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ORIGINAL ARTICLE

Taste, smell and mouthfeel disturbances in patients with gastrointestinal stromal tumors treated with tyrosine-kinase inhibitors

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Abstract

Context Taste, smell, and mouthfeel disturbances are underrated and underreported, but important side effects of anti-cancer medication. These symptoms are associated with a lower quality of life (QoL). The prevalence and the impact of taste, smell, and mouthfeel disturbances on daily life in patients with a gastrointestinal stromal tumor (GIST) are largely unknown.
Objectives This exploratory study assessed the prevalence and type of taste, smell, and mouthfeel disturbances and their impact on daily life and QoL in patients with a GIST treated with a tyrosine-kinase inhibitor (TKI).
Methods Patients currently treated with TKIs for GIST completed a standardized questionnaire. The questionnaire addressed changes in taste, smell, and mouthfeel and, if changes occurred, impact on daily life and QoL. Statistics are descriptive.
Results A total of 65 GIST patients on TKI treatment completed the questionnaire. Of these patients, 79%, 12%, and 9% currently used imatinib, sunitinib, and regorafenib respectively. Taste, smell, and mouthfeel disturbances were reported by 25 (38%), 15 (23%), and 36 (55%) patients respectively. Salty and sweet tastes were mostly affected, respectively in 14 and 13 patients. A dry mouth was experienced by 29 (45%) patients. Taste disturbances were more often reported to have impact on daily life and QoL (80% and 60%) than smell (47% and 31%) and mouthfeel disturbances (47% and 30%).
Conclusion Taste, smell, and mouthfeel disturbances are frequent side effects of TKIs in GIST patients. Daily life and QoL are affected in a considerable number of those patients.
Trial registration ClinicalTrials.gov Identifier: NL7827 (2019–06-25).

Keywords Gastrointestinal stromal tumor · Taste disturbances · Smell disturbances · Tyrosine-kinase inhibitors · Imatinib

Introduction

Taste disturbances are important side effects of systemic anti-cancer therapies in general and are associated with a lower quality of life (QoL) and a decreased nutritional intake [1–5]. The development of taste alterations is related to changes in smell and food texture perception. Patients receiving chemotherapy are after losing their hair but before tiredness and nausea, mostly bothered by changes in the way food tastes [6]. However, taste and smell disturbances are underreported due to lack of spontaneous communication of these alterations by patients. Besides, taste and smell changes are considered as unavoidable by both patients and healthcare professionals, so routine assessment is not daily practice [7].

Gastrointestinal stromal tumors (GISTs) are a rare cancer type of the gastrointestinal tract with an incidence of 10–15 per million per year [8]. The majority of GIST patients are treated in a (neo-)adjuvant or palliative setting with a tyrosine-kinase inhibitor (TKI). TKIs are a type of targeted therapy and are taken daily orally. Standard first-line systemic therapy in GIST is imatinib. In case of intolerance or

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progression, second-line treatment is sunitinib and third-line is regorafenib [9].

Taste disturbances are commonly present in patients using TKIs. The prevalence of taste alterations depends on the type and treatment dose of the TKI, but it is not clear if, when reported, taste disturbances are mentioned spontaneously by patients or are asked for specifically [10]. In GIST patients, taste disturbances (Common Terminology Criteria for Adverse Events (CTCAE) grades 1–2) are reported in 2–14% and 8–18% of patients using a standard dose of respectively imatinib and sunitinib [11–14]. However, most studies on imatinib and sunitinib in GIST patients do not mention changes in taste as a side effect, so it is arguably underrated and underreported. Oral mucosal changes, which can lead to taste disturbances, are common in patients treated with sunitinib, but only present in few patients on imatinib [15]. The prevalence of taste disturbances and a dry mouth was reported in 1–10% patients using regorafenib; however, this study included not only GIST patients [16].

Patients usually take TKIs for years and therefore have to cope with side effects for a long period of time [17]. The course of taste alterations as a side effect of TKIs is not known yet. Therefore, side effects may be more prevalent than was described in TKI studies that focused on early side effects. In addition, previous studies do not mention the type of changes in taste, smell, and mouthfeel and their impact on daily life and QoL. At last, considered the many factors that determine taste disturbances, it is not unreasonable to assume that different tumors are related to differences in taste disturbances. Thus taste, smell, and mouthfeel disturbances should be studied in GIST patients only. For example, GIST and chronic myeloid leukemia (CML) have a different impact on the immune system, and as a result, even if treated both with the same TKI imatinib, taste disturbances may be different. Therefore, this exploratory study assessed the prevalence and type of taste, smell, and mouthfeel disturbances specifically in GIST patients using TKIs and the impact of these disturbances on daily life and QoL.

Methods

Outcome

The primary outcome of this study was the proportion of patients reporting taste, smell, and mouthfeel alterations. Secondary outcomes were data on the type of taste disturbances and in particular alterations of bitter, sweet, salt, sour, and the presence of a metallic or continuous taste in the mouth. Furthermore, insight on the impact of taste, smell, and mouthfeel alterations on daily life and QoL of the patients was investigated.

Participants

This study was conducted in three Dutch specialized GIST centers: the University Medical Center Groningen (UMCG), the Netherlands Cancer Institute (NKI), and the Erasmus MC Cancer Institute (EMC). Potential participants were selected from these centers by convenience sampling. All potential participants from the UMCG who were registered in the Dutch GIST registry, a database containing all patients with GIST treated in one of the Dutch GIST centers since 2009, were approached for this study [18]. The same number of potential participants was randomly selected from the Dutch GIST registry from the NKI and the EMC. Patients, who were currently treated with a TKI for a GIST, understood spoken and written Dutch and were older than 18 years were included. The study was approved by the medical ethical committees of the UMCG, NKI, and EMC and was performed according to the Dutch law and registered at the Netherlands Trial Register (NL7827).

Procedure

Data collection took place from July 2019 to January 2020. Potential participants were sent a letter by mail that explained the study design. Within 2 weeks, they were contacted by telephone and asked explicitly for consent to participate and to collect information from their medical records. After consent, the questionnaire as described below was completed by the patient by phone. Information about patient and tumor characteristics (including gender; age; medical history; current medication; location of primary tumor; resection history; and indication, duration of current use, and previous use of TKI treatment) was collected from the patients electronic medical file after consent was given. Data were pseudonymized during data collection by use of a code list. The code list was kept separately from the data in an electronic file. Patients were excluded if they had a history of disease with taste and smell disturbances or currently used medication that strongly affect taste and smell.

Questionnaire

The questionnaire was developed specifically for this study, as we are not aware of any questionnaire that focuses on taste, smell, and mouthfeel perception and impact. The questionnaire was based on two previously used questionnaires and consisted of three parts (supplement A) [19, 20].

The first part of the questionnaire addressed changes in taste, smell, and mouthfeel, with changes of the preferred temperature on which food and drinks should be served as a specific component of mouthfeel. A participant could

address more than one type of change in taste, smell, or mouthfeel. This part of the questionnaire was completed by all participants. If a participant had taste, smell, or mouthfeel disturbances, questions regarding impact on daily life and QoL were asked about this specific disturbance with a 4-point Likert scale (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much).

The second part was only completed by patients who reported changes in taste in the first part. First, the level of severity of taste alterations was asked using the same 4-point Likert scale as mentioned before and the course of changes in taste was asked using a 5-point Likert scale (1 = decreases, 2 = decreases a bit, 3 = stable, 4 = increases a bit, 5 = increases). Open questions on specific food likings and coping with changes in taste were asked next. Specific changes in intensity in basic tastes (salty, bitter, sweet, and sour) were reported using a 5-point Likert scale (1 = much weaker, 2 = slightly weaker, 3 = no change, 4 = slightly stronger, 5 = much stronger). If changes in basic tastes were reported, impact and coping were asked with respectively the previously used 4-point Likert scale and with an open question. At last, questions regarding the presence of metallic taste and a continuous taste were answered.

The third part of the questionnaire was completed only by patients who reported changes in smell in the first part. The level of severity of smell perception was asked first with the 4-point Likert scale. Next, open questions concerning coping with bad or distorted smells, specific odors, and avoiding of these specific odors were asked.

Statistical analyses

Statistics are descriptive and are reported as percentage or mean with standard deviation (*SD*). Possible correlations between prevalence of taste, smell, and mouthfeel disturbances were investigated with cross tables. The correlation between impact on daily life and QoL was studied with Spearman's rank correlation coefficient. $p < 0.05$ was considered significant. SPSS Statistics 23 (IBM Corporation, Armonk, NY) was used to perform the analyses.

Results

Baseline characteristics

In total, 84 patients (26 from the UMCG, 28 from the NKI, and 30 from the EMC) were contacted and asked to participate. Of those, 68 (81%) gave informed consent and responded to the questionnaire. Completing the questionnaire took about 15 min. Three patients were excluded: two patients were excluded due to a history of diseases with possible taste and smell disturbances and one patient was excluded because of a recent treatment with chemotherapy, leaving 65 patients for further analysis. Imatinib, sunitinib, and regorafenib were currently used by 51 (79%), 8 (12%), and 6 (9%) patients, respectively. The median duration of current TKI treatment was 30 months (IQR 13–58 months). Characteristics of the participating patients are shown in Table 1.

Prevalence of taste and smell disturbances

Of the 65 evaluable patients, 25 (38%) reported at least one taste disturbance, of whom 14 tasted less than before treatment, 18 experienced changes in taste, and one reported new unpleasant tastes in the mouth (Fig. 1A). Smell alterations occurred in 15 of the 65 patients (23%). Of these 15 patients, four had a diminished smell, nine had changes in familiar scents, and three experienced new unpleasant scents (Fig. 1B). Fourteen patients experienced solely alterations in taste and 11 patients reported both taste and smell disturbances. Gender did not influence the presence of taste and smell disturbances.

Table 1 Baseline characteristics

Characteristics	Patients ($n = 65$)
Gender	
Male	38 (59%)
Age (years), median [IQR[a]]	67 [58–75]
Location of primary tumor	
Stomach	25 (38%)
Small intestines	30 (46%)
Rectum	5 (8%)
Other/unknown	5 (8%)
Resected primary tumor	45 (69%)
Time since resection primary tumor (months), median [IQR]	75 [36–130]
Intention of current treatment	
Neo-adjuvant	4 (6%)
Adjuvant	10 (15%)
Palliative	51 (79%)
Current TKI[b] type	
Imatinib	51 (79%)
Sunitinib	8 (12%)
Regorafenib	6 (9%)
Duration of current TKI treatment (months), median [IQR]	30 [13–58]
TKI dose	
Imatinib (mg), median [IQR]	400 [400–400]
Sunitinib (mg), median [IQR]	31 [20–38]
Regorafenib (mg), median [IQR]	120 [70–160]

[a]*IQR*, interquartile range, [b]*TKI*, tyrosine-kinase inhibitor

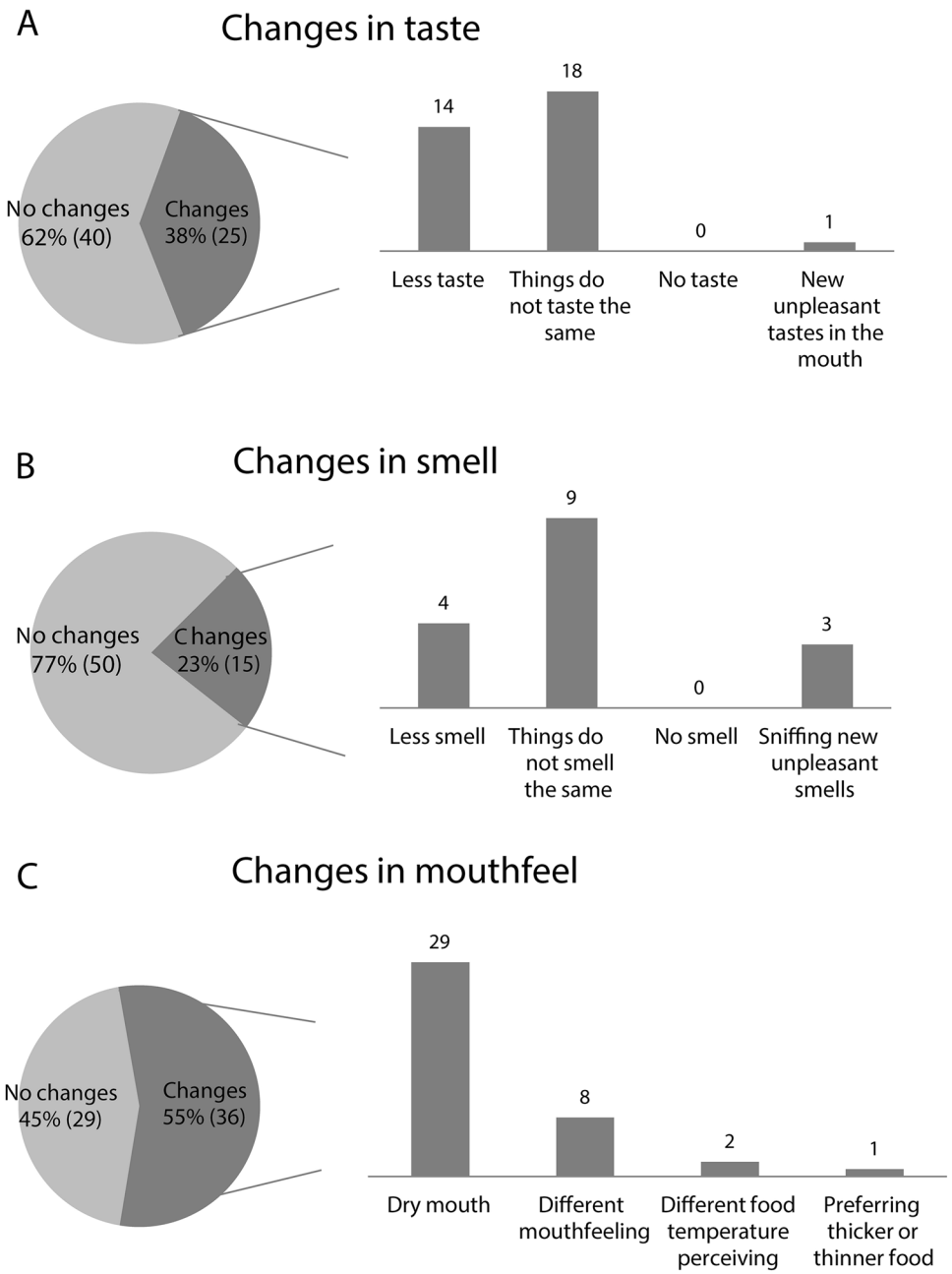

Fig. 1 Reported taste, smell and mouthfeel disturbances in patients with GIST ($n=65$) using tyrosine-kinase inhibitors. More than one type of change in taste, smell, or mouthfeel could be addressed. **A** Changes and type of changes in taste. **B** Changes and type of changes in smell. **C** Changes and type of changes in mouthfeel

Changes in mouthfeel were described by 36 of the 65 patients (55%). Of those patients, 29 experienced a dry mouth, eight had a different tactile sensation in the mouth, two perceived temperature of foods differently, and one preferred other textures (Fig. 1C). Of the 29 patients who reported a dry mouth, 13 (45%) did not report taste or smell disturbances. The preferred temperature on which food and drinks should be served was altered in 15 of the 65 patients (23%). Of these patients, nine preferred food and drinks served at room temperature, three preferred at fridge temperature, and three a bit warmer.

Characteristics of taste and smell disturbances

In patients with taste disturbances ($n=25$), nine (36%) reported that their taste had changed a little, 13 (52%) that it had changed quite a bit, and three (12%) reported that it had changed very much. A stable course of these alterations was experienced by 14 (56%) patients, two (8%) were almost back at their normal level of taste, and five (20%) experienced a small decrease in the alterations. Four (16%) patients reported an increase in taste disturbances. As displayed in Fig. 2, patients reported

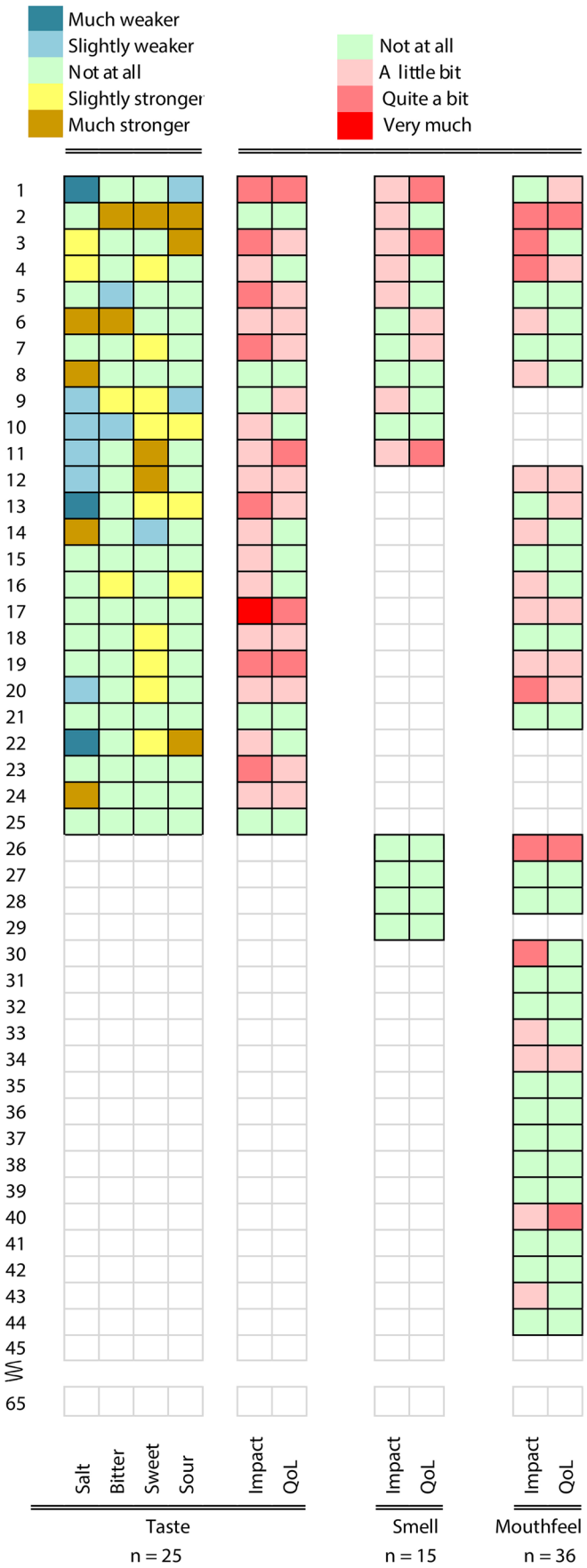

Fig. 2 Changes of salt, bitter, sweet, and sour in patients with taste disturbances and impact on daily life and QoL in patients with taste ($n=25$), smell ($n=15$), and mouthfeel ($n=36$) disturbances. Each number (y-axis) and corresponding row represents one patient. Patients with no disturbances are not displayed

a high variation in alterations of the four basic tastes. Some patients reported taste disturbances in general, but did not report changes in salt, bitter, sweet, or sour. Salt and sweet were the tastes most often altered, respectively in 14 (56%) and 13 (52%) of the patients with taste disturbances. Some patients experienced an increased taste in sweet and salt. However, salt was also reported to have less taste by some patients. A metallic taste was reported by three (12%) patients with taste alterations, of whom two beyond meals and one during meals. Two (8%) patients experienced a continuous taste, calling it respectively a musty and chemical taste. Food or drinks that tasted good before the TKI treatment, but not anymore, were reported by 17 (68%) patients with taste disturbances. Seven (28%) patients reported food and drinks that they did not like before treatment, but now did.

Of the 15 patients reporting smell disturbances, nine (60%) reported a little change in their smell, four (27%), and one (7%) patient respectively reported that smell had changed quite a bit and very much. One patient reported smell disturbances in the first part of the questionnaire, but stated that smell experience had not changed in the second part of the questionnaire. The smells that patients reported most frequent to be stronger were smells from the kitchen, meat, fish, perfume, and smoke. These were also the smells that most of them tried to avoid, except for perfume. Some patients did not avoid any smells.

The impact on daily life and QoL of taste and smell disturbances

Taste, smell, and mouthfeel disturbances had respectively impact on daily life in twenty (80%), seven (47%), and 17 (47%) of the patients with these alterations. With taste disturbances, 12 of the 20 patients experienced a little bit impact on daily life, seven quite a bit, and one very much. Smell had less impact on daily life; all seven patients reported a little bit impact. Mouthfeel had a little bit impact on daily life in eleven patients and quite a bit impact in six patients. QoL was lower due to taste, smell, and mouthfeel disturbances in respectively 15 (60%), five (33%), and 11 (31%) of the patients (Fig. 2).

To cope with changes in taste intensity in general, most patients did nothing or experimented with new flavors or avoided stronger flavors. To cope with smell alterations, eight out of the 14 (57%) patients did not do anything. Avoiding certain scents and increased room ventilation were mostly used as coping styles.

Impact on daily life and QoL were correlated in taste ($\rho = 0.64$ ($p < 0.05$)) and mouthfeel ($\rho = 0.51$ ($p < 0.05$)), but not for smell ($p = 0.28$).

Discussion

In this study, taste, smell, and mouthfeel disturbances were found to be a side effect with high prevalence in GIST patients treated with TKIs. Furthermore, impact on daily life and diminished QoL were reported due to the disturbances in taste, smell, and mouthfeel.

Our study reveals a more than twofold higher prevalence of taste disturbances than described previously [12–14, 16]. This seemingly discrepancy could be due to underreporting of taste disturbances in previous studies or a different timing of asking about taste and smell disturbances. Whereas previous studies report all side effects in GIST patients, this study is, to our knowledge, the first to explore the occurrence of taste, smell, and mouthfeel alterations exclusively in GIST patients. Next, this study measured the effects of the TKI in patients with a high variance in current treatment duration, with the majority of patients using TKI longer than 12 months (with a median treatment duration of 30 months). In contrast, other studies measured side effects at an earlier time point [12–14, 16]. Another factor that could explain the high prevalence of taste, smell, and mouthfeel disturbances in this study is that explicitly asking for these disturbances might have increased awareness for them. However, it should be noted that this study has a small sample size and therefore meaningful statistics could not be performed.

Studies on alterations of specific tastes in GIST patients using TKIs have not been performed so far. In CML, imatinib is the first-line treatment [21]. The pharmacokinetics of imatinib in GIST and CML patients are similar [13]. Taste disturbances have been reported in 12.8% of the CML patients using imatinib [22]. However, this is, again, a study on side effects in general of imatinib in CML patients and not specifically a study on taste disturbances. The long-term safety of imatinib in CML patients has been studied, but taste disturbances are not mentioned in these studies. Further studies are needed to determine whether taste alterations in patients with different tumors treated with similar TKIs are corresponding.

In patients treated with chemotherapy, the threshold to detect sweet and salty tastes is usually described to be higher, while our patients reported a lower detection for sweet and a varying higher and lower detection for salt [23]. It should be noted that our study used subjective data and the detection could therefore be misperceived by the patients. A high prevalence of dry mouth is also reported in patients using chemotherapy (56%), but not in studies on TKIs [12, 24]. This could, again, be an underreported side effect. The occurrence of a dry mouth can be an isolated symptom and does not have to accompany taste or smell disturbances.

The underlying mechanisms of taste and smell disturbances in patients treated with a TKI are not yet

established. Several hypotheses on the potential mechanisms exist, but it is not understood why differences in the perception of taste and smell occur between patients using TKIs. A diminished amount of saliva and also oral mucositis can occur in both patients using chemotherapy and TKIs, which could lead to diminished taste and smell [10, 23, 25]. A mechanism that may explain specific changes in sweet, salt, bitter, and sour taste is the inhibitory effect of imatinib, sunitinib, and regorafenib on β-catenin. β-catenin regulates the differentiation of progenitor cells into taste cells [10, 26]. Taste cells have distinct receptors for the different basic tastes. Type II taste cells express receptors for sweet and bitter and require high levels of β-catenin for differentiation and could therefore be more affected by TKIs. Type III cells express receptors for sour and possibly salt and need less β-catenin to differentiate. Therefore, type III cells could be less affected by TKIs. It is less known if type III cells can identify salt, so the disturbance of salty taste in this study could be explained by this uncertainty. At last, taste and smell changes could be a result of a degenerative effect of TKIs on neurons, which has been shown in vivo with sunitinib [10, 27].

The reduction in QoL due to taste, smell, and mouthfeel disturbances in this study is in line with previous studies [2, 4, 28]. Despite reported impact of taste, smell, and mouthfeel disturbances on daily life and QoL, most patients did nothing to cope with changes in taste and smell intensity. This could be explained by acceptance of the taste and smell disturbances and the feeling of helplessness, for patients could possibly think a remedy against taste and smell disturbances is not available. In addition, patients do not always comply to dietary recommendations and relapse to old nutritional habits [29].

Both a limitation and strength of this study is the focus on patients using imatinib. The sample size in the sunitinib and regorafenib group is small, so no firm conclusions can be drawn on sunitinib and regorafenib separately. On the contrary, the majority of patients were on imatinib, which is the clinically the most relevant TKI in GIST patients.

Due to lead-time bias, underreporting of taste and smell disturbances cannot be ruled out in the current study. Patients that use TKIs for a long time could have forgotten that their taste and smell changed shortly after starting using a TKI. Furthermore, reporting of the alterations by patients is subjective and some patients could find it hard to assess the exact type of changes. Most of the patients reporting smell disturbances also experienced taste disturbances. Since flavor is the combination of perceptions of smell, taste, and mouthfeel, it is possible that patients reported smell alterations as taste alterations [30].

As taste, smell, and mouthfeel disturbances lead to a lower QoL and could decrease nutritional intake, healthcare professionals should be aware of this side effect. Taste, smell, and mouthfeel disturbances should be discussed with the patient before starting with a TKI. Furthermore, patients with taste, smell, and mouthfeel disturbances can be referred to a dietician for support and advise on the adjustments of their diet [31]. In addition, timely referral to a dental surgeon is important for oral hygiene education and oral care to improve comfort.

Further research with more patients using sunitinib and regorafenib should be performed. This exploratory study could be enlarged and prospectively performed, in order to allow testing for statistical significance for associations between taste, smell, and mouthfeel disturbances and TKI type, the treatment duration and the course of the alterations, with consideration of the patients baseline situation and nutritional intake of patients to assess intake fluctuations and impact upon oral intake, diet, and nutrition. In addition to the custom made questionnaire applied in the present study, the use of validated questionnaires such as the Appetite, Hunger and Sensory Perception (AHSP), Patient-Generated Subjective Global Assessment (PG-SGA), and chemotherapy-induced taste alteration scale (CiTAS) is recommended [32–34]. Considered the burden of taste and smell disturbances for patients, patient-reported outcome measures should become important study endpoints. In daily life, the taste disturbances that patients experience are more important than disturbances that can be measured objectively but that do not cause problems. Therefore, in this explorative study, the use of a questionnaire as a subjective measure was selected. In a future in-depth study however, also objective taste and smell testing, saliva analysis, and oral mucosal changes should be addressed for better understanding of the pathophysiology. Furthermore, the course of taste, smell, and mouthfeel disturbances from the pre-treatment setting until the situation after quitting a TKI should be assessed. Finally, further studies should also be extended to patients with non-GIST cancer types who are treated with TKIs.

To conclude, taste, smell, and mouthfeel disturbances are more frequent side effects of TKIs in GIST patients than earlier reported. QoL and daily life is affected in a considerable number of patients.

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Author contribution J.M. van Elst, A.K.L. Reyners, and J.J. de Haan contributed to the study conception and design. Material preparation and data collection were performed by J.M. van Elst and N.S. IJzerman. Analysis was done by J.M van Elst. The first draft of the manuscript was written by J.M. van Elst and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the UMCG, NKI, EMC (Ethics approval number: UMCG: METc 2019/360, NKI: IRBd19-258, EMC: MEC-2019–0669).

Consent to participate Verbal informed consent was telephonically obtained prior to the interview.

Conflict of interest The authors declare no competing interests.

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