

Exploring Multi-Disciplinary Cancer Care for Immunotherapy-Related Dermatological Symptoms

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Short Report

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Abstract

Context and objectives: The present study examined the perspectives of healthcare providers (HCPs) in designing a multi-disciplinary model of supportive cancer care for the relief of dermatology-related symptoms caused by immunotherapy.

Methods: This qualitative study identified patients undergoing oncology therapy with MoAB, anti-HER2 and anti-PD-L1 monoclonal antibodies among a cohort of patients referred to an integrative oncology (IO) consultation for symptom relief and improved quality of life (QoL). Case-studies with significant dermatology-related concerns were selected and presented to a panel of 6 HCPs trained in medical oncology, oncology nursing, family medicine, supportive cancer care and IO. HCP narratives were qualitatively analyzed and assessed using ATLAS.Ti software for systematic coding.

Results: Of 924 patients referred to the IO consultation, 208 were treated with immunotherapy, from which 50 were selected for further evaluation. Of these, and 7 cases were presented to the HCP team which then identified treatment gaps requiring a multi-disciplinary approach. Qualitative analysis identified 3 major themes: a biophysical perspective; a psycho-social-spiritual perspective; and the implementation of integrated care.

Discussion: There is a need for a multi-disciplinary approach when treating patients suffering from immunotherapy-related skin toxicities. HCP-reported themes highlight the need to identify patients where such an approach is warranted; conditions where a psycho-social-spiritual perspective should be considered in addition to the bio-physical approach; and considerations of who should be appointed as the patient's case manager.

Key Message

In order to provide personalized care to oncology patients, a multi-disciplinary approach is needed. In the present study, it was shown that integrative oncology practitioners may serve as one of the case managers responsible for co-designing a supportive care model for patients with dermatological symptoms resulting from immunotherapy.

Introduction

The introduction of targeted immunotherapy (or biological therapy) has led to significantly better outcomes in the treatment of cancer. At the same time, these drugs have led to an increase in treatment-related dermatological symptoms such as acne, rashes, itching, etc [1]. Skin-related symptoms are frequently accompanied by emotional distress, with social and functional implications [2].

Immunotherapy-induced dermatological symptoms are being addressed by a wide spectrum of healthcare providers (HCPs), including oncology physicians and nurses, dermatologists, supportive cancer care professionals, family physicians and others.

Many of today's leading cancer centers provide complementary medicine within an evidence-based and integrative oncology (IO) setting, often as part of the center's supportive care service [3]. The research supporting the impact of IO on symptom relief and quality of life (QoL) has led to the inclusion of many of these modalities in clinical practice guidelines of organizations such as the American Society for Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO), among others [4]. However, little has been published on the impact of IO on dermatological symptoms related to the use of immunotherapy drugs. The present study examined the extent to which immunotherapy-treated patients with dermatological symptoms are being referred to IO services, and qualitatively assessed a multi-disciplinary approach in treating these and related concerns. Recurrent themes were identified and analyzed, using the narratives of HCPs working in a patient-centered multi-disciplinary supportive care setting.

Methods

Study design and setting

The study took place as part of an ongoing prospective registry protocol study. The electronic files of patients participating in the study were scanned to identify those receiving immunotherapy agents who had been referred by their HCP to the IO service for the treatment of QoL-related indications. A qualitative analysis of 6 in-depth interviews with the oncology HCPs treating 7 of the identified patient files, focusing on dermatological symptoms related to either the underlying cancer or immunotherapy agents. Predominant themes derived from these interviews were identified.

Patients participating in the prospective study had been recruited between from August 2013 and February 2021 at the Oncology Service, Lin and Zebulon Medical Centers, Clalit Healthcare Services Haifa, Israel [5]. These two community-based oncology centers provide ambulatory oncology treatments, with an IO service offering a wide range of modalities for reducing QoL-related concerns. IO treatments are provided by a multidisciplinary team of 6 integrative physicians (IPs), medical doctors trained in supportive cancer care and integrative medicine; 6 IO-trained nurses; 4 paramedical practitioners; and 6 integrative-medicine therapists, all with extensive training in integrative and supportive cancer care and with over 5 years of IO work experience.

Study population and IP consultation

Oncology patients eligible for study inclusion were aged ≥ 18 years and undergoing adjuvant, neo-adjuvant, or palliative oncology treatments for solid tumors. Patients unable to read and sign informed consent were excluded, as were patients with hemato-oncological disease. Patients were required to have been referred to the IO consultation by an oncology HCP for at least one QoL-related indication (e.g., pain, nausea, itching, etc.). Following an IP consultation assessing the patient's leading QoL-related concerns, treatment goals were co-defined with the patient and an IO treatment plan co-designed.

Selection of patient files

The files of eligible patients undergoing immunotherapy, whether alone or in conjunction with other anti-cancer agents, were identified (**Figure 1**). The agents being used included the MoAB (anti-EGFR monoclonal antibody) drug Cetuximab (Erbix); the anti-HER2 monoclonal antibody agent Pertuzumab (Perjeta); and the anti-PD-L1 monoclonal antibody drugs Nivolumab (Opdivo) and Pembrolizumab (Keytruda). Patient files mentioning dermatological-related symptoms, as reported by one of their treating HCPs were selected, with 7 of these files selected for further qualitative assessment. A panel of 6 HCPs working in oncology, dermatology, integrative medicine, family medicine, or supportive cancer care was asked to read all 7 selected clinical cases, and then interviewed by the first author (D.K.). Qualitative analysis of the HCP narratives was conducted systematically using ATLAS.Ti Scientific Software (V.8). A qualitative content analysis was performed using a conventional content analysis approach in order to avoid the need for pre-established categories for coding [6].

Results

Characteristics of Study Groups

The IO registry protocol database consisted of the electronic files of 924 oncology patients, of which 208 (22.51%) were receiving immunotherapy agents. The median age of this cohort was 60 years, the majority of which were female (152, 73%) and listed Hebrew as their primary language (139, 66.8%). There was a wide variety of primary cancer sites (breast, 99; gastro-intestinal, 37; lung, 23; gynecological, 18), with most having a diagnosis of advanced disease (121, 58.2%). The most frequently used immunotherapy were Cetuximab, Pembrolizumab, Nivolumab and Pertuzumab, for which 14 patients reported suffering from dermatological-related adverse effects.

Identified Themes

Qualitative analysis of the HCP narratives identified 3 major thematic groupings: a biophysical perspective; a psycho-social-spiritual perspective; and implementation of integrated care.

Theme I: Bio-physical perspective

The first theme identified from the HCPs narratives addressed a comprehensive bio-physical perspective of immunotherapy-induced dermatological symptoms. The study dermatologist differentiated between localized (simple) and systemic (complicated) dermatological effects of the treatment, pointing out the danger of over-diagnosing these effects.

"I see many oncology patients with dermatological conditions which are not related to their oncology treatment. And even for those cases where the link between symptom and drug is clear, I am frequently reluctant to stop the oncology treatment, because of the implications for the patient's disease."

The dermatologist's approach was one of open discussion with the patient, starting prior to and continuing throughout the treatment period. This approach was also evident in the oncology nurse's narrative, which addressed preventive treatment strategies to decrease skin-related toxicities of the

treatment. The supportive care physician, much like the dermatologist, first looked for other causes for the patient's skin condition, which are not necessarily related to the immunotherapy drugs:

First, you'll think of anything that can be treated and reversible. You'd like to check if she's taking any other herbs or supplements causing rashes.... And then you want to make sure that this rash doesn't look like anything that could be related to the disease.

All of the participating HCPs addressed the need for a multi-disciplinary and inter-disciplinary approach, as well as the need to look beyond the skin condition "per se". The nurse addressed behavioral aspects; the supportive care physician suggested dietary changes and the use of pro-biotic products; and the integrative physician considered the use of acupuncture, as well herbal and Anthroposophic medicine to reduce dermatological symptoms and emotional distress.

Theme II: Psycho-social-spiritual perspective

The second theme identified from the HCP narratives presented a psycho-social-spiritual perspective, addressing the effect of the dermatological symptoms beyond their physical manifestation. The dermatologist approached this theme using a metaphor of "widening" the biophysical diagnosis' "borders" of the skin lesion, emphasizing the importance of effectively communicating with the patient on what they were experiencing and how they were coping.

"It's very important to be alert regarding the emotional impact on the patient...on her faith in her body. There is a tragedy here, and it requires the involvement of a social worker for emotional support. It's not something you can deal with on your own. The scariest thing is that they lose faith in their body, in themselves."

The emotional aspects of the symptoms, as well as the patient's relationship with their partner, were the focus of the nurse's narrative. The family doctor's narrative also addressed the psycho-social-spiritual perspective of patient care, viewing the effectiveness of treatment within the emotional response, especially with respect to how the patient's skin condition related to their role within the family and society, including sexual identity and role as caregiver:

"I ask the patient about whether the skin condition has an effect on her sexual role, her self-image. If she agrees, then I would ask her partner how he sees it; and how he thinks she feels about it...I would also talk with other family members. It really depends on the woman...she could be of a strong character, with many resources, and then it might be easier for her. But she could also suffer from depression, or a poor relationship with her partner...it affects everyone differently."

The integrative physician emphasized the importance of the relationship between dermatological symptoms related to the oncology treatment and depression, as well as general QoL:

"Metastases and skin-related symptoms can severely impair QoL, and may lead to an avoidant personality (doesn't want to leave home, doesn't meet with friends or family), and even depression. It's as

if it constantly reminds them that they are a cancer patient."

In this narrative, the integrative physician also addressed the need for compassion, which may be difficult in light of the unpleasant appearance of and sometimes strong odor from the skin condition:

"Even if there is an off-putting feeling, talking about it makes it normal ...It's not something to be embarrassed about. Ask her about how much it bothers her, how it bothers her relationship with her partner..."

The supportive care physician's narrative was reflective of her specialty in family medicine, with extensive training in integrative medicine. In her opinion, the psycho-social aspects of the dermatological symptoms were primarily a function of the patient's health-belief model:

It's really trying to understand the person`s belief system. You need to find a way to engage them in a way that's therapeutic. Sometimes you'll meet somebody and he'll show you his rash, but that's two minutes of the consultation...and then for the other 58 minutes of the consultation I'll take the person's history and ask about their main concerns. The symptom that gets the patient through the door, opens the way to treat the whole person. If people are anxious or in distress, often the first thing would be a massage or a reflexology treatment. Engaging people, touching their skin very early on is helpful.

Theme III: Implementation of Integrated Care

While the need for inter-disciplinary communication was emphasized by all HCPs in their narratives, the question of who is responsible for the patient's care varied, as well as the need to ensure continuity of care. The dermatologist considered herself a counselor, with the oncologist as the case manager. The oncology nurse saw her role as that of a "case manager", the most readily available HCP responsible for the patient's QoL:

"This [the patient`s trust in the medical team] is the most important challenge facing nurses; from the first meeting with the patient...it is our responsibility not to "brush off" the patient...the way it is done is that there is one doctor, one nurse...to make it clear to the patient that they have come to the right place...that they are in good hands."

All narratives addressed the need for a multi-disciplinary model of care based on effective communication. The dermatologist recommended including a psychologist in the team, as well as nurses and therapists to treat mouth sores. The oncologist emphasized the role of the social worker and the oncology nurse. The family physician referred patients to the oncologist, to the dermatologist and to the integrative physician. The supportive care physician considered referring the patient to the psycho-oncologist, as well as to the team of IO practitioners for touch therapy, acupuncture, yoga, and mindfulness treatments. The collaboration within the multi-disciplinary team referred to both design and implementation of the patient-tailored treatment program:

"Once a week there`s a meeting of my integrative team for one hour, where we discuss 'difficult' patients... I present patients I have seen or that have changed their status, and we discuss them. I am the 'bridge' between my team and the oncology team, as well as the family physician and community clinic nurse".

In contrast, the integrative physician pointed out barriers to the multi-disciplinary teamwork, specifically regarding patients with skin-related concerns:

"The oncology team does not refer enough of their patients suffering from skin conditions to our service. At the same time, we as an integrative medicine team are often not as aware of dermatological symptoms as we are of other conditions, such as chemotherapy-induced peripheral neuropathy...it's not sufficiently embedded in our lexicon...I do not ask my patients enough about skin-related symptoms..."

At the same time, she admitted that she doesn't usually address dermatological complications of immunotherapy drugs, or their on patient adherence to the oncology treatment regimen:

"Our primary objective is QoL improvement. We're not 'supposed' to treat the cancer itself, but rather focus more on improving QoL-related symptoms. However, If the patient is receiving immunotherapy...there needs to be an awareness about the side effects...skin-related symptoms need to be seen as a 'red flag', requiring special attention..."

Discussion

The three narrative themes identified in this qualitative study highlight the need for a multi-disciplinary approach in the treatment of immunotherapy-induced dermatological symptoms in the oncology setting. In contrast to the often "fragmented" approach of today's health care, the narrative themes addressed both biophysical and emotional, social, familial and spiritual aspects of patient care. The first of these themes focused on the biophysical, identifying patient concerns from a comprehensive and systemic perspective shared by varied medical disciplines. The second theme addressed the psychosocial domain, recognizing the potential impact of skin lesions on the patient's body image, sexual and spouse/partner-related concerns; and in which a social, cultural and spiritual context interacts with the patient's health-belief model, faith, hope, and ability to cope with uncertainty. The third and final theme acknowledged the complexity and challenges of multi-disciplinary care, in which effective communication can ensure integration with continuity of care. This requires a case-manager, a role which can be filled by the HCPs described in the present study, including the integrative physician with training and experience in supportive care. These 3 themes can be better identified and addressed by asking a group of directed questions during the oncology HCP's interactions with the patient, including those undergoing immunotherapy for their cancer (Table 1).

Table 1

Questions to ask while treating patients with dermatological complications of immunological cancer therapies.

<p>1. Is the patient in need of a multi-disciplinary/multi-team approach, or is a single modality/HCP enough?</p>
<p>2. Is the patient open to a discussion on aspects of their skin condition, which go beyond the physical symptoms?</p> <p>a. What do the patient's physical symptoms (itching, pain, burning sensation, etc.) mean to them?</p> <p>b. Are there elements of suffering which go beyond the physical (emotional, spiritual)?</p> <p>c. What is the impact of the skin condition on the patient's body image and perception of their disease?</p> <p>d. Can aspects related to the patient's sexuality, as well as those of their partner, be addressed?</p> <p>e. Are there any indications of psychological/emotional co-morbidity?</p> <p>f. What are the social (e.g., avoidance) and functional (e.g., carrying, walking) implications of the skin condition?</p>
<p>3. Who among the patient's healthcare providers (if any) should be delegated as their Case Manager? To whom should the other HCPs turn to in order to update, advice, consult about the patient's care?</p>

The present study has a number of methodological limitations which need to be addressed in future research of the model described. These include the pragmatic nature of the prospective database, with a potential for a referral bias among patients referred to the IP consultation and IO treatment program. In addition, the qualitative assessment of narratives from the panel of 6 HCPs, examining a select case series of patients may not reflect the cohort as a whole.

In conclusion, the present study examined a multi-disciplinary approach in the treatment of immunotherapy-related dermatological symptoms, in which oncology, supportive cancer care, dermatology, primary care and integrative medicine HCPs work together to improve the QoL of their patients. Further research is needed, expanding the model described to other IO centers and settings, identifying the challenges they are facing in their own model of supportive cancer care; discuss approaches for improving inter-communication between the integrative teams; and assess the effectiveness of IO treatments for immunotherapy-related dermatological symptoms, including their impact on adherence to the oncological treatment regimen.

Declarations

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Data Availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

References

1. Sibaud V. Dermatologic Reactions to Immune Checkpoint Inhibitors: Skin Toxicities and Immunotherapy. *Am J Clin Dermatol*. 2018 Jun;19(3):345-361. doi: 10.1007/s40257-017-0336-3. PMID: 29256113.
2. Romito F, Giuliani F, Cormio C, Tulipani C, Mattioli V, Colucci G. Psychological effects of cetuximab-induced cutaneous rash in advanced colorectal cancer patients. *Support Care Cancer*. 2010 Mar;18(3):329–34. doi:10.1007/s00520-009-0656-9. Epub 2009 May 31. PMID: 19484487.
3. Witt CM, Balneaves LG, Cardoso MJ, Cohen L, Greenlee H, Johnstone P, Küçük Ö, Mailman J, Mao JJ. A Comprehensive Definition for Integrative Oncology. *J Natl Cancer Inst Monogr*. 2017 Nov 1;2017(52). doi: 10.1093/jncimonographs/lgx012. PMID: 29140493.
4. Greenlee H, DuPont-Reyes MJ, Balneaves LG, Carlson LE, Cohen MR, Deng G, Johnson JA, Mumber M, Seely D, Zick SM, Boyce LM, Tripathy D. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. *CA Cancer J Clin*. 2017 May 6;67(3):194-232. doi: 10.3322/caac.21397. Epub 2017 Apr 24. PMID: 28436999; PMCID: PMC5892208.
5. Ben-Arye E, Schiff E, Shapira C, Frenkel M, Shalom T, Steiner M. Modeling an integrative oncology program within a community-centered oncology service in Israel. *Patient Educ Couns*. 2012 Dec;89(3):423-9. doi: 10.1016/j.pec.2012.02.011. Epub 2012 Mar 7. PMID: 22401792.
6. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res*. 2005 Nov;15(9):1277-88. doi: 10.1177/1049732305276687. PMID: 16204405.

Figures

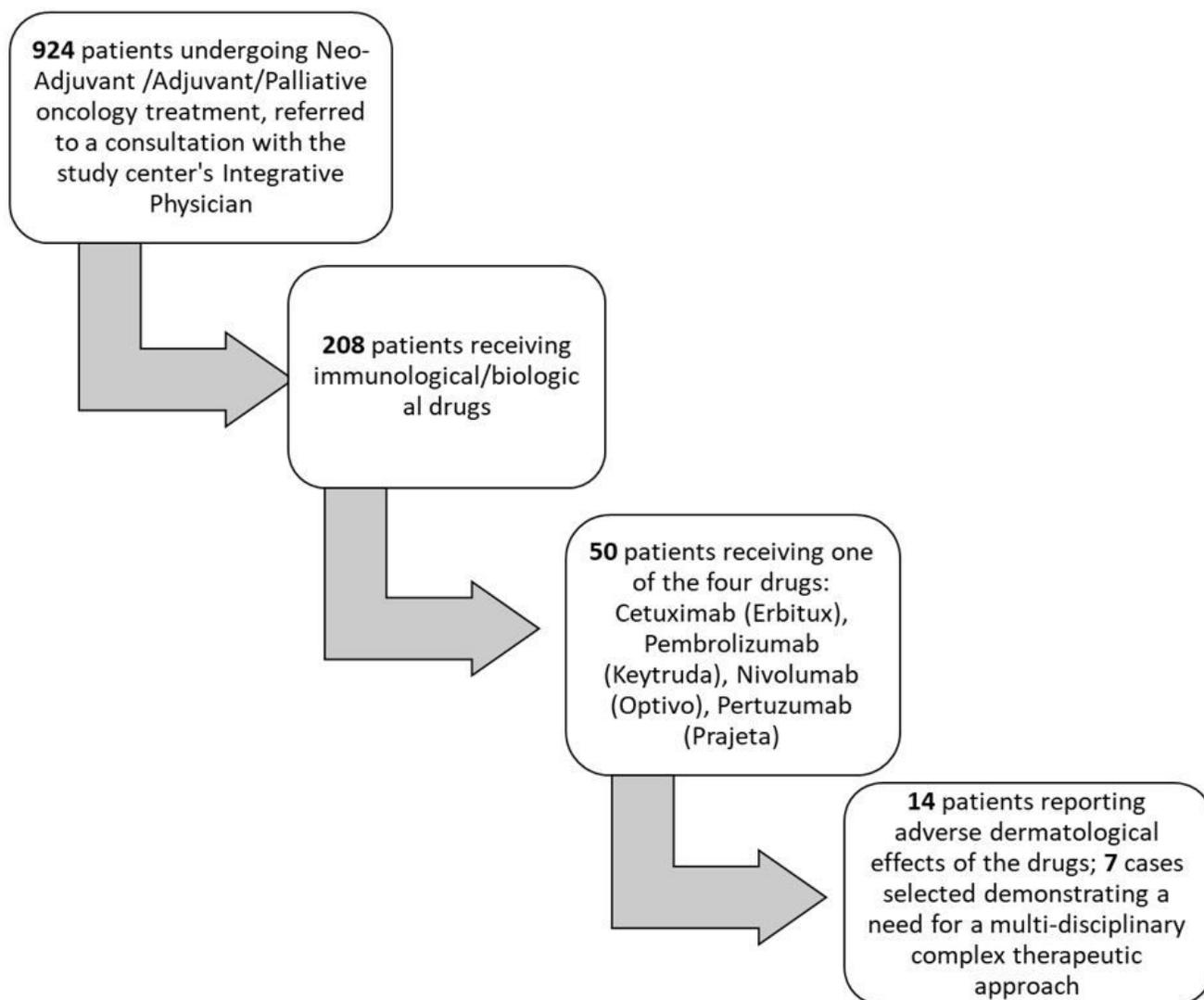


Figure 1

Legend not included with this version