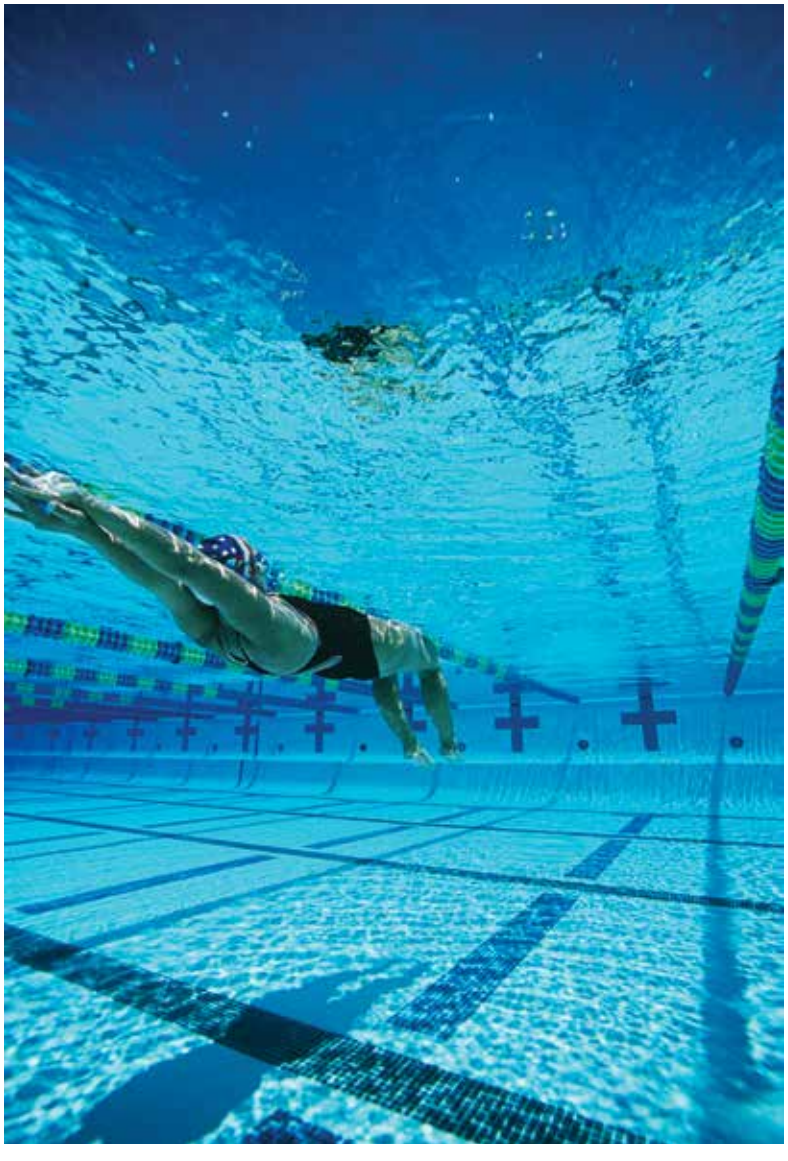
CRF relief: Exercise still trumps pharmaceutical interventions

Recent studies show the evidence continues to support exercise and holistic measures as the most effective intervention for cancer-related fatigue.



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The pathophysiologic roots of cancer-related fatigue (CRF) remain poorly understood, but CRF is a pervasive problem, affecting the vast majority of patients with cancer and frequently persisting for months or even years after treatment. CRF is debilitating and can profoundly impact a patient's quality of life; its severity correlates with depression and prognosis. Yet patients do not always raise concerns about their fatigue with clinicians. Although the evidence base for managing CRF is relatively small, physical exercise and dexamethasone appear to be helpful interventions. Communication with patients about CRF symptoms and treatment options might improve detection and assessment.

Cancer-related fatigue is defined as persistent tiredness, weakness, or exhaustion that interferes with a patient's ability to function physically, emotionally, cognitively, or socially.[1,2] Patients report that CRF is both physically debilitating and socially isolating—more so even than pain or nausea.[3]

"CRF is associated with decreased survival and interferes with employment, enjoyment of life, relationships, and motivation to battle the cancer," notes Tami Borneman, RN, MSN, CNS, FPCN, of the City of Hope Cancer Center, in Duarte, California.[4]

Onset of cancer-related fatigue can precede treatment, but clearly becomes more acute in many patients undergoing traditional anticancer therapies; symptoms persist for months or years

in a third of cancer survivors, studies suggest.[1,5] A recent study found that 45% of patients undergoing active anticancer treatment report moderate to severe CRF.[5] CRF is also being reported by patients receiving targeted therapies such as sunitinib (Sutent, generic).[6] With improving survival times for cancer patients, CRF among patients undergoing treatment and survivors seems unlikely to wane—and might well become even more common in the near future.

Despite its impact, however, patients do not always volunteer that they are experiencing CRF, and clinicians do not always ask. For example, documenting fatigue in the patient's medical record is uncommon.[4] As a result, CRF is believed to be underdetected and undertreated.[1,4]

CRF is typically measured via patient self-report using a scale of 0 to 10 (0 representing no fatigue, and 10 representing severe fatigue), although several formal instruments have been developed and validated (eg, the Brief Fatigue Inventory [BFI] and the Functional Assessment of Cancer Therapy Instrument-Fatigue [FACIT-F] scale).[4,7] The National Comprehensive Cancer Network (NCCN) recommends all patients with cancer be assessed for CFR at diagnosis and at each chemotherapy appointment.[2]

PATHOPHYSIOLOGY

Contributing factors include comorbidities, radiation therapy, chemo- and targeted anticancer therapies, surgery, and polypharmacy.[4] The underlying pathophysiologic underpinnings of CRF are poorly understood, although various lines of evidence implicate central nervous system neuroendocrine-immune inflammatory processes, including proinflammatory cytokines, and suggest that peripheral (muscular) fatigue does not play as important a role.[1,8-11] Cytokine antagonists were recently proposed as a potential pharmacotherapy for CRF.[10]

Genotype and gene expression research underway includes work on the role of proinflammatory cytokine gene variants in CRF associated with breast cancer.[1,10,12] If early findings are confirmed in larger studies, genotyping might allow meaningful stratification of patients by risk for CRF, and identify targets for drug development.[10]

Meanwhile, however, even though evidence-based guidelines for CRF interventions have been promulgated, there are not yet simple, sure-bet answers to the question of how best to manage CRF.[2,3,13-15] More studies have recruited cancer survivors than currently treated cancer patients, and more advanced/palliative treatment patients have been studied, than patients with early stage cancers.

Patient education is important, including communication about the potential fatigue-worsening effects of opiates for pain control and the importance of hydration, nutrition, energy-conservation, and physical activity in maintaining better alertness and energy levels.[4] In general, patients with mild CRF should be encouraged to engage in physical activity and try other nonpharmaceutical interventions, whereas patients with moderate or severe CRF may require pharmacotherapeutic interventions.[4]

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PHYSICAL ACTIVITY

Some evidence shows modest improvements in CRF associated with physical activity regimens, and physical exercise is the only intervention "supported by a body of evidence of sufficient rigor to … be considered for carefully screened patients with cancer experiencing fatigue."[15]

The authors of a 2012 meta-analysis of data from 34 randomized controlled clinical studies concluded that physical exercise offers "significant but small" reductions in CRF among patients with breast cancer.[16] Adding resistance exercise to aerobic exercise appears to yield larger benefits in patients' physical and functional quality-of-life scores.[16] Recent studies also suggest CRF symptom improvements associated with deep-water aquatic exercise regimens (eg, deep-water running, three times a week) among breast cancer survivors.[17,18]

Early research has also yielded preliminary support for cognitive-behavioral therapy (CBT), CBT with hypnosis, massage, relaxation training, education and information provision, yoga, and acupuncture.[16,19-21] Omega-3 polyunsaturated fatty acid supplements also may decrease inflammation and fatigue among cancer survivors, leading to calls for additional study of omega-3 PUFA supplements and CRF among breast cancer survivors.[22]

PHARMACOTHERAPIES

In addition to nonpharmaceutical interventions, several investigational pharmacotherapies have been proposed for

CRF. Unfortunately, few of these enjoy clear evidence of benefits. A recent meta-analysis of erythropoietin-stimulating agents, for example, found no overall evidence of improved CRF symptoms.[13] As described below, the promise of psychostimulants as an effective treatment for cancer-related fatigue has yet to receive definitive support in recent clinical studies.

A 2013 double-blind, randomized, placebo-controlled clinical trial of 84 patients with advanced cancers reported that the anti-inflammatory corticosteroid dexamethasone offered improved CRF and quality of life compared with placebo.[14] The study used the FACIT-F scale, and measured outcomes at days 8 and 15 after initiation of dexamethasone or placebo administration, but not at later points in time.[14]

"Our data suggest that dexamethasone acts rapidly in relieving CRF," the authors reported, adding that the effect might reflect the effect of dexamethasone on proinflammatory cytokines rather than mood-related neurotransmitters.[14]

Methylphenidate is a psychostimulant used to treat attention deficit disorder (ADD).[3] Methylphenidate, which increases brain levels of the neurotransmitter dopamine, has been used off-label in the treatment of depression and fatigue.[3] Preliminary study suggested it might also alleviate CRF, particularly among patients who are administered opiates for pain management.[23] However, given concerns about potential side effects and addictiveness, compelling clinical trial outcomes would be necessary to justify the widespread or routine use of methylphenidate to prevent or treat CRF.[1]

Disappointingly, recent studies provide little such support for methylphenidate's widespread use. A 2013 randomized, placebo-controlled clinical trial concluded that neither methylphenidate nor nursing telephone support interventions (either alone or in combination) improve CRF compared with placebo.[23] The finding appears to be consistent with the randomized controlled clinical trial evidence as a whole. The authors of a recently published meta-analysis of data from five other randomized controlled clinical trials of methylphenidate for CRF treatment concluded that further confirmation is needed before firm recommendations on their usage and safety can be promulgated.[3]

Although the meta-analysis suggested that the efficacy of methylphenidate might improve with prolonged treatment durations ($P = 0.03$), the available clinical trial data provided limited evidence overall that methylphenidate is effective against CRF.[3]

Modafinil, another psychostimulant, has been studied as a potential pharmacotherapy for docetaxel chemotherapy-associated severe CRF. However, a newly reported phase 3 randomized double-blind, placebo-controlled clinical study of 83 patients, found no statistically significant difference in CRF between patients receiving 200 mg/day modafinil and those assigned to receive placebo.[24] There is therefore, to date, no evidence that modafinil is an effective intervention against CRF.

The challenge is to identify CRF and quantify its severity, but many patients may not report experiencing the effect.

IN SUMMARY

Cancer-related fatigue is a common side effect, and almost half of patients undergoing treatment for cancer will experience moderate to severe CRF. The challenge is to identify CRF and quantify its severity, but many patients may not report experiencing the effect. Furthermore, despite the availability of validated formal tools for measuring CRF, it is typically measured via subjective patient self-report.

Evidence on effective management is limited. Physical exercise and nonpharmaceutical interventions are helpful for patients with mild to moderate CRF. For more severe cases, dexamethasone was shown to be more effective than placebo. However, no studies to date support the use of methylphenidate and modafinil, both psychostimulants, as effective agents for managing CRF. ■

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