Gastrointestinal Cancer

Development of a New Tool to Assess the Quality of Life of Patients with Hand–Foot Syndrome Receiving Capecitabine-Based Therapy: A Pilot Study

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Abstract

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Background Hand–foot syndrome (HFS) can result in significant deficits in health-related quality of life (HRQOL) and can lead to poor compliance, dose reduction, or interruption. This study was performed to assess the HRQOL with HFS on physical, psychological, social, and sexual aspects of patients receiving capecitabine-based chemotherapy with gastrointestinal cancer along with validating and assessing the reliability score of the questionnaire.

Patients and Methods HFS-related QOL (HF-QOL) questionnaire was developed and validated in a sample of 30 patients randomly selected for this pilot study. The internal consistency of the tool was tested by calculating the Cronbach's α coefficient, while content and construct validity were assessed by Pearson's correlation. Statistical analyses were performed using SPSS version 25.0.

Results Out of 30, 22 (73%) patients were males, mean age was 44 ± 13 years; 21 (70%) patients had grade 1 HFS, while 6 (20%) and 3 (10%) patients had grades 2 and 3 HFS, respectively. Cronbach's α coefficient was high for physical (0.79) and sexual scales (0.79), while it was moderately low for psychological (0.65) and social (0.53) domains. The average HF-QOL scores were 70.6 ± 13.2 in physical domain and 71.3 ± 23.7 in sexual domain indicating poor quality of life (QOL), while it was 50.9 ± 9.9 in social domain indicating moderately worse QOL. Grades 2 and 3 of HFS were found to have statistical significance on physical (0.0001), psychological (0.05), and social (0.02) domains, whereas sexual domain did not have any statistical significance (0.594).

Conclusion This pilot study showed the feasibility of use and validity of a new patient-reported instrument, the HF-QOL, which measures the effect of HFS on daily activities (physical, psychological, social, and sexual domains) after capecitabine-based chemotherapy.

Keywords

- hand–foot syndrome
- quality of life
- patient-reported outcomes
- gastrointestinal cancer
- capecitabine

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Introduction

Hand–foot syndrome (HFS) is one of the common adverse effects of anticancer agents, which is characterized by dysesthesia and tingling of the palms, fingers, and soles.[1] HFS is usually self-limiting and rarely leads to hospitalization or life-threatening manifestation. However, the symptom burden can result in significant deficits in health-related quality of life (HRQOL) and can lead to poor compliance, dose reduction, or interruption.[2] In treatment regimens with an expected probability of significant HFS, recognizing the early symptoms could hasten the use of management strategies. Most of the available clinical studies report only more severe (i.e., grades 2 and 3 skin toxicities), thus fail to provide sufficient information on the extent of HRQOL impairment with HFS.[3,4] HRQOL has become secondary goal of treatment in standard clinical trials and a primary outcome with treatment alternatives effective in prolonging life or controlling disease progression. A 14-item HFS-14 tool has been reported that assesses the functional implications of HFS such as pain, but not the wider symptom burden associated with the condition.[5] The questionnaire of HFS-14 tool focuses only on physical dimension and does not address other domains of life. Thus, there is an unmet need for development of a tool to assess HRQOL related to HFS in cancer research settings. This study was performed to assess the HRQOL with HFS on physical, psychological, social, and sexual aspects of patients receiving capecitabine-based chemotherapy with gastrointestinal (GI) cancer along with validating and assessing the reliability score of the questionnaire.

Materials and Methods

HFS-Related QOL Questionnaire Development

The HFS-related QOL (HF-QOL) questionnaire was formulated taking into account four aspects to determine the quality of life (QOL) that is physical, psychological, social, and sexual aspects of patients who were receiving capecitabine-based chemotherapy and had HFS. The development of questionnaire required multiple and interactive steps that included input from both patients and clinicians. Also, the available dermatology patient-related outcome questionnaires assessing HF-QOL were reviewed, these included the Skindex,[6] the Dermatology Quality of Life Index,[7] and the Dermatology Specific Quality-of-Life questionnaire.[8,9] HF-QOL questionnaire[10] included demographic and disease-related parameters such as age, gender, disease, number of cycles, and grade received by patients who have received capecitabine. QOL was assessed in term of four domains of life. These were physical (16 items), psychological (5 items), social (7 items), and sexual (4 items). The study was conducted over a period of 8 weeks and started after institutional ethics committee approval.

Questionnaire Validation and Statistical Analysis

Data gathered were analyzed by using descriptive statistics and inferential statistics. Based on the analysis, the interpretation was made. The validation of tool was done by the experts which included five doctors and four nurses. Descriptive analysis was performed to identify the distribution of variables of HFS under study. The content and construct validity (the extent to which the instrument measures the concept it is intended to measure) was assessed by Pearson's correlation. The internal consistency of HFS tool (the extent to which items in a scale are all measuring the same concept) was assessed by calculating the Cronbach's α coefficient $\geq$70 being acceptable. Standardization was done by using linear transformation ranging from 0 to 100. The higher score represented worst QOL and lower score indicated good QOL. To assess concurrent validity, Pearson's correlation coefficients (small effects 0.10–0.29; medium effects 0.30–0.49; and large effects $\geq$0.50). Referring to the existing literature, the correlations should be at least in the medium effect size range for internalizing problems and in the large effect size range for externalizing problems.

Because of the lack of a reference standard, we performed known group comparison at baseline by comparing the mean score of domains with different clinical characteristics. Mann–Whitney's *U*-test and *t*-test were used to compare the disease and number of chemotherapy cycles received by patients who had received capecitabine and grades with QOL. All analysis was two sided with significance *p*-value level set at 0.05. Statistical analysis was performed using SPSS version 25.0.

Study Procedure

This study reports a pilot study conducted at the Tata Memorial Hospital, Mumbai. Participants who had GI cancer and received capecitabine-based chemotherapy had HFS of any grade. Participants older than 18 years who understood English language and were willing to participate in the study were included. Patients with a history of any allergic condition and having psychiatric disorder were excluded from the study. A sample of 30 patients were randomly selected for this pilot study.

The investigator personally contacted the patients and explained the purpose of the study and ascertained the willingness to participate. The confidentiality of the information was maintained. The questionnaire prepared was given to the participants in English language. A convenient and calm place was selected for this purpose and time taken to complete the questionnaire was ~25 to 30 minutes for every individual. The questionnaire was explained to the participants again if they did not understand the same and any related queries were solved by the investigator. The primary objectives of this study were (1) to validate and assess the reliability score of questionnaire of HFS of patients receiving capecitabine-based chemotherapy, (2) to assess the HF-QOL on physical, psychological, social, and sexual aspects of patients receiving capecitabine-based chemotherapy with GI cancer, and (3) to compare the age, gender, disease, number of cycle, and grade with QOL of patients with HFS.

Results

Study Population

Between April and May 2019, 30 patients completed this study. The demographic and clinical characteristics of these

Table 1 Demographic and clinical characteristics at baseline

Characteristics	*n* (%)
Age, mean ± SD	44 ± 13 y
Gender	
Male	22 (73.3%)
Female	8 (26.7%)
Comorbidities	
Yes	2 (6.6%)
No	28 (93.3%)
Addictions	
Yes	12 (40%)
No	18 (60%)
Site of primary	
Colorectal	17 (56.7%)
Stomach	7 (23.3%)
Gallbladder	6 (20%)
Number of chemotherapy cycles	
≤3	16 (53.3%)
>3	14 (46.7%)
Grade of HFS	
Grade 1	21 (46.7%)
Grade 2	6 (20%)
Grade 3	3 (10%)

Abbreviations: HFS, hand–foot syndrome; SD, standard deviation.

patients are listed in ►Table 1. Out of 30, 22 (73%) patients were males, and mean age was 44 ± 13 years. Two (7%) patients had comorbidities, while 12 (40%) patients had habits such as smoking, alcohol, chewing pan; 17 (57%) patients had colorectal cancer, 7 (23%) patients had stomach cancer, while 6 (20%) had gallbladder cancer. At the time of study, 16 (53%) patients had received less than three cycles, 21 (70%) patients had grade 1 HFS, while 6 (20%) and 3 (10%) patients had grades 2 and 3 HFS, respectively. Dose reductions were considered as per standard guidelines in these patients with grade 2/3 HFS.

Cronbach's α coefficient was high for physical (0.79) and sexual scales (0.79), while it was moderately low for psychological (0.65) and social domains (0.53) (►Table 2). Construct validity from item–item correlation of the physical domain

Table 2 Domain wise HF-QOL tool and Cronbach's α coefficient

Scale (domain)	Cronbach's α coefficient
Physical	0.79
Psychological	0.65
Social	0.53
Sexual	0.79

Abbreviation: HF-QOL, hand–foot syndrome-related quality of life.

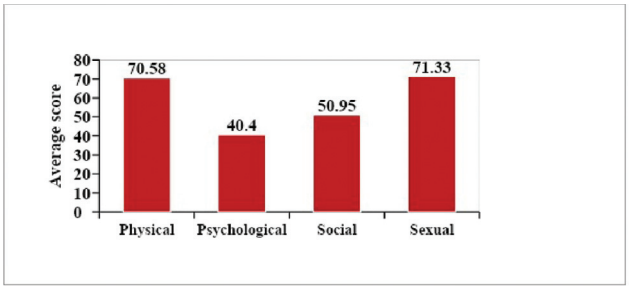

Fig. 1 Quality of life average score for hand–foot syndrome.

(<0.65), psychological domain (<0.57), social domain (<0.50), and sexual domain (<0.56) were in the medium effect which needed minimal change in the questionnaire for the larger effect. In construct validity from scale–scale, high correlation was found for psychological to social (0.63), medium effect between physical to psychological (0.52) and physical to social (0.58) was found. Correlation of sexual to physical (0.07), sexual to psychological (0.14), and sexual to social (0.22) had a low effect probability as a result of unwillingness of patients to respond for sexual domain. The average HF-QOL scores were 70.6 ± 13.2 in physical domain and 71.3 ± 23.7 in sexual domain indicating poor QOL, while it was 50.9 ± 9.9 in social domain indicating moderately worse QOL. The average score for psychological domain was 40.4 ± 13.2 (►Fig. 1).

Correlation of QOL with Prespecified Baseline Characteristics

The site of primary disease (colorectal, stomach, and gallbladder) did not have any statistically significant correlation with physical, psychological, social, and sexual domains (►Fig. 2). Patients with more than three cycles of chemotherapy had statistically significant correlation with physical and social domains (0.001 and 0.023) indicating more number of cycles of chemotherapy had an impact on physical and social domains, whereas psychological and sexual domains were not significantly affected (0.179 and 0.593, respectively) (►Fig. 2). Grades 2 and 3 of HFS were found to have statistical significance on physical (0.0001), psychological (0.05), and social (0.02) domains, whereas sexual domain did not have any statistical significance (0.594) (►Table 3).

Discussion

The present pilot study describes the development and validation of a new patient-reported instrument, the HF-QOL, which measures the effect of HFS on daily activities (physical, psychological, social, and sexual domains) after capecitabine-based chemotherapy. Previous studies which have reported QOL in patients developing HFS have usually concentrated only on physical symptoms while overlooking the overall status of the patient. Sibaud et al developed and validated an HFS-specific QOL questionnaire (HFS-14).[5] The mean HFS-14 score was significantly higher in patients with clinical grades 2 and 3 HFS than in those with grade 1 HFS. In the population of patients with severe grade 3 National

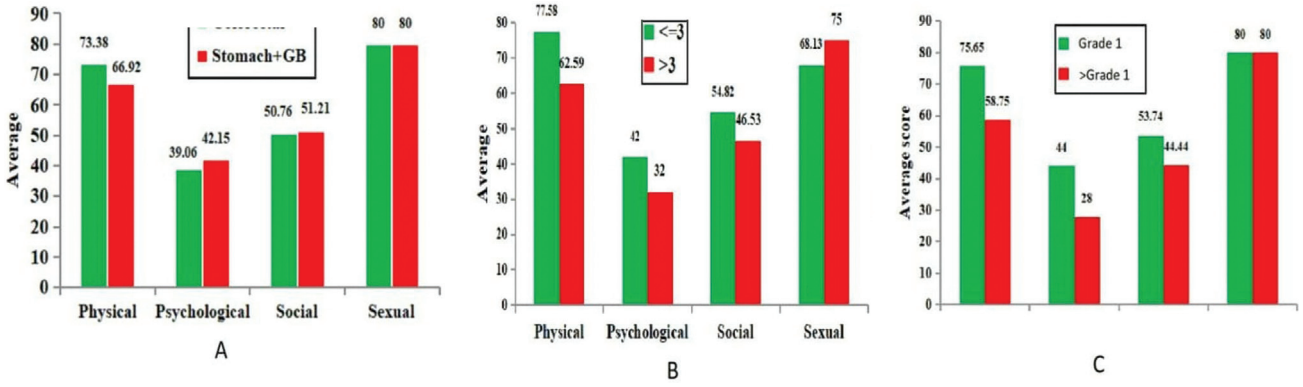

Fig. 2 Bar charts showing average hand–foot syndrome (HFS)-related quality of life (QOL) score versus QOL domain for (A) site of primary disease, (B) number of chemotherapy cycles, and (C) grade of HFS.

Table 3 Comparison of clinical characteristic with domains scores of HFS tool

Variable	Physical	Psychological	Social	Sexual
Site of primary				
Colorectal	73.38 ± 10.35	39.06 ± 12.61	50.76 ± 10.18	80 ± 15.81
Stomach and gallbladder	66.92 ± 15.88	42.15 ± 14.29	51.21 ± 10.13	80 ± 13.42
p-Value	0.189	0.535	0.905	0.779
Number of cycles				
≤3	77.58 ± 8.79	42 (37–51)	54.82 ± 8.30	68.13 ± 25.35
> 3	62.59 ± 13.05	32 (27–49)	46.53 ± 10.17	75.00 ± 22.88
p-Value	0.001*	0.179	0.023*	0.593
Grade of HFS				
Grade 1	75.65 ± 9.25	44.00 (34–50)	53.74 ± 9.24	80 ± 14.21
> Grade 1	58.75 ± 13.86	28 (24–42)	44.44 ± 8.23	80 ± 12.42
p-Value	<0.0001*	0.05*	0.02*	0.594

Abbreviation: HFS, hand–foot syndrome.
*Statistically significant

Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) HFS, the HFS-14 score was significantly higher in patients having both hands and feet severely involved than in those with severe involvement of one limb (hands or feet) with the other one less severely affected.[5] It included 12 questions on physical functioning along with one question related to social relationship and one question related to work. Thus, HFS-14 touches upon social functioning, but it does not include any question related to psychological and sexual domains. In our study, all the important domains of QOL were included while preparing the questionnaire and involved iterative development with input from both patients and clinicians with experience of the condition, supporting the instrument's content validity.

The HF-QOL tool was administered to 30 patients who were having HFS on capecitabine-based chemotherapy, and this pilot study showed evidence of its validity and reliability in this patient population. The clinical validity of the HF-QOL was ascertained by comparing adverse event reporting by NCI-CTCAE. Although the NCI-CTCAE grading has been constructed based on a physician's perspective, it might fail to capture the patient's HRQOL symptom burden.[11] The HF-QOL average score displayed concurrence with increasing NCI-CTCAE level of HFS and scores in all domains (except sexual) dipped with higher grade of HFS as compared with grade 1 HFS. Since this study involved a small sample size, grades 2 and 3 HFS were clubbed together while doing the calculations, else it would have been interesting to observe further dip in HF-QOL average score from grade 2 to grade 3 HFS. Different results for sexual domain as compared with other domains might be related to unwillingness of patients to respond to questions related to sexual domain.

The costs of the diagnosis and treatment of dermatologic adverse effects of antineoplastic therapy are large and usually under described. Borovicka et al reported that HFS reaction associated with sorafenib therapy was the most costly dermatologic toxicity.[12] Also, patient-reported outcome (PRO) measures are now considered as an important

adjunct to physician assessment due to the complexity of adverse effects that can occur on an individual's daily life. Capturing such information is impossible based on objective assessment of toxicity grading. This clearly demonstrates the value of developing and validating PROs to quantitate HFS. These tools can highlight the need to develop treatments and the use of prophylactic therapies to address adverse events and thus, improve the QOL of cancer patients.

The important limitations of this study include the small sample size, use of only English questionnaire, and including patients of HFS only as a result of capecitabine-based chemotherapy. The study had 53% of patients with less than three cycles of chemotherapy and 47% of patient with more than three cycles of chemotherapy. The time point of assessment for more cycles of capecitabine could not be planned due to logistics issues. However, it highlights that QOL studies should focus on including all the possible domains of life. Further studies are required to determine the HF-QOL properties for other conditions and therapies.

Conclusion

This pilot study showed the feasibility of use and validity of a new patient-reported instrument, the HF-QOL, which measures the effect of HFS on daily activities (physical, psychological, social, and sexual domains) after capecitabine-based chemotherapy. Larger studies are required to confirm the findings of this pilot study.

Funding

None.

Conflict of Interest

We do not have any financial or any other conflict of interest. We have full control of all primary data and we agree to allow the journal to review their data if requested.

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