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REVIEW

Targeted therapy of desmoid-type fibromatosis: mechanism, current situation, and future prospects

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Abstract **Desmoid-type fibromatosis (DF) is a rare monoclonal fibroblastic proliferation that is characterized by locally infiltrative but rarely metastatic lesions. Tyrosine kinase and γ-secretase inhibitors are primarily used in the targeted therapy of DF. The use of these drugs, however, is mainly based on the recommendations of retrospective studies with small sample sizes. Previous studies that focused on the mechanism, efficacy, and safety of targeted therapy for DF were reviewed to provide references for clinical applications and research. The efficacy and safety of targeted therapy were compared with those of other systemic therapy options. Targeted therapy does not provide considerable advantages in efficacy and safety over other medical treatments and is usually applied after the failure of antihormonal therapies, nonsteroidal anti-inflammatory drugs, and chemotherapy. Further studies are required to explore the mechanism, indications, and appropriate drug dosage of the targeted therapy of DF.**

Keywords targeted therapy; desmoid-type fibromatosis; tyrosine kinase inhibitor; γ-secretase inhibitor

Introduction

Desmoid-type fibromatosis (DF) is a rare monoclonal fibroblastic proliferation that is characterized by locally infiltrative but rarely metastatic lesions [1,2]. Trauma, surgery, pregnancy, and oral contraceptives are high-risk factors of DF development [3,4]. Gene mutations, particularly β-catenin and APC gene mutations, play key roles in DF pathogenesis [4,5]. The Wnt (β-catenin) pathway has been verified to play an important role in DF pathogenesis [5–9]. Most cases of sporadic DF involve a mutation in the β-catenin gene [5,8,10,11]. Similarly, most cases associated with familial adenomatous polyposis (FAP) involve mutations in APC, which regulates β-catenin degradation [6,12,13].

DF has a variable and unpredictable clinical course. Some tumors progress, whereas others will not grow and may even regress spontaneously [14]. The consensus on the treatment of DF has changed over the past decade, with most centers moving away from primary radical surgery toward a frontline "watchful waiting" policy [1,2,15–18]. Medical therapy is an important strategy for the treatment of progressive DF, particularly cases with unresectable lesions that are adjacent to important organs. Drugs used in targeted therapy mainly include tyrosine kinase inhibitors (TKIs) and γ-secretase inhibitors [1,19–24].

Targeted therapy, however, is mainly applied on the basis of the results of retrospective studies with small sample sizes. Moreover, few works have compared the safety and efficacy of different drugs used for the targeted therapy of DF. Therefore, we summarize the mechanisms, current situation, and the future of targeted therapy for DF. Our review will provide a reference for the research and clinical application of targeted treatments for DF.

TKIs

TKIs block ligand-activated receptor phosphorylation and mitogen-activated kinase activation and proliferation; these effects ultimately inhibit cellular growth and proliferation [25,26]. TKIs that have been reported effective in DF therapy include imatinib, nilotinib, pazopanib, sorafenib, and sunitinib [1,4].

Imatinib

Imatinib exerts an inhibitory effect on multiple class 3

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receptor tyrosine kinases, including platelet-derived growth factor receptor (PDGFR), PDGFRβ, and cKIT, which are associated with the Wnt pathway and may play important roles in DF development [4,25,27]. In 2002, Mace *et al*. characterized 9 DF cases through immunohistochemistry (IHC) and reverse transcriptase-polymerase chain reaction (RT-PCR) analyses and reported that all cases were positive for PDGFR and PDGFRβ and 6 cases (66.7%) were positive for cKIT [26]. Whether the inhibition of these imatinib targets resulted in imatinib-mediated clinical responses, however, remains unclear.

Heinrich *et al*. detected cKIT, PDGFR, PDGFRβ, and β-catenin mutations in tumor specimens to determine the molecular basis for tumor responses to imatinib [28]. They were unable to identify cKIT, PDGFR, and PDGFRβ mutations and failed to find correlations between β-catenin and APC mutations and clinical responses to imatinib. In contrast to Mace *et al*. [26], they did not detect PDGFR expression or activation in the analyzed DF tumors, and they failed to detect phosphorylation despite the comparable levels of PDGFRβ expression in DF tumors and normal fibroblasts. The plasma levels of PDGFR and PDGFRβ in patients with DF were elevated relative to those in normal patient controls. In addition, they found that the level of plasma PDGFRβ was inversely correlated with time to treatment failure. All their results provide evidence that the response of patients with DF to imatinib may be mediated through the inhibition of PDGFRβ kinase activity [28].

Wcislo *et al*. [29] reported a case that achieved 3 years of sustained response with imatinib despite presenting negative results for PDGFRβ and c-kit (PDGFR was not assessed). Chugh *et al*. [30] analyzed the expression of cKIT, PDGFR, PDGFRβ, AKT, PTEN, FKHR, and β-catenin in specimens through IHC and the mutations of PDGFR exon 18 and APC through allelic discrimination PCR. They reported that all the tested samples were positive for PDGFR and PDGFRβ and that 1 of the 7 tested cases was positive for cKIT. None of the laboratory findings showed any statistically significant correlation with outcome or response. Therefore, further studies are required to confirm the hypothesis of Heinrich *et al*. [28] and to identify biomarkers that can be used to predict patients who will respond to imatinib.

Mace *et al*. [26] performed a study based on IHC and RT-PCR. In their study, 2 cases received imatinib therapy after the failure of chemotherapy, nonsteroidal anti-inflammatory drug (NSAID) therapy, and antiestrogen therapy. The cases received imatinib at the dose of 400 mg twice daily. Both cases responded to imatinib. The tumor masses of 1 case showed an overall size reduction of 50%. The other case showed tumor stability and ongoing reductions in tumor internal density and enhancement. Despite its small sample size, this study provided important information regarding the use of imatinib and other types of TKIs in DF treatment. Heinrich *et al*. reported the results of a phase II clinical study that was performed to further define the efficacy of imatinib in DF treatment [28]. In this study, 19 patients received 400 mg of imatinib twice daily. Among the patients, 3 (15.7%) exhibited reductions of 50% in tumor volume, and 4 patients (21.1%) had stable disease for more than 1 year before treatment failure. Wcislo *et al*. [29] reported a patient treated with 400 mg of imatinib once daily. The tumor dimensions of this patient showed sustained shrinkage from 65 mm × 31 mm to 35 mm × 20 mm during 3 years of follow-up. In a study by Chugh *et al*. [30], imatinib was prescribed to 51 patients at the dosage of 100–300 mg twice daily on the basis of body surface area. The follow-up results showed progression-free survival (PFS) rates of 94%, 88%, 66%, and 58% at 2 months, 4 months, 1 year, and 3 years, respectively. Five patients (9.8%) remained progression-free after 4 years of treatment, and the tumor volumes of 3 patients (5.9%) reduced by more than 30%. The efficacy of imatinib in the treatment of progressive and recurrent DF was investigated in an FNCLCC/French Sarcoma Group phase II trial [20]. All 40 patients received imatinib at the initial dose of 400 mg/day, which was later increased to 600 mg/day in 1 case (2%) and to 800 mg/day in 8 cases (20%) because of progression. The PFS of the patients at 3, 6, and 12 months were 91%, 80%, and 67%, respectively. The 2-year PFS and overall survival rates of the patients were 55% and 95%, respectively. A phase II study by the German Interdisciplinary Sarcoma Group involved 38 patients with DF who received 800 mg of imatinib per day [19]. The PFS at 9, 12, 15, 18, 21, and 24 months were 65%, 59%, 53%, 53%, 50%, and 45%, respectively, and the tumor volumes of 7 patients (19%) reduced by more than 30%. A review of 151 previously reported patients revealed overall response rates of 13% and PFS at 6, 12, and 24 months of 78%, 61%, and 51%, respectively. Moreover, the overall response rate of the high-dose group was better than that of the low-dose group ($P = 0.039$). Studies on the treatment of DF with imatinib are summarized in Table 1.

The toxic effects of imatinib in the treatment of gastrointestinal stromal tumors (GISTs) has been evaluated. Side effects occurred in almost all of cases, and grade 3–4 events occurred in approximately 41% of cases; however, 2/3 of the patients did not require a dose reduction [31]. Side effects occurred in almost all GIST cases in the 800 mg/day group. In addition, more instances of edema, anemia, rashes, lethargy, nausea, bleeding, diarrhea, and dyspnea were recorded in the 800 mg/day group than in the 400 mg/day group [31]. The majority of patients with DF who received 800 mg/day imatinib required dose reduction because of grade 3 or 4 toxicity [28]. Grades 1, 2, 3, and 4 side effects occurred in 86.8%, 34.2%, 10.5%, and 2.6% of patients, respectively [19]. Among DF patients who received 400 mg/day imatinib,

Table 1 Summary of previous studies on systemic therapy for desmoid-type fibromatosis

Treatment protocols	Study	Patient number	Overall response rate	PFS	Grade 3–4 side effects/ dose reduction due to side effects	Characteristics
Imatinib	Mace *et al*. (2002) [26]	2	100%	100% (FUT: 9 and 11 months)	0%	–
	Heinrich *et al*. (2006) [28]	19	16%	6-M 53%; 12-M 37%; 36-M 12%	Majority	–
	Wcislo *et al*. (2007) [29]	1	100%	100% (FUT 24-M)	0%	–
	Chugh *et al*. (2010) [30]	51	6%	6-M 84%; 12-M 66%; 36-M 58%; 60-M 52%	39%	–
	Penel *et al*. (2011) [20]	40	10%	6-M 80%; 12-M 67%; 24-M 55%; 36-M 40%	45%	–
	Kasper *et al*. (2017) [19]	38	19%	12-M 59%; 24-M 45%	13%	–
	Total[#]	151	13%	–	33%	
Nilotinib	Kasper *et al*. (2017) [19]	8	–	3-M 88%	13%	Had the potential to stabilize DF after the failure of imatinib treatment
Pazopanib	Martin-Liberal *et al*. (2013) [39]	2	50%	100% *	50%	–
	Szucs *et al*. (2017) [22]	8	38%	6-M 75%; 12-M 75%; 36-M 12.5%	13%	–
	Total[#]	10	40%	–	20%	
Sorafenib	Gounder *et al*. (2011) [40]	26	25%	6-M 95%	15%	Clinical improvement was noted within 2 weeks
Sunitinib	Skubitz *et al*. (2009) [24]	1	100%	36-M 100%	0%	–
PF-903084014	Messersmith *et al*. (2015) [53]	7	71%	Response time ranged from 1.74 + months to 24 + months	43%	–
	Kummar *et al*. (2017) [21]	17	29%	94% (median FUT>25 months)	47%	–
	Total[#]	24	42%	–	46%	
Antihormone and/or NSAIDS	Hansmann *et al*. (2003) [70]	27	37%	50%*	0%	30% of the cases developed ovarian cysts; 22% CR
	Tanaka *et al*. (2008) [80]	1	100%	100%*	0%	–
	Bocale *et al*. (2011) [81]	168	50%	80%*	0%	–
	Quast *et al*. (2016) [68]	134	33%	85%*	0%	–
	Total[#]	330	42%	–	0%	
Anthracycline-based regimens	Gega *et al*. [74]	7	100%	Average PFS was 74 months (32.5–107.5)	43%	43% CR
	Bertagnolli *et al*. [79]	10	90%	90%*	–	–
	Camargo *et al*. [73]	35	37%	88%*	6%	–
	Garbay *et al*. [76]	13	54%	100% (median PFS was 40.8 months)	–	–
	Total[#]	65	55%	–	12%	
Methotrexate and/or vinblastine	Weiss *et al*. [77]	15	60%	87%*	20%	–
	Azzarelli *et al*. [78]	30	40%	6-M 96%; 12-M 92%; 36-M 80%; 60-M 67%	13%	–
	Bertagnolli *et al*. [79]	4	25%	75%*	–	–
	Camargo *et al*. [73]	22	27%	82%*	–	–
	Garbay *et al*. [76]	27	15%	67% (median PFS 40.8 months)	–	–
	Li *et al*. [82]	71	35%	24-M 80%; 36-M 68%; 60-M 36%	–	–
	Total[#]	169	34%	–	16%	

Overall response, cases that showed DF shrinkage. PFS, progression-free survival. M, month. CR, complete response. FUT, follow-up time. NSAIDS, nonsteroidal anti-inflammatory drugs.
*The follow-up time was unavailable. [#]Only available data were analyzed.

45% experienced grade 3 side effects but none suffered grade 4 side effects. The safety and efficacy of imatinib at the initial dose levels of 400 and 800 mg/day for patients with GIST were assessed in EORTC 62005 and S0033/CALGB 150105 studies [31–33]. Both studies showed equivalent response rates and overall survival for both dose levels. In both studies, more side effects were associated with high doses of imatinib than with low doses of imatinib. The results of the GIST studies provided important references for DF despite the absence of evidence indicating that high doses of imatinib cause severe side effects in patients with DF. Therefore, the suitable initial dose of imatinib in patients with DF that will exhibit low toxicity but equivalent efficacy as high doses of imatinib must be identified. The Italian Sarcoma Group, Heidelberg University, and Yonsei University are currently conducting the phase II trials NCT00928525, NCT01137916, and NCT02495519, respectively, to assess the safety and efficacy of imatinib in DF.

Nilotinib, pazopanib, sorafenib, and sunitinib

Nilotinib, an orally bioavailable selective second-generation TKI, is 30 times more potent than imatinib [34]. It is used as second-line therapy for imatinib-resistant BCR-ABL positive CML [35]. In addition to inhibiting BCR-ABL, nilotinib, similar to imatinib, has a potent effects against cKIT and PDGFR [34,36,37]. Kasper *et al*. investigated the efficacy of nilotinib (800 mg/day) in patients with progressive disease or intolerance under imatinib treatment. In this study, 8 patients were treated with nilotinib for a median duration of 377 days (range: 88–751 days). A total of 88% of the patients showed PFS of 3 months. Nilotinib had mild side effects. Grades 1, 2, 3, and 4 side effects were observed in 75%, 0%, 13%, and 0% of the patients, respectively. No case required dose reduction because of toxicity. The mechanism underlying the therapeutic effect of nilotinib on DF remains unclear. Nevertheless, Kasper *et al*. presented encouraging results. The treatment mechanism, safety, and efficacy of nilotinib in the targeted therapy of DF need to be further studied.

Pazopanib is a multitargeted TKI of cKIT, PDGFR, and PDGFRβ. The results of the PALETTE study, a randomized, double-blind, placebo-controlled phase III trial, demonstrated that pazopanib is a safe and effective treatment option for patients with metastatic nonadipocytic soft-tissue sarcoma after previous chemotherapy [38]. Randomized controlled trials on the use of pazopanib in DF remain unavailable. Martin-Liberal *et al*. [39] reported 2 cases that underwent therapy with pazopanib after the failure of surgery, chemotherapy, NSAIDS therapy, and antiestrogen therapy. The cases received an initial pazopanib dose of 800 mg/day. Both cases responded to pazopanib, and 1 of the cases maintained stable disease and had a sustained drop in T2 signal intensity for more than 1 year. The dose of pazopanib, however, was reduced from 800 mg/day to 200 mg/day because of side effects. The other case showed marked tumor shrinkage and reduced T2 signal intensity and suffered no toxicity. Szucs *et al*. [22] reported that the tumors of 37.5% of 8 patients reduced by more than 30%, and the remaining patients maintained stable disease. Meanwhile, 75% of the patients derived clinical benefit from treatment in terms of improved function and/or pain reduction. Only 1 patient experienced grade 3 toxicity that resulted in early treatment discontinuation. In the PALETTE study, the most common adverse side effects were fatigue, diarrhea, nausea, weight loss, and hypertension; these side effects were mostly controllable through dose adjustments [38]. The results of these studies are encouraging. Nevertheless, the efficacy and tolerability of pazopanib needs to be further confirmed because of the retrospective nature and the small sample size of these studies. The French Sarcoma Group is currently conducting a phase II trial (NCT01876082) that assesses the safety and efficacy of pazopanib in the treatment of DF [39].

Sorafenib is another orally multitargeted TKI that has been reported useful in DF therapy. Gounder *et al*. [40] studied 26 patients with DF who received sorafenib at the initial dose of 400 mg/day. The initial dose was adjusted in accordance with the severity of side effects. The tumors of 25% and 29% of the cases shrank by more than 30% and by 10%–29%, respectively. Meanwhile, 42% of the cases showed disease stability, whereas 4% showed progression. Notably, this study reported the rapid derivation of clinical benefit in 73% of the symptomatic cases. Clinical improvement was typically noted within 2 weeks of initiating sorafenib therapy. This period was shorter than that observed for imatinib. Side effects were controlled through dose adjustments and the inclusion of antidiarrheal and antihypertensive drugs. The National Cancer Institute is conducting a phase II trial (NCT02066181) to assess the safety and efficacy of sorafenib in DF [4].

Skubitz *et al*. [24] reported a case of aggressive multicentric extra-abdominal DF that was responsive to sunitinib but resistant to imatinib. The spectrum of tyrosine kinases that is inhibited by sunitinib is broader than that is inhibited by imatinib and includes vascular endothelial growth factor receptors (VEGFRs). Direct evidence verifying the hypothesis that VEGFR inhibition accounts for the different responses to sunitinib and imatinib remains unavailable. Therefore, further studies are required to confirm this hypothesis and to identify biomarkers that can be used to identify patients who will respond to certain TKIs.

γ-secretase inhibitor

The Notch signaling pathway plays a key role in the differentiation of bone marrow cells, peripheral immune

cells, and gastrointestinal cells [41–43]. Abnormalities in the Notch pathway are associated with the poor prognosis of solid tumors and hematologic malignancies [44–47]. Remarkably, the Notch pathway cross-talks with the Wnt pathway, which plays a key role in DF development [48,49]. These observations provide evidence for the relationship between the Notch pathway and DF development. Kummar *et al*. reported that the response of DF to GSI is not associated with the status of β-catenin and the APC gene [21]. This finding suggests that DF can respond to GSI simply by inhibiting the Notch pathway instead of inhibiting the Wnt pathway synchronously. Given the limitation of the small sample sizes of previous studies on the relationship between Notch pathway and DF development, further studies are required to confirm this hypothesis.

γ-secretase cleaves the Notch intracellular domain, which then translocates to the nucleus where it modulates gene transcription [50]. Therefore, γ-secretase inhibitors (GSIs) may inhibit DF by inhibiting the Notch pathway. The results of a study based on a preclinical cancer model showed that the combination of GSI with an inhibitor of the ERK pathway enhances gastric cancer cell death through the downregulation of Wnt/β-catenin pathways [51]. Arcaroli *et al*. reported that GSI may be beneficial for patients with elevated levels of components of the Wnt and Notch pathways [52]. These results provide theoretical support for the effectiveness of GSI as a DF therapy.

A phase I study on the use of the GSI PF-903084014 in DF treatment showed that among 7 patients, 5 (71.4%) experienced partial response and 2 (28.6%) experienced stable disease [53]. Treatment-related grades 3 and 4 side effects occurred in 35.9% and 1.6% of the patients, respectively. Meanwhile, the expression of the Notch pathway-related HES4 gene was inhibited in the peripheral blood samples of all evaluable patients. The results of a phase II study on the use of PF-903084014 in the treatment of adult DF showed that 5 patients (29%) achieved more than 30% tumor shrinkage after a median of 2 years of treatment [21]. Remarkably, 4 of these 5 patients had no response to imatinib and/or sorafenib before therapy with PF-903084014. During the follow-up time (median 25 (3–30) months), 65% of patients showed sustained stable disease. All patients suffered grades 1 and 2 side effects, and 2 needed dose reduction. Grade 3 treatment-related side effects occurred in 47% of the patients. These results suggested that GSI is an option for the medical treatment of DF, especially when other treatments are ineffective. Meanwhile, the safety and efficacy of GSI must be confirmed in further studies.

Role of targeted therapy

The options for DF treatment include watchful waiting, surgery, radiation, and medical therapy. The results of previous studies have shown that targeted therapy is a completely novel option for DF treatment. Few researchers have discussed the role of targeted therapy in DF treatment. The role of targeted therapy in neoadjuvant and adjuvant therapy in combination with surgery must be assessed by further research. The role of targeted therapy in systemic therapy must be evaluated by comparing the therapeutic effects and adverse reactions of targeted therapy and commonly used chemotherapy protocols.

The rate of the spontaneous regression of DF is 20%–30% and can be observed at all sites of body, including extremities, abdominal wall, abdomen, etc. [14,54]. Given the variable and unpredictable clinical course of DF, the consensus on treatment has changed from primary radical surgery to a front-line "watchful waiting" policy [1,2,15–18]. A series of retrospective studies involving asymptomatic patients managed with a "watchful waiting" policy has shown PFS rates of 50% at 5 years [16–18,55]. Therefore, similar to immediate surgery, targeted therapy should not be considered as the initial therapy for asymptomatic patients. Furthermore, the efficacy of targeted therapy should be assessed under the full consideration of the clinical course of DF because tumor shrinkage and disease stability in some cases are the clinical course rather than the effects of therapy.

The rate of local recurrence after operation falls in the range of 25%–60% at 5 years of follow-up [4,16,56–65]. Crago *et al*. [66] reported that extremity location, young age, and large tumor size but not tumor margin are associated with recurrence. Surgery can cause postoperative complications and loss of function. Thus, the observation of Crago *et al*. [66] led to the comprehensive reassessment of DF management and the prioritization of the preservation of function [1]. Neoadjuvant therapy with targeted medicine may facilitate the regression of DF. This finding may be helpful in efforts to preserve function, reduce postoperative complications, and improve clinical outcomes. Multiple studies have shown that recurrent DF after surgery responds to targeted therapy [26,29]. These results provide further support for the use of targeted therapy for recurrent tumors after surgery. Nevertheless, the role of targeted therapy as a supplement to surgery in neoadjuvant and adjuvant therapy requires further study.

Medical therapy strategies for DF includes antihormonal therapy, NSAID therapy, chemotherapy, and targeted therapy. Previous studies on medical therapies for DF are summarized in Table 1, Fig. 1, and Fig. 2. Tamoxifen is the most commonly used antihormonal chemotherapeutic drug and may be used alone or in combination with NSAIDs [67,68]. The response rate of patients to hormone-based therapy varies from 33% to 50% (Table 1 and Fig. 1) [69,70]. The overall response rate of patients who received antihormone and/or NSAIDS therapy was significantly higher than that of patients who received imatinib ($P < 0.001$) (Table 2, Fig. 3). Antiestrogens can increase

Table 2 Comparison of the overall response rates and grade 3–4 side effect rates of antihormone and/or NSAIDS therapy and various targeted therapies

Treatment protocols	Overall response				Grade 3–4 side effects			
	N	Yes	No	*P*	*N*	Yes	No	*P*
Antihormone and/or NSAIDS	330	139 (42%)	191 (58%)		330	0 (0%)	330 (100%)	
Imatinib	151	20 (13%)	131 (87%)	<0.001	132	43 (33%)	89 (67%)	<0.001
Nilotinib	8	–	–	–	8	1 (13%)	7 (87%)	0.024
Pazopanib	10	4 (40%)	6 (60%)	0.893	10	2 (20%)	8 (80%)	0.001
Sorafenib	26	7 (25%)	19 (75%)	0.129	26	4 (15%)	22 (85%)	<0.001
PF-903084014	24	10 (42%)	14 (58%)	0.965	24	11 (46%)	13 (54%)	<0.001

Overall response, cases that showed DF shrinkage. NSAIDS, nonsteroidal anti-inflammatory drugs.

the occurrence of thromboembolic events and can also increase the incidence of endometrial cancer and ovarian cysts [71,72]. The rate of side effects of antiestrogens, however, is considerably lower than that of surgery, chemotherapy, and targeted therapy (Table 2, Fig. 3). Therefore, because of its low cost and limited toxicity, hormone-based therapy is used as the first-line medical treatment for DF.

Chemotherapy for DF treatment includes conventional dose chemotherapy and low-dose chemotherapy. Conventional dose chemotherapy is based on anthracycline-based regimens and is usually administered for 6 to 8 cycles [1]. This regimen can achieve long-term PFS and even complete responses and is often used as second-line therapy after the failure of hormone-based regimens (Table 1) [73,74]. In our study, the overall response rate of anthracycline-based regimens is higher than that of imatinib and sorafenib regimens (Table 3, Fig. 3).

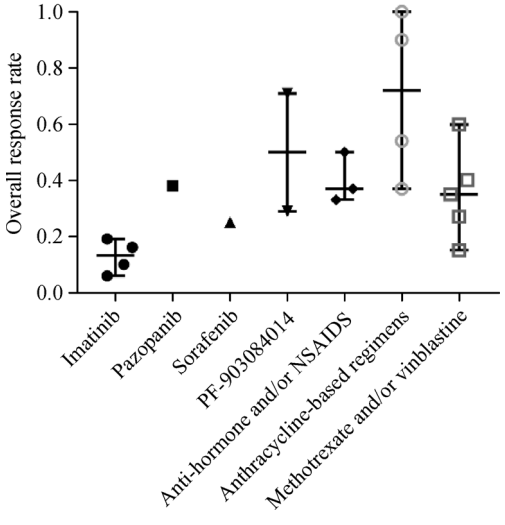

Fig. 1 Overall response rates of systemic therapies for DF (case number > 5). The median overall response rates and ranges are shown in the figure. Overall response rate, the rate of the cases that showed DF shrinkage. NSAIDS, nonsteroidal anti-inflammatory drugs. DF, desmoid-type fibromatosis.

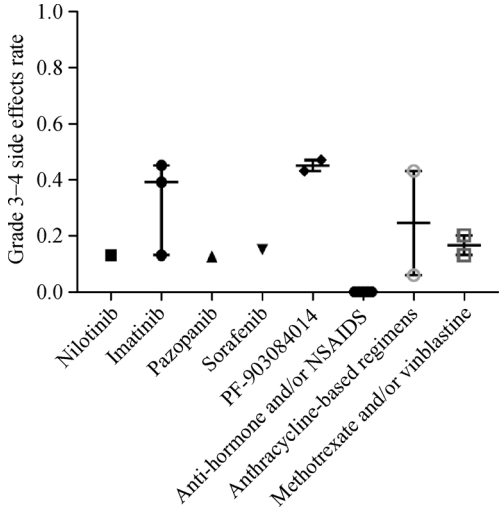

Fig. 2 Rates of grade 3–4 side effects of systemic therapies for DF (case number > 5). The median overall response rates and ranges are shown in the figure. NSAIDS, nonsteroidal anti-inflammatory drugs. DF, desmoid-type fibromatosis.

Conventional dose chemotherapy is associated with high toxicity and can cause cardiac and hematological toxicities. Grade 3–4 toxicities occurred in approximately 31%–43% of patients [73,74]. However, we found that the rates of grade 3–4 side effects of imatinib and PF-903084014 were higher than those of anthracycline-based chemotherapy (Table 3, Fig. 3). Furthermore, pegylated liposomal doxorubicin is a better choice than conventional doxorubicin because of its low cardiac toxicity, which is an important consideration when treating young patients [75]. Therefore, anthracycline-based chemotherapy should be selected before targeted therapy.

Low-dose chemotherapy is typically administered using methotrexate and vinblastine and has response rates of 15% to 60% (Table 1 and Fig. 1) [73,76]. The overall response rates of patients receiving chemotherapy is significantly higher than those of patients receiving imatinib ($P < 0.001$) (Table 4, Fig. 3). Grade 3–4 side

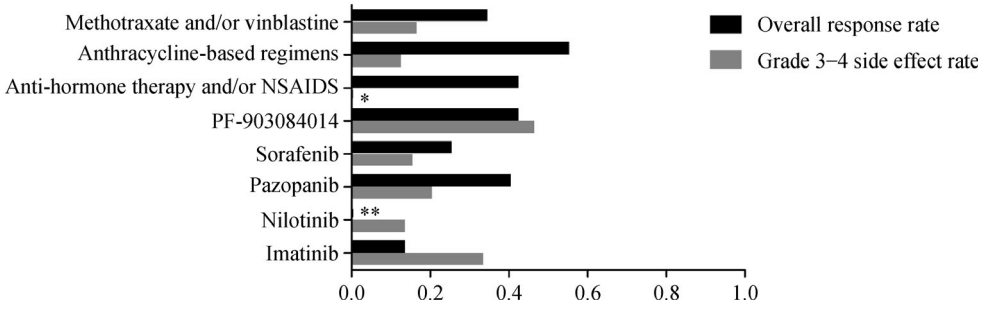

Fig. 3 Overall response and grade 3–4 side effects of various systemic therapies. NSAIDS, nonsteroidal anti-inflammatory drugs. Overall response rate, the rate of the cases that showed DF shrinkage. *Grade 3–4 side effects occurred in none of the patients that underwent antihormone and/or NSAIDS therapy. **The overall response rate of nilotinib is unavailable. NSAIDS, nonsteroidal anti-inflammatory drugs. DF, desmoid-type fibromatosis.

Table 3 Comparison of the overall response rates and grade 3–4 side effect rates of anthracycline-based regimens and various targeted therapies

Treatment protocols	Overall response				Grade 3–4 side effects			
	N	Yes	No	*P*	*N*	Yes	No	*P*
Anthracycline-based regimens	65	36 (55%)	29 (45%)		42	5 (12%)	37 (88%)	
Imatinib	151	20 (13%)	131 (87%)	0.001	132	43 (33%)	89 (67%)	0.009
Nilotinib	8	–	–	–	8	1 (13%)	7 (87%)	0.962
Pazopanib	10	4 (40%)	6 (60%)	0.570	10	2 (20%)	8 (80%)	0.874
Sorafenib	26	7 (25%)	19 (75%)	0.014	26	4 (15%)	22 (85%)	0.965
PF-903084014	24	10 (42%)	14 (58%)	0.250	24	11 (46%)	13 (54%)	0.002

Overall response, cases that showed DF shrinkage.

Table 4 Comparison of the overall response rates and grade 3–4 side effect rates of methotrexate and/or vinblastine regimens and various targeted therapies

Treatment protocols	Overall response				Grade 3–4 side effects			
	N	Yes	No	*P*	*N*	Yes	No	*P*
Methotrexate and/or vinblastine	169	57 (34%)	112 (66%)		45	7 (16%)	38 (84%)	
Imatinib	151	20 (13%)	131 (87%)	<0.001	132	43 (33%)	89 (67%)	0.029
Nilotinib	8	–	–	–	8	1 (13%)	7 (87%)	1.000
Pazopanib	10	4 (40%)	6 (60%)	0.950	10	2 (20%)	8 (80%)	1.000
Sorafenib	26	7 (25%)	19 (75%)	0.492	26	4 (15%)	22 (85%)	1.000
PF-903084014	24	10 (42%)	14 (58%)	0.445	24	11 (46%)	13 (54%)	0.006

Overall response, cases that showed DF shrinkage.

effects occurred in 13% to 20% cases undergoing methotrexate and vinblastine treatment [77,78]. The grade 3–4 side effect rates of methotrexate and vinblastine are significantly lower than those of imatinib and PF-903084014 (Table 4, Fig. 3). The most common side effect of vinblastine is neurotoxicity, which may be reduced by alternating vinblastine with vinorelbine [77,79]. Targeted therapy is mostly given after chemotherapy failure. Targeted therapy combined with chemotherapy has not been studied before, and studies should fully consider drug tolerability by patients.

Conclusions

Previous studies have shown the encouraging safety and

efficacy of targeted therapy for DF. To the best of our knowledge, however, targeted therapy has not shown considerable advantages in efficacy and safety over other medical treatments. Furthermore, the application of targeted therapy, particularly in developing countries, is limited by its high costs. Therefore, targeted therapy is mainly used in cases after the failure of antihormonal therapies, NSAIDs, and chemotherapy. Future research on targeted therapy for DF should focus on the following aspects. First, the mechanisms and targets of targeted therapy should be further clarified through gene detection to help provide individualized treatment to patients. Second, the application of targeted therapy in preoperative neoadjuvant therapy and postoperative adjuvant therapy and in combination with other types of systemic therapies should be explored. Third, the appropriate dosage of various targeted drugs must be identified to improve the patient's tolerance without reducing the therapeutic effect.

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Compliance with ethics guidelines

Zhen Wang, Jianhui Wu, Xiuyun Tian, and Chunyi Hao declare no competing financial interests. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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