Cancer-Related Fatigue

Persistent, Pervasive, and Problematic

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KEYWORDS

• Cancer • Rehabilitation • Fatigue exercise • Cognitive behavioral therapy

KEY POINTS

- Cancer-related fatigue (CRF) is common, persistent, and difficult to treat.
- Causes for CRF are not known, but associations with anemia, high body mass index, diabetes with some tumor types (breast, colon, liver), inflammatory cytokines, insomnia, and cortisol dysregulation are reported.
- One of the most effective treatments for CRF is exercise. Aerobic and resistance exercise are both effective.
- Cognitive and behavioral therapy mitigate symptoms, as does modafinil.

BACKGROUND

Cancer and its treatments have been reported to be associated with fatigue in a significant number of patients. Fatigue has been a finding during all phases of treatment, from pretreatment through treatment completion and survivorship.[1–3] Additionally, it was noted to be associated with significant patient distress.[4–6] These early reports helped establish an awareness that fatigue was common in patients with cancer diagnoses. What also resulted from these descriptive studies was the belief, later substantiated, that this fatigue was pathologic; that is, persistent and not easily resolved with the usual antidote to fatigue, rest. The early reports proposed that this fatigue was unusual and possibly specific to cancer, in part because its onset was often related to the diagnosis and became almost universal during treatment. Consensus was reached about identifying this as cancer-related fatigue (CRF).[1,2]

The National Comprehensive Cancer Network (NCCN), a network of practitioners from many disciplines who treat and study patients with cancer, has helped spearhead an effort to bring the needs of patients with cancer into a forum that can help

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improve and possibly prolong their lives. CRF is one area that NCCN has provided a forum for discussion to raise awareness, and provide data and written guidelines and other tools for management.[7]

NCCN has defined CRF as "an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning."[8] Others have suggested that possibly a better approach might be to use a case definition to describe CRF. This approach suggests 4 criteria to establish the diagnosis: (1) a period of 2 weeks or longer within the preceding month during which significant CRF or diminished energy was experienced each day or almost every day along with additional CRF-related symptoms; (2) the experience of CRF results in significant distress or impairment of function; (3) the presence of clinical evidence suggesting that CRF is a consequence of cancer or cancer therapy; and (4) CRF is not primarily a consequence of a concurrent psychiatric condition, such as major depression. Many agree that CRF is associated with significant distress; interferes with usual activity; is not the result of a psychiatric condition; is likely to be the result of multiple causes, as a result of the disease itself or its treatments; and is difficult to treat.[9,10]

Because of its prevalence, consensus about the criteria for diagnosis and its impact of function and well-being, CRF has been accepted as a diagnosis in the *International Classification of Diseases, 10th Revision* (World Health Organization. International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Version for 2003: http://www.who.int/classifications/icf/en/). Many have stated that fatigue is nearly a universal symptom in patients with cancer, mainly during treatment. However, nearly 30% of cancer survivors with no existing disease still have significant fatigue symptoms.[11–14] Cella and colleagues[12] demonstrated that patients with cancer with anemia, even after successful anemia therapy, and patients with cancer without anemia were significantly more fatigued than controls without either.

In general, CRF is a descriptive term widely accepted by practitioners and patients. The criteria for establishing the diagnosis and its importance as a symptom that needs be followed over time and treated are not questioned. Nonetheless, diagnosis is dependent on a mix of clinical observations and patient self-reports. As of this writing, no metric establishes the diagnosis of CRF and its etiology is not known.

Is CRF a unique form of fatigue? Does it differ from other pathologic fatigue conditions associated with chronic illness? Does it share similar clinical and physiologic findings with chronic fatigue syndrome? In part, the answers to these questions depend on the way fatigue is measured. Improvements in understanding have resulted through the use of operationalized criteria, but classification methods and the validity of diagnostic criteria also are important. Some common findings from other diseases and syndromes may help answer these questions and are discussed in the sections pertaining to clinical presentations and possible biological associations or mechanisms of fatigue.

CLINICAL PRESENTATIONS

One of the most frequently heard comments from my patients over the decades of treating them is "Why am I so tired? I am exhausted all the time and I am terribly frustrated by this." My approach has been to enable them to describe their experiences in their own words and hopefully enable me to sort out the contributors to their symptom. I often begin with a thorough evaluation of their medical status and try to identify comorbidities that are treatable, conditions resulting from the cancer and its treatments that might resolve with time, and an overall assessment of the impact fatigue has had on the individual's life activities. Specifically, it is helpful to ask about the duration, frequency, onset, pattern, and intensity.