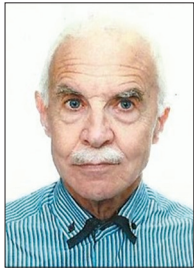


Cancer-Related Fatigue: Some Clinical Aspects

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Fatigue is the very frequently reported symptom of cancer and cancer treatment. Cancer patients invariably report that fatigue is a major obstacle in maintaining their routine daily activities. The proportion of patients experiencing cancer-related fatigue (CRF) varies widely in the literature, but it has generally been reported to be between 40% and 100% of the overall number of patients with cancer. This variation in rates is likely owing to the lack of commonly accepted diagnostic criteria and assessment tools and the effect of disease stage and status on fatigue. However, the malignant tumor itself and treatment factors were not found to be related to severe fatigue.

CRF is the most frequently anticipated side effect of cancer treatment: 95% of patients who are scheduled to receive chemotherapy or radiotherapy are expected to suffer from some degree of fatigue during their treatment.

An exploration of this disorder exemplifies a conceptual approach to a clinical problem. In disorder beginning to study, the concept of fatigue as a mental phenomenon was predominant. Accordingly, rest remained the crucial factor in the care of cancer patients' fatigue. Later, CRF was increasingly seen as a symptom of a disease or even

a disease itself (neoplastic [malignancy]-related fatigue, ICD-10-CM R53.0).^[1]

The 2018 National Comprehensive Cancer Network (NCCN) defines CRF as “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.”^[2] CRF is distinct from the “normal” tiredness/weakness experienced by healthy individuals in that, it is not relieved by rest or sleep. Besides, it may interfere with therapy compliance and even limit the effects of active antitumor treatment. Approximately one-third of patients experience CRF for months and sometimes, for years after treatment.

The effect of CRF on a patient's quality of life (QoL) is both profound and pervasive. This disorder diminishes a person's ability to work, to participate in social, leisure, and other activities, and to sustain meaningful relationships with his/her family and others.

Despite the availability of some treatment options as well as extensive ongoing research, fatigue is nevertheless often viewed by clinical staff, caregivers, and the patients themselves as an inevitable consequence of cancer and cancer treatment. This view needs to change.

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In addition, CRF is underreported, under-assessed, and undertreated partially because it is not clearly understood. Many patients with fatigue do not discuss treatment options for this disorder with their oncologists; therefore, only a quarter of them receive any treatment recommendations.

The etiology of CRF is complex, involving many potentially contributing elements. Identifying the etiological factors that contribute to fatigue often proves to be complicated, as multiple causes typically coexist and may have additive effects. These factors include the direct effect of cancer, side effects associated with anticancer therapies or other medications, comorbid medical/psychological conditions, and psychosocial state. Possibly, there is dysregulation of several interrelated physiological, biochemical, and psychological factors. To further complicate matters, the effect of each of these disruptions on CRF not only varies among individuals but also during different phases of the disease and with treatment type.

Specific mechanisms involved in the pathophysiology of CRF are unknown. Serotonin levels, adenosine triphosphate and hypothalamic–pituitary–adrenocortical axis dysregulation, skeletal muscle wasting, circadian rhythm desynchronization, and cytokine levels (primarily pro-inflammatory cytokines) are considered to be related to the development of CRF. The authors examined the contribution of comorbid conditions, such as depression, anemia, cachexia, and hypothyroidism, to CRF.

Activation of the immune system by infection, injury, or trauma leads to the release of pro-inflammatory cytokines and other immune factors, including receptor antagonists, soluble receptors, and products of cellular activation. These cytokines orchestrate local and systemic immune responses and mediate neural symptoms such as fatigue.

Some conditions are commonly associated with fatigue, such as anemia, cachexia, fever, infection, and depression. Fatigue may occur as a part of a cluster of symptoms including pain, difficulty in sleeping, and perceived muscle weakness. The associations among these symptoms might encourage the development of effective integrated treatment strategies.

With respect to the clinical picture, we emphasize the multiple biopsychosocial dimensions of fatigue. CRF is a multidimensional condition with both subjective and objective components. Individuals may perceive fatigue as physical tiredness or exhaustion, a need for reduced activity, reduced motivation (including lack of initiative, pessimism, and expectation of negative outcomes), and/or mental fatigue. The latter can be expressed as a reduced capacity for attention and learning. They are related to cognitive symptoms, such as disturbances in short-term memory and the ability to concentrate.

The experience of CRF involves multiple signs and symptoms; the patients usually refer to them as concurrent cancer- or treatment-related side effects. Physiological signs and symptoms include anemia, hypothyroidism, shortness of breath, muscle atrophy, physical weakness, low aerobic capacity, and sleep disruption. Mood symptoms include depression and anxiety. Social symptoms generally include a reduction in the patients' ability to work and to participate in leisure activities, their capacity to sustain meaningful relationships with their families and to engage in social and other activities during and after treatment. No two individuals experience CRF in the same way, making it difficult to develop an effective treatment, and most likely, impossible to develop an effective intervention targeting a single pathopsychological/physiological mechanism that will provide relief to the majority of patients with cancer.^[3]

The standards of care for fatigue were proposed by the NCCN, and the first set of guidelines was published in 2000. Since then, the NCCN Fatigue Practice Guidelines have been updated annually using the treatment algorithm, which combines the available research and clinical experience to provide concise recommendations for supportive care. Nowadays, the management of CRF is based on the current understanding of the symptom and the development of new therapies. Fatigue should be screened, assessed, and managed according to these guidelines.^[2]

As fatigue is a symptom that is perceived by the patient, the most accurate description can be obtained through self-reporting by patients. The NCCN recommends the use of a single item to assess fatigue severity on a scale of 0–10.^[4] This approach permits identification of cancer patients who may benefit from the assessment and treatment for fatigue. Multidimensional CRF measures may be useful in assessing physical, emotional, and cognitive domains. The patient's medical history and physical examination, data on laboratory tests and descriptions of his/her behavior by family members are important sources of necessary information.

Screening for fatigue should include screening for possible contributing factors (e.g., pain, emotional distress, sleep disruption, anemia, and nutrition) as well as comorbid conditions (e.g., infection, cardiac dysfunction, pulmonary dysfunction, renal dysfunction, hepatic dysfunction, neurologic dysfunction, hypothyroidism, and other endocrine dysfunctions). Identification of CRF and its contributing factors does not alleviate the problem. Given the diverse etiological factors that contribute to fatigue and its multidimensional nature, a comprehensive assessment of patients with fatigue is required for the development of effective treatments. Clinical practice guidelines for fatigue assessment and management emphasize the need

to evaluate^[1] fatigue characteristics and^[2] disease status and treatment. Guidelines also recommend obtaining the medical history and physical checkup results of the patient and conducting the prescribed laboratory studies to rule out common, treatable causes of fatigue, such as anemia and thyroid dysfunction.

NCCN CRF guidelines recommend a two-stage approach for the treatment of CRF. The first step is to identify and address any treatable factors contributing to fatigue. NCCN guidelines identify several common contributing factors, including pain, emotional distress, anemia, sleep disturbance, nutritional inadequacies, and comorbidities (e.g., infection, cardiac dysfunction, and renal dysfunction). Significant improvement in QoL has been observed in cancer patients with anemia after treatment with erythropoietic agents. The second step involves the management of any residual fatigue that continues after the resolution of treatable contributing factors or of fatigue that continues despite the lack of any identifiable contributing factors. To develop treatment strategies tailored to the patient's clinical status, separate algorithms are provided for patients receiving active cancer treatment, patients receiving disease-free long-term follow-up, and patients receiving care at the end of life. Fatigue management includes:

1. Providing education and counseling for all cancer patients and their families regarding fatigue and its natural history. It should be emphasized that fatigue is commonly experienced by patients undergoing treatment for cancer and is not necessarily an indicator of disease progression (if appropriate)
2. Nonpharmacologic interventions
3. Pharmacologic treatments.

The NCCN guidelines recommend the use of a variety of integrative nonpharmacologic interventions. The integrative nonpharmacologic behavioral interventions are organized into three main categories as follows: (a) exercise, (b) psychosocial interventions, and (c) other integrative therapies (mindfulness relaxation, yoga, and so on).^[2]

The above-mentioned concept that describes fatigue as a mental phenomenon and rest as the best method of care has been disregarded, as more studies have provided data that invalidate this concept.

Physical exercise is an intervention modality that shows great promise in mitigating acute CRF experienced by cancer patients during treatment as well as chronic CRF they experience after completion of treatment. Exercise is defined as physical activity performed in a systematically dosed manner (e.g., a specific frequency, intensity, duration, and mode) with the intention of improving health-related outcomes, such as fatigue, depression, and others. Exercise

is safe and well tolerated by cancer survivors with various diagnoses.^[3] The outcomes are similar for patients throughout the cancer care continuum.

Persistent psychological distress detrimentally affects the patient's well-being, QoL, work productivity, and personal relationships. The psychosocial needs of the patient diagnosed with cancer are considered important in providing comprehensive care. Psychosocial interventions include activities such as support interventions (either individually or in groups), education, stress management, coping strategy training, and providing behavioral modalities designed to assist patients with managing their CRF.

Meaning (alternatively, "purpose") of life – the perception that one's previous and present life is useful and that one finds satisfaction in daily activity – is considered an important aspect of QoL.^[5] Patients are recommended to find meaning in their current situation with an emphasis on meaningful interaction and maintaining their dignity.^[2]

Clinicians often encourage patients experiencing CRF to rest and conserve energy. Such conservation is a part of the planned management of personal energy resources to prevent their depletion. It encompasses a common sense approach, which helps patients set realistic expectations, prioritize and pace activities, and delegate less essential activities. Daytime naps can replenish energy, but it is advisable to limit these to less than an hour, to avoid disturbing nighttime sleep.

New treatment options will likely emerge from the several ongoing large-scale clinical trials examining the efficacy of a variety of treatments for CRF, for example, those involving modafinil, buspirone, American ginseng, L-carnitine, and coenzyme Q10.

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Conflicts of interest

There are no conflicts of interest

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