A systematic review of cancer related fatigue

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SUMMARY

Fatigue is one of the most common symptoms among cancer patients that impacts quality of life. The prevalence of fatigue reaches 80% in patients undergoing active anticancer therapy. Oncologists commonly underestimate fatigue and do not recommend any treatment for this condition, while patients consider fatigue as one of the most important symptoms affecting their daily lives. Cancer-related fatigue is multifactorial and can be related to many potential causes that need to be evaluated. Interdisciplinary approach to the management may be the most beneficial for individuals suffering from fatigue.

Empirical support for activity enhancement and psychosocial therapies has been suggested. Methods of pharmacological treatment are limited due to the lack of reliable well-designed clinical trials. Further investigations of precise pathophysiological mechanisms of cancer-related fatigue are necessary to develop novel, more effective treatment interventions.

Key words: cancer, chemotherapy, fatigue.

INTRODUCTION

Fatigue is one of the symptoms most frequently reported by cancer patients which impacts patients’ quality of life [1, 2]. It is usually characterized as an overall lack of energy, cognitive impairment, somnolence, mood disturbance, or muscle weakness [3]. These symptoms occur with cancer and cancer therapy and are not relieved by rest or additional sleep and often interfere with daily activities [4]. Cancer-related fatigue (CRF) is more severe and more distressing than fatigue experienced by healthy people and can persist from fatigue.

Remarkable progress that was made in cancer research and treatment has resulted in longer survival of cancer patients. Therefore, better understanding the etiology and clinical management of symptoms that affect the quality of life is needed. Results of a multi-centre patient survey revealed that cancer patients identify fatigue as an important problem which affects their daily activities for more of the time than either nausea/vomiting or cancer pain. Despite the importance of this symptom half of patients suffering from fatigue do not report this to their oncologist and do not discuss strategies of management of this debilitating complaint. Many physicians consider fatigue a “normal condition” among cancer patients and believe that it is less serious problem for patients than other symptoms like pain. Results of cancer patient survey found that just 14% of patients get treatment or recommendations about the management of their fatigue [5]. These results show that cancer-related fatigue is downplayed and underestimated symptom. As novel cancer treatments are associated with longer patient survival research into the etiology and clinical management of CRF should receive heightened attention and be considered as a priority for advancing cancer care [5, 6].

EPIDEMIOLOGY OF CANCER-RELATED FATIGUE

National Comprehensive Cancer Network (NCCN) Cancer-Related Fatigue Panel describes fatigue as a nearly universal symptom among patients with cancer receiving chemotherapy, radiation therapy, bone marrow transplantation, or biological therapy [7]. Survey of 1,569 patients with cancer revealed that 80% of patients suffer from this distressing symptom during treatment with chemotherapy and/or radiotherapy [1, 8]. The prevalence of fatigue in patients who have metastatic cancer reaches 78% [9]. Many cancer survivors report persistent fatigue that can last months or years post treatment. According to results of studies, a third of individuals who had been cured of their cancer for 5 years suffered from chronic fatigue and its devastating effects on their lives [10].

ASSESSMENT OF FATIGUE

Cancer-related fatigue has been under-diagnosed and under-treated. As this symptom significantly interferes with the person’s normal routine, occupational (or academic) functioning, or usual social activities it is very important...
to identify all cancer patients who experience fatigue [7]. Comprehensive assessment of fatigue is essential for better clinical management of this distressful symptom.

Fatigue is subjectively perceived symptom and can be accurately described by self-reporting but additional information is also necessary to confirm the right diagnosis. In about 50% of cancer patients experiencing fatigue, reversible and treatable cause of this symptom can be identified. The diagnosis of CRF is usually achieved when no other treatable contributing factors like hypothyroidism, anemia, sleep disorders, pain, emotional distress, climacterium, adverse effects of drugs, electrolyte imbalances and metabolic disturbances, or organ dysfunction such as heart failure, myopathy, or pulmonary fibrosis are found [11–14]. To detect these factors it may be necessary to obtain specific information by combining anamnestic, physical, laboratory examinations and discussions with family members of the patient. When all potentially treatable factors are evaluated or none is found, patients should be screened for fatigue by using standardized evaluation instruments. For the first step of evaluation of fatigue the simplest assessment tools should be used such as Visual Analog Scale (VAS) [15] and Brief Fatigue Inventory (BFI) [16, 17]. Several longer and more detailed measures (Functional Assessment of Cancer Therapy – Fatigue subscale, FACT-F [18]; Multidimensional Fatigue Symptom Inventory-Short Form [19] and others) have also been used but usually in clinical research. VAS and FACT-F can be very useful CRF monitoring tools, as both demonstrate remarkably high sensitivity to changes of fatigue levels [15]. Detailed fatigue evaluation is recommended for patients who have positive results of preliminary screening. This in-depth evaluation should include severity of the symptom, duration, specific factors associated with fatigue, impact on the daily functioning, psychosocial well-being and quality of life, and other symptoms that occur with fatigue.

**MANAGEMENT STRATEGIES**

There is a lack of reliable therapeutic interventions due to limited knowledge about CRF and its pathogenesis and evidence from placebo-controlled randomized trials. Therefore future research on pharmacological treatment of CRF should be based on double-blind randomized clinical trials [20].

Management of CRF should be interdisciplinary as clinical, psychological and social factors interact and impact fatigue characteristics. The first step is to evaluate and to correct other contributing factors if it is possible. Correction of these factors may significantly improve the quality of life of cancer patient. Major improvements in quality of life after the use of erythropoietin in anemic cancer patients have been reported in prospective study [12]. Recent meta-analysis of ten clinical trials revealed that correction of anemia with erythropoietin of cancer patients undergoing chemotherapy resulted in reduced levels of fatigue [7]. As some clinical trials showed association of erythropoietin with higher risk for thrombotic embolic complications, higher mortality and shorter progression free survival, this agent should be avoided in patients who are not treated with chemotherapy and have hemoglobin level higher than 100 g/L [21, 22]. Some patients may need red blood cells transfusion to correct anemia that is not a rare cause of cancer fatigue but this may be not helpful in reducing fatigue level in terminal stages of cancer [23]. It also very important to correct pain, metabolic or electrolyte disorders, and infections as these conditions often interfere with CRF. Megestrol acetate may be beneficial in improving appetite [24, 25] but its effect on CRF is not proven [25, 26]. Depression can be a contributing factor for development of fatigue but meta-analysis of clinical trials with cancer patients who were treated with selective serotonin reuptake inhibitor (SSRI) paroxetine did not show benefit in relieving fatigue [27]. Additional medications including even vitamins or herbal agents may also lead to increased fatigue levels. All unnecessary agents that could influence development of CRF should be discontinued. It is always recommended to evaluate possible drug interactions. Correction of dosage or administration intervals may be beneficial in some cases.

Despite a comprehensive work-up causes of fatigue remains unknown in a big part of cancer patients [12]. The pathogenesis of this ‘idiopathic’ fatigue is poorly understood and seems to involve a variety of central and peripheral mechanisms such as changes of hypothalamic-pituitary-adrenal (HPA) axis and hypothalamic-pituitary-thyroid (HPT) axis, dysfunction of immune system, abnormal regulation of arousal mechanisms, abnormal muscle energy metabolism [28], and high cytokine levels [29]. Changes of hypothalamic-pituitary-adrenal (HPA) axis may lead to abnormal circadian rhythm that is also associated with higher level of fatigue.

As CRF is complex symptom both pharmacologic and non-pharmacologic methods of treatment need to be considered if fatigue remains after resolution of contributing factors [20]. Education of patients and their families, discussions about possible reasons of fatigue and its management strategies, and providing information about self-management are recommended to all cancer patients [30]. It is important to inform patients that fatigue can occur as a consequence of chemotherapy, radiation therapy or treatment with biological agents, and it is not necessarily an indicator of disease progression. It is also a good option to recommend self-monitoring of fatigue intensity for cancer patients [7].

In addition to pharmacologic and non-pharmacologic methods of treatment, it is recommended to advice patients about self-management techniques that could be helpful in coping with fatigue. Such techniques include energy conservation and distraction. It is recommended for patients experiencing fatigue to refuse not so important and exhausting activities, to organize daily routine with the biggest activity at times of peak energy, to take short sleep naps during daytime (if they do not impact night-time sleep), to prioritize activities, and to use some devices that facilitate everyday’s life [7, 31]. Excessive energy saving (like long rest periods during daytime, long sleep naps) can be harmful for fatigued patients as it interferes with night rest and may
cause increased fatigue levels [32]. Distraction techniques include doing activities that are pleasant like reading, games, music, and socializing. Although some suggestions about usefulness of distraction exist, the actual mechanism is not known [33, 34].

In most cases CRF will relieve from some non-pharmacologic methods of treatment. Randomized trials showed benefit of psychosocial interventions, physically based therapy, and activity enhancement (exercise). It is important to note that exercise is considered to be one of the most effective method according to clinical trials while oncologists commonly advise bed rest for patients experiencing CRF [35]. According to NCCN exercise should be used with caution when bone metastases, thrombocytopenia, anemia, fever or acute infection, and limitations due to other illnesses are present. It is recommended to allow patient to choose the type of exercise and to individualize this treatment according to the type of cancer, patient’s age, physical condition, and gender. The intensity of physical activity should be lower at the beginning of treatment and get more intensive as patient’s condition gets better [7].

Psychosocial interventions also have support according to randomized clinical trials [36–41]. Supportive programs, stress management techniques, coping skills training and behavioral interventions were found to be beneficial in reducing CRF levels.

Physically based therapies include acupuncture and massage. The effect of these methods on fatigue remains unclear due to the lack of randomized clinical trials. One retrospective study and one randomized clinical trial revealed that massage was effective in reducing fatigue for cancer patients [7]. Another study randomized 47 cancer patients to acupuncture, acupressure, or sham acupressure therapy. Acupuncture showed a significant benefit in treating fatigue and no effect on fatigue was observed in acupressure and sham acupressure groups [42].

Other methods like diet consulting and cognitive behavioral therapy for sleep have less evidence but some suggestions about effectiveness of these methods exist [7]. However, randomized clinical trial with breast cancer patients did not find the benefit of individualized sleep promotion plan on CRF [43].

Pharmacological treatment of cancer related fatigue

Pharmacological treatment may also be useful for patients suffering from CRF. One of the classes of medications that can be effective in relieving fatigue is psychostimulants. The examples of agents of this group are methylphenidate, dexamethylphenidate, modafinil, pemoline and dextroamphetamine.

Several experimental and small open-label studies reported possible effect of methylphenidate in reducing fatigue levels [44–47] but one randomized controlled trial did not show any benefit of this medication as compared to placebo. 112 cancer patients who suffered from fatigue took placebo or methylphenidate for 7 days in this study.

All patients were interviewed by telephone everyday and the level of fatigue was assessed by FACT-F questionnaire at the eighth day. Reduced levels of fatigue were noticed in both groups. These results show us non-pharmacologic methods such as contact with health care provider are very important in improving patient’s condition [48].

The effect of dexamethylphenidate was also investigated in randomized clinical trial where cancer patients had taken dexamethylphenidate or placebo for fatigue. Higher improvement of fatigue but also more adverse events were seen in dexamethylphenidate group as compared to placebo [49].

Modafinil was evaluated in a big randomized placebo controlled study with patients undergoing active treatment with chemotherapy and experiencing fatigue. Treatment group showed better results in relieving fatigue but the effect was worse in patients with severe fatigue [50].

Limited clinical trials suggest positive effect of corticosteroids on fatigue, especially when used in low doses for short periods. Long-term treatment with dexamethasone or prednisolone is not recommended as it may cause side effects such as hyperglycemia, insomnia, infections, myalgia, and rapid changes in mood.

In sum, there is a lack of reliable evidence concerning pharmacological treatment of CRF. Some medications hold promise, especially psychostimulants but it is clear that well-designed randomized trials are needed urgently to provide data on effectiveness of pharmacological approaches to the management of this incapacitating problem.

CONCLUSION

Fatigue is a very common symptom among cancer patients. Its etiopathogenesis is poorly understood. Despite impact on cancer patients’ quality of life, this symptom is underestimated and commonly remains untreated. As cancer-related fatigue is multifactorial symptom a multidisciplinary and combined approach that includes individualized treatment may be the most beneficial in the management of this distressing symptom affecting lives of millions of people diagnosed with cancer. Further clinical research focusing on investigations of relationships between fatigue and contributing factors, pathogenesis, and treatment intervention is necessary to develop effective management strategies.
REFERENCES:


