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Unmet needs of cancer patients with chemotherapy-related hand-foot syndrome and targeted therapy-related hand-foot skin reaction: A qualitative study

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ABSTRACT

Purpose: The objective of this qualitative study was to understand the perceived needs of advanced-stage cancer patients with chemotherapy-related hand-foot syndrome (HFS) and/or targeted therapy-related hand-foot skin reaction (HFSR).
Method: Face-to-face interviews were conducted with 20 outpatients with advanced/recurrent cancer and chemotherapy-related HFS and/or targeted therapy-related HFSR using a semi-structured interview guide at Keio University Hospital, Tokyo, Japan. Thematic analysis was used to analyse the data.
Results: The unmet needs of cancer patients with chemotherapy-related HFS and/or targeted therapy-related HFSR was identified through four themes: a sense of helplessness with persistent symptoms, noticeable appearance as a barrier to social participation, decreased willingness to work and continue treatment, and need of individual coping strategies.
Conclusion: This study revealed unmet needs of cancer patients with chemotherapy-related HFS and/or targeted therapy-related HFSR that are not often voiced. Health care providers should provide full information in advance and find the best coping strategy for individual patients.

1. Introduction

Hand-foot syndrome (HFS) is associated with traditional cytotoxic chemotherapies, including cytarabine, anthracyclines, fluoropyrimidines, and taxanes (McLellan et al., 2015). HFS is distinct from hand-foot skin reaction (HFSR) which is reversible (Gomez and Lacouture, 2011) and associated with multikinase inhibitors (e.g. sorafenib, sunitinib, and regorafenib) and BRAF inhibitors (e.g. vemurafenib and dabrafenib) (McLellan et al., 2015). Although HFS/HFSR is usually not life threatening (Hoesly et al., 2011; Chanprapaph et al., 2016), it can lead to the cessation of therapy or a dose reduction and impaired quality of life and treatment outcomes (Huang et al., 2018; Rosen et al., 2013). Optimum prevention and treatment strategies for HFS/HFSR are needed to enhance quality of life and treatment efficacy (Huang et al., 2018; De Wit, 2014).

Despite no standard prevention for HFS/HFSR, recommendations for prevention and management of HFS through the use of specific drugs are available based on expert opinions and literature reviews which also emphasize the importance of management based on the accurate grading of HFS/HFSR and patient education given by healthcare teams (Nikolaou et al., 2016; McLellan et al., 2015). Charalambous and Charalambous (2016) reported that skin toxicities distorted patients' daily activities and negatively affected on their self-image, social engagement, and intimate relationships. Another qualitative study also suggested that skin toxicities were related to actual physical discomfort, appearance concern, social isolation, and high medical morbidity (Coleman et al., 2011).

The literature suggests that HFS occurrence is a predictor of prolonged survival in patients with locally recurrent/metastatic breast cancer (Zielinski et al., 2016). According to the recent risk/benefit trade-off analyses, patients prefer a more efficacious therapy with more severe skin toxicities to a less efficacious therapy with less severe skin toxicities (Tischer et al., 2018). To our knowledge, there is no study on patients' perspectives of skin toxicities focusing on HFS/HFSR during

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cancer therapy. Accordingly, we conducted a qualitative study to understand perceived needs of advanced-stage cancer patients with chemotherapy-related HFS and/or targeted therapy-related HFSR.

2. Methods

2.1. Study design

We conducted a qualitative study using individual interviews with outpatients with advanced/recurrent cancer and chemotherapy-related HFS and/or targeted therapy-related HFSR at Keio University Hospital, Tokyo, Japan. This study was approved by the Institutional Review Board of the Faculty of Nursing and Medical Care, Keio University (No. 267), and the Institutional Review Board of the Keio University School of Medicine (No. 20170251).

2.2. Setting and participants

Eligible participants were outpatients with chemotherapy-related HFS and/or targeted therapy-related HFSR aged 20 and older who did not have hearing or cognitive disorders and were able to agree or withdraw in regard to study participation. Patients who had strong physical pain, discomfort, anxiety, or depression were excluded. Potential participants were invited to meet the investigators of the study by their attending physicians at their visit to the Cancer Centre, Department of Gastroenterology and Hepatology, or Department of Dermatology, Keio University Hospital, Tokyo. One of the investigators (KY) explained the objective and methods (e.g. interview method and audiotaping) of the study to those who were interested in the study. Before obtaining the informed consent, four patients withdrew mainly because of ‘no time’. All approached participants gave their oral and written informed consent to participate in the study and chose a suitable date for the interview.

2.3. Data collection

The investigators (HK and KY), with extensive experience in cancer field and qualitative study, conducted in-depth interviews with 20 patients using a semi-structured interview guide in a private room at the hospital between March and June 2018.

After the completion of the 3rd, 8th, and 14th interviews, the investigators (HK and KY) conducted an interim analysis, and based on the results, we reviewed the interview guide and refined it to facilitate extracting unmet needs.

The following questions were included in the interview guide:

- What problems do you have with HFS/HFSR?
- How does HFS/HFSR affect your daily life? What problems do you want to improve in your daily life?
- Does the treatment, care or support for HFS/HFSR given by healthcare professionals meet your expectations? What do you want healthcare professionals to do for you?

Emerging themes were discussed, and data collection continued until the data reached saturation (Moser and Korstjens, 2018). The interviews were audiotaped and transcribed verbatim.

2.4. Data analysis

To reveal the content of and meanings behind themes present across entire data sets, thematic analysis was used to analyse the data. After all the interview data were transcribed, the investigator (KY) anonymised personally identifiable information. We used the qualitative analysis software NVivo10® to organize codes and passages.

To ensure the trustworthiness of the study, we adopted the following procedures: First, we reflected on preconception and preferences of the investigators about cancer patients and HFS/HFSR to minimize the bias, and made efforts to bracket the perceptions and subjectivity during analysing and interpreting the data. According to the principles of thematic analysis (Braun and Clarke, 2006), one of the investigators (KY) independently generated an initial list of codes and subthemes. Then, together with another investigator (HK) they reviewed and refined all codes, subthemes, and their corresponding passages for discrepancies in interpretation, until consensus was reached. The investigators combined related codes into larger thematic categories and confirmed that the data reached saturation. The themes were finalised by the peer debriefing of research team which included oncologists and dermatologists. The final themes and quotations that supported the themes were translated into English by a professional translator.

3. Results

3.1. Participant characteristics

Twenty participants (13 female and seven male) participated in this study. The mean age of the participants was 65.3 years (range: 36–83). The majority of the participants were employed (50%) and married (80%). Female participants accounted for 65%. The most common type of cancer was colon cancer (65%) followed by gastric cancer (20%). Participant demographic and clinical characteristics are described in Table 1 and Table 2, respectively. As shown in Table 2, 14 of 20 participants received both chemotherapy and targeted therapy, and most participants used multiple skin care products for HFS/HFSR grade 1 or 2. Mean interview duration was 26.6 min. Thematic analysis revealed four major themes (Fig. 1).

3.2. A sense of helplessness with persistent symptoms

As hands and feet are used in everyday life, participants experienced pain and change in sensitivity that prevented them from doing some daily activities. One of the participants said, ‘Anticancer medications caused more distress than surgery. (Because of numbness and pain) I hardly walked.’ (P11, 70-year-old male). One of the participants said, ‘It is painful. I barely walk ….’ (P10, 67-year-old female). Another participant described the inconvenience: ‘It is frustrating and stressful. Hand movements affect everything. For example, opening a bag or a zip, taking something out, or turning something.’ (P5, 68-year-old female).

Table 1
Demographic and clinical characteristics (n = 20).

Age		
Mean ± SD, range	65.3 ± 11.7, 36-83	
	n	%
Gender		
Female	13	65.0
Male	7	35.0
Employment status		
Full-time and part-time	10	50.0
Housewife	8	40.0
Unemployed/retired	2	10.0
Marital status		
Married	16	80.0
Single (including divorced/widowed)	4	20.0
Primary Cancer Diagnosis		
Colon cancer	13	65.0
Gastric cancer	4	20.0
Ovarian cancer	1	5.0
Duodenal GIST	1	5.0
Pancreatic cancer	1	5.0
Metastasis/recurrence		
Yes	20	100.0
No	0	0.0

Table 2
Patient list.

No	Sex	Age	Primary Diagnosis	Regimen	Skin care product	HFS/HFSR Grade
P1	F	48	Ovarian ca	TC (paclitaxel + carboplatin) + Bevacizumab	O	1
P2	F	79	Gastric ca	Paclitaxel + Ramucirumab	L and O	1
P3	F	77	Colon ca	FOLFIRI (folinic acid + fluorouracil + irinotecan) + Bevacizumab	O	1
P4	M	59	Colon ca	FOLFIRI (folinic acid + fluorouracil + irinotecan) + Bevacizumab	C and L	1
P5	F	68	Colon ca	XELOX (capecitabine + oxaliplatin) + Bevacizumab	C, L, and O	2
P6	M	83	Colon ca	XELOX (capecitabine + oxaliplatin) + Bevacizumab	L	1
P7	F	61	Colon ca	XELOX (capecitabine + oxaliplatin) + Bevacizumab	L and O	1
P8	M	46	Colon ca	XELIRI (capecitabine + irinotecan) + Bevacizumab	L and O	1
P9	F	36	Colon ca	XELOX (capecitabine + oxaliplatin) + Bevacizumab	Unknown (prescribed at another clinic)	2
P10	F	67	Colon ca	Regorafenib	C, L, and O	2
P11	M	70	Gastric ca	SOX (S1 + oxaliplatin)	C and O	1
P12	M	71	Colon ca	mFOLFOX 6 (oxaliplatin + folinic acid + 5-fluorouracil) + Bevacizumab	Unknown (prescribed at another clinic)	2
P13	F	61	Gastric ca	XELOX (capecitabine + oxaliplatin) + Trastuzumab	L and O	1
P14	M	65	Colon ca	XELOX (capecitabine + oxaliplatin) + Bevacizumab	C and O	1
P15	F	71	Colon ca	XELOX (capecitabine + oxaliplatin) + Bevacizumab	C and O	1
P16	F	74	Colon ca	mFOLFOX 6 (oxaliplatin + folinic acid + 5-fluorouracil) + Bevacizumab	C	1
P17	M	62	Duodenal GIST	Regorafenib	C and O	1
P18	F	81	Pancreatic ca	nab-Paclitaxel + Gemcitabine	O	1
P19	F	68	Colon ca	XELOX (capecitabine + oxaliplatin)	C and O	1
P20	F	58	Gastric ca	XELOX (capecitabine + oxaliplatin)	C and O	1

ca = cancer, GIST = Gastrointestinal stromal tumor, O = Ointment, L = Lotion, C = Cream.

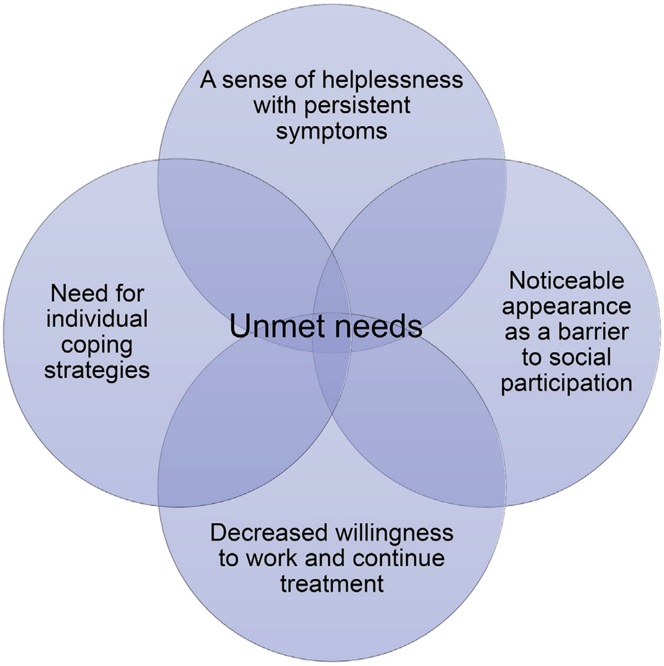

Fig. 1. Major themes deriving from the data.

This participant felt that she was just the same as her 90-year-old mother who had difficulty in taking out her medications.

Participants were at a complete loss as what to do with persistent HFS/HFSR. Without frequent skin care, HFS is easily worsened. Participants were frustrated that treatment does not cure HFS, and felt helpless. One of the participants had received the current chemotherapy and targeted therapy regime for four years. She used hand cream and band aids for cracked and dry skin on her hands and feet, but the condition was not improved. She was determined to ask her attending physician and be referred to a dermatologist. Although she understood that her condition might not improve during her cancer therapy, the frequent use of hands made her daily living difficult. She said, ‘I don't know what to do about the persistent terrible condition. It is not getting better at all. Hirudoid doesn't work at all. But I can't wear gloves all the time. I don't know what to do.’ (P1, 48-year-old female).

Another participant also used gloves but found difficulty. She said, ‘When it is rubbed by the gloves like this, the nails on my fingers are painful. The skin care product seems to work for only one or two days. I experience this repeated cycle.’ (P5, 68-year-old female). All participants felt a sense of helplessness. ‘Skin problems are beyond my control. It works against my efforts … ’ (P17, 62-year-old male).

Participants suffered from a feeling of discomfort from the sticky skin care products. Frequent application was necessary, but it adhered to everything. One of the participants described it as follows: ‘I can't do anything with my bare hands because the drug (skin care product) is sticky. So, I wear white cotton gloves all the time. Otherwise, the drug sticks to everything, and it's sticky.’ (P5, 68-year-old female). She used skin care products every morning, afternoon, and evening, so she had to wear gloves all day and night. A working participant had to reduce the number of applications because it affected her work: ‘I often use a PC for my work so I can't use the drug (skin care product) much or sometimes do not use it because it is sticky.’ (P9, 36-year-old female).

Despite much discomfort and inconvenience in daily living, participants did not feel that the drug was effective, as one of the participants (ointment, lotion, and cream were prescribed) said, ‘I think that they (skin reactions) do not disappear with the prescribed drugs.’ (P5, 68-year-old female). Another participant revealed that the hardest thing was that there were no effective drugs for skin reactions: which was the same situation with cancer: ‘My hands are getting darker and darker, swollen and painful. But there are no effective drugs.’ (P7, 61-year-old female). Participants desperately wanted a drug to cure these skin symptoms: ‘Development of a new drug that can cure the skin problems is the only way.’ (P17, 62-year-old male).

Since the exacerbation of HFS/HFSR may lead to dose reduction or drug change in cancer therapy, participants spend time managing HFS/HFSR. They felt stressed about always having to pay attention to their skin condition and providing frequent self-care to avoid it worsening. ‘If I forget to use the drug (skin care product), my hands get cracked. Once the skin is cracked, it is difficult to repair it. So, I try not to do so.’ (P12, 71-year-old male). The burden of self-care occupied their everyday life: ‘To avoid it (bleeding), I had to put on the cream so often. I had to have it in my mind all the time. It was so stressful.’ (P1, 48-year-old female).

3.3. Noticeable appearance as a barrier to social participation

Since hands are visible parts of the body, participants were concerned that other people stared at their altered hands. ‘When the condition is bad, I use four band aids for each hand. That means eight band aids for my hands. I can't use my fingers as usual. It is not convenient … People think, "Poor woman with eight band aids."' (P1, 48-year-old female). One of the participants said, 'When it is darker, I don't like that people may be thinking, "It's dark" … I am concerned that people think something is wrong with me.' (P13, 61-year-old female). Participants did not want other people to pry into their skin symptoms. They were sometimes misjudged as being a dirty person. 'If I tell people about the disease, they understand that the darkness due to the disease and it's OK. But people who do not know the reason are likely to think that it is because of poor hygiene. "Oh, this man has dirty hands." So I wear gloves to hide my hands.' (P11, 70-year-old male).

Embarrassment led to hiding the affected hands and there were negative effects on their social life. One of the participants said, 'It is depressing because it is clearly dark. My (finger) joints get dark. It's even worse. So, I paint my nails to cover it when I see somebody.' (P7, 61-year-old female). However, she found 'no means to hide it because they are hands.' Participants were also tired of being asked about their condition and having to give an answer every time. 'If the condition was not so bad and not so visible, people wouldn't notice it. But it is visible, so people ask me, "What's the matter with you?" and I reply. Such repetition is stressful.' (P1, 48-year-old female).

3.4. Decreased willingness to work and continue treatment

HFS affected participants' work. In particular, pain and perceptive change not only reduced working capacity but also their willingness to work: 'Pain discourages my willingness. I lose my drive for everything including work.'(P14, 65-year-old male). A mechanic was worried that he might be a burden rather than contributing to productivity. He said, 'I have to use my hands for work … Yes, it is critical … I am losing the ability to feel what I touch. It is hard. It hinders my work. I have to decrease such kind of work. I barely go to work.' (P8, 46-year-old male). Another participant tried to think his condition was not bad and encouraged himself to continue treatment. However, he said, 'If it continues forever, it is annoying. Typing errors are increasing. I have to write an article with 800 characters today, but it is bothersome and I may not do it.' (P4, 59-year-old male).

Because of a great impact of HFS/HFSR on daily activities, some participants reviewed the meaning of anticancer therapies: 'Persistent side effects are depressing because I can't do anything. I wonder whether treatment is meaningful because my condition is so bad.' (P13, 61-year-old female).

3.5. Need for individual coping strategies

Participants want specific information on the outlook of HFS/HFSR. They want to know how the symptoms of HFS/HFSR will change, worsen or improve during the period of cancer treatment. They did not have enough information to decide dose reduction or discontinuation of anticancer therapy. One of the participants said, 'This is the 10th course (of chemotherapy and targeted therapy). It is getting worse. I am worried how far it will go. If I am informed and given guidance, it would offer me some relief.' (P7, 61-year-old female). Another participant read the leaflet given by the healthcare provider but could not judge whether she should stop medication. 'The doctor prescribes many kinds of medicines … The leaflet said that I should stop "if a prickly condition develops". I wonder my condition is applicable. I need a more detailed explanation from the healthcare provider. I can't judge by myself.'(P15, 71-year-old female).

Participants were seeking coping strategies and trying to find their own coping strategies by themselves. One of the participants said, 'Maybe I know better than the nurse. When I say that I am doing this, the nurse says "Oh, that's a good idea." I know that the nurse is busy, so she does not tell me what to do from one to 10.' (P19, 68-year-old female). She wished that the healthcare provider would give her a list of management methods.

4. Discussion

This study reveals that patients cry for help with persistent skin symptoms. HFS/HFSR restricts cancer patients' daily activities, impairs their social functioning (Sibaud et al., 2011; Nardone et al., 2012), and has psychosocial consequences that can lead to a reduced quality of life (Sehgal et al., 2009). As hands are an integral part of our personal and social life (Ahmed et al., 2015) and feet are related to mobility, the present study found that HFS/HFSR negatively affected almost every activity of daily life. Moreover, the participants were stressed about visible hand symptoms that might be misinterpreted by other people. Telling others that the skin symptoms were caused by cancer treatment was also a psychological burden for the participants.

Interestingly, this study suggests that HFS/HFSR is related to a loss of productivity and questions the meaning of cancer treatment. Persistent painful symptoms reduce the willingness of patients to continue treatment and work. Some participants began to question whether the current cancer treatment was really needed if the trade-off was persistent with terrible skin symptoms, because the treatment goal was often to improve survival and to maintain or improve quality of life for patients with advanced cancer.

Patients are suffering not only from skin symptoms but also from caring for the skin with the skin care products. The high level of burden caused by skin care could lead to reduction of the number of drug applications or discontinuation. However, such decision-making is difficult for patients with advanced cancer. In clinical settings, specific information is often not provided to patients to help with their decision-making. Although patients understand their symptoms, they are not sure whether they have the specific symptoms that the physician and nurse have told them to pay attention to. In the present study, some participants hesitated to talk about their skin symptoms with their physician. Even though they received skin treatment, the skin care product was not as effective as they expected and they often sought their own coping strategies by themselves. The participants in this study recognized the importance of moisturizers by themselves and frequently used them. Indeed, skin care with moisturizers improves skin barrier function and hydration (Bensadoun et al., 2013).

The difference of attitudes and perceptions about skin toxicities between the patient and the healthcare provider is often reported (Basch et al., 2009; DiMaio et al., 2015; Tischer et al., 2018). As standard practice, patients are informed about skin protection and observation of HFS/HFSR; however, they do not know what to do with persistent HFS/HFSR. While specific indicators are required for self-identification of skin symptoms, effective health education should be offered to patients for appropriate use of the drug to minimize discomfort in daily skin care. Since optimal management remains uncertain aside from dose reduction and treatment interruption, healthcare providers should seek suitable coping strategies for individual patients. In this study, most participants had Grade 1 skin toxicities. Only one third of them were referred to the dermatologist, and the rest was treated by the oncologist. Skin care education for the oncology team based on appropriate drug selection and use, including order, volume, and interval in skin care is necessary. In addition, future clinical trials are needed to address appropriate interventions for the management of HFS/HFSR (Hofheinz et al., 2015; Chanprapaph et al., 2016). Furthermore, development of a cream that minimizes discomfort and impacts on daily living is desirable.

This study has several limitations. As with all qualitative studies, our sample size was small. In addition, the selection of the participant population and of a single institution might influence the results of the study. Since all the participants had metastasis and recurrence and talked about symptoms other than skin toxicities, it was very difficult to isolate the experience of HFS/HFSR. Most of the participants received both chemotherapy and targeted therapy and did not take biopsies, we did not know clearly whether they developed a HFS or HFSR or both. In addition, whether the hands, feet or both were affected was not specifically described in the medical chart. The participants used multiple skin care products and we could not identify which one caused discomfort (e.g. stickiness).

5. Conclusions

This study revealed unmet needs of cancer patients with chemotherapy-related HFS and/or targeted therapy-related HFSR that were not often voiced. Persistent and visible symptoms of HFS/HFSR seriously hinder patients' daily activities including work and social functions. The physical and psychological burden of HFS/HFSR even leads to patients questioning the meaning of cancer treatment. To meet the unmet needs of patients, first, full information should be given at the beginning of the cancer therapy so that the patients are prepared for management of HFS/HFSR. Second, indicators help patients for self-identification of HFS/HFSR. Third, healthcare providers should carefully listen to patients' problems and find the best coping strategy for each individual patient.

Conflicts of interest

None declared.

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