Cancer-Related Fatigue in Cancer Survivorship

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KEYWORDS

• Cancer-related fatigue • Cancer survivors • Screening • Exercise
• Cognitive behavioral therapy • Psycho-educational therapy • Yoga
• Psychostimulants

KEY POINTS

- Cancer-related fatigue (CRF) is 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 that significantly interferes with usual functioning.
- Screening should be performed at the time of the cancer diagnosis, throughout cancer treatment, and following completion of the essential cancer treatment. A fatigue scoring scale (mild-severe) can be used to evaluate fatigue in cancer survivors. Cancer survivors with moderate to severe CRF require an additional detailed evaluation.
- The general approach to CRF management includes education, counseling, and other strategies. This approach should be used for survivors at all fatigue levels.
- Nonpharmacologic interventions include psychosocial interventions, exercise, yoga, physically based therapy, dietary management, and sleep therapy. Cognitive behavioral therapy, psychoeducational therapy, yoga, and exercise have the most supporting evidence for CRF management (category 1).
- The psychostimulant, methylphenidate, is a pharmacologic intervention that may be considered in CRF. It does not have category 1 supporting evidence and is not US Food and Drug Administration approved for CRF. Antidepressants may also benefit cancer survivors when CRF and depression are both present. Corticosteroids are usually limited to patients with cancer with advanced disease.

INTRODUCTION

Fatigue is perceived as one of the most common and distressing adverse effects of cancer and cancer therapy.[1] The National Comprehensive Cancer Network (NCCN) defines cancer-related fatigue (CRF) as a distressing, persistent, subjective sense of

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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] Cancer survivors are characterized as individuals who have a diagnosis of cancer from the time of diagnosis until death.[3]

The general overall predominance of CRF is approximately 48%, despite the fact that it is higher in certain malignancies (eg, pancreatic, breast, lymphoma) and during treatment.[4] Studies report 58% to 94% of patients with breast cancer experience CRF during treatment and 56% to 95% have CRF following adjuvant chemotherapy.[4]

Before cancer treatment, fatigue may be present; however, it generally increases during radiotherapy,[5] chemotherapy,[6] and hormonal and/or biological therapies.[7] The fatigue prevalence is estimated at 25% to 99% while undergoing treatment.[5–8] Henry and colleagues[9] conducted a cross-sectional survey of 1569 patients with cancer. CRF was experienced by 80% of those who received chemotherapy and then radiotherapy. The prevalence of CRF surpasses 75% in patients with metastatic disease.[10–12] Factors such as the population studied, treatment received, and evaluation type (type of screening tool) contribute to the prevalence of fatigue during treatment.[1] However, despite the predominance and negative effect of CRF, this symptom is underreported by patients, and underestimated and undertreated by clinicians.[13] Patients may not talk with their physicians about fatigue because of their fear of not receiving maximum cancer treatment; their belief it is an expected symptom and is untreatable; their belief they will be thought of as a "complainer"; or their belief that fatigue is a sign of recurrent or advancing disease. In response, physicians and other health care providers may not ask about fatigue because they often lack knowledge regarding management and their perception of limited treatment options or because of time constraints in a busy clinical environment. Reports acquired from cancer survivors suggest that fatigue may persevere for a considerable length of time or even years after treatment.[14] Despite some improvement in fatigue symptoms following the first year of treatment completion, approximately 25% to 30% of patients will continue to experience these symptoms up to 5 years after successful completion of treatment and in some cases longer.[15–17] A significant variable driving the assessment and treatment of CRF has been the developing recognition of the negative effect of fatigue on quality of life.[18]

PATHOPHYSIOLOGY

The cause of CRF is often vague. Although unproven, there have been several hypotheses of the pathophysiology of CRF. The hypotheses include serotonin (5-HT) dysregulation, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, circadian rhythm disruption, muscle metabolism/ATP dysregulation, vagal afferent nerve activation, and cytokine dysregulation.

5-HT dysregulation hypothesizes that the malignancy and/or associated treatment causes an expansion in brain 5-HT levels including upregulation of a population of 5-HT receptors resulting in a decreased somatomotor drive, a modified HPA axis function, and a sensation of decreased ability to exhibit physical work.[19]

Another potential cause of fatigue is the aggravation of the HPA axis. This hypothesis suggests that cancer, and/or cancer treatment, modifies the function of the HPA axis, resulting in endocrine changes that cause or add to fatigue.[20]

Circadian rhythms are described as endogenous hereditary and physiologically based patterns that are controlled by the body's "clock." These rhythms operate on a 24-hour cycle and are sensitive to environmental (eg, alterations in light and dark) and psychological factors (eg, stress, anxiety, and illness). Relative to patients with