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Development of a Patient-Reported Outcome Measure (PROM) for Dysgeusia During Treatment With Smoothened (SMO) Inhibitors for Basal Cell Carcinomas: The SMO-iD Questionnaire

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ABSTRACT

Introduction: Dysgeusia may occur during conventional or target-therapies and affect patients adherence-to-treatment. Therefore, it should be monitored to improve clinical outcome. To date, available questionnaires on dysgeusia relate to traditional antineoplastics and do not apply to target-therapies as the pathogenetic mechanism and clinical expression differ.

Objectives: To develop a patient-reported outcome measure (PROM) to screen for and monitor the occurrence and severity of dysgeusia in patients under Smoothened (SMO) inhibitors: the SMO-iD questionnaire.

Methods: Patients with locally advanced basal cell carcinomas referring dysgeusia under SMO inhibitors at the University Hospital of Naples Federico II, were enrolled between January-December 2020. The PROM was elaborated based on chemotherapy-induced dysgeusia (CiTas) scale (development phase) and then validated by measuring internal consistency and reliability (validation phase).

Results: Thirty-nine patients were enrolled and interviewed every 8 weeks. In the first phase, 160 CiTas questionnaires were collected, and the SMO-iD questionnaire was developed. In the second phase, 195 SMO-iD questionnaires were recorded, and reliability and validity assessed. Cronbach alpha was 0.89.

Conclusions: The SMO-iD questionnaire is a validated questionnaire that shows high face and content validity as well as high internal consistency and reliability. Hence, it may be introduced in daily clinical setting to monitor dysgeusia in patients under SMO-inhibitors.

Introduction

Dysgeusia is a prominently subjective gustatory disturb that may occur during chemotherapies and affect patients adherence to treatment and quality of life with severe implications on clinical outcome [1,2]. Therefore, physicians should thoroughly monitor the occurrence of any taste alteration in order to undertake strategies to address it and at the same time not compromise the therapeutic goal. To date, there are several questionnaires that investigate dysgeusia and related symptoms following traditional chemotherapies and radiotherapy [2,3]; however, the advent of new target therapies has led to the occurrence of selective side effects, including taste impairment, that are different under both the qualitative and quantitative aspects and brought out the need of new reporting tools.

Objectives

In detail, dysgeusia occurring during treatment with Smoothened (SMO) inhibitors results from the blockade of the Sonic Hedgehog (SHH) pathway, that has been proven to be a fundamental regulator of the gustatory functioning without impacting the olfactory one [4,5]. For this reason, we developed a new and specific patient-reported outcome measure (PROM) to characterize it: the SMO inhibitors-induced Dysgeusia (SMO-iD) questionnaire.

Methods

The COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments) 'study design for PROMs' checklist was followed during the process of questionnaire creation [6]. A prospective study was conducted on patients affected by locally advanced basal cell carcinomas (laBCCs) treated with Smoothened inhibitors (Sonidegib and Vismodegib) referring dysgeusia, that were admitted to the University Hospital Federico II of Naples, Italy, between January 2020 and December 2020. Informed consent was required before participation. Inclusion criteria were laBCCs treated with SMO inhibitors and age ≥ 18 years old. By contrast, exclusion criteria included any pre-existing gustatory and/or olfactory disturbs, gastrointestinal and/or mental diseases that could interfere with the analysis. The study was drawn according to the ethical standards laid down in the World Medical Association Declaration of Helsinki (June 1964) and its later amendments and was approved by the local Ethical Committee. The questionnaire creation was structured in two phases: development and validation.

The Development Phase (January 2020- June 2020)

An extensive literature research concerning questionnaires on dysgeusia was performed. Above all, the Chemotherapy-induced Taste alterations (CiTas) scale developed by Kano and Kanda in 2013 was selected and employed as theorical model from which developing the questionnaire in issue, given its high consistency in literature [3,7,8]. Such questionnaire consists of 18 items exploring taste alterations, nausea/discomfort, food temperature intolerability and olfactory disturbs [7]. The Citas scale was administered by 5 investigators (EC, AV, MS, SS OG, MM) to enrolled patients together with broader and open questions to better define the quality and severity of dysgeusia and any potential impact on eating habits. Interviews were conducted in-person every 8 weeks from study start and patients answers were recorded and transcribed verbatim.

The Validation Phase (July 2020-December 2020)

All enrolled patients took part in the second phase of PROM development. They were administered the SMO-iD questionnaire by the same investigators with the same schedule and procedure of the previous one (the CiTas), ie, every 8 weeks, and answers recorded. The validation process of PROM went through qualitative and quantitative analysis as follows.

Results

Preliminary Results of the Development Phase

Thirty-nine patients meeting the inclusion and exclusion criteria were enrolled in the study. Overall, 160 interviews were made and recorded. From the answers analysis, some

questions of the Citas scale resulted redundant and inappropriate: indeed, they explored aspects not reported by the study population nor in literature concerning SMO inhibitors side effects, such as olfactory impairment and food temperature intolerance [9,10]. Moreover, from the open questions, patients referred variable impact of dysgeusia on social life and eating habits (appetite, nausea and weight) and better detailed the quality and severity of their taste alteration. On this basis, a new and specific questionnaire consisting of 4 domains and 14 items was developed as illustrated in Table 1: the SMO-iD questionnaire. The herein provided version was translated from Italian into English according to the COSMIN-principles. No scoring was provided since the questionnaire is intended to give physicians a toll to screen for and monitor the occurrence of dysgeusia and related symptoms in patients under SMO inhibitors. Moreover, as displayed in the last domain, patients' self-assessment of dysgeusia severity may guide physicians in changing drug posology or eating behaviors during treatment to improve their quality of life and increase compliance.

Preliminary Results of the Validation Phase

The qualitative validation of the PROM in issue derived from investigators interviews recording participants' opinion about accuracy of questions and standardized answers as well as overall approval of the questionnaire. A total of 195 SMO-iD questionnaires were collected and analyzed. In general, the questionnaire was appreciated by patients and defined as more focused to describe their taste alterations compared to the previous one. Moreover, it was depicted as easily understandable, repeatable, and fast. Also, the quantitative validation was performed employing the Cronbach alpha (CA), a test that measures the internal consistency of a survey, since it makes inferences about the health status of individuals (ie, dysgeusia), which is an unobservable variable for the practitioner, using available evidence (questions), which instead is observable. The test gave an alpha coefficient of 0.89 which indicates high internal consistency (note that a reliability coefficient of .70 or higher is considered "acceptable" in most social science research situations). Also, the 95% confidence intervals were computed based on 1000 bootstrapped samples which resulted in [0.83, 0.950]. The narrow bands, small standard errors, also supported the accuracy of the survey. In addition to computing the alpha coefficient of reliability, the dimensionality of the scale was investigated, since the unobservable variable was assumed unidimensional. Factor analysis is one method of checking dimensionality (Table 2). Looking at the table labeled "Total Variance Explained", the eigenvalue for the first factor is significantly larger than the eigenvalue for the next factor

Table 1. Smoothened inhibitors-induced dysgeusia (SMO-iD) questionnaire: it is composed by 4 domains that investigate the quality of taste perception and distortion, the impact on food habits and an overall patient self-assessment of dysgeusia severity.

Assessing taste perception	
Do you perceive the salty taste?	□ no □ little □ tolerably □a lot
Do you perceive the sweet taste?	□ no □ little □ tolerably □a lot
Do you perceive the bitter taste?	□ no □ little □ tolerably □a lot
Do you perceive the sour taste?	□ no □ little □ tolerably □a lot
Do you perceive the umami taste?	□ no □ little □ tolerably □a lot
Assessing taste distortion	
Do you have a metallic taste in your mouth?	□ yes □no
Do you have a bitter taste in your mouth?	□ yes □no
Do you have a foul taste in your mouth?	□ yes □no
Do you have a salty taste in your mouth?	□ yes □no
Do you have a sickly-sweet taste in your mouth?	□ yes □no
Assessing impact on food habits	
Do you have nausea?	□ yes □no
Have you lost appetite?	□ yes □no
Have you lost weight?	□ yes □no
Assessing severity of dysgeusia	
How would you grade your dysgeusia?	□ mild □moderate □severe

Table 2. Principal component analysis: the table shows the results of principal component analysis applied to domains survey.

Components	Eigenvalues	Percentage variance %	Cumulative percentage%
1	3.10	76.23	76.23
2	0.52	11.22	87.45
3	0.20	9.40	96.85
4	0.18	3.15	100.00

(3.10 versus 0.52). Additionally, the first factor accounts for 76.23% of the overall variance. This suggests that the scale domains are unidimensional, that is, the questions in the survey are inherent to one single common factor, ie, the presence of dysgeusia.

Conclusions

The rationale of creating a new questionnaire to investigate chemotherapy-induced dysgeusia derives from development of the so called "target therapies"- ie, agents that selectively target a specific pathogenetic mechanism that sustains an oncological disease [11]. Hence, the concept of chemotherapy -induced side effects has changed dramatically as they are not the result of a generalized antimitotic effect common to the category of traditional antineoplastics but appears to be class-specific [11]. Moreover, the development of target therapy implies a complete knowledge of the role of certain molecules in the pathogenesis of the disease and in some way may foresee its side effects [11]. Concerning the SMO inhibitors, the SHH pathway has been proven to be crucial for taste functioning maintenance, and its tackle predictably leads to gustatory impairment [5,12]. In fact, an alteration of the morphology of fungiform papilla, a reduction in the number of taste buds and an impairment in the chorda tympani response to all taste quality has been described in patients with laBCCs treated with such agents [4]. By contrast, SHH pathway is not involved in olfactory functioning, that is not affected [4,5]. In those patients, taste alterations have been proven to affect quality of life as well as therapeutic compliance and efficacy [13,14]. In literature, no PROMs or questionnaire on target-chemotherapy induced dysgeusia exist, as the available questionnaires relate to conventional chemotherapies or radiotherapy, and do not perfectly apply to the condition in issue, with the risk of not completely understanding patients' discomfort. For this reason, we decided to create a target-therapy specific questionnaire to investigate the peculiarity of dysgeusia under SMO inhibitors, that manifests with different characteristics compared to conventional antineoplastic agents. A validated and certified questionnaire, the CiTas, has been used as theoretical model and frame [3,7,8]. On the basis of the answers given by interviewed patients, the CiTas questionnaire was restructured and modified, reducing the number and topic of items as to make it more focused and specific. Moreover, such new version, the SMO-iD, gives the possibility to have a direct esteem of patients self-assessment of dysgeusia, that may guide the development of tailored treatment strategies. Hence, the SMO-iD questionnaire was developed and subsequently validated, showing high face and content validity as well as high internal consistency and reliability. Such results suggest its potential important applicability in daily clinical practice to collect, monitor and screen for such side effect with a specific tool. Hence, further and real-life studies are needed to support our findings.

The SMO-iD questionnaire has been proven to be characterized by high face and content validity as well as high internal consistency e reliability. Hence, it may be promisingly introduced in daily clinical settings to help physicians screen for and monitor the occurrence and the social impact of dysgeusia in patients under SMO-inhibitors.

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