Fatigue

10

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10.1 Problem

Fatigue, the number one symptom reported by cancer patients, is a subjective experience associated with the underlying disease, anticancer treatments, and other comorbid factors. Cancer-related fatigue (CRF) is defined by the National Comprehensive Cancer Network (NCCN) as "a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual activity" and is the most common cancer-related side effect occurring in up to 80 % of chemotherapy and radiotherapy patients [1]. Over the past two decades, there has been a greater interest in research and an increased awareness of CRF in both professional and lay publications.

CRF is recognized as an underdiagnosed and undertreated problem in most patients living with cancer, not only at the time of diagnosis but throughout treatment and even during disease-free intervals. Unfortunately, many patients continue to suffer greatly from this perplexing symptom. The fatigue experienced by cancer patients is quite distinct from that experienced by those without cancer; patients with CRF describe themselves as "feeling tired, weak, worn out, heavy, slow, or that they have no energy or get-up-and-go" [2]. Cancer patients become tired after much less activity than those without cancer, and their fatigue is longer lasting and not ameliorated by rest or sleep. CRF can significantly interfere with a patient's activities of daily living (ADLs) and may persist for months or years after treatment ends

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[3]. Fatigue is often associated with depression, but the relationship between these two factors remains unclear. It has been observed that preexisting depression may be a risk factor for CRF [4].

CRF negatively impacts quality of life and affects patients on multiple levels. Daily activities that bring joy and satisfaction to life may be compromised and diminished. Fatigue can impact relationships with friends and loved ones and reduce job performance [5]. CRF often causes patients to end employment which can lead to financial problems, loss of health insurance, and decreased access to health care.

The causes of CRF are multiple and complex, and its mechanisms have not been well defined. Disease patterns and treatment effects are clearly related to the onset and intensity of fatigue. However, each patient's experience is different, suggesting a variety of host factors. Various biological and psychological mechanisms contributing to CRF have been identified that are potentially treatable such as anemia, anxiety, drug effects, hypothyroidism, malnutrition, physical deconditioning, etc. (Fig. 10.1). CRF is rarely reported as an isolated symptom but rather in combination with others such as depression, pain, sleep disorders, etc. This cluster effect [6], along with wide variability in the presentation of CRF, adds to the complexity of understanding the biology and host factors of underlying cause.

There is a direct correlation between treatment and fatigue, with different treatment modalities such as surgery, radiotherapy, chemotherapy, immunotherapy, and bone marrow transplantation, exhibiting distinct patterns of fatigue. This fatigue can lead to interruption or intolerance of therapy, thus negatively impacting response to therapy and potentially overall survival. Often, treatment-related fatigue lasts even beyond the cessation of therapy.

Although the incidence of CRF varies between patient subgroups, it affects many throughout the cancer spectrum; it appears worse in minorities, unmarried patients, those with lower household income, and patients with metastatic cancer [4]. The

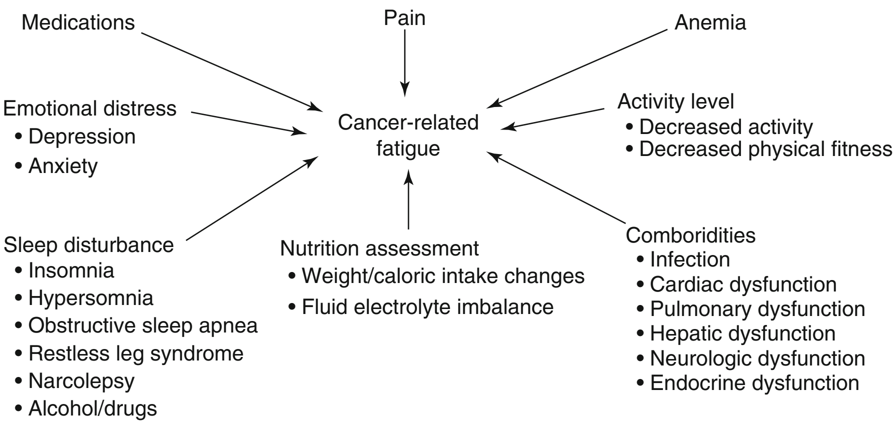

Fig. 10.1 Contributing factors to cancer-related fatigue (Reproduced with permission from Mortimer et al. [1])

incidence of CRF is expected to increase in the coming years with ongoing improvement in cancer treatments and overall survival. Thus, fatigue is recognized as a major problem in cancer patients and survivors.

10.2 Evidence

It must be noted that most studies of CRF have been conducted in populations of breast cancer patients and far less often in patients with other solid and liquid tumors [7].

Fatigue has been reported in patients with most types of cancer and during all stages of disease. In a recent multicenter study, outpatients with breast, prostate, colorectal, or lung cancer undergoing active treatment rated their severity of fatigue and interference with function on a 1–10 scale (1–3 mild, 4–6 moderate, 7–10 severe); 983 of 2177 patients (43 %) reported moderate to severe fatigue. Among those patients with no evidence of disease and not currently receiving cancer treatment, 150 of 515 patients (29 %) had moderate to severe fatigue that was also associated with poor performance status and a history of depression [8].

Cancer treatment-related fatigue appears to display distinct patterns which correlate to the type of treatment the patient undergoes. Patients experiencing fatigue after a successful surgical tumor resection tend to display the most severe fatigue immediately after surgery that subsides over time. Fatigue related to chemotherapy displays a definitive pattern, worst immediately after a cycle of treatment and improving up until the next cycle with fatigue lasting up to a month after treatment [9]. The severity may become worse with each successive treatment cycle, likely due to the accumulation of toxic by-products [2]. Radiation therapy, on the other hand, shows a pattern of fatigue that increases throughout the course of treatment until mid-treatment and then plateaus [10, 11]. It may end after treatment or could extend beyond treatment for months or years. Many personal factors may influence the degree of fatigue. In women receiving treatment for breast cancer, the degree of fatigue is severely correlated with employment during treatment, the presence of children in the home, depression, anxiety, lack of sleep, younger age, and being underweight [12].

Fatigue also persists in patients who are cancer-free and long-term survivors. A longitudinal study of long-term breast carcinoma survivors revealed that 34 % of patients report significant fatigue even 5–10 years post-diagnosis and that the fatigue was worse in patients that had received chemo and radiation combination therapy [13].

10.3 Ongoing Research

Current research efforts in CRF include the study of etiologic mechanisms, development of assessment tools, descriptive studies of patients' experiences, and intervention efforts. A review of ClinicalTrials.gov reveals hundreds of studies related to fatigue and cancer, targeting patients of differing age groups, ethnicities, and disease types. Some are observational in design, including the study of molecular genetics to identify possible risk factors. Bench research has focused primarily on identifying the mechanisms of CRF. In recent years, chief among these have been studies on the neuroimmune basis of fatigue and the role of inflammation and pro-inflammatory cytokines. Other studies focus on a wide range of interventions such as activity-based and psychological interventions, pharmaceuticals, supplements, acupuncture, light therapy, and diet modification, to name a few.

10.3.1 Neuroimmune Basis of Fatigue

Recent research has expanded our understanding of possible causes of CRF including inflammatory and immune responses from the cancer and/or its treatment. Inflammation is present at all stages of cancer, before treatment, during treatment, and even persisting up to a year posttreatment, which seems to correspond well with the onset and duration of fatigue [4]. In fact, a study comparing the levels of a number of markers in patients' serum found that the pro-inflammatory cytokine IL-6 was the single best indicator differentiating healthy controls, patients with locoregional breast cancer, and those with metastatic breast cancer [14]. This is of particular interest due to the observation that elevation in the blood levels of pro-inflammatory cytokines, secreted proteins which influence the behavior of other cells, are known to generate fatigue-like symptoms in both humans and animal models [15], potentially through alterations in neuronal dopamine synthesis, release, and reuptake [16].

In early-stage cancer the tumor itself appears to be the source of inflammatory cytokines [17, 18], while after treatment cytokines are generated in the course of the response to treatment-induced tissue damage [19]. Clinical observation of patients with untreated breast cancer, acute myeloid leukemia (AML), and myelodysplastic syndrome reveals that inflammatory markers such as C-reactive protein (CRP) and a number of interleukins are present pretreatment [20–22].

It is well known that many cancer patients who undergo radiation or chemotherapy exhibit a marked increase in their fatigue [12] and a sharp increase in circulating levels of inflammatory markers [23, 24]. The levels of these markers of inflammation appear to correlate with severity of CRF from patient to patient [25]. In a within-subject study of early-stage breast cancer and prostate cancer patients before, during, and after radiation therapy, elevations in the levels of inflammatory markers CRP and IL-1RA correlated with increases in fatigue; however, elevations in IL-6 and IL-1β did not [26], indicating that there may be no single pathway by which inflammation contributes to fatigue.

Studies in animal models have been somewhat informative in unraveling the effects of inflammation and appear to confirm a role for inflammatory cytokines in CRF. Growth of ovarian tumors in mice causes increases in the levels of a number of inflammatory markers, including IL-6 and TNF-α, both locally and in systemic circulation and that these animals, while still physically capable of movement, display a reduction in spontaneous locomotion [27]. Total body irradiation of mice, the best model of radiation therapy, causes an increase in several inflammatory markers, including plasma IL-6, that lasts up to 24 h after treatment [28]. Increase in those markers correlates with a reduction in locomotion, the most common metric of animal fatigue, that persists up to 2 weeks after treatment mirroring the human tissue recovery response to irradiation [28, 29].

Overall, while the correlation between CRF and inflammation in patients remains strong, whether inflammation causes that fatigue remains unclear, and in fact one study of newly diagnosed breast cancer patients found no correlation between levels of CRP and fatigue severity [30]. This confusion exists in no small part due to uncertainty of the neurological mechanism by which inflammation causes fatigue. Further work, both at the clinical and preclinical level, is needed to uncover the mechanisms by which cancer and its treatments influence inflammation both locally and systemically, determine how inflammation affects CRF, and identify biomarkers for diagnosis and targets for intervention that may reduce fatigue.

10.3.2 Activity-Based and Psychological Interventions for CRF

10.3.2.1 Exercise

To date, the most convincing data of an effective intervention for CRF is that related to exercise. Exercise has been shown in multiple studies to improve patients' level of fatigue [31–33]. In 2009 the American College of Sports Medicine (ACSM) convened a round table and, after an in-depth review of the literature, concluded that exercise training during and after adjuvant chemotherapy is safe and results in improvement in physical functioning, quality of life, and cancer-related fatigue in several groups of cancer survivors. ACMS recommended that cancer survivors avoid inactivity and follow the 2008 Physical Activity Guidelines for Americans with exercise adaptations based on disease and treatment-related adverse events [34]. These recommendations include aerobic exercise at least 150 min per week and strength training at least two days per week.

Exercise has been studied in a variety of patient populations and at various time points throughout the cancer experience. One prospective study explored whether the type of cancer affects exercise-mediated improvements in cardiorespiratory function and fatigue; 319 cancer survivors with 7 different types of cancer participated in fatigue inventories, cardiorespiratory function assessments, and an individualized, multimodal exercise intervention with cardiorespiratory, flexibility, balance, and muscular strength training 3 days per week for 3 months. Cancer types included breast cancer (BC, $n=170$), prostate cancer and other male urogenital neoplasia (PC, $n=38$), hematological malignancies (HM, $n=34$), colorectal cancer (CC, $n=25$), gynecological cancers (GC, $n=20$), glandular and epithelial neoplasms (GEN, $n=20$), and lung cancer (LC, $n=12$). Trends toward improved cardiorespiratory function and fatigue reached statistical significance in some groups, and no significant differences were seen between cancer types, suggesting that these improvements are not dependent on specific cancer types. Mean fatigue indices decreased by at least 17% in all groups, with changes significant in BC, HM, CC, and GC groups. The authors concluded that it is appropriate to prescribe exercise interventions to cancer patients based on individual needs without emphasis on cancer type and recommend further research to investigate a relationship between cancer type and exercise-mediated rehabilitation [35].

One meta-analysis reviewed the effectiveness of exercise intervention on overall health-related quality of life (HRQOL) in cancer survivors who had completed primary treatment. The review included 40 trials with 3,694 participants exposed to exercise interventions. At 12 weeks, cancer survivors who participated in an exercise intervention had greater improvement in overall HRQOL including a significant reduction in fatigue [36].

10.3.2.2 Yoga

Many studies suggest that yoga practice offers multiple health benefits. A large randomized controlled trial in breast cancer patients studied yoga's impact on inflammation, mood, and fatigue [37]. Two hundred breast cancer survivors who had completed cancer treatment (between 2 months and 3 years from last therapy), including surgery, adjuvant chemotherapy, or radiation therapy, were assigned to either 12 weeks of 90 min twice per week hatha yoga classes or a wait list control with no yoga intervention. The study included the biological measures interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and interleukin-1b (IL-1b). Findings showed that immediately posttreatment, fatigue was not lower but vitality was higher in the yoga group. At 3 months posttreatment, comparing the women who had practiced yoga to the non-yoga group, fatigue was 57% lower, and pro-inflammatory cytokines were decreased up to 20% in the yoga group. A secondary analysis noted that more frequent yoga practice correlated with larger changes [37].

10.3.2.3 Qigong/Tai Chi

A double-blind, randomized control trial (RCT) tested 12 weeks of Qigong/Tai Chi (QC/TCE) versus sham Qigong (SQG) on fatigue, depression, and sleep among 87 postmenopausal, breast cancer survivors with persistent fatigue. Participants' mean characteristics included: age 58, BMI 26.8, time to last treatment 2 years, and baseline fatigue 4.2, as measured by the Fatigue Symptom Inventory (FSI) on a 1–10 scale with ≥3 being clinically meaningful. QC/TCE showed a significant improvement in fatigue levels over time (baseline 4.6, at 1 month 2.1, at 3 months 2.3), compared to SQG (fatigue levels of 3.8, 2.6, 2.5, respectively). Both interventions showed improvement in depression and sleep quality. The authors conclude that adding gentle, low-intensity exercise in this patient population, as was done in both groups, may be beneficial in reducing several symptoms. However, the QC/TCE intervention, adding the focus on breath and meditative states to create a deep sense of relaxation, showed an advantage over gentle physical activity in improving fatigue levels in these breast cancer survivors [38].

10.3.2.4 Acupuncture/Acupressure

Acupuncture and acupressure have been studied in CRF with results suggestive of benefit in treating cancer-related fatigue. In a recent review of 11 RCTs conducted in adults with CRF, eight studies utilized acupuncture and three acupressure; the authors concluded that due to the methodological flaws of these studies, no firm conclusions could be drawn regarding the effectiveness or the optimal intensity and duration of the intervention. However, acupuncture and acupressure were noted to be safe in this patient population and warrant further investigation [39].

10.3.2.5 Psychosocial Interventions

Psychological issues arising from the cancer and its treatment contribute strongly to cancer fatigue. Fifteen to twenty-two percent of cancer patients become depressed and the stress, anxiety, and fear that follow a cancer diagnosis contribute as well. The cortisol response to stress is known to be blunted in cancer patients, further exacerbating cancer fatigue [40, 41].

Psychosocial interventions, including education on self-care, coping techniques, and energy management, have demonstrated beneficial effects on fatigue. For example, an Internet-based educational program providing information regarding fatigue, energy conservation, physical activity, nutrition, sleep hygiene, pain control, and stress management versus no intervention demonstrated a reduction in fatigue in the intervention group [42].

10.3.3 Pharmacologic Agents

A number of pharmacologic agents including psychostimulants, corticosteroids, supplements, and antidepressants have been tested in the treatment of CRF with mixed results.

10.3.3.1 Psychostimulants

Over the past two decades, there has been a growing interest in the use of psychostimulants in treating CRF. Methylphenidate, a dopamine and norepinephrine reuptake inhibitor, has been the most studied pharmacologic agent in the treatment of CRF. Although several studies demonstrated benefit [43], most recent large RCTs have been disappointing, showing no statistically significant benefit of psychostimulants in the treatment of CRF [44–46]. One study that showed no overall benefit of methylphenidate in patients with CRF did note a positive effect in a subset analysis of patients with more severe fatigue in advanced cancer [46].

Although recommended by the National Comprehensive Cancer Network in 2014, current data does not support the general use of psychostimulants in treating fatigue outside a clinical trial unless new data supporting use become available [47]. However, in certain situations such as severe fatigue in advanced disease, a psychostimulant may briefly palliate the patient’s fatigue and improve quality of life.

10.3.3.2 Corticosteroids

Although limited evidence is available, corticosteroids are often used to palliate cancer-related symptoms [48]. Two recent placebo-controlled double-blind randomized trials in advanced cancer patients demonstrated benefit of corticosteroids in alleviating cancer-related symptoms, including fatigue in advanced cancer patients [49, 50]. Hydrocortisone, cortisone, prednisone, methylprednisolone, and dexamethasone have been studied with no evidence of a difference between these agents in the management of fatigue. Dexamethasone has been studied most extensively. The mechanism of action of corticosteroids in improving cancer-related fatigue is unclear. Several mechanisms have been suggested including modulation of pro-inflammatory cytokines including IL-6, TNF-a, and C-reactive protein [51], decrease in tumor mass and associated edema, and modulation of adrenergic activity in the dorsal horn [48].

A study of patients with advanced cancer experiencing fatigue compared dexamethasone 8 mg daily x 14 days versus placebo. Significant improvement in CRF was noted at both days 8 and 15 in the dexamethasone-treated patients [50].

Another study compared the effects of oral methylprednisolone 32 mg daily versus placebo on analgesic efficacy, fatigue, and anorexia, for a period of seven days in 50 patients with advanced cancer. Significant improvement in CRF and anorexia as measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 was noted: fatigue (−17 vs. 3; $P=0.003$) and anorexia (−24 vs. 2; $P=0.003$). No significant improvement was observed in pain intensity, and no significant difference in adverse events between the two arms was seen [49].

These studies have looked at the benefit and safety of only very short-term use of corticosteroids. The long-term use and associated risks of corticosteroids in palliating CRF have not been studied. However, these risks in the general population are known to include hyperglycemia, prolonged HPA axis suppression, myopathy, infections, osteoporosis, aseptic necrosis, and mood changes. Future studies are needed to evaluate the benefits and risks of moderate- and long-term use in patients with CRF [48].

10.3.4 Supplements

Although there is significant interest in the utilization of herbal and dietary supplements in treating fatigue, few controlled studies have been conducted in cancer patients.

10.3.4.1 Ginseng

A large RCT of 364 cancer patients from 40 institutions evaluated the effect of Wisconsin ginseng 2,000 mg/day on fatigue in cancer survivors. Statistically significant improvement in fatigue was seen at 8 weeks in the ginseng group compared with placebo. Greater benefit was noted in the patients receiving active treatment compared to those who had completed treatment. No discernable toxicities from the ginseng were observed [52].

10.3.4.2 L-Carnitine

In an RCT of cancer patients with moderate to severe fatigue ($n = 376$), most with metastatic disease undergoing chemotherapy or radiotherapy, patients received L-carnitine (2 g/day) or placebo for 4 weeks. The intervention group demonstrated no improvement in fatigue compared to placebo [53].

10.3.5 Antidepressants

Antidepressants as treatment for CRF are being studied in animal models, but limited data are available in human trials. One placebo-controlled RCT of paroxetine 20 mg daily in patients with mixed solid tumors showed no difference in CRF between the placebo and paroxetine groups [54].

10.3.6 Sleep

Lack of quality sleep can impact one's level of fatigue. Cancer treatment and CRF both correlate strongly with a range of sleep disorders often brought on by a disruption in circadian rhythms. Commonly reported issues are insomnia, hypersomnia, and disrupted sleep patterns [55]. Sleep disorders including insomnia are more common in cancer patients compared to the general public [56]. This may be due to the psychological, behavioral, and physical effects of a cancer diagnosis and treatment. The American Association of Sleep Medicine recommends cognitive behavioral therapy for insomnia (CBT-I). CBT-I is defined as "a non-pharmacological treatment that incorporates cognitive and behavior-change techniques and targets dysfunctional attitudes, beliefs, and habits involving sleep" [56].

Results of a systematic review of CBT-I in cancer patients suggest that CBT-I is associated with statistically and clinically significant improvements in subjective sleep outcomes and may improve mood, fatigue, and overall QOL in patient with cancer [56].

10.3.7 Cancer Cachexia/Nutrition

Cancer cachexia (CC) is a multifactorial paraneoplastic syndrome characterized by anorexia, body weight loss, and loss of adipose tissue and skeletal muscle and is associated with impaired function, quality of life, and fatigue [57]. Interventions under study in cancer cachexia include anabolic steroids, appetite stimulants, ghrelin analogs, and anti-myostatin agents, to name a few. Anabolic steroids are being studied in cancer cachexia but end points are muscle mass and strength and weight and have not included fatigue measures. Novel agents inhibiting myostatin which is a normal negative regulator of muscle growth have shown the ability to increase muscle volume [58]; however correlation between change in the volume of muscle mass and level of fatigue is yet unknown.

Physical activity is reduced in many cancer patients at some time throughout their disease experience. There are few studies that discern the potential contribution of muscle disuse and muscle wasting to CRF. Research is needed to better define skeletal muscle changes that may contribute to CRF and the utility of exercise and other muscle-building strategies in treating fatigue associated with muscle disuse and wasting [59].

10.4 Solutions

Although the full mystery of CRF is yet to be unraveled, much has been learned regarding contributing factors, biochemical mediators, and actions that patients and health-care providers can implement to improve frequency of diagnosis, identification of treatable causes, and implementation of evidence-based interventions in managing CRF.

10.4.1 Assessment

Current recommendations include that all patients at the time of diagnosis of cancer undergo an evaluation of the level of fatigue and continue regular assessments throughout treatment and recovery [1, 60]. A variety of validated assessment tools are available to health-care providers to assess for the presence and severity of fatigue, from a simple 1–10 rating scale which is the gold standard to more complex multidimensional scales commonly used in research (Table 10.1). Patients who report moderate or severe fatigue (e.g., ≥4 on a 1–10 scale) should be further assessed and examined for any underlying conditions and treated appropriately.

10.4.2 Evaluation and Treatment of the Cancer Patient with Fatigue

Evaluating a cancer patient with existing fatigue requires a careful history and physical examination looking for symptoms and signs that suggest contributing factors

Table 10.1 Examples of validated instruments to assess fatigue [65–73]

Fatigue instruments
Brief Fatigue Inventory [65]
The Functional Assessment of Cancer Therapy – Fatigue [66]
The Piper Fatigue Scale (long and short versions) [67, 68]
The Schwartz Cancer Fatigue Scale [69]
Fatigue Symptom Inventory [70]
Lee's Visual Analogue Scale for Fatigue [71]
Cancer Fatigue Scale [72]
Multidimensional Fatigue Symptom Inventory – short form [73]

to the fatigue (Table 10.2). Patients are most worried about the status of their cancer and fear that recurrence or progression of disease is causative. Concurrent medications, especially narcotics, can contribute to sedation and fatigue. In some cases, adding a nonnarcotic such as an NSAID, if not contraindicated to the patient's analgesic regimen, can decrease the need to escalate the dose of narcotic. A review of the patient's alcohol and illicit drug use along with any social or financial stresses and symptoms of depression can open a discussion of available resources of support in the community. Sleep quality and disruption should be assessed. Patients who are dehydrated note significant fatigue and can benefit promptly with IV hydration. Attention to the patient's endocrine function can reveal an undiagnosed hypothyroidism or a low testosterone level. Of note, men who are chronically ill or on chronic narcotics commonly have low testosterone levels that can easily be supplemented. Hemoglobin and hematocrit levels should be assessed and anemia treated according to the ASCO/ASH guidelines [61]. Identifying and treating other organ

Table 10.2 Assessment/evaluation checklist for patients with CRF

Evaluation checklist	
Assessment of cancer disease status	☐
Patient self-assessment 1–10 analogue scale	☐
Concurrent medication review with special attention to: Analgesics/narcotics	☐
Sedatives/sleep aids	☐
Antihistamines	☐
Psychosocial history Depression/anxiety	☐
Social/financial issues	☐
Alcohol intake	☐
Illicit drug use	☐
Review of systems/Physical exam Fatigue – detailed description of onset, duration, aggravating/relieving factors, impact on QOL	☐
Anemia	☐
Pain	☐
Sleep quality and quantity	☐
Fluid/electrolyte disturbance	☐
Endocrine dysfunction – thyroid, adrenal axis, gonadal	☐
Other organ dysfunction – cardiac, hepatic, neurological, renal, pulmonary	☐
Laboratory Hemoglobin/hematocrit	☐
Sodium/potassium/magnesium	☐
Thyroid function tests	☐
Testosterone level	☐
Cortisol level/cortrosyn stimulation test	☐

Table 10.3 Management of CRF

Management checklist	
Treat co-morbid conditions when possible	☐
Prescribe exercise: Aerobic, 30 min/day, 5 days/weeks	☐
Mind/body interventions: Meditation, yoga, qigong/tai chi	☐
Nutrition consult	☐
Maximize sleep	☐
Educate on self-help techniques	☐
Psychosocial counseling such as cognitive therapy	☐
Consider psycho-stimulant if narcotic-related or advanced disease	☐

system dysfunctions, such as CHF from prior anthracycline use, can make a significant impact in the patient's level of fatigue. A thorough assessment and identification of contributing factors of fatigue in each patient will lead to potential individualized management strategies (Table 10.3).

10.4.3 Strategies to Help Patients Cope with Fatigue

Along with treating and managing the medical causes of fatigue, many patients find that lifestyle changes can help them better cope with fatigue.TherapyandCounseling Talking with a therapist or counselor specially trained to work with cancer survivors can help reduce fatigue. Specifically, a type of counseling called cognitive behavioral therapy or behavioral therapy can help patients reframe their thoughts about fatigue and improve poor coping skills and/or sleep problems that could contribute to fatigue.

10.4.3.1 Mind-Body Interventions

In addition to the already discussed mindfulness-based approaches such as yoga, meditation, etc., massage, music therapy, relaxation techniques, and a form of touch therapy called reiki are harmless and may also benefit patients experiencing fatigue, but more research is needed on these strategies.

10.4.3.2 Patient Education

Educating patients and family members to regularly discuss the presence and degree of fatigue with their health-care providers is key to accurate reporting and symptom management. Patients can empower themselves with knowledge of evidence-based treatments and self-help strategies (Table 10.4). Patients must be instructed that supportive care and symptom management are an important part of overall treatment and quality of life throughout the cancer experience and beyond. Multiple reliable resources addressing CRF are available to patients and family members (Table 10.5).

Table 10.4 List of simple recommendations to help cancer patients minimize fatigue

Recommendations for patients
Avoid inactivity
Gradually increase your activity. Do so gradually in order to conserve energy
Keep a log of which time of day seems to be your best time Plan, schedule and prioritize activities at optimal times of the day
Eliminate or postpone activities that are not your priority
Change your position and do not just stay in bed
Use sunlight or a light source to cue the body to feel energized
Try activities that restore your energy, such as music, or spending time outdoors in nature or meditation
Allow caregivers to assist you with daily activities such as eating, moving or bathing if necessary.
Plan activities ahead of time
Encourage your family to be accepting of your new energy pace
Rest and sleep better
Listen to your body – rest as needed
Establish and continue a regular bedtime and awakening
Avoid interrupted sleep time and try to get continuous hours of sleep
Plan rest times or naps during the day late morning and mid afternoon
Avoid sleeping later in the afternoon which could interrupt you night time sleep
Ask if using oxygen when you sleep will help you to sleep better
Try nutritious, high protein food
Small frequent meals
Add protein supplements to foods or drinks Ask about possible use of medications to stimulate your appetite or relieve fatigue

Adapted from www.HPNA.org[74]

Table 10.5 Patient resources

Patient resources for more information
American Cancer Society (ACS) http://www.cancer.org
American Society of Clinical Oncologists (ASCO) http://www.cancer.net
Cancer Care http://www.cancercare.org
National Comprehensive Cancer Network (NCCN) http://www.nccn.org/patients
National Cancer Institute (NCI) http://www.cancer/gov

10.4.4 Supporting Exercise Behavior Change

Based on the current evidence, cancer care professionals can expect that fewer than 10 % of cancer survivors will be active during their primary treatments, and only about 20–30 % will be active after they recover from treatments. Consequently,

Table 10.6 American cancer society guidelines on nutrition and physical activity for cancer survivors (Reproduced with permission from [62])

Achieve and maintain a healthy weight. If overweight or obese, limit consumption of high-calorie foods and beverages and increase physical activity to promote weight loss.
Engage in regular physical activity Avoid inactivity and return to normal daily activities as soon as possible following diagnosis. Aim to exercise at least 150 min per week. Include strength training exercises at least 2 days per week.
Achieve a dietary pattern that is high in vegetables, fruits, and whole grains. Follow the American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention.

unless behavioral support interventions are provided, the majority of cancer survivors will not benefit fully from regular physical activity. Patients may be fearful of injury or harm while exercising, especially if their lifestyle has been sedentary. Some successful strategies include short-term supervised exercise (e.g., 12 weeks), support groups, telephone counseling, motivational interviewing, and cancer survivor-specific print materials [62]. Health-care providers can be instrumental in motivating and guiding patients in developing a safe, sustainable exercise program. Assessing current exercise habits and building slowly toward the goal of 30 min of aerobic exercise five days a week are feasible with many patients during and after cancer therapies (Table 10.6). Recommending 5–10 min of walking two to three times a day may be more appealing to the patient. Utilizing the expertise of an exercise physiologist or personal trainer aware of the individual needs of the patient can enhance patient motivation and cooperation with treatment goals. Another strong motivator for exercise in this patient population is the evolving evidence that exercise offers a potential survival benefit as demonstrated in an exercise study of breast cancer patients likely due to exercise's effect on reduction of inflammation and modulation of the insulin pathway [63].

10.5 Future Directions

Increased research in recent years has provided a greater understanding of the characteristics, prevalence, and course of fatigue in cancer patients. Ongoing work is beginning to uncover underlying mechanisms, risk factors, and effective treatments [4]. A more complete understanding of the mechanisms of CRF will lead to the identification of many more targets for therapeutic intervention.

Still many questions remain unanswered regarding the specific causes and patient predisposition to developing CRF. Further research is desperately needed in the following areas:

- Genomic and epigenomic factors that may predispose an individual to CRF and influence response to therapeutic interventions. It will be very useful to be able

to identify those subgroups of patients at higher risk and those more likely to benefit from specific interventions.
- The role of inflammation and pro-inflammatory cytokines. Greater understanding of which cytokines are causative in specific patients, diagnoses, and treatments.
- Pharmacologic and non-pharmacologic interventions.
- Prevention strategies.

Knowing that the variables affecting CRF are numerous, well-designed smaller studies of more homogenous groups of patients may reveal more accurate and applicable data. Also, a greater consensus in the selection of assessment tools will allow for more consistent results and clearer data analysis between studies. The FDA encourages investigators to use standardized, validated patient-reported outcome measures in symptom intervention clinical trials [64].

Although advances have been made in the identification and treatment of CRF, many cancer patients continue to suffer with fatigue. Ongoing research is surely needed in order to fully understand, prevent, and treat this multidimensional phenomenon lacking an integrative approach.

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