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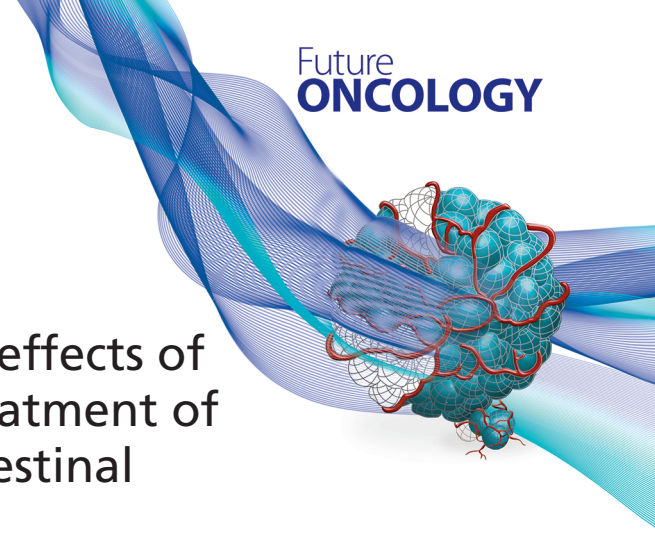

A patient's perspective on the side effects of tyrosine kinase inhibitors in the treatment of advanced and metastatic gastrointestinal stromal tumors

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Aim: To provide the gastrointestinal stromal tumor patient's perspective on side effects of tyrosine kinase inhibitors and compare this with that of healthcare professionals. **Materials & methods:** Semi-structured interviews were conducted with 19 patients with an advanced or metastatic gastrointestinal stromal tumor, as well as six healthcare professionals, and five patients participated in a focus group. Thematic analysis was used to interpret the data. **Results**: Most participants (n = 29) reported gastrointestinal symptoms followed by tiredness (n = 25), edema (n = 22), muscle cramps (n = 21), skin problems (n = 21), eye problems (n = 11) and trouble sleeping (n = 10). Patients, but not healthcare professionals, reported cognitive problems or symptoms of depression. **Conclusion:** These results underline the importance of including the patient's perspective, as there is a gap in symptom reporting between patients and healthcare professionals.

Plain language summary: In this study, the authors report on the side effects of targeted therapies used in the treatment of gastrointestinal stromal tumors from the patient's perspective and draw comparisons with reports from healthcare professionals. The authors conducted interviews with both patients and healthcare professionals. Most participants reported gastrointestinal symptoms followed by tiredness, fluid retention, muscle cramps, skin problems, eye problems and trouble sleeping. Gastrointestinal stromal tumor patients reported cognitive problems and symptoms of depression, which were not reported by healthcare professionals. In conclusion, the authors' results highlight the importance of including the patient's perspective, as there is a gap in symptom reporting between patients and healthcare professionals.

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Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract. GIST is a rare cancer, with an incidence of 5–20 people per million per year, and because of its diverse presentation, it is not uncommon for patients to receive a late or incorrect diagnosis [1,2]. Historically, treatment for advanced and metastatic GISTs has been limited because of resistance to conventional chemotherapy [3]. Over the

last few decades, there have been dramatic improvements in the treatment of GISTs as a result of the development of targeted therapies. The introduction of tyrosine kinase inhibitors (TKIs), specifically imatinib, has resulted in a substantial gain in median overall survival from 14–18 months up to 57 months [4]. In the event of nonresponse or resistance to imatinib, sunitinib, regorafenib and ripretinib are registered as second-, third- and fourth-line therapies, respectively, and avapritinib is registered specifically for GISTs harboring a *PDGFRα* exon 18/D842V mutation [5].

TKIs are described as tolerable drugs. Compared with conventional chemotherapy, TKIs are more selective in their mechanism of action. However, they are not without side effects. In a systematic review, the authors identified a total of 64 symptoms related to TKI treatment in GIST patients. Symptoms covered both physical side effects such as fatigue, nausea and edema, as well as psychological symptoms of depression, confusion and concentration problems [6]. The gold standard for reporting toxicities in clinical trials of cancer treatment is for clinicians to apply the Common Terminology Criteria for Adverse Events (CTCAE) [7]. In contrast to the acute and severe side effects of conventional chemotherapy, side effects of TKIs are often subacute, daily and long-lasting, which makes the CTCAE less suitable as a measure for reporting TKI-related side effects [8]. Limitations of the CTCAE are underlined by the fact that treatment adjustments are regularly needed in clinical practice to continue TKI treatment.

Furthermore, previous research suggests a lack of concordance between healthcare professionals (HCPs) and patients in symptom reporting, especially for symptoms that are more subjective in interpretation, such as fatigue, nausea and pain [9,10]. Patients tend to report symptoms earlier and more frequently with worse symptom severity than HCPs [11,12]. This suggests that HCPs may underreport symptoms. In addition, in imatinib-treated patients with chronic myeloid leukemia, HCPs have been found to underestimate the severity of long-term side effects, in particular for muscle cramps and musculoskeletal pain [13]. This underscores the need to evaluate the impact of treatment from the patient's perspective.

The widespread impact of receiving a GIST diagnosis as well as treatment on health-related quality of life (HRQoL), as reported by the patient, has been largely overlooked. Studies that include patient-reported outcomes are scare. A recent review of HRQoL and side effects in GIST patients treated with TKIs reported that of the 104 studies reviewed, only 13 used patient-reported outcomes [14]. This is a concern, given that tools are available to collect patient-reported side effects (e.g., patient-reported outcomes version of the CTCAE [15] and MD Anderson Symptom Inventory for GISTs [16]), yet it is argued that including the patient's perspective should be a primary concern of HCPs and researchers considering that GIST patients with advanced or metastatic disease are experiencing prolonged survival but often at the expense of their HRQoL [17].

The current study forms part of a larger program of work carried out on behalf of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group to develop symptom lists for patients receiving targeted therapies [18]. Here, the authors report the qualitative findings of the interviews and focus group conducted as part of the first phase of this work. The authors' work builds on that of Fauske *et al.*, who presented the patient's perspective on GIST treatment [19], but the present study also includes the perspective of HCPs. The aim of the current study is to provide the GIST patient's perspective on side effects of TKIs and compare this perspective with that of HCPs.

Materials & methods

Participants

Patients with unresectable, advanced or metastatic GIST treated with a TKI were recruited from the Royal Marsden Hospital, University Hospital Southampton (UHS) and GIST Cancer UK. HCPs from different hospitals across the UK with experience delivering care to patients with GIST were also invited for an interview.

Procedure

UK ethics and research governance approvals were obtained (National Research Ethics Service Committee South Central Southampton B 11/SC/0412). All participants were given verbal and written information about the study and gave written informed consent prior to the interview. Case report forms, including details related to educational attainment, employment status and domestic situation, were completed together with participants. Participants were asked to self-report comorbidities and to complete a measure of performance status. Clinical data were collected from medical files. For HCPs, collected information included sex, specialist discipline and number of years working with GIST patients. An overview of the details recorded is provided in Table 1.

Table 1. Participant characteristics.

Patient characteristics	Interviewed (n = 19), n (%)	Focus group (n = 5), n (%)	Total (n = 24), n (%)
Sex			
Female	8 (42.1)	2 (40.0)	10 (41.7)
Male	11 (57.9)	3 (60.0)	14 (58.3)
Age (years)			
Mean (SD)	60.8 (12.6)	52.5 (6.4)	59.1 (11.9)
Range	38–82	44–62	38–82
Education level			
Compulsory school education	7 (36.8)	2 (40.0)	9 (37.5)
Post-compulsory education	3 (15.8)	2 (40.0)	5 (20.8)
University	9 (47.4)	1 (20.0)	10 (41.7)
Employment status			
Full-time	2 (10.5)	1 (20.0)	3 (12.5)
Part-time	3 (15.8)	1 (20.0)	4 (16.6)
Homemaker	1 (5.3)	0 (0)	1 (4.2)
Retired	12 (63.1)	1 (20.0)	13 (54.1)
Sick leave	1 (5.3)	0 (0)	1 (4.2)
Unemployed	0 (0)	1 (20.0)	1 (4.2)
Student	0 (0)	1 (20.0)	1 (4.2)
Living situation			
Alone	2 (10.5)	1 (20.0)	3 (12.5)
Partner	16 (84.2)	2 (40.0)	18 (74.9)
Parents	1 (5.3)	0 (0)	1 (4.2)
Other	0 (0)	1 (20.0)	1 (4.2)
Missing	0 (0)	1 (20.0)	1 (4.2)
Disease status			
Localized	8 (42.1)	2 (40.0)	10 (41.7)
Metastatic	11 (57.9)	3 (60.0)	14 (58.3)
Years since initial diagnosis			
<2	4 (21.0)	3 (60.0)	7 (29.2)
2–5	7 (36.8)	1 (20.0)	8 (33.3)
5–10	6 (31.6)	1 (20.0)	7 (29.1)
10–15	1 (5.3)	0 (0)	1 (4.2)
>15	1 (5.3)	0 (0)	1 (4.2)
Comorbidities			
None	12 (59.2)	2 (40.0)	14 (58.3)
Arthritis	3 (15.8)	0 (0)	3 (12.5)
Thyroid	2 (10.5)	1 (20.0)	0 (0)
Cardiac	1 (5.3)	0 (0)	1 (4.2)
Chronic fatigue syndrome	1 (5.3)	0 (0)	1 (4.2)
Renal	0 (0)	1 (20.0)	1 (4.2)
Parkinson's disease	0 (0)	1 (20.0)	1 (4.2)
Eye	0 (0)	1 (20.0)	1 (4.2)
Depression	0 (0)	1 (20.0)	1 (4.2)
Karnofsky performance status			
100	8 (42.1)	2 (40.0)	10 (41.6)
90	4 (21.0)	2 (40.0)	6 (25.0)
85	1 (5.3)	0 (0)	1 (4.2)
80	2 (10.5)	0 (0)	2 (8.3)

GIST: Gastrointestinal stromal tumor; HCP: Healthcare professional; SD: Standard deviation.

Table 1. Participant characteristics (cont.).

Patient characteristics	Interviewed (n = 19), n (%)	Focus group (n = 5), n (%)	Total (n = 24), n (%)
75	2 (10.5)	1 (20.0)	3 (12.5)
60	1 (5.3)	0 (0)	1 (4.2)
Missing	1 (5.3)	0 (0)	1 (4.2)
HCP characteristics	**Interviewed (n = 6), n (%)**		
Sex			
Female	4 (67)		
Male	2 (33)		
Specialist discipline			
Medical/clinical oncology	4 (67)		
Nursing	2 (33)		
Number of years specializing in care of patients with GIST			
<1	1 (17)		
1–5	2 (33)		
5–10	0 (0)		
>10	3 (50)		

GIST: Gastrointestinal stromal tumor; HCP: Healthcare professional; SD: Standard deviation.

Interviews

Semi-structured interviews with patients and HCPs were carried out by one researcher (SC Sodergren), either face-to-face or over the telephone. A face-to-face focus group was run at UHS by a facilitator (SC Sodergren) with the help of a moderator. The content of the interview schedules was informed by the EORTC Quality of Life Group guidelines [20] for the first phase of module development, where the aim was to identify an exhaustive list of 'issues' (symptoms) related to TKIs. Patients were asked to consider their experiences while on TKIs and to report side effects of their treatment. They were also asked to consider which symptoms were the most troublesome. The interviews commenced with open-ended questions and were followed up with prompts to stimulate further discussion. HCPs were asked to describe the symptoms they encounter in their interactions with patients. The patient, HCP and focus group interview schedules can be found in Supplementary Materials. Steps to protect the confidentiality of focus group participants were adopted.

Analysis

Data extracted from the case report forms were analyzed descriptively. Interviews were audio-recorded and transcribed verbatim. The content of the interviews was organized within NVivo software (LUMIVERO, CO, USA) [21] to facilitate analysis according to the principles of thematic analysis [22]. Transcripts were independently reviewed by two reviewers (SC Sodergren and S Venkatesan). Coding assumptions were continually reviewed, and an audit trail was kept of all reviewer discussions and modifications to the codebook.

Examples of each symptom code were extracted from the interviews as direct quotes or summaries of issues raised. The following definition of symptoms was applied and guided the extraction of data from participants' narratives: "*a physical or psychological disturbance from normal biological function, sensation or appearance*" [17]. Symptoms attributable by the patient to treatment rather than a marker of the disease itself were coded. In addition, the reviewers coded references made to participants' experience of symptoms in terms of their impact on life (personally or from the perspective of HCPs) as well as to symptom management.

Results

Participant characteristics

Nineteen patients with GIST were interviewed: five from UHS, five from the Royal Marsden Hospital and nine members of a patient support group for people with GIST across the UK. In addition, five patients formed part of a focus group conducted at UHS. There was a slightly higher representation of males (58%) and a mean age of 59 years. Time since diagnosis ranged from 4 months to 24 years. Imatinib had been given as first-line treatment to all patients, six had progressed on to sunitinib, three of whom were currently on regorafenib as third-line treatment. Eighteen participants had previously received some form of surgery and ten had at least one comorbidity. Six HCPs,

including four medical oncologists and two nurses, involved in the care of GIST patients and working for National Health Service trusts across the UK were interviewed. Three HCPs had over 10 years of experience in the care of patients with GIST, two HCPs between 1 and 5 years of experience, and one HCP having less than 1 year of experience. A complete overview of participant characteristics is provided in Table 1.

Gastrointestinal (GI) problems

Symptoms relating to GI problems were reported by all participants, with the exception of one patient in the focus group (Table 2). GI symptoms covered diarrhea (n = 23); nausea (n = 18); lack of appetite (n = 13); indigestion (n = 8); change in taste (n = 8); constipation (n = 5), which often alternated with diarrhea; vomiting (n = 5); flatulence (n = 3); inability to eat (n = 2); reflux (n = 2); stomach pain (n = 2); and gastritis (n = 1). Diarrhea was not only the most commonly reported symptom, but was also identified by five participants as the most troublesome symptom affecting everyday activities, including social functioning, and requiring careful management, resulting in the introduction of antidiarrheal medications or dose reductions.

> "*Diarrhea's the main thing; it does affect my day*" (FG002, 62 years, imatinib).
> "*I just wish I could do something to stop the diarrhea. Really, that affected me on all three but most with the Sutent and the regorafenib. It really interferes with your life because you end up taking spare clothes with you in case you have an accident, and you get weary on certain days if I know it's going to be bad. Even if I've been invited somewhere I might not go because I'd be worried about my stomach. Even if you know it's going to happen sometimes you just get caught short, so it's actually – however careful you are – it's actually quite difficult to manage and it's quite embarrassing*" (GSUK006, 52 years, regorafenib).

Whereas imatinib is administered daily, sunitinib can be administered as a fractionated dose (4 weeks on followed by 2 weeks off treatment), and one patient described some respite during the days off treatment:

> "*. . . quite a lot of diarrhea when I'm on it, and as soon as I have that 7 days off, I dry up without being rude . . . the diarrhea I can guarantee as soon as I'm on it*" (RMG003, 38 years, sunitinib).

One HCP reasoned that patients who had already undergone GI surgery were more vulnerable:

> "*. . . quite a number of our patients have had GI surgery, so it may be that they are set up to be more likely to have the diarrhea, if you see what I mean, because they've already got a shortened bowel*" (HCP005).

This was reinforced by one of the focus group participant's attributions:

> "*I put diarrhea down to the fact that food's getting through a lot quicker*" (FG002, 62 years, imatinib).

The second most commonly reported GI symptom was nausea (n = 18), which was mentioned by 14 patients, one focus group participant and three HCPs. Nausea was often managed by altering the timing of medication intake to coincide with mealtimes or taking it later in the day.

> "*A lot of patients, they start it first thing in the morning, and as time goes on they tend to take it when they go to bed or they find a time that suits them better because of the nausea*" (HCP004).

Vomiting (n = 5) was reported by only four patients and one HCP. The HCP underlined that vomiting was an unusual side effect of imatinib and probably dose-dependent:

> "*Occasionally, it's a problem in patients, where I don't know whether it's to do with the drug or where probably the dose is too high. We had a very tiny lady – obviously the standard dose is 400 mg – and she did have vomiting. It's quite unusual, and I think it's probably because her blood level, I mean I don't know for definite, she's too tiny and it's too high a dose. So vomiting is quite rare, but I have seen it*" (HCP006).

Another frequently reported GI symptom was lack or loss of appetite (n = 13), to which a change in taste (n = 8) could have contributed. One focus group participant expressed a change in appetite:

> "*I've got to admit, I was a real chip lover, greasy foods and McDonald's I found revolting and now it's reversed.*" (FG002, 62 years, imatinib).

HCPs described that change in taste is more common in sunitinib-treated patients, which was acknowledged by one of the sunitinib-treated patients:

Table 2. Reported issues in alphabetical order.

Reported issue	Patients (n = 19)	Focus group (n = 5)	HCPs (n = 6)	Total (n = 30)
Blackouts	–	–	1	1
Blood pressure, high	1	–	2	3
Cognitive problems	5	1	–	6
Forgetfulness	3	1	–	4
Difficulty concentrating	2	–	–	2
Cold hands and feet	2	–	–	2
Dehydration	–	–	1	1
Dizziness	2	–	–	2
Edema	14	2	6	22
Exacerbation of existing condition	1	1	2	4
Eye problems	7	3	1	11
Subconjunctival hemorrhages	2	3	1	6
Watery eyes	4	–	–	4
Dry eyes	2	–	–	2
Gritty eyes	1	–	–	1
Facial paralysis	1	–	–	1
Fainting	1	–	–	1
Fever and chills	1	–	–	1
GI problems	19	4	6	29
Diarrhea	14	3	6	23
Nausea	14	1	3	18
Lack of appetite	8	3	2	13
Indigestion	6	1	1	8
Change in taste	5	1	2	8
Constipation	2	3	–	5
Vomiting	4	–	1	5
Flatulence	–	3	–	3
Inability to eat	2	–	–	2
Reflux	2	–	–	2
Stomach pain	2	–	–	2
Gastritis	1	–	–	1
Hair problems	7	–	2	9
Hair loss or thinning	5	–	1	6
Hair color change	4	–	–	4
Depigmentation	–	–	2	2
Change in hair structure	2	–	–	2
Headache	3	–	–	3
Heart problems	–	–	2	2
Inability to walk	3	–	–	3
Laboratory abnormalities				
Hematology (e.g., anemia, leukopenia, neutropenia, thrombocytopenia)	1	–	3	4
Thyroid function problems	1	–	3	4
Liver function abnormalities	–	–	1	1
Lack of energy	2	–	–	2
Mouth problems	4	–	4	8
Sore mouth	2	–	4	6
Mouth ulcers	2	–	1	3
Sensitive mouth or tongue	2	–	1	3

GI: Gastrointestinal; HCP: Healthcare professional.

Table 2. Reported issues in alphabetical order (cont.).

Reported issue	Patients (n = 19)	Focus group (n = 5)	HCPs (n = 6)	Total (n = 30)
Mucositis	–	–	1	1
Dry mouth	–	–	1	1
Thrush	1	–	–	1
Muscle and joint pain	5	–	1	6
Muscle cramps	12	5	4	21
Night sweats	1	–	–	1
Nose problems (sores, blockages, bleeds)	1	–	–	1
Psychological problems	8	1	3	12
Anxiety	4	–	3	7
Depression	5	1	–	6
Easily irritated	3	–	–	3
Getting emotional easily	1	1	–	2
Mood swings	1	–	–	1
Frustration	1	–	–	1
Loss of motivation	1	–	–	1
Sensitivity to temperature	2	1	–	3
Shortness of breath	6	–	2	8
Skin problems	13	3	5	21
Hand–foot syndrome	6	–	3	9
Rash	4	1	3	8
Skin color change	5	–	1	6
Dry skin	3	1	1	5
Fragile skin	2	1	1	4
Itchy skin	2	–	1	3
Bruising	1	–	2	3
Photosensitivity	2	–	–	2
Delayed healing	1	–	–	1
Swollen glands	1	–	–	1
Throat problems (pain, excess mucus)	2	–	–	2
Tiredness	16	3	6	25
Trouble sleeping	8	1	1	10
Urinary problems	3	–	–	3
Urgency	2	–	–	2
Urinary tract infection	1	–	–	1
Nighttime urination	1	–	–	1
Voice alteration	1	–	–	1
Weakness	6	–	–	6
Weight gain	2	–	–	2
Weight loss	5	1	–	6

GI: Gastrointestinal; HCP: Healthcare professional.

"*I think you do get taste changes more with sunitinib than you do with imatinib*" (HCPSU004).
"*I found things like wine just took on a very metallic taste*" (GSUK001, 56 years, sunitinib).

Indigestion was also a commonly reported GI complaint (n = 8), which can result in loss of appetite, as was expressed by one patient:

"*. . . getting terrible indigestion, and as I say my consumption of food has really dropped because I can't eat an awful lot. If I eat an awful lot, I get pains down the left side*" (GSUK007, 66 years, imatinib).

Tiredness

The second most prevalent symptom reported by 16 patients, three focus group participants and all six HCPs was tiredness (n = 25), which was also described as fatigue or exhaustion. Ten patients referred to fatigue as the most troublesome of all side effects, leading to adjustments in their daily lives (e.g., needing more rest, going to bed early), dose reductions or the need to take sleeping tablets. For example, one patient reported the following:

> "*Those days I really suddenly hit a wall, feeling really exhausted, so that decided me that third cycle onwards I would stick to half dose*" (GSUK002, 62 years, regorafinib).

One focus group participant described the fatigue as always being there:

> "*I could have a restful weekend but wake up feeling tired and spend the best part of the day yawning. I'm normally in bed by 9 or half past 9 at night. I just can't stay up any longer. I get a good night's sleep I'll wake up tired*" (FG003, 53 years, imatinib).

One patient referred to the fatigue getting worse because of the inability to sleep:

> "*Yes, there's exhaustion, the fatigue, very bad fatigue, and then I couldn't sleep. Because I was absolutely exhausted and couldn't sleep, it was going around in a circle. You can't sleep, so the fatigue gets worse and more worse [sic] and then you still can't sleep, so in the early days I was on sleeping tablets*" (RMG004, 61 years, imatinib).

One HCP pointed out fatigue as a challenging symptom to discuss, as there is no treatment available:

> "*. . . we like discussing things we can do things about. Fatigue's one of those sort of things that's difficult to help, so if somebody says, I've got diarrhea, we say, oh, great, I can give you something for that, whereas with tiredness it's much more difficult to help people, so I suppose we aren't going to focus on that because we can't help so much. That may be the patient's perception at least*" (HCP005).

Another HCP acknowledged the impact of fatigue on patients:

> "*I think the fatigue can affect patients psychologically*" (HCP001).

Edema

Edema, comprising swelling or fluid retention in any region of the body, including the limbs, face, eyes (referred to by HCPs as periorbital edema) and scrotum, was the third most prevalent symptom (n = 22) and was reported by 14 patients, two focus group participants and all HCPs. One patient described edema as the most bothersome of symptoms experienced and the cause of headaches:

> "*The biggest side effect, the worst side effect, is water retention. I get it quite badly, particularly in my face, and my face really puffs up, my eyes are swollen, and because of that I believe that's what gives me a headache most days because I believe it's a buildup of water*" (GSUK003, 44 years, imatinib).

Skin, eye, mouth & hair problems

Twenty-one participants (13 patients, three focus group participants and five HCPs) reported skin problems. Skin problems covered a wide range of symptoms, including sore skin, which overlapped with hand–foot syndrome (n = 9); rash (n = 8); skin color change, such as pale skin (n = 6); dry skin (n = 5); fragile skin (n = 4); itchy skin (n = 3); bruising (n = 3); and photosensitivity (n = 2). One patient expressed the following:

> "*The only other thing is my skin. It's like paper, it rips so easily*" (SUGF005, 53 years, imatinib).

One HCP described:

> "*Skin problems are certainly a problem for people with GISTs, but again, it's more with sunitinib than with imatinib*" (HCP004).

Both sunitinib and regorafenib are known to cause a specific skin condition, hand–foot syndrome, which was reported by nine participants (six patients and three HCPs). One patient who had previously been treated with sunitinib and suffered from hand–foot syndrome expressed the following:

> "*The Sutent, initially made my hands and feet worse than before, so I had more problems with, well, it was mild hand–foot syndrome, but blisters on my feet and hard skin and sore feet*" (GSUK006, 52 years, regorafenib).

Rash and hand–foot syndrome were referred to by four patients as being the most troublesome, including one patient who indicated the following:

> "*I think without a doubt it's the hand–foot syndrome because walking can be extremely painful*" (GSUK001, 56 years, sunitinib).

A total of 11 participants (seven patients, three focus group participants and one HCP) reported eye problems, including subconjunctival hemorrhages or bloodshot eyes (n = 6), watery eyes (n = 4), dry eyes (n = 2) and gritty eyes (n = 1). Problems of the mouth and tongue were described by eight participants (four patients and four HCPs) and included sore mouth (n = 6), mouth ulcers (n = 3), sensitive mouth or tongue (n = 3), mucositis (n = 1), dry mouth (n = 1) and thrush (n = 1). One patient described the following:

> "*My tongue was more sensitive, more sensitive to hot tea and things like that. It almost felt a bit numb. Kind of warm and tingly kind of describes how my tongue felt*" (GSUK002, 62 years, regorafenib).

Nine participants reported hair-related symptoms. Two HCPs described depigmentation of hair, other symptoms included hair loss or thinning (n = 6), hair color change (n = 4) and change in hair structure (n = 2). One patient experienced hair changes on both imatinib and sunitinib:

> "*I've had significant hair loss or color change, and in fact I should say when I was on Glivec 800, my hair when it grew back after having fallen out, it changed color and kind of texture, and it went slightly orangey, in fact, having been dark brown. Back to Sutent, my hair has gone quite gray and white – various friends refer to it as a badger-like effect – and it's got finer, it's got straighter because it used to be wavy, but it's still there*" (GSUK001, 56 years, sunitinib).

Cramps, muscle & joint pain & weakness

Muscle cramps were reported by 21 participants (12 patients, five focus group participants and four HCPs). One HCP described cramps as a less common, but troublesome side effect:

> "*One of the less common side effects, or at least it's one that the patients complain about, is cramps, particularly cramps in their hands or feet, and that can be quite troublesome, again, for patients and difficult to manage*" (HCP005).

However, from the patients' perspective, cramps were common, leading to insomnia or trouble sleeping:

> "*. . . cramps . . . which I think is quite common. Nighttime incidence and cause of insomnia*" (GSUK001, 56 years, sunitinib).
>
> "*The other major thing is leg cramps as well. I used to suffer really badly with stomach cramps, but leg cramps would be so bad they'd wake you up in the middle of the night. You'd go from sound asleep to wide awake in a split second. It's not very fun to wake up like that*" (FG003, 53 years, imatinib).

Muscle and joint pains were less common and expressed by five patients and one HCP. Six patients experienced weakness or loss of strength, and one patient acknowledged that it might also be an age-related problem:

> "*I'm not as strong as I used to be, and that's quite new, the weakness, and again, I don't know whether that's drug-related or age-related. I wouldn't like to blame the drug when it's not the drug. I can't say. I know I'm not as strong as I used to be*" (RMG004, 61 years, imatinib).

Cognitive problems

Cognitive problems, including forgetfulness (n = 4) and difficulty concentrating (n = 2), were reported only by patients. One patient clearly related concentration problems to imatinib use:

> "*. . . an inability to concentrate is how I describe it, but that seems to have gone since coming off Glivec*" (GSUK002, 62 years, regorafenib).

Forgetfulness was attributed by a patient to a changed lifestyle in combination with lack of stimulation:

> "*. . . I mean I have got a fairly poor memory now, but I sort of put that down to not working and using my brain quite as much as I used to, so it may just be situational or it may be something to do with the medication.*

> *I couldn't really say, but I can't remember names. If I'm watching the telly, I can't remember names of actors and things*" (GSUK008, 66 years, imatinib).

Psychological problems

A total of 12 participants (eight patients, one focus group participant and three HCPs) noted psychological symptoms since starting treatment. Both patients (n = 4) and HCPs (n = 3) reported anxiety, with HCPs describing a specific anxiety called 'scanxiety':

> "*. . . there's a very particular thing, 'scanxiety', because they get regular CT scans when they're on these medications*" (HCP002).

The presence of scanxiety was also acknowledged by patients:

> "*. . . I get anxious just before going to the hospital for scans only because I've been through two treatments, which have failed to respond [sic] after a while, and I'd like to think this will last a bit longer*" (RMG003, 38 years, sunitinib).

Another patient described anxiety decreasing over time:

> "*I think it was the shock of a cancer diagnosis. Inevitably, most of us have shock, disbelief and a degree of anxiety. I was going up and down to the hospital quite regularly for scans, and that in itself brings about a certain level of anxiety. What if it's come back? . . . the diagnosis sat on my shoulder for quite a while. I mean it's still there, but it's receded a lot as time has gone by*" (GSUK005, 61 years, imatinib).

By contrast, symptoms of depression (n = 6) were expressed only by patients:

> "*I did start to get a bit depressed, I think, earlier this year. I don't know whether that was treatment so much as just dealing with the reality of having cancer*" (GSUK004, 40 years, imatinib).

In addition, three patients emphasized getting easily irritated (n = 3), which one patient attributed to the side effects experienced:

> "*. . . I've been suffering from the side effects. That makes me irritable, but otherwise I haven't been feeling irritable*" (GSUK002, 62 years, regorafenib).

One patient struggled with frustration related to lower levels of activity as a result of loss of strength and concentration problems. The same patient also described loss of motivation and suffered from mood swings:

> "*I do suffer from mood swings. I've always been very even-tempered. I can cope with most things, but now I do have some quite dramatic mood swings*" (RM001, 71 years, imatinib).

Two other patients expressed getting emotional easily and the need to stay positive.

Trouble sleeping

Trouble sleeping was mentioned by ten participants (eight patients, one focus group participant and one HCP), although the HCP indicated that it is difficult to determine whether this is actually treatment-related:

> "*I think insomnia is something people mention, but again, it's one of those symptoms that it's difficult to pin down to being because of the treatment, but it may be something to look at, definitely*" (HCP006).

Shortness of breath

Shortness of breath was reported by eight participants (six patients and two HCPs), regarded by patients as not particularly serious. Patients reasoned that age and not being physically fit contributed to shortness of breath:

> "*I put it down to perhaps not being fit, yes, but whether it's drug-related, I'm not too sure*" (RMG004, 61 years, imatinib).

One HCP meanwhile mentioned shortness of breath in relation to a serious side effect:

> "*They can get pulmonary infiltrates, causing cough and shortness of breath*" (HCP002).

Side effects mentioned mostly by HCPs

Three HCPs made references to 'medically defined' symptoms in the form of abnormalities detected by laboratory tests, such as neutropenia and anemia:

> "*They are mildly myelosuppressed. Most of them are anemic to a degree. Some of them are leukopenic, neutropenic, sometimes thrombocytopenic, usually not to a clinically significant level, but maybe the anemia is contributing to the tiredness. They can also have liver function abnormalities*" (HCP002).

In addition, high blood pressure induced by sunitinib or regorafenib was emphasized by two HCPs as something patients do not necessarily notice:

> "*Well, the commonest adverse effect would be the hypertension, but that's not something the patient notices. That's something we pick up*" (HCP005).

Three HCPs and one patient reported thyroid function issues (e.g., hypothyroidism), which were mostly seen in the laboratory findings of sunitinib-treated patients without clinical symptoms:

> "*Thyroid function depression is frequent*" (HCP002).

Two HCPs noted heart problems:

> "*We had a patient who went into heart failure on sunitinib, a young girl, but it was reversible, so she's – it improved when she came off the drug*" (HCP005).

Impact of side effects

For some side effects, it might be difficult to assign causality fully to TKI treatment. In the authors' study, 21 participants mentioned possible difficulty in attributing causality and could not rule out other influencing factors. For example, side effects could be attributed to or influenced by comorbidities, older age, the disease itself or previous surgery. The impact of side effects on the lives of patients was described differently by HCPs than by the patients themselves. Most of the HCPs described patients as doing well while on TKIs, especially imatinib, and side effects as tolerable. In addition, almost all HCPs noted a difference in the side effect profile of imatinib compared with other TKIs, with sunitinib and regorafenib being more toxic. By contrast, patients described acceptance of symptoms:

> "*I wanted to have my life back really . . . but I didn't get my life back because of the effects of the drug. It never happened. Now I look upon it as I got my life and 'this' is a small price I have to pay for having my life*" (RMG004, 61 years, imatinib).

Patients also indicated that they had learned to live with the side effects:

> "*I respect Sutent's toxicity and listen to my body. It's a lot easier to live with. Some cycles I get away pretty scot-free, and other times it's not so easy*" (GSUK001, 56 years, sunitinib).

However, other patients also acknowledged the detrimental impact:

> "*On the whole, it is an awful drug to take because you do get those things, and you try and fix these little things by doing that and doing this, but they are all kind of happening, but just try and work at it. But it's a big whack, you know. Even the 400 mg I think people struggle with. It is big, it isn't easy, it's doing the job. I had a scan recently, and everything is still all clear*" (GSUK003, 44 years, imatinib).

One focus group participant expressed that being alive was more important than the experienced side effects:

> "*We're still here. That's the main thing, isn't it?*" (FG001, 51 years, imatinib).

Focus group participants also valued the fact that fellow TKI-treated GIST patients recognized the noted side effects and experienced them too:

> "*It's nice to hear that someone else is going through this when you sit in your little ivory tower away from everybody and nobody in your family has ever heard of it. So it's quite nice to meet people who are in the same boat really*" (FG001, 51 years, imatinib).

Another participant in the focus group admitted not mentioning side effects because of the fear of having to stop treatment:

> "*I'm not complaining about 'them' because, you know, you can have these symptoms or, you know, we'll stop the Glivec and everything will get worse. I'll have the symptoms. None of them are really life-changing*" (FG002, 62 years, imatinib).

Management of side effects

Both HCPs and patients had different strategies for managing and reducing the experienced side effects. With regard to HCPs, supportive medications (e.g., antiemetics, antidiarrheals, antidepressants, iron supplements, painkillers) were prescribed and dose reductions were applied to manage side effects. A patient described knowing what to expect and how to anticipate this:

> "*. . . because I've been on it 8 years, you learn what you've got to do to combat each symptom*" (FG001, 51 years, imatinib).

Several patients adjusted their daily lives, mainly to manage fatigue:

> "*. . . I don't get generally to the point where I'm absolutely exhausted. Like if I go to the theater, for example, I won't book any activities for the next day because I know I'll need to have a kind of quiet day. So because of that I don't suffer too badly, but I know I would if I carried on regardless. So it's a question of managing that, and it was one of the major reasons why I gave up work because it was just too much, day after day, and the exhaustion just overwhelmed me, but I've been a lot better since I gave up work*" (GSUK008, 66 years, imatinib).

Other patients also indicated modifying their diet, quitting their job or taking a drug holiday. One patient expressed carrying on with life in spite of the side effects and being grateful that treatment is available:

> "*I don't have a lot of energy, but I ignore that and do carry on with the things I used to do . . . I think we have been very lucky, haven't we, with Glivec*" (SUG003, 82 years, imatinib).

Discussion

To the authors' knowledge, this is the second qualitative study to report the side effects of TKIs in the treatment of advanced and metastatic GIST from the patient's perspective and the first to draw comparisons with reports from HCPs. In the authors' study, all patients experienced multiple TKI-related side effects. GI problems were most frequently reported followed by fatigue, edema, muscle cramps and skin problems. Interestingly, cognitive problems and psychological problems other than anxiety were expressed only by patients. Fatigue, diarrhea and skin problems were experienced as the most troublesome of all side effects by both patients and HCPs.

The majority of the reported side effects in this study, including tiredness, diarrhea, nausea, lack of appetite, edema, muscle cramps and rash, are well-known side effects of TKI treatment [6]. In addition, specific side effects associated with sunitinib and regorafenib, including hand–foot skin reactions and mouth problems [23,24], were commonly reported by HCPs and patients treated with either sunitinib or regorafenib. For some reported side effects, it was difficult to assign causality fully to the TKI treatment, as side effects could be attributed to or influenced by comorbidities, older age, the disease itself or previous surgery. In a review about the safety profile of imatinib in chronic myeloid leukemia and GIST, severe nausea and diarrhea were more common in GIST patients when treated with the same dose of imatinib [25], suggesting that the origin of GIST and the fact that GIST patients often had previous GI surgery might have been responsible for GI symptoms.

As shown in Table 2, patients in the authors' study also reported side effects that were less recognized by HCPs, including eye problems (in particular subconjunctival hemorrhages and bloodshot eyes), hair loss, trouble sleeping, shortness of breath, cognitive problems and psychological problems. Impaired cognitive functioning was previously reported in sunitinib-treated patients [26] and also in qualitative research [19]. Understandably, previous research in GIST patients focused on clinical outcomes (e.g., response rate, time to progression, progression-free survival) and safety [24,27–29]. The number and severity of adverse events during study treatment usually determine safety, which is traditionally measured by applying the physician-reported CTCAE. This might not be the appropriate measure for reporting TKI-related side effects [8], especially in light of the fact that HCPs tend to underreport symptoms [11,12]. Using the physician-reported CTCAE may result in an underestimation of the side effects of TKI treatment. The use of patient-reported outcome measures such as the patient-reported outcomes version of

the CTCAE or EORTC symptom-based questionnaire [18] could be a better strategy for measuring TKI-related side effects. Nevertheless, a recently published study reported that some frequently reported TKI-related symptoms (e.g., alopecia) were not fully covered by the currently available patient-reported outcome measures [30].

Cognitive problems such as forgetfulness and difficulty concentrating, and psychological problems other than anxiety were underreported by HCPs. A minority of HCPs reported anxiety, their statements often related to the stress or worries patients experienced around scans and follow-up visits (referred to as 'scanxiety'). A limited number of studies have addressed psychological problems. Custers *et al.* specifically studied fear of cancer recurrence or progression – a common psychological issue among GIST patients – with 52% of patients experiencing high levels of fear, resulting in lower global quality of life and more distress compared with patients experiencing lower levels of fear [31]. A qualitative study addressed the emotional journey of GIST patients, which consists of five stages: crisis, hope, adaptation, 'new normal' and uncertainty [32]. A more recent qualitative study by Fauske *et al.* reported that side effects of the required life-prolonging TKI treatment led to changes that limited the daily lives of GIST patients with metastatic disease [33]. Patients emphasized the detrimental impact on their family life, vocational life, social life and leisure time due to tiredness, impaired memory and physical limitations.

During the interviews and focus group, GIST patients were asked to consider which symptoms were the most troublesome. Troublesome symptoms were symptoms that were either always present or came unexpectedly and were difficult to manage. The majority of patients expressed that fatigue was the most troublesome because they had to plan their days and needed to rest more. Severe fatigue and its impact on the HRQoL of GIST patients were previously studied, and it was found that the prevalence of severe fatigue was higher among GIST patients (30%) compared with healthy controls (15%) [34]. Severely fatigued patients reported a lower global quality of life as well as increased impairment in all functional domains of HRQoL, less favorable physical functioning, lower self-efficacy and more distress. Fatigue is a difficult and challenging symptom to manage for HCPs, as there is no supportive medication that can be prescribed to reduce it. Internet-derived cognitive behavioral therapy or an online psychoeducation program may be more helpful for patients in managing their fatigue [35]. In the authors' study, focus group participants acknowledged that it was nice to hear that fellow GIST patients recognized and experienced the same side effects. Consequently, participants felt heard and not alone. Therefore, connecting with other GIST patients via support groups and online patient forums may also be helpful.

Symptoms that can arise unexpectedly, such as diarrhea, can also have a significant impact on the social lives of patients. In the case of diarrhea, urgency and incontinence were embarrassing for these patients. Hand–foot syndrome was described as extremely painful, and patients felt they were not able to go out and enjoy life. All troublesome side effects hampered the daily lives of patients and forced patients to adjust their lives. This was also reported by Fauske *et al.*, where more than half of metastatic GIST patients described partially debilitating side effects that had a detrimental impact on their lives and compelled them to adapt to 'a new normal' [19].

The strength of this study is that it provides a unique insight into how GIST patients themselves experience the side effects of TKI treatment. Because of the qualitative approach, the authors were able to provide a more complete overview of the broad spectrum of TKI-related side effects and its impact on the daily lives of patients. This study raises awareness of the diversity of side effects experienced by patients, which might not always be picked up or asked about by HCPs. Some limitations also need to be taken into account. First, the small sample size and the fact that only participants from the UK were included may limit the generalizability of this study. Second, most interviews were conducted with imatinib-treated patients, and few patients were on treatment with either sunitinib or regorafenib. This may seem off balance but is an actual representation of the patient population in the clinic, as today's treatment consists of first-line imatinib, second-line sunitinib and third-line regorafenib. Fourth-line ripretinib and avapritinib were only recently approved, and therefore no patients on these newer treatments were interviewed. Third, this study focused only on side effects of TKI treatment rather than all domains of HRQoL and side effects were not specified per type of TKI; both were outside the scope of this study. In the interviews, patients were asked to consider their experiences while on TKI treatment and to report side effects of their treatment.

Conclusion

The authors' results underline the importance of including the patient's perspective, as all GIST patients experienced TKI-related side effects that were not always recognized by HCPs. The authors found a gap in symptom reporting – in particular for cognitive and psychological symptoms – between patients and HCPs, which is a worrying conclusion that can easily be overcome if HCPs include a question during consultations about how the disease and treatment affect the patient's daily life. In addition, patients should be made aware that HCPs are interested in all

side effects, including mood problems or difficulty remembering things, as some patients may feel they should just be grateful that treatment is available and that they are still alive. Capturing this currently missed information may have important implications for the patients' HRQoL, patient–HCP communication, decision-making (shared), engagement with treatment and clinical outcomes. In addition to the side effects and limitations patients experience as a consequence of TKI treatment, GIST patients also face psychological and social challenges that hamper their HRQoL. It remains unknown whether patients with GIST who depend on life-prolonging TKI treatment find it worthwhile to continue TKI treatment at the expense of HRQoL. Future studies should include the patient's perspective, focusing on physical as well as psychological and social challenges.

Summary points

- This study provides a unique insight into how gastrointestinal stromal tumor patients themselves experience the side effects of tyrosine kinase inhibitor treatment.
- The most troublesome symptoms were fatigue, diarrhea and skin problems, including hand–foot syndrome and rash. All troublesome symptoms were either always present or came unexpectedly and were difficult to manage.
- There is a gap in symptom reporting – specifically for cognitive and psychological symptoms – between patients and healthcare professionals (HCPs).
- HCPs seem to underestimate the impact of side effects on the daily lives of patients. Most HCPs described patients as doing well while on tyrosine kinase inhibitors and side effects as tolerable. By contrast, patients described acceptance of symptoms and found ways to adapt to and manage side effects that hamper their everyday activities.
- This study raises awareness of the diversity of side effects experienced by patients, which might not always be picked up or asked about by HCPs.
- Raising awareness may have important implications for the patients' health-related quality of life, patient–HCP communication, decision-making (shared), engagement with treatment and clinical outcomes.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2022-0730

Author contributions

Study design: SC Sodergren. Data collection: SC Sodergren. Data interpretation: D van de Wal, S Venkatesan and SC Sodergren. Original draft preparation: D van de Wal and SC Sodergren. Review and editing: D van de Wal, S Venkatesan, C Benson, WTA van der Graaf, CD Johnson, O Husson and SC Sodergren. Project administration: SC Sodergren. All authors have read and agreed to the final version of the manuscript.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Søreide K, Sandvik OM, Søreide JA, Giljaca V, Jureckova A, Bulusu VR. Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies. *Cancer Epidemiol.* 40, 39–46 (2016).
2. Judson I, Bulusu R, Seddon B, Dangoor A, Wong N, Mudan S. UK clinical practice guidelines for the management of gastrointestinal stromal tumours (GIST). *Clin. Sarcoma Res.* 7, 6 (2017).
3. D'Amato G, Steinert DM, McAuliffe JC, Trent JC. Update on the biology and therapy of gastrointestinal stromal tumors. *Cancer Control* 12(1), 44–56 (2005).
4. Blanke CD, Demetri GD, von Mehren M *et al.* Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J. Clin. Oncol.* 26(4), 620–625 (2008).

• **Illustrates the improved overall survival of gastrointestinal stromal tumor (GIST) patients with advanced and metastatic disease.**

5. Casali P, Blay J, Abecassis N *et al.* Gastrointestinal stromal tumours: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 33 (1), 20–33 (2021).
6. Sodergren SC, White A, Efficace F *et al.* Systematic review of the side effects associated with tyrosine kinase inhibitors used in the treatment of gastrointestinal stromal tumours on behalf of the EORTC Quality of Life Group. *Crit. Rev. Oncol. Hematol.* 91(1), 35–46 (2014).

•• **Provides information on the diversity of physical and psychological side effects of tyrosine kinase inhibitors in the treatment of GIST.**

7. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) (2021). https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm
8. Edgerly M, Fojo T. Is there room for improvement in adverse event reporting in the era of targeted therapies? *J. Natl Cancer Inst.* 100(4), 240–242 (2008).
9. Basch E, Iasonos A, McDonough T *et al.* Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. *Lancet Oncol.* 7(11), 903–909 (2006).
10. Fromme EK, Eilers KM, Mori M, Hsieh YC, Beer TM. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. *J. Clin. Oncol.* 22(17), 3485–3490 (2004).
11. Atkinson TM, Ryan SJ, Bennett AV *et al.* The association between clinician-based common terminology criteria for adverse events (CTCAE) and patient-reported outcomes (PRO): a systematic review. *Support. Care Cancer* 24(8), 3669–3676 (2016).
12. Di Maio M, Basch E, Bryce J, Perrone F. Patient-reported outcomes in the evaluation of toxicity of anticancer treatments. *Nat. Rev. Clin. Oncol.* 13(5), 319–325 (2016).
13. Efficace F, Rosti G, Aaronson N *et al.* Patient- versus physician-reporting of symptoms and health status in chronic myeloid leukemia. *Haematologica* 99(4), 788–793 (2014).
14. van de Wal D, Elie M, Le Cesne A *et al.* Health-related quality of life and side effects in gastrointestinal stromal tumor (GIST) patients treated with tyrosine kinase inhibitors: a systematic review of the literature. *Cancers (Basel)* 14(7), 1832 (2022).

•• **Provides an overview of the available literature on health-related quality of life and side effects of different TKIs in the treatment of GIST and underlines the lack of studies using patient-reported outcomes.**

15. Basch E, Reeve BB, Mitchell SA *et al.* Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *J. Natl Cancer Inst.* 106(9), dju244 (2014).
16. Williams LA, Araujo DM, Shi Q *et al.* Symptoms in gastrointestinal stromal tumors. *J Clin. Oncol.* 32(15), 9637–9637 (2014).
17. Cottone F, Collins GS, Anota A *et al.* Time to health-related quality of life improvement analysis was developed to enhance evaluation of modern anticancer therapies. *J. Clin. Epidemiol.* 127, 9–18 (2020).
18. Sodergren SC, Wheelwright SJ, Fitzsimmons D *et al.* Developing symptom lists for people with cancer treated with targeted therapies. *Target. Oncol.* 16(1), 95–107 (2021).

• **Provides information on the development of a symptom-based questionnaire for patients receiving targeted therapies and is the larger body of work this study is a part of.**

19. Fauske L, Hompland I, Lorem G, Bondevik H, Bruland ØS. Perspectives on treatment side effects in patients with metastatic gastrointestinal stromal tumour: a qualitative study. *Clin. Sarcoma Res.* 9(1), 6 (2019).

• **First qualitative study to report on the side effects of tyrosine kinase inhibitors in the treatment of advanced and metastatic GIST from a patient's perspective.**

20. EORTC QUALITY OF LIFE GROUP. Guidelines for Developing Questionnaire Modules (2011). www.eortc.org/app/uploads/sites/2/2018/02/guidelines_for_developing_questionnaire-_final.pdf
21. Lumivero. NVivo (2020). www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home

22. Braun V, Clarke V. What can 'thematic analysis' offer health and wellbeing researchers? *Int. J. Qual. Stud. Health Well-being* 9, 26152 (2014).
23. Reichardt P, Kang YK, Rutkowski P *et al.* Clinical outcomes of patients with advanced gastrointestinal stromal tumors: safety and efficacy in a worldwide treatment-use trial of sunitinib. *Cancer* 121(9), 1405–1413 (2015).
24. Demetri GD, Reichardt P, Kang YK *et al.* Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 381(9863), 295–302 (2013).
25. Thanopoulou E, Judson I. The safety profile of imatinib in CML and GIST: long-term considerations. *Arch. Toxicol.* 86(1), 1–12 (2012).
26. Mulder SF, Bertens D, Desar IME *et al.* Impairment of cognitive functioning during sunitinib or sorafenib treatment in cancer patients: a cross sectional study. *BMC Cancer* 14(1), 219 (2014).
27. Casali PG, Zalcberg J, Le Cesne A *et al.* Ten-year progression-free and overall survival in patients with unresectable or metastatic GI stromal tumors: long-term analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group intergroup phase III randomized trial on imatinib at two dose levels. *J. Clin. Oncol.* 35(15), 1713–1720 (2017).
28. Demetri GD, Garrett CR, Schoffski P *et al.* Complete longitudinal analyses of the randomized, placebo-controlled, phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. *Clin. Cancer Res.* 18(11), 3170–3179 (2012).
29. Blay JY, Serrano C, Heinrich MC *et al.* Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 21(7), 923–934 (2020).
30. den Hollander D, Dirkson AR, Verberne S *et al.* Symptoms reported by gastrointestinal stromal tumour (GIST) patients on imatinib treatment: combining questionnaire and forum data. *Support. Care Cancer* 30(6), 5137–5146 (2022).
31. Custers JAE, Tielen R, Prins JB, de Wilt JHW, Gielissen MFM, van der Graaf WTA. Fear of progression in patients with gastrointestinal stromal tumors (GIST): is extended lifetime related to the sword of Damocles? *Acta Oncol.* 54(8), 1202–1208 (2015).
32. Macdonald N, Shapiro A, Bender C, Paolantonio M, Coombs J. Experiences and perspectives on the GIST patient journey. *Patient Prefer. Adherence* 6, 253–262 (2012).
33. Fauske L, Hompland I, Lorem G, Hall KS, Bondevik H. Striving towards normality in daily life: a qualitative study of patients living with metastatic gastrointestinal stromal tumour in long-term clinical remission. *Sarcoma* 2020, 1814394 (2020).
34. Poort H, van der Graaf WTA, Tielen R *et al.* Prevalence, impact, and correlates of severe fatigue in patients with gastrointestinal stromal tumors. *J. Pain Symptom Manage.* 52(2), 265–271 (2016).
35. Carbajal-Lopez EB, Juarez-Garcia DM, Espinoza-Velazco A, Calderillo-Ruiz G. Internet-delivered cognitive behavioral therapy and psychoeducation program for patients with gastrointestinal stromal tumors. *J. Cancer Educ.* 37(3), 668–674 (2022).