

ADVANCES IN SUPPORTIVE CARE

Current Developments in Side Effect Management, Palliative Care, and Quality of Life

Management of Cancer-related Fatigue

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H&O What causes cancer-related fatigue?

JB The causes of cancer-related fatigue still remain to be conclusively determined. Fatigue is a complex symptom that can be influenced by many factors. These factors include direct effects of the tumor or tumor burden, physiologic changes induced by cancer treatment, and treatment side effects such as insomnia or pain. Patients' psychologic response to the experience of cancer and their coping style may also cause or exacerbate fatigue. In particular, studies have shown that depression correlates with fatigue, but this correlation is not necessarily a causal relationship.

With regard to biologic factors, anemia can lead to fatigue. Often, treating anemia alleviates the associated fatigue. However, anemia accounts for only a small portion of the cases of cancer-related fatigue.

H&O What other factors might play a role in cancer-related fatigue?

JB There is some evidence that the immune system might be involved in fatigue among cancer survivors. Preliminary data from studies with breast cancer survivors have documented elevated levels of pro-inflammatory cytokines among patients experiencing fatigue, suggesting a chronic inflammatory process. In addition, fatigue in breast cancer survivors appears to be associated with alterations in stress hormones, specifically cortisol. These data provide novel insights into potential mechanisms for cancer-related fatigue.

H&O How are pro-inflammatory cytokines produced in association with cancer therapy?

JB Cytokines can be produced by the tumor, by immune cells in response to the tumor, or by the immune system as a result of treatment effects. We are currently conducting studies to identify changes in the immune system that occur during and after treatment that may set the stage for a chronic inflammatory state.

H&O Is cancer-related fatigue now well recognized in the literature?

JB Yes. Fatigue is now widely recognized as the most common and distressing side effect of cancer treatment. Studies have shown that the majority of patients experience fatigue during treatment, and a significant minority continue to experience fatigue for months or years after successful treatment completion. Among breast cancer survivors, approximately 30% experience fatigue.

H&O What are future research directions?

JB The first generation of research on cancer-related fatigue documented the presence of fatigue in cancer patients and survivors and identified correlates of fatigue. There are several important next steps for this area of research. Longitudinal studies that follow patients before, during, and after treatment will provide a more accurate picture of the prevalence and course of fatigue and identify those at risk for severe or enduring fatigue. These studies are just beginning to be reported. Mechanistic studies that test theory-driven models of cancer-related fatigue are also key for identifying the causes of this symptom. As mentioned earlier, there is a great deal of interest in understanding the potential role of the immune system in driving cancer-related fatigue. Psychologic factors are also being examined here, including a catastrophizing coping style.

H&O Could you further describe the research regarding the role of the immune system?

JB Studies done in the field of psychoneuroimmunology have shown that the immune system can signal the brain, leading to a variety of behavioral effects, including fatigue and changes in sleep, mood, and cognitive function. This

connection has been demonstrated in animal models, and we are now conducting studies in order to determine whether a similar process occurs in cancer patients and survivors. It may be that an immune process is switched on by cancer or cancer treatment, leading to the release of pro-inflammatory cytokines, which then trigger symptoms of fatigue and possibly other behavioral changes. It is possible that this type of inflammatory process is sustained in cancer survivors, even though the treatment has ended and the cancer has supposedly been eradicated.

Our group has reported studies showing that breast cancer survivors who experience fatigue have elevated levels of inflammatory markers compared with nonfatigued breast cancer survivors.

H&O What potential treatments might come from these findings?

JB If pro-inflammatory cytokines are indeed driving symptoms of fatigue, it may be possible to treat cancer-related fatigue with pharmacologic agents that block the action of these cytokines. For example, in a study reported by Monk in 2006 in the *Journal of Clinical Oncology*, pharmacologic agents were used to block cytokines in order to improve the tolerability of chemotherapy in cancer patients.

However, before such treatments can be attempted, we need more data showing that the immune system is involved in cancer-related fatigue. Such confirmation is necessary before cytokine blockage could be recommended.

H&O How is cancer-related fatigue currently managed?

JB Perhaps the best-studied intervention for cancer-related fatigue is exercise. There is very strong evidence that moderate exercise diminishes fatigue. These data are predominantly from patients undergoing treatment, but there are some data from survivors as well.

We recently conducted a very small pilot study of Iyengar yoga as a treatment for cancer-related fatigue and found considerable benefit among breast cancer survivors. Based on the positive findings of this initial study, we are now seeking to conduct larger, randomized controlled trials.

Psychosocial interventions have also been found to be effective in reducing cancer-related fatigue. These include stress management interventions, psychoeducational group interventions, and supportive expressive group therapy. In some cases fatigue has not been the focus of these interventions but has still been positively affected.

Finally, as mentioned earlier, treating anemia will be helpful for those patients experiencing this side effect of cancer or cancer therapy.

H&O Is it possible to isolate fatigue in terms of data collection?

JB Fatigue generally occurs with other problems. For example, in all of the studies we have conducted, women who were experiencing fatigue also tended to experience symptoms of depression. These states are often linked and it can be difficult to separate them. However, there are data showing that depression and fatigue are not the same. Many fatigued women do not experience elevated depressive symptoms. Further, treating depression does not necessarily relieve cancer-related fatigue. In a study by Morrow and colleagues in 2003 in the *Journal of Clinical Oncology*, fatigued patients were given antidepressants, and although depression was alleviated in these individuals, fatigue was not.

In our studies, we try to limit enrollment to women who have fatigue as their primary symptom and who are not clinically depressed. However, it would be impossible to exclude all individuals with an elevated depression score from studies of cancer-related fatigue. The symptoms are closely related and often co-occur.

Suggested Reading

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