clinical symptoms such as pain and emotional functioning decreased or stabilized, whereas global health status decreased in the MTX–VBL group. To understand the role of many of the discussed compounds on QoL, future studies should include PRO items to assess the effect of drugs. Nearly all clinical trials with patients with DTF use standard endpoints such as tumor response rates (RECIST) and PFS to measure treatment efficacy. DTF poses a low risk of death but the unpredictable growth behavior, the high tendency of local recurrence after surgical resection, and the chronicity of symptoms such as pain can have a huge impact on HRQoL. Therefore, radiological endpoints are not optimal. Tumor response can be overestimated as DTFs can spontaneously regress (or remain dimensionally stable).[28] Additionally, treatment might follow clinical benefit, even in the absence of tumor regression, but can also induce other effects than changes in tumor size. Therefore, desmoid-specific HRQoL tools or PRO measures are needed to capture symptoms and how they affect daily living.[29] There are currently two validated DTF-specific HRQoL questionnaires available, both primarily developed for adults. For the GODDESS PRO, a pediatric validation study (NCT04195399) is currently ongoing, the developers of the DTF-QoL are considering developing an age-specific questionnaire for children with DTF.[29,30] In this way, appropriate support and analgesic treatment can be provided.[29,31] For YAs who are in an important developmental stage of their lives, age-specific support is crucial.[10,11]

TABLE 5 Pediatric studies compared to adult studies

	Pediatric study (Skapek et al., 2013)	Adult study (Anter et al., 2019)
Study population	Children with measurable DTF that is recurrent or not amenable to surgery or radiation	Patients with measurable histologically confirmed recurrent or newly diagnosed tumors, not amenable to R0 resection, or those who underwent tumor excision with gross residual DTF
Treatment	Sulindac and tamoxifen 3 mg/kg × 2/day, with the maximum daily dose of 300 mg for each agent	Tamoxifen 20 mg/day and sulindac 100 mg × 3/day for 12 months
Number of patients	59	25
Tumor response outcomes and response criteria	1 CR, 4 PRs, ORR[a] 8% (>50% decrease in product of maximum perpendicular dimensions)	2CRs, 13 PRs, 7 SD, 3 PDs, ORR 60% (RECIST v1.0)
Survival rates	2-year PFS: 36% [95% CI: 0.23–0.48]	2-year PFS: 55%, mPFS: 25 months [95% CI: 21.6–28.3]
Adverse events	Total number of grade 3 AE: 5 Most common grade 3: abdominal pain (3) (NCI-CTCAE v.3.0) 12 (40%) of 30 females developed ovarian cysts, which were asymptomatic in 11 cases	No grade 3 or grade 4 (NCI-CTCAE version 3) During the course of therapy, 2 out of 13 females developed 1–4 ovarian cysts
	Pediatric study (Skapek et al., 2007)	**Adult study (Toulmonde et al., 2019)**
Study population	Children with recurrent DTF or with newly diagnosed disease not amenable to surgery or radiation	Patients with progressive, histologically confirmed DTF
Treatment	Vinblastine 5 mg/m^2 and methotrexate 30 mg/m^2, both administered by intravenous injection weekly for 26 weeks and every other week for an additional 26 weeks	Intravenous methotrexate 30 mg/m^2 plus vinblastine 5 mg/m^2, once a week for 6 months and then every 2 weeks for 6 months
Number of patients	26	20
Tumor response outcomes and response criteria	1 CR, 4 PRs, 3 MRs, 10 SD, 8 PD, ORR 19.2% [95% CI: 6.6–43.7] (>50% decrease in product of maximum perpendicular dimensions)	5 PRs, 10 SD, 4 PD, ORR 25%[1] (RECIST v1.1)
Survival rates	2-year PFS: 46% [95% CI: 25–65][2] mTTP: 9.1 months [range: 2.1–47.3] (n = 18)	1-year PFS: 79.0% [95% CI: 53.2–91.5] 2-year PFS: 79.0% [95% CI: 53.2–91.5]
Adverse events	Total grade 3/4 AE: 31 Most common grade 3: neutropenia (9), anemia (2), nausea (2), vomiting (2), elevated hepatic transaminases (2) Grade 4: neutropenia (5), cortical (1), mood (1) (NCI-CTCAE)	Total grade 3/4 AE: 20 Most common grade 3/4: neutropenia (9), liver transaminitis (6) Grade 4: neutropenia (1), liver transaminitis (1) (NCI-CTCAE version 4.0)

Abbreviations: AE, adverse events; CI, confidence interval; CR, complete response; DTF, desmoid-type fibromatosis; mPFS, median progression-free survival; MR, minor response; mTTP, median time to progression; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.0/1.1, Response Evaluation Criteria in Solid Tumors version 1.0/1.1.

[a]Analyzed results: (ORR = CRs + PRs)/number of patients.

[b]Results found in the study of Skapek et al. (2013).

Remarkably, TKIs were not reported in the pediatric studies of this systematic review. This suggests that the treatment has not yet been implemented into the management of children with DTF, while TKI therapies were common in the adult studies. Five out of eight adult studies reported on multiple targeted compounds. Also, regarding the limited amount of RCTs for pediatric patients with DTF, they seem to have less accessibility to new therapeutic options compared to adult populations. When comparing the adult and pediatric trials, adult patients show more favorable outcomes (Table 5). A similar, relatively low PFS (42.8% [95% CI: 27.2–57.6]) was found in children treated with chemotherapy in an international prospective study.[5] This suggests that DTF could be more aggressive in children. A prospective comparative trial in children or adults is needed to explore this further.[32]

The TKI studies were recently published (publications between 2011 and 2019); 43 TKIs were approved by the Food and Drug Administration for oncological indications in 2019, but DTF is not yet one of them.[33] The toxicity profile of TKIs is manageable when analyzing the grade 3–4 adverse events, but relatively many grade 1–2 adverse events occur.[14] The exact working mechanisms of these

targeted agents in DTF remain unclear. It is suggested that the various mechanisms of action of TKIs cause a variety of unknown side effects.[34] A better understanding of the exact molecular mechanisms that could influence DTF progression will enable the development and implementation of new targeted therapies for both pediatric and adult patients.[35] The working mechanism of the γ-secretase inhibitor nirogacestat (PF-03084014) is better understood. The Notch pathway, which plays an important role in the carcinogenesis of several tumor types, is activated in desmoid tumors. Nirogacestat inhibits this pathway, which results in significant antitumor activity against human desmoid tumors in vitro.[36] Very recently the first results of the global phase3, double-blind, placebo controlled clinical trial (DeFi, NCT03785964) conducted in adults with progressing desmoid fibromatosis were reported on line, showing a 71% decrease in risk of progressive disease as compared to placebo (HR, 0.29, 95% CI, 0.15–0.55; $P < 0.001$) (www.cancernetwork.com, May 28, 2022). For the pediatric population, an open-label, single-arm, phase 2 clinical trial with nirogacestat in children and adolescents with progressive, surgically unresectable desmoid tumors is actively accruing (NCT04195399). Besides nirogacestat, another γ-secretase inhibitor is being investigated. A phase 2/3, randomized study evaluating the efficacy and safety of AL102 is now recruiting patients with progressive desmoid tumors (RINGSIDE, NCT04871282).

The only clinical trial on local therapy found in our search was about radiotherapy. Overall, this local treatment with low-dose radiotherapy showed the most favorable outcomes (ORR: 50%, 2-year PFS: 81.5%) in the treatment of DTF. However, it was only reported in one study and the well-known toxic effects of radiotherapy, such as pain, muscle and joint stiffness, and limb edema, were reported in patients. Radiation-related damage may over time translate to increased risks for functional problems or even induce second malignancies in the irradiated area.[37] The median follow-up (57.6 months) in the study of Keus et al. was insufficient to evaluate this on the longer term.[26] Because of these potential negative long-term side effects, radiotherapy is nowadays restricted to highly symptomatic patients for whom no other valuable alternative is available. Other local therapies like cryoablation (a clinical trial was published after our search), radiofrequency ablation, and high-frequency ultrasound techniques are potential alternatives with good local control outcomes and improved quality of life.[38–40]

One of the main limitations of this review is the low quality of the included trials. Of the 14 studies, only one was considered as high quality, according to the CONSORT 2010 checklist. The CONSORT 2010 checklist is not an official quality assessment tool, which caused the scoring of the articles to be more subjective. It focuses on RCTs and has limited value in the remainder of the studies. Also, in nonrandomized studies, it is challenging to interpret the efficacy of systemic and targeted therapies. Lastly, this review is limited in terms of its descriptive synthesis of the data. Comparisons were difficult to make due to the heterogeneity of the selected clinical trials, the heterogeneity of patients included in the studies, and the variable outcome data assessed with diverse criteria and at variable time points.

In conclusion, this systematic review showed the paucity of randomized trials for DTF, while the oncologists in charge of these patients must select the optimal treatment for their patients. The treatment principles of DTF are similar in pediatric and adult oncology, but the actual treatment for unresectable and/or symptomatic patients is different. In children, the lack of TKI accessibility and the uncertainty of the impact of long-term TKIs on safety explains that the current focus is still on chemotherapy. Although at this point in time, our review is in favor of pazopanib and sorafenib as most effective drugs and radiotherapy as an effective alternative for adult patients, there is a need for larger randomized trials. In addition, the value of desmoid-specific patient-reported outcome cannot be underestimated in this chronic disease and needs to be studied for existing and novel compounds in future studies. Lastly, the accessibility of children to targeted agents seems insufficient, and for DTF it would be an important improvement to include children at age 12 in clinical studies with novel drugs.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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