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Real-word experience of pazopanib and sorafenib in patients with desmoid tumors: A CanSaRCC multi-center study

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ABSTRACT

Background: Sorafenib and pazopanib, two tyrosine kinase inhibitors (TKI), are widely used in patients with progressive symptomatic desmoid tumors (DT). Limited real-word data is available on long-term outcomes of patients who progressed on, stopped, or continued TKIs.

Methods: Patients diagnosed with DTs and treated with sorafenib or pazopanib between 2011 and 2022 at 11 institutions were reviewed. Patient history, response to therapy and toxicity were recorded. Statistical analyses utilized Kaplan-Meier and log-rank tests.

Results: 142 patients with DT treated with sorafenib (n = 126, 88.7 %) or pazopanib (n = 16, 11.3 %) were analyzed. The median treatment duration was 10.8 months (range: 0.07- 73.9). The overall response rate and the disease control rate were 26.0 % and 95.1 %, respectively. The median tumor shrinkage was − 8.5 % (range −100.0 %- +72.5 %). Among responders, the median time to an objective response was 15.2 months (range: 1.1 to 33.1). The 1-year and 2-year progression-free survival rates were 82 % and 80 %. Dose reductions were necessary in 34 (23.9 %) patients. Grade 3 or higher adverse events were reported in 36 (25.4 %) patients. On the last follow-up, 55 (38.7 %) patients continued treatment. Treatment discontinuation (n = 85, 59.9 %) was mainly for toxicity (n = 35, 45.9 %) or radiological or clinical progression (n = 30, 35.3 %). For the entire cohort, 36 (25.4 %) patients required subsequent treatment. In the 32 responders, only 1 (3.1 %) patient required a subsequent treatment. In patients who discontinued TKI, 25 (44.6 %) with stable disease received subsequent treatment compared to 0 (0.0 %) of responders.

Conclusion: This retrospective study represents the largest cohort of DT patients treated with sorafenib or pazopanib to date. Discontinuation of treatment in responders is safe. The optimal treatment duration in patients with stable disease remains to be defined.

1. Background

Desmoid tumors (DT) are rare soft-tissue tumors characterized by monoclonal fibroblastic proliferation, accounting for less than 3 % of all soft-tissue tumors [1]. They are also called aggressive or deep fibromatosis because of their characteristic infiltrative growth and tendency to recur locally despite the absence of any metastatic potential. These tumors are usually diagnosed between 15 and 60 years, with a peak

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around 30 years of age, without a gender predilection [2]. They can arise anywhere in the body, with most cases found in the abdominal wall, the neurovascular bundle of the limb and shoulder, the root of the mesentery, and the head and neck. The exact etiology is unknown; some physical factors (surgical or accidental trauma), hormonal factors (pregnancy), and genetic factors (Gardner's syndrome) have been associated with the development of DTs [3,4]. Symptomatology varies depending on tumor location and biology. It ranges from a slow-growing asymptomatic mass to a fast-growing infiltrative mass, leading to severe pain and functional impairment. Occasionally, it can even be life-threatening due to bowel obstruction or invasion of vital organs.

The natural evolution of DTs is unpredictable. Close to two-thirds of tumors may be associated with an indolent behavior and periods of prolonged growth arrest or spontaneous regression over time [5]. Presently, there is little insight into clinical and molecular determinants that govern the clinical course of disease. Owing to its high local recurrence rates and unpredictable clinical behavior, the management of DTs has distanced itself from initial wide resection [6]. Because a significant proportion of cases may stabilize or spontaneously regress during a period of observation, the current consensus is to adopt a wait-and-see approach and intervene only in patients with truly progressive or symptomatic disease [7]. Current management options range from surgery in select cases to systemic therapy. In routine practice, standard options to treat DTs are chemotherapy like weekly methotrexate-vinblastine, liposomal doxorubicin or doxorubicin, and targeted agents like imatinib [8–11]. However, no convincing high-level data was ever produced with these agents through randomized clinical trials.

Sorafenib, a tyrosine kinase inhibitor with activity against many protein kinases, including VEGFR, PDGFR and RAF kinases is the first drug to have shown activity in a phase III trial in DTs [12]. At a starting dose of 400 mg once a day, the reported objective response rate (ORR) was 33 % (95 % 95 % confidence interval [CI], 20 to 48) and the 2-year progression-free survival (PFS) rate was 81 % (95 % CI, 69 to 96). Sorafenib was well tolerated, with most reported adverse effects being rash (73 %), fatigue (67 %), hypertension (55 %), and diarrhea (51 %). Treatment was only discontinued upon disease progression or unacceptable toxicity. Patients responding to treatment with acceptable tolerance were to continue treatment indefinitely until study withdrawal. Pazopanib, another tyrosine kinase inhibitor targeting VEGF receptors 1, 2, and 3, platelet-derived growth factor receptor-like protein (PDGFR) α and β, and c-KIT tyrosine was also shown to be active in DTs [9]. In a randomized phase II trial, patients were treated with a starting dose of pazopanib at 800 mg once a day for a year compared to weekly methotrexate-vinblastine. The 6-month PFS rate was 83.7 0 % (95 % CI 23.1–68.5) and the objective response was 37 %. The most common adverse effects were hypertension (21 %) and diarrhea (15 %).

Although these agents now represent new standards of care for DTs, there remains many unknowns. The activity and tolerance of sorafenib and pazopanib outside a clinical trial in a general population with DTs is unknown. Duration of treatment is still ill defined. Outcomes of patients who failed, stopped or progressed on TKIs are not well documented. For patients responding to treatment, the timing and safety of treatment discontinuation is currently unknown. Predicting which patients may respond to therapy is still a challenge. Therefore, the main purpose of this multicenter retrospective study is to collect real-world data to better guide physicians in managing these rare tumors.

2. Methods

The prospectively maintained databases of Canadian Sarcoma Centers participating in the Canadian Sarcoma Clinical and Research Collaboration (CanSaRCC) registry and two American sarcoma centers were searched to identify patients diagnosed with a desmoid tumor who were treated with either sorafenib or pazopanib between 2011 and 2022. All diagnoses of desmoid tumor were confirmed by soft-tissue pathologists. Prior to data collection, approval from the Ethics Committee of each hospital was obtained under the CanSaRCC Consortium agreement.

Baseline characteristics included age, sex, tumor location, underlying genetic predisposition, previous surgery, radiation therapy and lines of systemic therapy in addition to the reason for treatment initiation were collected. Treatment characteristics regarding choice of TKI, starting dose, dose reductions, dose interruptions and total treatment duration were analyzed. Adverse events according to CTCAE 5.0 criteria were extracted from medical charts. Patients were imaged using computed tomography or magnetic resonance after three or four months according to local hospital guidelines. Response to TKI treatment was assessed via retrospective viewing of radiology reports using Response Evaluation Criteria In Solid Tumours (RECIST) criteria 1.1 by local investigators. Outcomes of patients discontinuing TKI therapy were also recorded in addition to response to subsequent therapies. Final outcomes were recorded as of July 2023.

2.1. Statistical analysis

Kaplan-Meier and log-rank tests were used to estimate progression-free survival (PFS), defined as the time from start of TKI to progressive disease per radiological or clinical assessment in addition to the time to next treatment defined as the time from the end of TKI to the start of a new treatment. Data on objective response rates (ORR), defined as partial or complete response as well as disease control rate (DCR), defined as ORR + stable disease were also collected. Exploratory analyses using univariate and multivariate linear and logistic regression were respectively performed on the degree of tumor shrinkage on TKI therapy in addition to tumor response according to RECIST 1.1 criteria.

3. Results

3.1. Baseline characteristics

142 DT patients initially treated with sorafenib (n = 126, 88.7 %) or pazopanib (n = 16, 11.3 %) were included in the study. Baseline patient characteristics are summarized in Table 1. The median age at diagnosis was 36 years (range 5–86). Patients were predominantly female (n = 88, 62.0 %) with lower extremity DTs (n = 32, 22.5 %). A history of familial polyposis was documented in 8.5 % of patients. Negative immunohistochemical expression of beta-catenin was observed in 17 (12,1 %) patients. Prior to TKI therapy, 62 (43.7 %) received systemic therapy (median 1, range 1–5 lines) and 122 (85.9 %) were symptomatic. The median largest tumor size diameter at TKI initiation was 8.8 cm (range 0.7–30.0). Radiological progression in the previous 6 months before TKI initiation was objectified in 97 (68.3 %) patients (data not available in

Table 1
Demographic and clinical characteristics.

Median age (range)–yr	36 (5–86)
Sex– no.(%)	
Male	54 (38.0)
Female	88 (62.0)
Primary Tumor site– no.(%)	
Intraabdominal	22 (15.5)
Extraabdominal	120 (84.5)
Largest tumor size—cm	8.8 (0.7-30.0)
Symptomatic disease– no.(%)	122 (85.9 %)
Familial Polyposis– no.(%)	12 (8.5)
Previous surgical resection– no.(%)	33 (23.2)
Previous cryoablation—no.(%)	3 (2.6)
Previous radiation therapy– no.(%)	9 (6.3)
Previous systemic therapy– no.(%)	62 (43.7)
Number of lines of therapy—Median(range)	1(1–5)
Choice of TKI	
Sorafenib–no.(%)	126 (88.7)
Pazopanib–no.(%)	16(11.3)

30 (21.1 %) patients). Overall, the most commonly reported baseline symptoms were chronic pain in 110 (77.4 %) and functional impairment in 12 (8.5 %) patients. The most frequent reasons for TKI treatment initiation were combined symptomatology and radiological progression (59, 41.5 %), radiological progression only (35, 24.6 %) or symptomology progression only (45, 31.7 %).

3.2. Treatment characteristics

The median treatment duration was 10.8 months (range 0.07- 73.9). The median starting dose for sorafenib and pazopanib were respectively 400 mg once daily and 800 mg once daily. Dose reductions were necessary in 34 (23.9 %) patients (19.0 % of patients on sorafenib and 62.5 %, on pazopanib), and dose interruptions were observed in 42 (29.8 %) patients (27.0 % of patients on sorafenib and 50.0 %, on pazopanib). Treatment interruptions lasting more than a month were documented in 10.6 % of patients. The median well-tolerated dose was 400 mg once a day for sorafenib and 400 mg once a day for pazopanib.

3.3. Treatment efficacy

The best overall response as per RECIST 1.1 criteria is summarized in Table 2. The overall response rate for the entire cohort was 23.2 %. Response could not be assessed in 18 (12.7 %) patients because the initial TKI was modified for a subsequent treatment prior to the first imaging assessment. Patients who were previously exposed to prior systemic therapy were less likely to experience an overall response compared to patients who were never exposed to systemic therapy (16.1 % vs 26.3 %).

Figure 1 illustrates a waterfall plot of the percentage of change in tumor size from baseline according to RECIST, version 1.1. Overall, 87 (61.3 %) of patients experienced some degree of tumor shrinkage on TKI therapy. The mean best percentage in tumor size change was − 14.1 % (range −100 to 72.5). In patients who reached a RECIST defined response, the median time to an objectified response was 15.2 months (range 1.1–33.1) (Fig. 2). Desmoid-related symptom improvement was reported in 74 (52.1 %) patients (Data not available in 31 (21.8 %) patients). Throughout the entire duration of follow-up, the median progression-free survival was not reached. (Fig. 3) The estimated 1-year and 2-year PFS rates were 82 % and 80 %, respectively.

Univariate and multivariate linear regression on the degree of tumor shrinkage were done as exploratory analyses to determine predictive factors of TKI response. Previous radiation and previous systemic treatment were associated with less tumor shrinkage in univariate analysis, and previous radiation remained significantly associated with less tumor shrinkage in multivariate analysis (adjusted beta: 36 [6.8–65.4] $p = 0.01$) (Appendix Table A1 and A2). Univariate and multivariate logistic regression according to RECIST response were also performed. Patients with a history of previous surgery or Beta-catenin negative expression were almost 5 times and 8 times more likely to achieve a RECIST response on multivariate analysis. (OR = 4.8, 95 % CI: 1.4 to 17.1) and (OR = 7.8, 95 % CI: 1.4 to 41.1). However, patients undergoing previous systemic treatment were 69 % less likely to achieve a complete or partial remission (OR = 0.31, 95 % CI:0.11 to 0.88). (Appendix Table B1 and B2).

Table 2
Overall response rates per RECIST 1.1.

Response	No previous systemic treatment n (%)	Previous systemic treatment n (%)	Overall n (%)
Complete response	2 (1.6)	0 (0.0)	2 (1.6)
Partial response	21 (26.3)	10 (16.1)	31 (21.8)
Stable disease	42 (52.5)	43 (69.4)	85 (59.9)
Progressive disease	3 (3.8)	3 (4.8)	6 (4.2)
Not available	12 (15)	6 (9.7)	18 (12.7)

Table 3
Toxicity grade according to CTCAE.

	Grade 1-2 (%)	Grade 3-4 (%)
Bleeding	1 (0.7 %)	2 (1.4 %)
Diarrhea	30 (21.1 %)	6 (4.2 %)
Elevated Bilirubin	0 (0.0 %)	1 (0.7 %)
Elevated Liver Enzymes	0 (0.0 %)	2 (1.4 %)
Hand-Foot Syndrome	32 (22.5 %)	5 (3.5 %)
Hypertension	8 (5.6 %)	7 (4.9 %)
Fatigue	18 (12.7 %)	2 (1.4 %)
Oral Mucositis	5 (3.5 %)	1 (0.7 %)
Skin Rash	22 (15.5 %)	8 (5.6 %)
Other	29 (20.4 %)	11 (7.7 %)
Any adverse event	101 (71.1 %)	38 (26.8 %)

3.4. Toxicity

Toxicity graded according to CTCAE is summarized in Table 2. Overall, 101 (71.1 %) patients experienced low grade (g1–2) toxicity and 38 (26.8 %) patients, high grade (g3–4) toxicity. For low grade toxicity, hand-foot syndrome (32, 22.5 %), diarrhea (30, 21.1 %) and skin rash (22, 15.5 %) were the most common reported side effects. For high grade toxicity, skin rash (8, 5.6 %), hypertension (7, 4.9 %) and diarrhea (6, 4.2 %) were the most prevalent. Treatment discontinuation because of toxicity was reported in 39 (27.4 %) patients.

3.5. Treatment discontinuation

On the last follow-up, 55 (38.7 %) patients were still on TKI treatment. The median duration of follow-up was 23.0 months (range 0.5–111.7). Among patients who discontinued treatment (85, 59.9 %), the main reasons for treatment discontinuation were toxicity (39, 45.9 %) or radiological or clinical progression (30, 35.3 %). In 12 (14.1 %) patients, there was a shared patient-physician decision to discontinue treatment following a good response. Among patients who achieved an overall response per RECIST, only 1 out of 33 (3.0 %) patients required a subsequent treatment. Furthermore, none of the 16 responding patients who discontinued treatment required subsequent therapy. In addition, despite TKI discontinuation, 9 patients experienced further tumor regression to the point of reaching a RECIST response on follow-up. In the subgroup of patients who achieved stable disease as their best RECIST response, 56 (65.0 %) patients discontinued treatment. Among them, 25 (44.6 %) required a subsequent treatment.

3.6. Subsequent therapy

Overall, 36 (25.4 %) patients required a subsequent treatment for their DT. The median time to next treatment was 1.5 months (range 0.2–57.7). Subsequent treatments varied and included surgery (3, 8.3 %), radiation therapy (4, 11.1 %), local cryo-ablation (6, 16.7 %) or further systemic therapy (23, 63.9 %). Systemic therapies included methotrexate-based regimens (7, 30.4 %), anthracycline-based therapies (9, 39.1 %), another TKI (4, 17.4 %) or other therapies (3, 13.0 %). The combined ORR of any subsequent therapy was 26.1 %. Of note, there were no observed responses in the 4 patients receiving a subsequent TKI.

4. Discussion

This multi-center retrospective study is the largest reported international cohort of DT patients treated with either sorafenib or pazopanib to our knowledge. The characteristics of our cohort are comparable to those reported in the current literature being predominantly young

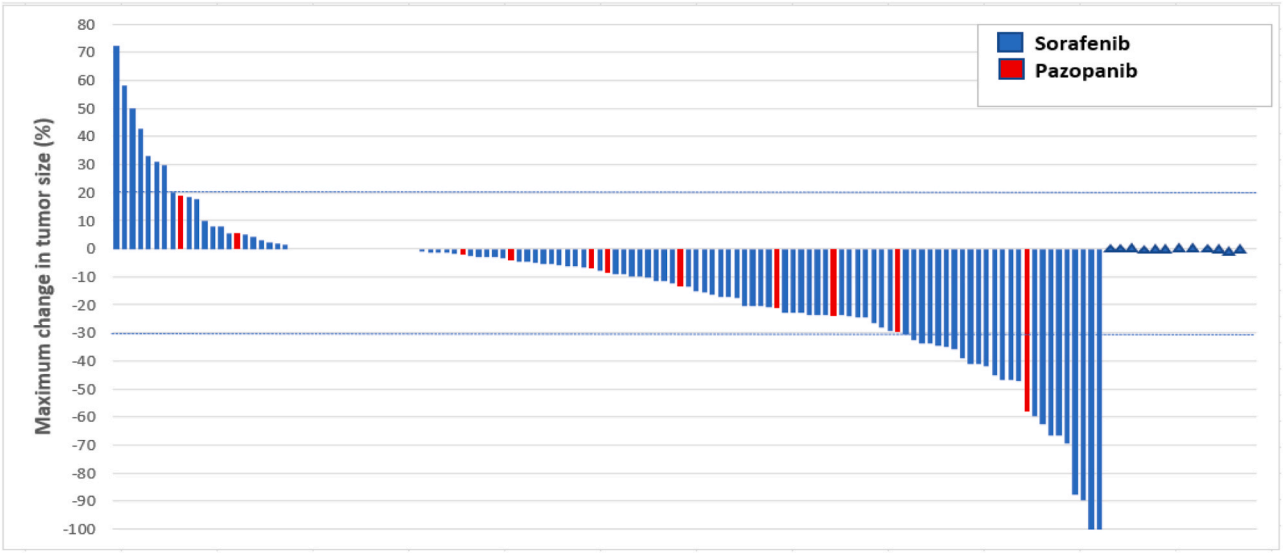

Fig. 1. Percentage change in tumor size from baseline. Fig. 1 shows waterfall plots of percentage changes from baseline in tumor size as according to RECIST, version 1.1.

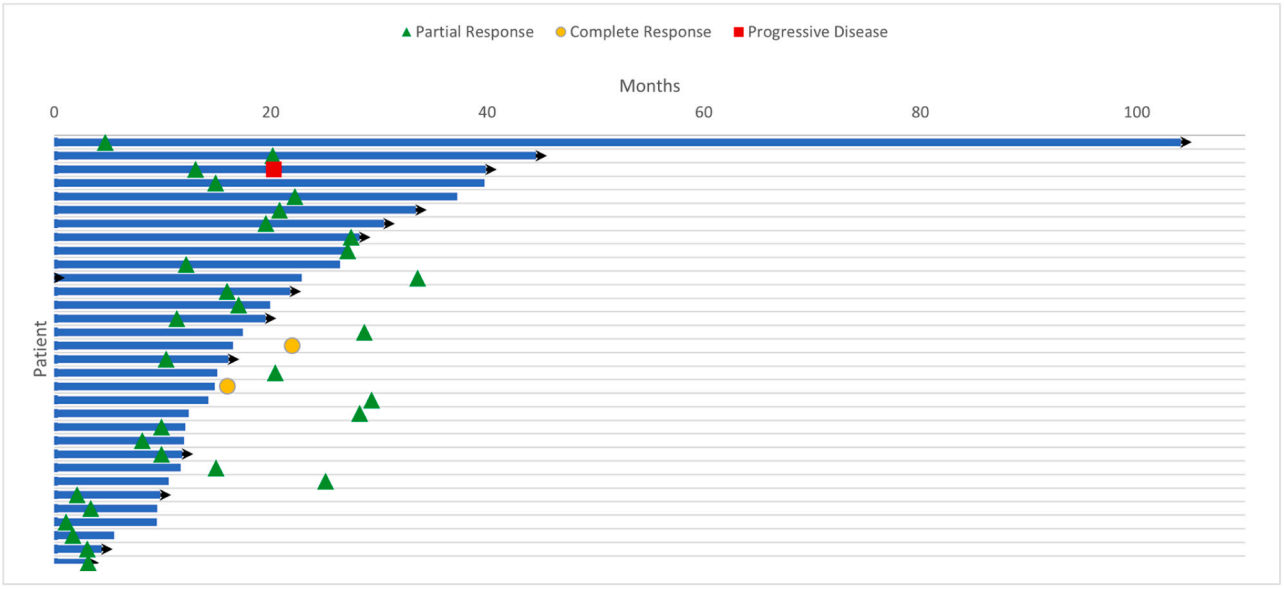

Fig. 2. Duration of response. A swimmer plots of the duration of response and clinical outcomes among patients having a response to sorafenib or pazopanib. * Patient 19 was on pazopanib.

females with extremity DTs [13]. In contrast to the published phase III trial comparing sorafenib to placebo, our cohort was less likely to undergo previous surgery in keeping with the current Desmoid Tumor Working Group (DTWG) guidelines favoring active surveillance as an initial approach for newly diagnosed DTs and systemic therapy compared to surgery for patients experiencing disease progression [14].

In a real-world setting, the effectiveness of sorafenib and pazopanib are comparable to the activity reported in the published randomized phase II and phase III trials [9,11]. Our study may suggest that patients derive more clinical benefit in being exposed to TKI therapy earlier than later in their disease management, as reflected by the higher response rate observed in patients who were not previously exposed to systemic therapy (26,3 % vs 16.1 %). However, it is also possible that another explanation for the lower level of TKI activity in previously more heavily treated patients may be that this subgroup represents a more biologically aggressive selected form of DT. Current guidelines from the DTWG do not propose a definitive sequence of existing systemic treatment options [14]. It is suggested to employ a less toxic therapy initially followed by more toxic treatments in a stepwise fashion. Since the publication of the DTWG guidelines, a novel class of drug, the gamma-secretase inhibitor nirogacestat had demonstrable activity in DTs with a reported ORR of 41 % and a 2-yr PFS of 76 % [15]. The lack of comparative studies makes it impossible to assess whether one drug class is superior to another. However, key differences in tolerance between TKIs and gamme-secretase inhibitors can be highlighted. In the nirogacestat study, 75 % of female patients experienced some form of ovarian dysfunction which may be concerning for a predominantly young female patient cohort similar to our study. Therefore, a careful balance between toxicity and effectiveness must be considered in treatment selection. In subsequent updates, careful attention should focus on the ideal sequencing of systemic treatments including the novel class of gamma-secretase inhibitors.

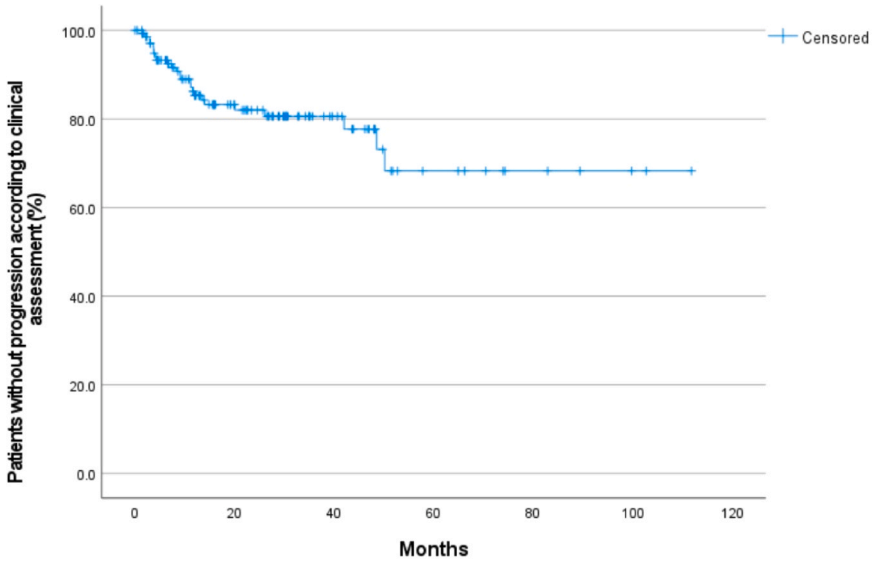

Fig. 3. A Kaplan–Meier estimates of the duration of progression-free survival at the time of the last assessment.

In our cohort, the starting dose of 400 mg OD for sorafenib was better tolerated compared to the 800 mg OD starting dose of pazopanib. This is comparable to the findings of the randomized studies that documented 31 % dose reduction for sorafenib and 73 % for pazopanib, but in contrast to a real-world retrospective Indian study that documented a challenge to maintain 400 mg of sorafenib for Indian patients [16]. Reported toxicity in our study was comparable to the published literature. The rate of treatment discontinuation due to toxicity was high (45.9 %). This observation can be partly explained by the protracted course of treatment (median 10.8 months) thereby emphasizing the need to consider treatment discontinuation as early as possible in this patient population. Owing to the retrospective nature of this study, patient related quality of life outcomes could not be assessed.

Our study offers some valuable clinical insight on treatment duration and outcomes following treatment discontinuation. The randomized sorafenib study was designed with the intent to carry on sorafenib until disease progression or unacceptable toxicity. It was therefore unknown whether sorafenib discontinuation may be safe and associated with long term favorable outcomes. Our study suggests that patients experiencing a documented radiological RECIST response may discontinue safely their treatment with the vast majority not requiring any subsequent treatment on long term follow-up. The same however cannot be applied for patients achieving only RECIST defined stable disease. In the latter subset of patients, nearly half required a subsequent treatment following TKI discontinuation. How to select which patients with SD may safely discontinue treatment remains an unanswered question. A phase II prospective Indian evaluation sorafenib discontinuation after 1 year of therapy that is ongoing may provide some answers [17].

Furthermore, we also observe that a subset of patients continues to have objective tumor regression beyond the time of TKI discontinuation. However, whether or not TKIs may be discontinued earlier then the timepoint of a documented RECIST defined response remains unknown. This study illustrates once more that RECIST may not be the most suitable radiological criteria to assess response and treatment effectiveness in DTs [18]. Current research focused on T2-weighted signal intensity assessment or radiomics correlates may help identify earlier true responders to TKI therapy [19].

As the number of effective systemic treatments increase, further research should focus on predictive biomarkers to better select patients that are more likely to respond to systemic treatment, including TKIs. Exploratory analyses done in our study may suggest that Beta-Catenin IHC negative DTs have a higher likelihood of responding to TKI therapy. As the number Beta-Catenin IHC negative DTs is relatively small, these findings will need to be reproduced in other studies before any conclusions can be drawn. It has been recently suggested that there may be other signaling pathways involved in DT progression beyond Beta-Catenin signalling activation [20]. Therefore, there is a possibility that the mechanism action of sorafenib in DT is beyond inhibition of PDGFR signaling, which needs to be further explored in translational studies.

Another interesting observation from our study is that patients who had surgical resection prior to TKI therapy seem to have a higher likelihood of response in our cohort. Again, these findings will require further studies to validate. It is possible that patients who had prior surgery were actively progressing and had less fibrotic tumors compared to patients who were not previously operated who were less likely to respond because of more predominant fibrotic tissue in the tumor bed. MRI T2 evaluations could help in assessing these possible differences. Indeed, differences between responders and non responders from TKI may be better appreciated on the textural differences of DT and their state of "activation/inflammation " rather than volumetric changes that are probably a poorer surrogate of this biological state. At the time being, one can only hypothesize that surgery may potentially modify the desmoid micro-environment, leading to potential activation of inflammation pathways within the desmoid tumor that makes them more likely to respond to TKI therapy. It would have been of interest to study whether the delay between surgery and TKI initiation may impact response to treatment, however, available data in this study was insufficient.

Finally, this study highlights the importance of national and international collaboration to gain meaningful clinical insight in rare tumors like DTs. Although this study presents some limitations owing to its retrospective design, it provides valuable information that can help physicians managing DTs on TKI therapy.

5. Conclusion

This retrospective study represents the largest cohort of DT patients treated with sorafenib or pazopanib to date. Sorafenib and pazopanib are both effective therapies in treating patients with progressive or symptomatic DTs. The real-world activity and tolerance of both agents are comparable to the published randomized trials. Discontinuation of treatment in responders is safe and associated with favorable long-term outcomes. The optimal treatment duration in patients with stable disease remains to be defined.

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CRediT authorship contribution statement

Jonathan Noujaim: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Abha Gupta:** Writing – review & editing, Data curation, Conceptualization. **Caroline Holloway:** Writing – review & editing, Data curation. **Ramy Saleh:** Writing – review & editing, Investigation, Data curation. **Amirrtha Srikanthan:** Investigation, Data curation. **Christopher Lemieux:** Investigation, Data curation. **Hagit Peretz Soroka:** Writing – review & editing, Project administration, Data curation. **Pauline Tibout:** Data curation. **Robert Turcotte:** Data curation. **Xiaolan Feng:** Writing – review & editing, Investigation, Data curation. **Albiruni R Abdul Razak:** Writing – review & editing, Investigation, Data curation. **Philippos Costa:** Writing – review & editing, Investigation, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114119.

References

[1] Kasper B, Strabel P, Hohenberger P. Desmoid tumors: clinical features and treatment options for advanced disease. oncologist 2011;16(5):682–93.
[2] Anneberg M, Svane HML, Fryzek J, Nicholson G, White JB, Edris B, et al. The epidemiology of desmoid tumors in Denmark. Cancer Epidemiol 2022;77:102114.
[3] Lazar AJF, Hajibashi S, Lev D. Desmoid tumor: from surgical extirpation to molecular dissection. Curr Opin Oncol 2009;21(4):352–9.
[4] Debaudringhien M, Blay JY, Bimbai AM, Bonvalot S, Italiano A, Rousset-Jablonski C, et al. Association between recent pregnancy or hormonal contraceptive exposure and outcome of desmoid-type fibromatosis. ESMO Open 2022;7(5):100578.
[5] Colombo C., Fiore M., Grignani G., Tolomeo F., Merlini A., Palassini E., et al. A prospective observational study of Active surveillance in primary desmoid fibromatosis. Clin Cancer Res, 2022.
[6] Gronchi A, Casali PG, Mariani L, Lo Vullo S, Colecchia M, Lozza L, et al. Quality of surgery and outcome in extra-abdominal aggressive fibromatosis: a series of patients surgically treated at a single institution. J Clin Oncol 2003;21(7):1390–7.
[7] Briand S, Barbier O, Biau D, Bertrand Vasseur A. Larousserie Fdr, Anract P, et al. Wait-and-see policy as a first-line management for extra-abdominal desmoid tumors. JBJS J Bone Jt Surg 2014;96(8):631–8.
[8] Azzarelli A, Gronchi A, Bertulli R, Tesoro JD, Baratti D, Pennacchioli E, et al. Low-dose chemotherapy with methotrexate and vinblastine for patients with advanced aggressive fibromatosis. Cancer 2001;92(5):1259–64.
[9] Toulmonde Maud M. Pazopanib or methotrexate-vinblastine combination chemotherapy in adult patients with progressive desmoid tumours (DESMOPAZ): a non-comparative, randomised, open-label, multicentre, phase 2 study. Lancet Oncol 2019;20(9):1263–72.
[10] Constantinidou A, Jones R, Scurr M, Al Muderis O, Judson I. Pegylated liposomal doxorubicin, an effective, well-tolerated treatment for refractory aggressive fibromatosis. Eur J Cancer 2009;45(17):2930–4.
[11] Gounder MM, Mahoney MR, Van Tine BA, Ravi V, Attia S, Deshpande HA, et al. Sorafenib for advanced and refractory desmoid tumors. N Engl J Med 2018;379 (25):2417–28.
[12] Gounder Mrinal M.M. Sorafenib for Advanced and Refractory Desmoid Tumors. New England Journal of Medicine.379(25):2417–2428.
[13] Bonvalot S, Cozic N, Le Cesne A, Blay JY, Penel N, Fau M, et al. Initial active surveillance strategy for patients with peripheral sporadic primary desmoid-type fibromatosis: a multicentric phase II observational trial. Ann Surg Oncol 2023;30 (13):8653–9.
[14] ANON. The management of desmoid tumours: a joint global consensus-based guideline approach for adult and paediatric patients. Eur J Cancer 2020;127: 96–107.
[15] Gounder M, Ratan R, Alcindor T, Schöffski P, van der Graaf WT, Wilky BA, et al. Nirogacestat, a γ-secretase inhibitor for desmoid tumors. N Engl J Med 2023;388 (10):898–912.
[16] Garg V, Gangadharaiah BB, Rastogi S, Upadhyay A, Barwad A, Dhamija E, et al. Efficacy and tolerability of sorafenib in desmoid-type fibromatosis: a need to review dose. Eur J Cancer 2023;186:142–50.
[17] Bharath SR B, Garg V, Tansir G, Dhamija E, Barwad A, Kaur S, Gamanagatti S, Bhoriwal S, Khan M. The clinico-radiological outcome of desmoid type-fibromatosis after discontinuing the sorafenib treatment in responders: Single-arm phase II clinical trial. Ann Oncol 2023;34(suppl_2)). S1032-S1061 101016/annonc/annonc1313.
[18] Subhawong TK, Feister K, Sweet K, Alperin N, Kwon D, Rosenberg A, et al. MRI volumetrics and image texture analysis in assessing systemic treatment response in extra-abdominal desmoid fibromatosis. Radio Imaging Cancer 2021;3(4):e210016.
[19] Souza FF, D'Amato G, Jonczak EE, Costa P, Trent JC, Rosenberg AE, et al. MRI T2 mapping assessment of T2 relaxation time in desmoid tumors as a quantitative imaging biomarker of tumor response: preliminary results. Front Oncol 2023;13: 1286807.
[20] Hu J, Hameed MR, Agaram NP, Whiting KA, Qin LX, Villano AM, et al. PDGFRβ signaling cooperates with β-catenin to modulate c-Abl and biologic behavior of desmoid-type fibromatosis. Clin Cancer Res 2024;30(2):450–61.