**The patient’s perspective on side effects of tyrosine kinase inhibitors (TKIs) in the treatment of advanced and metastatic gastrointestinal stromal tumours (GISTs)**

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**Abstract**

***Aim*** This study aimed to provide the gastrointestinal stromal tumour patient’s perspective on side effects of tyrosine kinase inhibitors, and compare this with that of health-care professionals. ***Methods*** Semi-structured interviews were conducted with 19 patients with an advanced or metastatic gastrointestinal stromal tumour, six health-care 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), oedema (*n*=22), muscle cramps (*n*=21), skin problems (*n*=21), eye problems (*n*=11), and trouble sleeping (*n*=10). Patients, but not health-care 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 health-care professionals.

**Plain Language Summary**

In our study, we report on the side effects of targeted therapies used in the treatment of gastrointestinal stromal tumours from a patient’s perspective and draw comparisons with reports from health-care professionals. We conducted interviews with both patients and health-care professionals. Most participants reported gastrointestinal symptoms, followed by tiredness, fluid retention, muscle cramps, skin problems, eye problems, and trouble sleeping. GIST patients reported cognitive problems and symptoms of depression, which were not reported by health-care professionals. In conclusion, our results highlight the importance of including the patient’s perspective, as there is a gap in symptom reporting between patients and health-care professionals.

**Keywords:** gastrointestinal stromal tumours, tyrosine kinase inhibitors, side effects, adverse events, qualitative research, patient-reported outcome, interviews

**Introduction**

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract. GIST is a rare cancer with an incidence of 5–20 people per million per year, and due to 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 decades, there have been dramatic improvements in the treatment of GISTs due to the development of targeted therapies (TTs). 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 non-response or resistance to imatinib, sunitinib, regorafenib, and ripretinib are registered as second, third, and fourth-line therapies, and avapritinib is registered specifically for GISTs harboring a *PDGFRα* exon 18/D842V mutation [5].

TKIs are described as tolerable drugs. Compared to conventional chemotherapies, TKIs are more selective in their mechanism of action. However, they are not without side effects. In our systematic review, we identified a total of 64 symptoms related to TKI treatment in GIST patients. Symptoms covered both physical side effects such as fatigue, nausea, and oedema, 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 (CTCAETM) [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 to report TKI related side effects [8]. The 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 health-care 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. Also, in imatinib-treated patients with chronic myeloid leukaemia (CML), HCPs underestimated 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 and 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 on HRQoL and side effects in GIST patients treated with TKIs reported that of the 104 studies reviewed, only 13 used patients-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 (PRO-CTCAE) [15] or MD Anderson Symptom Inventory for GISTs (MDASI-GIST) [16]). Yet it is argued, including the patient 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 programme of work carried out on behalf of the European Organisation for Research and Treatment of Cancer Quality of Life Group (EORTC QLG) to develop symptom lists for patients receiving TTs [18]. Here, we report the qualitative findings of the interviews and focus group conducted as part of the first phase of this work. Our work builds on the exploration of that of Fauske and colleagues [19] which presents the patient perspective on GIST treatment, but we also include 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 to that of HCPs.

**Methods**

*Participants*

Patients with a non-resectable advanced, or metastatic GIST treated with a TKI were recruited from the Royal Marsden Hospital, University Hospital Southampton, and the GIST UK Support Group. HCPs from different hospitals across the UK with experience of delivering care to patients with GIST were also invited for an interview.

*Procedure*

UK Ethical and research governance approvals were obtained (NRES 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 relating to educational attainment, employment status and domestic situation were completed together with participants. Participants were asked to self-report co-morbidities and to complete a measure of performance status. Clinical data were collected from medical files. For HCPs, collected information included gender, specialist discipline and number of years working with GIST patients. See Table 1 for an overview of the details recorded.

*Interviews*

Semi-structured interviews with patients and HCPs were carried out by one researcher (SS), either face to face or over the telephone. A face-to-face focus group was run at the University Hospital Southampton (UHS) by a facilitator (SS) with the help of a moderator. The content of the interview schedules was informed by the EORTC QLG 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 from their interactions with patients. The patient, HCP and focus group interview schedules are available as supplementary material (supplementary material 1). Steps to protect 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 [21] to facilitate analysis according to the principles of thematic analysis [22]. Transcripts were independently reviewed by two reviewers (SS and SV). Coding assumptions were continually reviewed, and an audit trail was kept of all the 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 as 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 a GIST were interviewed: five from UHS, five from the Royal Marsden Hospital, and nine members of a patient support group for people with a GIST across the UK. In addition, five patients formed part of a focus group delivered 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 a first-line treatment to all patients, six had progressed onto sunitinib, of which three were currently on regorafenib as a third-line of 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 NHS trusts across the UK were interviewed. Three of the HCPs had over 10 years of experience in the care of patients with a GIST, the other HCPs had less than 5 years of experience of which one had less than 1 year of experience. For a complete overview of the participant characteristics, see Table 1.

**Table 1. Participant characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
| **Patient characteristic** | Total **Interviewed** (n=19) | Total **Focus Group** (n=5) | **Total**(n=24) |
| n (%) | n (%) | n (%) |
| Gender |  |  |  |
| 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 |  |  |  |
| Less than compulsory | 0 | 0 | 0 |
| 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 | 1 (4.2) |
| Retired | 12 (63.1) | 1 (20.0) | 13 (54.1) |
| Sick leave | 1 (5.3) | 0 | 1 (4.2) |
| Unemployed | 0 | 1 (20.0) | 1 (4.2) |
| Education | 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 | 1 (4.2) |
| Others | 0 | 1 (20.0) | 1 (4.2) |
| Missing | 0 | 1 (20.0) | 1 (4.2) |
| Disease status |  |  |  |
| Localised | 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 | 1 (4.2) |
| >15 | 1 (5.3) | 0 | 1 (4.2) |
| Co-morbidities |  |  |  |
| None | 12 (59.2)) | 2 (40.0) | 14 (58.3) |
| Arthritis | 3 (15.8) | 0 | 3 (12.5) |
| Thyroid | 2 (10.5) | 1 (20.0) | 0 |
| Cardiac | 1 (5.3) | 0 | 1 (4.2) |
| Chronic Fatigue Syndrome | 1 (5.3) | 0 | 1 (4.2) |
| Renal | 0 | 1 (20.0) | 1 (4.2) |
| Parkinsons disease | 0 | 1 (20.0) | 1 (4.2) |
| Eye  | 0 | 1 (20.0) | 1 (4.2) |
| Depression | 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 | 1 (4.2) |
| 80 | 2 (10.5%) | 0 | 2 (8.3) |
| 75 | 2 (10.5%) | 1 (20.0) | 3 (12.5) |
| 60 | 1 (5.3) | 0 | 1 (4.2) |
| Missing | 1 (5.3) | 0 | 1 (4.2) |
|  |  |
| **HCP characteristic** | Total **Interviewed** (n=6)n (%) |  |  |
| Gender |  |  |  |
| Female | 4 (67%) |  |  |
|  Male | 2 (33%) |  |  |
| Specialist discipline |  |  |  |
| Medical / Clinical Oncology | 4 (67%) |  |  |
| Nursing | 2 (33%) |  |  |
| Number of years specialised in the care of patients with GIST |  |  |  |
| <1 year | 1 (17%) |  |  |
| 1-5 years | 2 (33%) |  |  |
| 5-10 years | 0 |  |  |
| >10 years | 3 (50%) |  |  |

**Gastrointestinal problems**

Collectively, symptoms relating to gastrointestinal (GI) problems were reported by almost all participants except for one patient within the focus group (Table 2). Gastrointestinal symptoms covered diarrhoea (*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 diarrhoea, vomiting (*n*=5), flatulence (*n*=3), inability to eat (*n*=2), reflux (*n*=2), stomach pain (*n*=2), and gastritis (*n*=1). Diarrhoea was not only the most commonly reported symptom, but also identified as the most troublesome symptom by five participants affecting everyday activities including social functioning and requiring careful management, resulting in the introduction of anti-diarrhoea medications or dose reductions:

*”Diarrhoea’s the main thing, it does affect my day”* (FG002, 62 years, imatinib).

*“I just wish I could do something to stop the diarrhoea 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).

Where imatinib is administered daily, sunitinib can be administered in a fractioned 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 diarrhoea when I’m on it and as soon as I have that 7 days off, I dry up without being rude*… *the diarrhoea I can guarantee as soon as I’m on it*” (RMG003, 38 years, sunitinib).

One HCP reasoned that patients who had already undergone gastrointestinal 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 diarrhoea 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 diarrhoea 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), mentioned by 14 patients, 1 focus group participant, and 3 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 only reported by 4 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 of appetite:

*“I’ve got to admit I was a real chip lover, greasy and McDonalds I found revolting and now its reversed. Fatty foods I’m not so keen on and yes I can’t be bothered to eat is a problem”* (FG002, 62 years, imatinib)*.*

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

“*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).

Also indigestion was a common reported GI complain (*n*=8), which can result in loss of appetite as was expressed by one patient (GSUK007, 66 years, imatinib):

*“…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”.*

**Table 2. Reported issues in alphabetic 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 |
| Exacerbation of existing condition | 1 | 1 | 2 | 4 |
| Eye problems | 7 | 3 | 1 | 11 |
| * Subconjunctival haemorrhages
 | 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 |
| Gastrointestinal problems | 19 | 4 | 6 | 29 |
| * Diarrhoea
 | 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 |
| * Depigmentation
 | - | - | 2 | 2 |
| * Hair loss or thinning
 | 5 | - | 1 | 6 |
| * Hair colour change
 | 4 | - | - | 4 |
| * Change of hair structure
 | 2 | - | - | 2 |
| Headache | 3 | - | - | 3 |
| Heart problems | - | - | 2 | 2 |
| Inability to walk | 3 | - | - | 3 |
| Laboratory abnormalities |  |  |  |  |
| * Haematology (e.g. anemia, leukopenia, neutropenia, thrombocytopenia)
 | 1 | - | 3 | 4 |
| * Liver function abnormalities
 | - | - | 1 | 1 |
| * Thyroid function problems
 | 1 | - | 3 | 4 |
| Mouth problems | 4 | - | 4 | 8 |
| * Sore mouth
 | 2 | - | 4 | 6 |
| * Mouth ulcers
 | 2 | - | 1 | 3 |
| * Sensitive mouth or tongue
 | 2 | - | 1 | 3 |
| * 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 (sore, blocked, bleeds) | 1 | - | - | 1 |
| Lack of energy  | 2 | - | - | 2 |
| Oedema | 14 | 2 | 6 | 22 |
| 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 |
| * Frustrations
 | 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 colour 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 (painful, excess mucus) | 2 | - | - | 2 |
| Tiredness | 16 | 3 | 6 | 25 |
| Trouble sleeping | 8 | 1 | 1 | 10 |
| Urinary function  | 3 | - | - | 3 |
| * Urgency
 | 2 | - | - | 2 |
| * Urinary infection
 | 1 | - | - | 1 |
| * Night time urination
 | 1 | - | - | 1 |
| Voice alternation  | 1 | - | - | 1 |
| Weakness | 6 | - | - | 6 |
| Weight gain | 2 | - | - | 2 |
| Weight loss | 5 | 1 | - | 6 |

**Tiredness**

The second most prevalent group of symptoms reported by 16 patients, 3 focus group participants, and all six HCPs was tiredness (*n*=25), 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 in this one patient (GSUK002, 62 years, regorafinib):

*“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”.*

A focus group participant (FG003, 53 years, imatinib) 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”.*

One patient referred to the fatigue getting worse due to 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 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 diarrhoea 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).

**Oedema**

Oedema covering swelling or fluid retention in any region of the body including limbs, face, eyes (referred to by HCPs as periorbital oedema) and scrotum was the third most prevalent collective group of symptoms (*n*=22), reported by 14 patients, 2 focus group participants and all HCPs. The following patient described oedema 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 build-up of water*” (GSUK003, 44 years, imatinib).

**Skin, eye, mouth, and hair problems**

Twenty-one participants (13 patients, 3 focus group participants and 5 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 colour 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, recognized by nine participants (6 patients and 3 HCPs). One patient who had previously been treated with sunitinib suffered from hand-foot syndrome:

*“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 the following patient (GSUK001, 56 years, sunitinib):

“*I think without a doubt it’s the hand-foot syndrome because walking can be extremely painful”*

A total of 11 participants (7 patients, 3 focus group participants, 1 HCP) reported eye problems, including subconjunctival haemorrhages 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 8 participants (4 patients and 4 HCPs) and covered a 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 symptoms related to hair. Two HCPs described depigmentation of hair, other symptoms included hair loss or thinning (*n*=6), hair colour change (*n*=4) and change of hair structure (*n*=2). One patient experienced hair changes on both imatinib and sunitinib:

“*I’ve had significant hair loss or colour 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 colour and kind of texture and it went slightly orangey in fact having been dark brown. Back to Sutent, my hair has gone quite grey 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 and joint pain, weakness**

Muscle cramps were reported by 21 participants (12 patients, 5 focus group participants and 4 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).

While from the patients’ perspective, cramps were common and leading to insomnia or trouble sleeping:

“…*cramps …which I think is quite common. Night-time 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 5 patients and 1 HCP. Six patients experienced weakness or a loss of strength, where 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 only reported 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 twelve participants (8 patients, 1 focus group participant, 3 HCPs) mentioned psychological symptoms experienced since starting treatment. Both patients (*n*=4) and HCPs (*n*=3) reported anxieties, of which HCPs described 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 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 its come back? … the diagnosis sat on my shoulder for quite a while I mean it’s still there but its receded a lot as time has gone by”* (GSUK005, 61 years, imatinib).

In contrast, symptoms of depression (*n*=6) were only expressed 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 frustrations relating to lowered 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 keep positive.

**Trouble sleeping**

Trouble sleeping was mentioned by 10 participants (8 patients, 1 focus group participant, 1 HCPs), although one 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 maybe something to look at definitely*”(HCP006).

**Shortness of breath**

Shortness of breath was reported by eight participants (6 patients, 2 HCPs), regarded by patients as not particularly serious. Patients reasoned that age and not being physically fit attributed to the 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 mylosuppressed, most of them are anaemic to a degree, some of them are leucopenic, neutropenic, sometimes thrombocytopenic usually not to a clinically significant level but maybe the anaemia is contributing to the tiredness. They can also have liver function abnormalities”* (HCP002).

In addition, sunitinib or regorafenib induced high blood pressure 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, referred to thyroid function issues (e.g., hypothyroidism). An issue mostly seen in laboratory findings of sunitinib-treated patients without clinical symptoms:

“*thyroid function depression is frequent”* (HCP002).

Two HCPs referred to heart problems:

“W*e 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 its causality fully to the TKI treatment. In our study, 21 participants mentioned a possible difficulty in attributing causality and could not rule out other influencing factors. For example, side effects could be attributed to or influenced by co-morbidities, older age, the disease itself, or previous surgery. The impact of side effects on the patient's life were 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 pointed out a difference in the side effect profile of imatinib compared to other TKIs, with sunitinib and regorafenib being more toxic. Patients meanwhile 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. I look upon it as I’m got my life ‘this is a small price to pay for having my life”* (RMG004, 61 years, imatinib).

Patients also acknowledged that they have learned to live with it, referring to 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).

Although other patients also expressed 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 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 (FG001, 51 years, imatinib) expressed that being alive was more important than the experienced side effects:

“*We’re still here that’s the main thing, isn’t it?”*

Focus group participants also valued the fact that fellow TKI treated GIST patients recognized the mentioned 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 of the focus group admitted not to mention side effects due to 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 to manage and reduce the experienced side effects. From the side of the HCP, supportive medications (e.g. anti-emetics, anti-diarrhoeas, anti-depressants, 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 theatre 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).

In addition, other patients indicated modifying their diet, quitting their job, taking a drug holiday. One patient expressed carrying on with life despite 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”* (SUG003, 82 years, imatinib).

“*I think we have been very lucky haven’t we with Glivec*” (SUG003, 82 years, imatinib).

**Discussion**

To our knowledge, this is the second qualitative study to report the side effects of TKIs in the treatment of advanced and metastatic GIST from a patient’s perspective, and the first to draw comparisons with reports from HCPs. In our study, all patients experienced multiple TKI related side effects. GI problems were most frequently reported, followed by fatigue, oedema, muscle cramps, and skin problems. Interestingly, cognitive problems and psychological problems other than anxiety, were only expressed by patients. Fatigue, diarrhoea, 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 are the well-known side effects of TKI treatment, such as tiredness, diarrhoea, nausea, lack of appetite, oedema, muscle cramps, and rash [6]. In addition, the specific sunitinib and regorafenib associated side effects including hand-foot skin reaction and mouth problems [23, 24], were also commonly reported by HCPs and patients treated with either sunitinib or regorafenib. For some reported side effects, it was difficult to assign its causality fully to the TKI treatment as side effects could be attributed to or influenced by co-morbidities, older age, the disease itself, or previous surgery. In a review about the safety profile of imatinib in chronic myeloid leukaemia and GIST [25], severe nausea and diarrhoea were more common in GIST patients when treated with the same dose, suggesting that the origin of GIST and the fact that GIST patients often had previous gastrointestinal surgery might have been responsible for GI symptoms.

As shown in table 2, patients in our study also reported side effects less recognized by HCPs such as eye problems, in particular subconjunctival haemorrhages or 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 other 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 determines the safety, traditionally measured by applying the physician-reported CTCAE. This might not be the appropriate measure to report TKI related side effects [8], together with the fact that HCPs tend to underreport symptoms [11, 12]. Using the physician-reported CTCAE may have resulted in an underestimation of the side effects of TKI treatment. The use of patient-reported outcomes measures (PROMs), such as the PRO-CTCAE or the EORTC-SBQ [18], could be a better measure for TKI related side effects. Nevertheless, a recent published paper reported that some frequently reported TKI related symptoms, e.g. alopecia, were not fully covered by the currently available PROMs [30].

Cognitive problems including forgetfulness and difficulty concentrating, and psychological problems other than anxiety were underreported by HCPs. A minority of HCPs reported on anxiety, their quotes often related to the stress or worries patients experienced around scans and follow-up, referred to as ‘scanxiety’. A limited number of studies have addressed psychological problems. Custers et al. [31] specifically studied fear of cancer recurrence or progression, a common psychological issue among GIST patients with 52% of the patients experiencing high levels of fear, resulting in a lower global quality of life and more distress compared to patients experiencing lower levels of fear. A qualitative paper addressed the emotional journey of GIST patients, consisting of five different stages including crisis, hope, adaptation, ‘new normal’ and uncertainty [32]. A more recent qualitative study by Fauske et al. [33] 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. 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 health-related quality of life of GIST patients was previously studied. The prevalence of severe fatigue was higher among GIST patients, 30% compared to 15% in healthy controls [34]. Severely fatigued patients reported a lower global quality of life as well as increased impairment in all the functional domains of HRQoL, less favourable 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 fatigue. Internet-derived cognitive behavior therapy or an online psychoeducation program may be more helpful for patients to manage their fatigue [35]. In our 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 diarrhoea, can also have a significant impact on the social lives of patients. In the case of diarrhoea, the 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 effect hampered the daily lives of patients, and forced patients to adjust their lives. This was also reported by Fauske et al, more than half of the metastatic GIST patients described partially debilitating self-reported side effects that had a detrimental impact on their lives, which urged 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 we 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 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 generalisability 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. Only recently, fourth-line ripretinib and avapritinib were approved and therefore no patients on these newer treatments have been interviewed. Third, this study only focused 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**

In conclusion, our results underline the importance of including the patient´s perspective as all GIST patients experienced TKI related side effects that are not always recognized by HCPs. We found a gap in symptom reporting, in particular for cognitive and psychological symptoms, between patients and HCPs. A worrying conclusion, which can easily be overcome if during the consultations HCPs always include a question about how the disease and treatment affect the patient’s daily life. Besides, patients should be made aware that HCPs are interested in all side effects, also in their low mood or difficulties remembering things, as some patients may feel they should be grateful that treatment is available and that they are still alive. Capturing this now-missed information can have important implications for the patients’ HRQoL, patient-HCP communication, (shared) decision making, engagement with treatment, and clinical outcomes. Besides the side effects and the limitations patients experienced as a consequence of their TKI treatment, GIST patients also face psychological and social challenges that hamper their HRQoL. It remains unknown whether patients with a 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 GIST patients themselves experience the side effects of TKI treatment.
* The most troublesome symptoms were fatigue, diarrhoea, 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 HCPs.
* HCPs seem to underestimate the impact of side effects on the daily lives of patients. Most of the HCPs described patients as doing well while on TKIs, and side effects as tolerable. Patients meanwhile 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 can have important implications for the patients’ HRQoL, patient-HCP communication, (shared) decision making, engagement with treatment, and clinical outcomes.

**Tables and figures**: Table 1. Participant characteristics, Table 2. Reported issues in alphabetic order

**Supplementary Materials**: Supplementary material 1: Patient, HCP and focus group interview schedules.

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