Cancer-Related Fatigue: Research and Clinical Experience

Journal of Nursing Care & Reports

Short Article

I.Chernikowa[1], S. Savina[2] and B. Zaydiner[3*]

[1]*State Medical University, Rostov-on-Don, Russian Federation*

[2]*Medical Centre "Hippocrates", Rostov-on-Don, Russian Federation*

[3]*Regional Cancer Centre Rostov-on-Don, Russian Federation*

***Correspondence author**

Boris Zaydiner
Regional Cancer Centre Rostov-on-Don
Russian Federation

Submitted : 1 Apr 2021 ; Published : 19 Apr 2021

Cancer commonly results in patient distress, the most frequent aspect of which is fatigue. Fatigue is highly prevalent in patients with cancer. It is a major obstacle in maintaining patients' routine daily activities and has a significant impact on their quality of life (QoL). Fatigue may also be a predictor of shorter survival [1].

Fatigue is the syndrome of both cancer and cancer treatment. The proportion of patients experiencing cancer-related fatigue (CRF) varies widely in the literature, it has generally been reported to be between 40% and 100% of the overall number of patients with cancer. Such variation in rates is likely owing to the lack of commonly accepted diagnostic criteria and assessment tools, and the effect of disease stage and status on fatigue. These rates can still vary between studies when the same diagnostic criteria are used, reflecting a lack of consistency in how these criteria are applied.

Fatigue may be elevated before treatment onset and typically increases during cancer treatment, including treatment with radiation, chemotherapy, hormonal, and/or biological therapies.

CRF is the most frequently anticipated side effect of cancer treatment: 95% of patients who are scheduled to receive chemotherapy or radiotherapy are expected to suffer from some degree of fatigue during their treatment. In the majority of studies, 30% to 60% of patients report moderate to severe fatigue during treatment, which in some cases may lead to treatment discontinuation.

In the post-treatment population, reported CRF rates range from 17% to 21%.

When strict ICD-10 criteria [2] are applied, the reports suggest that approximately 20% of cancer survivors report persistent fatigue after curative treatment.

Meanwhile many patients with fatigue do not to discuss treatment options for this disorder with their oncologists; therefore, only quarter of them receive any treatment recommendations. Despite the availability of some treatment options as well as extensive ongoing research, fatigue is nevertheless often viewed by clinical staff, caregivers, and the patients themselves as an inevitable consequence of cancer and cancer treatment. This view is unfortunate and is contradicted by the available evidence; it needs to change.

Thus, CRF is underreported, underassessed and undertreated, partially because it is not clearly understood. An exploration of this disorder exemplifies a conceptual approach to a clinical problem. In the disorder beginning to study, concept of fatigue as a mental phenomenon was predominant. Accordingly rest remained the crucial care factor. Later CRF concept has become multifactorial and subjective. The tiredness /exhaustion was increasingly seen as a symptom of a disease or even a disease itself. The specific diagnostic criteria were developed and suggested. The International Statistical Classification of Diseases and Related Health Problems 10th edition (ICD-10) includes neoplastic (malignant)-related fatigue (ICD-10 CM R53.0).

This disorder can be defined in terms of perceived energy, mental capacity, and psychological situation. The 2018 National Comprehensive Cancer Network (NCCN) defines CRF as "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 interferes with usual functioning". CRF is distinct from the "normal" tiredness/weakness experienced by healthy individuals in that it is not relieved by rest or sleep. Besides it may interfere with therapy compliance and even limit the effects of active antitumor treatment.

The etiology of CRF is complex, involving many potentially contributing elements. Identifying the etiological factors that contribute to fatigue often proves to be complicated, as multiple causes typically coexist and may have additive effects. These factors include

- the direct effect of cancer,
- side effects associated with anti-cancer therapies (mentioned previously) or other medications,
- Comorbid medical/psychological conditions, and psychosocial systems.

Tumor-related factors consist of cachexia, hypoxia, electrolyte abnormalities, dehydration, thrombosis/pulmonary embolism, renal failure, liver failure, adrenal insufficiency, neurological deficit etc.

The comorbid conditions fall into fever, infection, mood disorders (the most common are depression and anxiety), anemia, hypothyroidism & other endocrine impairments.

Most likely there is dysregulation of several interrelated physiological, biochemical, and psychological systems. To further complicate matters, the effect of each of these disruptions on CRF not only varies among individuals but also during different phases of the disease and with treatment type.

Specific mechanisms involved in pathophysiology of CRF are unknown.
Factors related to the development of CRF were supposed to be serotonin, ATP and hypothalamic-pituitary-adrenocortical axis dysregulation, skeletal muscle wasting, circadian rhythm desynchronization.

Activation of the immune system by infection, injury, or trauma leads to the release of immune factors, including receptor antagonists, soluble receptors, products of cellular activation as well as cytokines, which have peptide structure, are generated by dendritic cells, macrophages and also in the gut, in adipose & other tissues. The cytokines possess specific receptors which are recognized as "crucial unit" on intercellular mediating; they orchestrate local and systemic immune responses. In physical illness (e.g. cancer), the immune system serves as a sensory organ communicating with the brain through the secretion of cytokines (primarily proinflammatory) which are released as part of the immune response and affect neural, neuroendocrine, behavioral functions.

Thus, the communication from the immune system to the brain is mediated by cytokines. In other hand, there were revealed association between high cytokine levels and psychological components of CRF. The converse is also true: a strong association between high levels of fatigue and elevated systemic inflammatory markers and high cytokine concentrations has recently shown.

Two "cytokine" hypotheses regarding the production of fatigue and related symptoms in cancer patients were formulated.

The first is based on the "sickness behavior model" that is thought to be related mechanistically to elevation of serum and brain levels of proinflammatory cytokines of the interleukin (IL) family (e.g., IL-1, IL-1Ra, and IL-6). Activation of this cytokine signaling in the peripheral and central nervous system by cancer or cancer treatment has been shown to lead to malaise, poor appetite, and social withdrawal, which are believed to underlie fatigue, cognitive disturbances, and depression. The second hypothesis is that symptoms could be due to the inhibition of circadian-signaling pathways. This hypothesis is based on extensive laboratory data showing inhibition of downstream hypothalamic signaling from the master clock in the suprachiasmic nucleus and corroborated by clinical observations. The inhibition of these hypothalamic signaling pathways can produce fatigue, suppress feeding activity, and cause malaise. Elevation of circulating levels of ligands of the epidermal growth factor receptor (EGFR), such as epidermal growth factor (EGF), transforming growth factor α (TGF-α), and neuregulin, can act to inhibit neural signaling that drives normal behaviors, in laboratory studies.

Higher levels of cytokines appear to be associated with a greater symptom burden. There are elevations in proinflammatory cytokines (IL-1 and IL-1Ra) and ligands of the EGFR family that are correlated with fatigue and depression in cancer patients.

Several studies have been conducted to examine whether targeted interventions based on molecular mechanisms could help alleviate fatigue.

CRF probably starts in the skeletal muscles due to a progressive reduction of physical activity (sometimes with physical interruption), but the brain is also critical as a central regulator of fatigue perception.

Some conditions are commonly associated with fatigue, such as anemia, cachexia and depression. These associations might encourage the development of effective integrated treatment strategies. In cancer patients there is significant correlation of fatigue with the level of depression. Both disorders' common features are well-known. Among demographic variables, higher levels of fatigue or depression were reported by younger cancer patients and female cancer patients. Among medical variables, prior surgery, distant metastases, and cancer site have been related to higher levels of fatigue or depression. For example, small cell lung cancer and medullary thyroid carcinoma produce hormones that can affect mental function and mood.

Psychological factors, such as heightened anxiety, anger, and confusion, or lowered vigor, have been associated with greater levels of fatigue and depression in cancer patients. However, the association between these constructs is complex; CRF is a symptom of depression, but depression also can result from the experience of fatigue. Fatigue may be the result of depressed mood. On the contrary, the person who continuously perceives his energy as insufficient may become depressed. To complicate matters, in cancer depression and fatigue may co-occur without having a causal relationship, because they can both originate from the same pathology. Such coexistence is commonly observed in patients undergoing chemotherapy, suggesting that administration of an antidepressant that alleviates symptoms of depression could also reduce fatigue. This speculation was tested of 94 female breast cancer patients who were delivered at least four cycles of chemotherapy.

Selective serotonin reuptake inhibitor (SSRI) paroxetine proved to be more effective than placebo in reducing depression but not in reducing fatigue. Results suggest that modulation of serotonin may not be a primary mechanism of fatigue related to cancer treatment. The SSRI have been particularly effective in reducing anxiety and cognitive components of depressive symptoms and less effective in reducing neurovegeta-

tive and somatic components of depression symptoms. These findings suggest that anxiety and cognitive dysfunction may be core features of depression, whereas somatic or arousal components might be tertiary features of depression, that instead may be core features of fatigue.

CRF and depression do not follow the same course overtime. Just after radiotherapy, fatigue had either increased or remained stable, depending on the dimension under consideration. Depression, in contrast, decreased. Nine months later fatigue had decreased, whereas levels of depression remained stable.

The opinion of these disorders' predictive value is established. Fatigue was considered a significant predictor of depressive symptoms and depression is a significant predictor of fatigue. However, results of some researches on the prediction of fatigue by depressive mood and vice versa have revealed the predictive power to be low in either direction. Neither of these symptoms had much predictive power with respect to the other, suggesting only weak causal relationships.

For general fatigue and physical fatigue, however, fatigue predicts depressive mood somewhat better than depressive mood predicts fatigue.

Underpinning the above data may be the hypothesis that emotional phenomena include two dimensions: arousal (alertness vs. boredom) and valence (positive vs. negative. Using this two-dimensional approach, the findings of a differential impact of pharmacological interventions on changes in depressive symptoms can be interpreted to suggest that changes in depressive symptoms may depend more on the valence dimension of emotion (e.g., anxiety and confusion), whereas changes in fatigue may depend more on the arousal dimension (e.g., anger and vigor).

Summing up, clear and noteworthy differences exist in the association between fatigue and depressive symptoms among cancer patients. Fatigue is not a valid criterion for depression in these patients.With respect to the clinical picture, we emphasize a multidimensional entity of CRF with both subjective and objective components. The assigning of 3 groups: biological, psychological, social dimensions - is generally accepted.

The experience of CRF involves multiple signs and symptoms; the patients usually refer them as concurrent cancer- or treatment-related side effects. Physiological disruption and self-reported tiredness or exhaustion are concerned. Mood symptoms include signs and symptoms include anemia, hypothyroidism, and shortness of breath, muscle atrophy, perceived physical weakness, low aerobic capacity, pain, sleep depression and anxiety. Motivational symptoms generally appear as hopelessness, pessimism or negative outcome expectancies. Cognitive symptoms manifest as reduced capacity for attention and learning that are related to impaired memory and the inability to concentrate. Social symptoms generally include a reduction in the patients' ability to participate in leisure activities, their capacity to sustain meaningful relationships with their families, their ability to work, and their capacity to engage in social and other activities during and after treatment.

In clustering concept CRF may occur as a part of a cluster of symptoms including pain, difficulty in sleeping, and muscle weakness. No two individuals experience the disorder in exactly the same way, making it difficult to develop an effective treatment and, most likely, impossible to develop an effective intervention targeting a single path psychological/physiological mechanism that will provide relief to the majority of patients with cancer.

The effect of CRF on a patient's QoL is both profound and pervasive. This condition dramatically impacts on a patients' physical, psychological, social and spiritual well-being; it diminishes a person's ability to work, to participate in social, leisure and previously enjoyable activities. The meaningful relationships with patient's relatives are disrupted. Such impairment is significantly greater than healthy controls.

NCCN have proposed Fatigue Practice Guidelines; they are the standards of care for CRF. The guidelines update annually using the treatment algorithm, which combines the available research and clinical experience to provide concise recommendations for supportive care. Nowadays the management of CRF is based on the modern conception of disorder and the development of new therapies. The distress should be screened, assessed, and managed according these guidelines.

As disorder's manifestations are perceived by the patient, the most accurate description can be obtained via self-reporting by patients. The NCCN recommends the use of a single item to assess fatigue severity on a scale of 0…10. This approach permits identification of cancer patients who may benefit from the assessment and treatment for fatigue. Multidimensional CRF measures may be useful in assessing physical, emotional, and cognitive domains. The patient's medical history and physical examination, data of laboratory tests and descriptions of his/her behavior by family members are important sources of necessary information.

Screening for CRF should include screening for possible contributing factors (e.g., pain, emotional distress, sleep disruption, anemia, and nutrition), as well as comorbid conditions (e.g., infection, cardiac dysfunction, pulmonary dysfunction, renal dysfunction, hepatic dysfunction, neurologic dysfunction, hypothyroidism and other endocrine dysfunctions). Identification of the disorder and its contributing factors does not alleviate the problem. Given the diverse etiological factors that contribute to CRF and its multidimensional nature, a comprehensive assessment of patients is required for the development of effective treatments. Clinical practice guidelines for assessment and management of the disorder emphasize the need to evaluate (1) fatigue characteristics and (2) disease status and treatment. Guidelines also recommend obtaining the medical history and physical checkup results of the patient, and conducting the prescribed laboratory studies to rule out common, treatable causes of fatigue, such as anemia and thyroid dysfunction.

At this time, there are no treatments (pharmacologic or non-pharmacologic) that have been proven effective in large randomized trials and replicated by other investigators in other groups of patients with cancer-related fatigue.

NCCN Cancer-Related Fatigue Guidelines recommend a two-stage approach for the treatment of CRF. The first step is to identify and address any treatable factors contributing to fatigue. NCCN guidelines identify several common contributing factors, including pain, emotional distress, anemia, sleep disturbance, nutritional inadequacies, and comorbidities (e.g. infection, cardiac dysfunction, and renal dysfunction). Significant improvement in QoL has been observed among cancer patients with anemia after treatment with erythropoietic agents. The second step involves the management of any residual fatigue that continues after the resolution of treatable contributing factors or of fatigue that continues despite the lack of any identifiable treatable contributing factors. To develop treatment strategies tailored to the patient's clinical status, separate algorithms are provided for patients receiving active cancer treatment, patients receiving disease-free long-term follow-up, and patients receiving care at the end of life.

CRF management includes:

1. Providing education and counseling for all cancer patients and their families regarding fatigue and its natural history. It should be emphasized that fatigue is commonly experienced by patients undergoing treatment for cancer and is not necessarily an indicator of disease progression (if appropriate),
2. Nonpharmacologic interventions and
3. Pharmacologic treatments.

The NCCN guidelines recommend the use of a variety of integrative nonpharmacologic interventions. The integrative nonpharmacologic behavioral interventions are organized into three main categories as follows:

- exercise,
- psychosocial interventions, and
- other integrative therapies (mindfulness relaxation, yoga and so on).

Physical exercise is an intervention modality that shows great promise in mitigating acute CRF experienced by cancer patients during treatment, as well as chronic CRF they experience after completion of treatment. Exercise is defined as physical activity performed in a systematically dosed manner (e.g., a specific frequency, intensity, duration, and mode) with the intention of improving fatigue and other health-related outcomes.

There is growing evidence that physical exercise can attenuate systemic inflammation and improve CRF, allowing patients with or without cachexia to become more capable of carrying out the activities of daily living (ADLs) and thereby to improve the functional QoL [3]. Exercise is safe and well tolerated by cancer survivors with various diagnoses. The outcomes are similar for patients throughout the cancer care continuum. Some observational and interventional studies have also suggested that patients with cancer who engage in at least 3–5 hours of moderate activity weekly may experience better outcomes and have fewer side-effects of anticancer therapy, including CRF [4].

Persistent psychological distress detrimentally affects the patient's well-being, QoL, work productivity, and personal relationships. The psychosocial needs of the patient diagnosed with cancer are considered important in providing comprehensive care. Recognizing that emotional distress is highly correlated with fatigue, psycheducational interventions should focus on identification of coping strategies to optimize the patient's ability to deal with anxiety, depression and psychosocial distress. The most important goal of psychoeducational intervention is to facilitate self-care for the person with cancer [5].

Psychoeducational interventions conducted in the post-treatment period have also demonstrated beneficial effects on fatigue. It may be helpful for patients to identify sources of psychosocial distress and to eliminate stress-producing activities where possible. Another important element is to focus the patient's attention on the patterns of fatigue and on finding a balance between rest and activity during the day. This can be done by using diary techniques, including subjective rating of each activity in terms of the perceived level of fatigue. An individual activity/rest program can be included, based on an assessment of the patient's fatigue patterns such as relaxation techniques or meditation, which may target underlying biological mechanisms and reduce cancer-related distress by diminishing activation of the hypothalamic pituitary adrenal (HPA) axis [6].

Psychosocial interventions include activities such as support interventions (either individually or in groups), education, stress management, coping strategy training, and providing behavioral modalities designed to assist patients with managing their CRF. Information and counselling help patients to gain a better understanding of CRF and to devise a personalized activity plan. There is some evidence showing that such strategies can improve QoL and reduce the subjective feeling of fatigue [7].

Cognitive behavioral therapy (CBT) in CRF takes into account the thoughts and functional behaviors relevant to the syndrome and focuses on the individual and their pattern of psychological factors [8]. The studies on the evaluation of CBT have been demonstrated a clinically significant decrease in fatigue severity and functional impairment.

A cognitive-behavioral approach combined with hypnosis also showed beneficial effects on fatigue among breast cancer patients undergoing radiation therapy; specifically, the intervention buffered the increase in fatigue observed in controls [9].

Meaning (alternatively, "purpose") of life - the perception that one's previous and present life is useful and that one finds satisfaction in daily activity – is considered seen an important aspect of QoL. Patients are recommended to find meaning in

their current situation with an emphasis on meaningful interaction and maintaining their dignity.

Symptomatic relief of distress is an important goal of psychotherapeutic treatment. Unique supporting approach was developed to relieve psychosocial and existential distress, it's called Dignity Therapy (DT). Prior studies of dignity have shown a strong association between an undermining of dignity and depression, anxiety, desire for death, hopelessness, feeling of being a burden on others, and overall poorer quality of life. Patients deem a sense of spiritual peace, relieving burden, and strengthening relationships with loved ones among the most important facets of end-of-life care. There was suggested that meaning, or a paucity of meaning, defines the essence of existential distress. An empirical model of dignity has permitted to obtain framework of questions which provides the basic content of the therapeutic process. These conversations are designed to accommodate the patient's needs and choices regarding what he/she specifically wishes to address. To decrease suffering, enhance quality of life, and bolster a sense of meaning, purpose, and dignity, patients are offered the opportunity to address issues that matter most to them or speak to things they would most want remembered. DT is audio-recorded and transcribed, with an edited version of the transcript returned to patients. In randomized controlled trial DT was compared with standard supportive approach, the former proving superior in lessening distress seemed to be particularly responsive from DT. This is also true for ones reporting more initial psychosocial despair and less satisfaction with pain relief before the intervention - the latter were more likely to report that DT yielded an increased sense of purpose. 72% reported that it heightened the meaning of life for the ones. This intervention is not only offered to alleviate distress, but also as a means of preventing distress, promoting well-being and establishing a sense of personal meaning and life purpose. Psychotherapeutic support helps patients face disappointments, process the reality of leaving behind loved ones; deal with feelings of sadness, loss, isolation and a damaged sense of identity and personal value [10, 11].

Clinicians often encourage patients experiencing CRF to rest and conserve energy. Such conservation is a part of the planned management of personal energy resources to prevent their depletion. It encompasses a common sense approach that helps patients set realistic expectations, prioritize and pace activities, and delegate less essential activities. Daytime naps can replenish energy, but it is advisable to limit these to less than an hour, to avoid disturbing nighttime sleep.

New treatment options will likely emerge from the several ongoing large-scale clinical trials examining the efficacy of a variety of treatments for CRF. A meta-analysis of this included 27 randomized controlled trials, including hematopoietic growth factors, presentational steroids, methylphenidate, and paroxetine (an antidepressant; 2 studies), among others. The hematopoietic growth factor trials were all conducted with anemic patients, the majority of whom were undergoing chemotherapy. In general, treatment with hematopoietic agents led to improvements in fatigue caused by chemotherapy-induced anemia [12].

Methylphenidate also led to greater reductions in fatigue than placebo, but progestational steroids and paroxetine did not. Another anti-depressant, sertraline, had no beneficial effect on fatigue in patients with advanced cancer who were neither fatigued nor depressed. A trial of dexamethasone for patients with advanced stage cancer who reported moderate to severe symptoms of cancer-related fatigue showed significant improvements in fatigue and QoL. Two recent studies conducted with larger samples of patients showed no benefit for methylphenidate vs. placebo for improving fatigue, although in subgroup analyses methylphenidate did appear to be effective for patients with severe fatigue and those with advanced disease [13].

The efficacy of modafinil was assessed in patients undergoing chemotherapy found beneficial effects of modafinil among patients who reported severe fatigue at baseline, but not among those with mild or moderate fatigue [14]. Based on research suggesting an inflammatory basis for CRF, anti-cytokine agents used in patients with advanced cancer. Beneficial effects of anti-TNF agents on fatigue have been observed.

Clinical trials investigating the effect of corticosteroids on fatigue in patients with advanced or metastatic cancer are scarce and partly based on observational studies [15]. As to administration of supplements, there was no evidence that of L-carnitine was more effective than placebo in improving fatigue; instead, fatigue improved in both the treatment and control groups. In contrast, a large multisite trial of American ginseng for patients with cancer-related fatigue did find beneficial effects, particularly among patients undergoing active cancer treatment [16]. Two randomized studies on the antioxidant Q10 showed no or limited effect [17]. RCTs on the herbal drug Guarana showed negative results. In contrast, Tualang honey, suggested to have anti-inflammatory and antioxidative properties, was reported to have a significant positive effect on both fatigue and QoL compared to vitamin C treatment in a randomized, open-label study on head-and-neck cancer patients [18].

Thus, when the optimal treatment for an individual patient is decided, several factors have to be taken into account, such as the performance status of the patient, the motivation and belief in the suggested treatment, and which adverse reactions that should be avoided to sustain the QoL of this specific patient.

References

1. Julienne E. Bower (2014) Cancer-related fatigue: Mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol.; 11*(10): 597–609.
2. The International Statistical Classification of Diseases and Related Health Problems 10th edition (ICD-10).
3. Mishra S.I., Scherer R.W., Geigle P.M.et al. (2012) Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev*. 2012; 15:

CD007566.
4. Mustian K.M., Alfano C.M., Heckler C.et al. (2017) Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. *JAMA Oncol*. 2017; 1: 961-968.
5. Williams S.A., Schreier A.M. (2005) The role of education in managing fatigue, anxiety, and sleep disorders in women undergoing chemotherapy for breast cancer. *Appl Nurs Res*. 2005; 18: 138-147.
6. Stanton A.L., Ganz P.A., Kwan L. et al. (2005) Outcomes from the Moving Beyond Cancer psychoeducational, randomized, controlled trial with breast cancer patients. *J Clin Oncol*. 2005; 23: 6009-6018.
7. Barsevick A.M.Dudley W.Beck S.et al. (2004) A randomized clinical trial of energy conservation for patients with cancer-related fatigue. *Cancer*. 2004; 100: 1302-1310.
8. Given C., Given B.,Rahbar M.et al. (2004) Effect of a cognitive behavioral intervention on reducing symptom severity during chemotherapy. *J Clin Oncol*. 2004; 22: 507-516.
9. Montgomery GH, et al. (2009) Fatigue during breast cancer radiotherapy: an initial randomized study of cognitive-behavioral therapy plus hypnosis. *Health Psychol.* 2009;28: 317–322.
10. Harvey Max Chochinov, Linda J. Kristjanson, William Breitbart, Susan McClement, Thomas F Hack, Tom Hassard, and Mike Harlos (2011) The effect of dignity therapy on distress and end-of-life experience in terminally ill patients: a randomised controlled trial. *Lancet Oncol*. 2011 Aug; 12(8): 753–762.
11. I Chernikowa , S Savina and B Zaydiner (2020) Some Aspects of Psychocorrection in Oncology *J Clin Rev Case Rep, 2020 5*(6):272-281.
12. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P (2008) A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. *J Natl Cancer Inst*. 2008;100: 1155–1166.
13. Moraska AR, et al. (2010) Phase III, randomized, double-blind, placebo-controlled study of long-acting methylphenidate for cancer-related fatigue: North Central Cancer Treatment Group NCCTG-N05C7 trial. *J Clin Oncol*. 2010;28: 3673–3679.
14. Jean-Pierre P, et al. (2010) A phase 3 randomized, placebo-controlled, double-blind, clinical trial of the effect of modafinil on cancer-related fatigue among 631 patients receiving chemotherapy: a University of Rochester Cancer Center Community Clinical Oncology Program Research base study. *Cancer*. 2010;116: 3513–3520.
15. Pinkerton E., Good P., Kindl K., Richard R., Fischer A., Hardy J.R. Palliat. (2019) Quality use of medicines: Oral corticosteroids in advanced cancer. *Med*. 2019;33: 1325–1326. doi: 10.1177/0269216319866647).
16. Barton DL, et al. (2013) Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. *J Natl Cancer Inst*. 2013; 105:1230–1238.
17. Iwase S., Kawaguchi T., Yotsumoto D., Doi T., Miyara K., Odagiri H., Kitamura K., Ariyoshi K., Miyaji T., Ishiki H., et al. (2015) Efficacy and safety of an amino acid jelly containing coenzyme Q10 and l-carnitine in controlling fatigue in breast cancer patients receiving chemotherapy: A multi-institutional, randomized, exploratory trial (JORTC-CAM01). Support. *Care Cancer*. 2015;24: 637–646. doi: 10.1007/s00520-015-2824-4.
18. Ramasamy V., Binti Mat Lazim N., Abdullah B., Singh A. (2019) Effects of Tualang Honey on Cancer Related Fatigue: A Multi-center Open-label Trial of H&N Cancer Patients. *Gulf J. Oncol*. 2019;1: 43–51.