Revista Brasileira de Enfermagem
REBEn

THEMATIC EDITION
ADVANCED NURSING PRACTICES

TECNOLOGICAL INNOVATION

Cancer symptom clusters: from the lab bench to clinical practice

Clusters de sintomas oncológicos: da bancada do laboratório à prática clínica

Clusters de síntomas oncológicos: de la mesa de laboratorio a la práctica clínica

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How to cite this article:
Lopes-Júnior LC. Cancer symptom clusters: from the lab bench to clinical practice. Rev Bras Enferm. 2022;75(5):e2022v75n5inov. https://doi.org/10.1590/0034-7167-2022v75n5inov

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Submission: 07-27-2022 **Approval:** 08-16-2022

ABSTRACT

Objective: to present and discuss the advancement of science in symptom management through research involving oncological symptom clusters (OSC). **Method:** a reflective study, supported by the scientific literature on OSC. **Results:** five key points are crucial to advancing the science of symptom management through research involving OSC: definition of OSC characteristics; underlying mechanisms and priority symptom clusters; OSC measurement; targeted and personalized interventions; new analytical strategies. **Final considerations:** a better understanding of the complex connections between different systems and biobehavioral aspects in patients, especially in the field of oncology nursing, is urgent. The study of these interactions has become increasingly promising and emerging for oncology nursing, since therapeutic interventions, whose target is the neuroimmunoendocrine axis, are relevant for personalized care, translating into greater scientific and nurse autonomy to care for patients. **Descriptors:** Concurrent Symptoms; Oncology Nursing; Neoplasms; Signs and Symptoms; Medical Oncology.

RESUMO

Objetivo: apresentar e discutir sobre o avanço da ciência no manejo de sintomas por meio da pesquisa envolvendo os clusters de sintomas oncológicos (CSO). **Método:** estudo reflexivo, sustentado na literatura científica sobre os CSO. **Resultados:** cinco pontos-chave são cruciais para o avanço da ciência no manejo de sintomas por meio da pesquisa envolvendo os CSO: definição de características dos CSO; mecanismos subjacentes e grupos de sintomas prioritários; mensuração dos CSO; intervenções direcionadas e personalizadas; novas estratégias analíticas. **Considerações finais:** uma melhor compreensão das complexas conexões entre os diversos sistemas e aspectos biocomportamentais em pacientes, especialmente no campo da enfermagem oncológica, é premente. O estudo dessas interações vem se tornando cada vez mais promissor e emergente para a enfermagem oncológica, pois as intervenções terapêuticas, cujo alvo é o eixo neuroimunoendócrino, são relevantes para o cuidado personalizado, traduzindo em maior cientificidade e autonomia do enfermeiro para cuidar dos pacientes.
Descritores: Sintomas Concomitantes; Enfermagem Oncológica; Neoplasias; Sinais e Sintomas; Oncologia.

RESUMEN

Objetivo: presentar y discutir el avance de la ciencia en el manejo de síntomas a través de investigaciones que involucran clusters de síntomas oncológicos (CSO). **Método:** estudio reflexivo, sustentado en la literatura científica sobre las OSC. **Resultados:** cinco puntos clave son cruciales para avanzar en la ciencia del manejo de los síntomas a través de la investigación que involucra a las CSO: definición de las características de las CSO; mecanismos subyacentes y grupos de síntomas prioritarios; medición de las CSO; intervenciones dirigidas y personalizadas; nuevas estrategias analíticas. **Consideraciones finales:** es urgente una mejor comprensión de las complejas conexiones entre los diferentes sistemas y aspectos bioconductuales en los pacientes, especialmente en el campo de la enfermería oncológica. El estudio de estas interacciones se vuelve cada vez más promisorio y emergente para la enfermería oncológica, ya que las intervenciones terapéuticas, cuyo objetivo es el eje neuroinmunoendocrino, son relevantes para la atención personalizada, traduciéndose en una mayor autonomía científica y de enfermería para cuidar a los pacientes.
Descriptores: Síntomas Concomitantes; Enfermería Oncológica; Neoplasias; Signos y Síntomas; Oncología Médica.

ONLINE VERSION ISSN: 1984-0446

For oncology nursing, one of the emerging themes is the timely management of oncological symptom clusters associated with cancer and its treatment[1-2]. In general, research in the field of oncology predominantly encompasses the prevalence of symptoms related to cancer and/or its treatment, analyzing them in isolation rather than considering them as concurrent symptoms. However, in daily professional practice, it is noted that symptoms rarely occur in isolation. In fact, numerous and complex symptoms of patients with cancer course in clusters sharing common molecular mechanisms in terms of frequency, intensity and severity[1-3].

Cancer symptom clusters comprise a set of symptoms that are related to each other, which can create a synergistic effect between them and be predictable[1]. Both the process of carcinogenesis and tumor progression and antineoplastic therapy can lead patients to experience numerous unpleasant symptoms, including cancer-related fatigue (CRF), cancer pain, sleep disorders, anxiety, depression, among others. Different oncological symptoms, which can occur alone or together (constituting clusters), when manifesting, have a negative impact on patients' functional status, culminating in a decrease in health-related quality of life[1-4].

Coming from experiments with laboratory animals submitted to the induction of infectious conditions and inoculation of pro-inflammatory cytokines, the history of oncological symptom clusters has evolved from a conceptual point of view and with applicability in clinical practice[1,5]. Initially, a cluster pattern of oncological symptoms was observed from the moment that mice exhibited a phenomenon that was called "sickness behavior", after induction of infectious and inflammatory conditions[1-5].

Sickness behavior was initially established by studying the effects of lipopolysaccharide (LPS) on the wall of Gram-negative bacteria, widely used to mimic systemic inflammation, or through the inoculation of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) in the paws of these animals[5]. Sickness behavior was related to a range of behavioral changes that accompanied pathological processes in mice, such as sleep disturbances, loss of interest in everyday activities such as foraging for food, decreased social contact and sexual interest[5].

Cytokines are signaling proteins released by a variety of cells (the main ones are defense cells, such as macrophages, NK, lymphocytes, mast cells, basophils, fibroblasts). Cytokines are released by these cells in response to different stressful events and are considered crucial for the interaction between the immune system and the central nervous system (CNS)[6-7]. Didactically, cytokines are classified into two general categories: pro-inflammatory and anti-inflammatory. Pro-inflammatory cytokines are directly or indirectly involved in inflammatory processes, with IL-1β (Interleukin 1), IL-6, IL-12, IL 17, INF-y and TNF-α (Tumor Necrosis Factor) making up this group[6-7]. Anti-inflammatory cytokines regulate the immune response by decreasing cell activation, as well as producing mediators such as IL-4, IL-10, IL-13 and TGF-β (Transforming Growth Factor)[6-7].

Preclinical and clinical studies have shown that pro-inflammatory cytokines modulate the effects of physical and psychological stressors, since its increased expression is associated with the emergence of several clusters of oncological symptoms and the occurrence of a worsening in patients' quality of life[5,8-11]. It is established that as relevant as the content of leukocytes produced by cells in the tumor microenvironment is the profile of soluble immunomodulatory mediators, such as cytokines and chemokines[6-7]. These factors mediate the communication between all elements of the microenvironment in which the tumor is inserted, since they can be produced by all cell types present there[6-7].

For example, the cytokines IFN-γ and IL-12 play an important role in antitumor immunity. While IFN-γ exerts a direct toxic effect on tumor cells and has anti-angiogenic activity, the antitumor role of IL-12 is largely due to the induction and activation of Th1 responses (T helper 1) and mediated by cytotoxic T lymphocytes (CTL). TGF-β and IL-10, on the other hand, are important cytokines in suppressing CTL effector functions and in inducing the differentiation of regulatory T cells (Tregs) in the tumor microenvironment. Additionally, cytokines, such as IL-6 and TNF-α, stimulate angiogenesis and metastasis[6-7,12].

Similarly, in relation to sickness behavior shown by mice in those experiments, symptoms such as CRF, sleep disturbances, pain, depression and cognitive disturbances were found in patients with cancer who also exhibited high levels of pro-inflammatory cytokines[1,8,13]. The manifestation of sickness behavior in patients with cancer resulted in the concept of neuropsychological symptom cluster: "set of emotional and/or behavioral symptoms that may be related to psychological and/or neurological dysfunction and that have a tendency to occur in patients with cancer"[1].

Common molecular mechanisms may underlie the interaction between the immune, endocrine and CNS systems, which orchestrate a set of responses capable of installing physiological and biobehavioral changes in both animal and human organisms[3-4]. Thus, research covering sickness behavior, via the assessment of neuropsychological symptom clusters in patients with cancer, supports the hypothesis that pro-inflammatory cytokines are closely linked to the molecular mechanisms of oncological symptom clusters[1,5,8].

One study determined that patients with high levels of CRF and sleep disturbances had more depressive symptoms and changes in behavior[14] and that changes in sleep patterns are strongly correlated with an increase in fatigue and a consequent worsening in quality of life. Thus, changes in cytokine levels, among other neuroimmunoendocrine processes, can be critical for the onset of symptoms and, potentially, a target for their prevention and treatment[1-4].

Evidence suggests that individuals with CRF have dysregulated circadian rhythms of activity/rest and sleep/wakefulness[1,8,10,12,15-16]. Furthermore, the hypothalamic-pituitary-adrenal (HPA) axis disruption or activation is a potential mechanism for fatigue, which is supported by dysregulation of cortisol concentrations[8,12-16]. During chronic exposure to HPA axis pro-inflammatory cytokines, sensitivity is likely to be abrogated and this decrease in cortisol production has been associated with CRF[10-11,16]. Furthermore, during chronic exposure to stress, the cytokine network is modulated, sensitizing the HPA axis (negative feedback)[8,16]. Indeed, circadian disruptions in cancer are mediated by both biological and behavioral factors. Studies indicate that psychosocial factors can lead to disruption of the neuroimmunoendocrine axis and circadian rhythms, which may contribute to the pro-tumor immune response and tumor progression[16-17].

According to the Expert Panel Proceedings and Recommendations, to advance the science of symptom management through research involving symptom clusters[18], five key points are crucial in this field: defining characteristics of symptom clusters (establish a common conceptual framework and approach to symptom cluster measurement assessment; assess the relationships between signs and symptoms within a cluster; replicate studies of subgroups of patients with common or different experiences for a pre-specified cluster of symptoms; assess, intervene and measure the results of symptom clusters along the disease trajectory; determine the phenotypic and molecular predictors and/or risk factors for the development of pre-specified symptom clusters in patients); underlying mechanisms and priority symptom clusters (assess mechanisms underlying symptom clusters, including immune system inflammation, sympathetic nervous system activation, HPA axis activation, and CNS changes; determine the best approaches to assess underlying genetic and epigenetic mechanisms for symptom clusters; determine the best methods to assess biobehavioral mechanisms for symptom clusters); symptom cluster measurement (use qualitative methods to identify generic and specific disease symptom clusters; use mixed methods approaches to identify disease-specific and generic symptom clusters; compare and contrast changes over time in the frequency and types of symptom clusters; build a common core dataset to gather data and assess comparability in symptom cluster studies); targeted interventions (assess the use of new clinical trial designs to determine whether they can be used to adapt interventions to treat single or multiple symptoms within a symptom cluster; determine the most effective interventions for various symptom clusters; determine the most appropriate outcomes for studies involving intervention on symptom clusters); and new analytic strategies (applying new advanced analytic techniques to symptom cluster research; establishing guidelines for choosing optimal analytic strategies for research involving symptom clusters)[18].

A better understanding of the complex connections between different systems and biobehavioral aspects in patients, especially in oncology, is urgent. The study of these interactions has become increasingly promising and emerging for oncology nursing, since therapeutic interventions, whose target is the neuroimmunoendocrine axis, are relevant for personalized care[19-20], translating into greater scientificity and autonomy of nurses to care for patients.

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