

Modern therapeutic management of patients with cancer is associated with many adverse side effects, including fatigue defined as weariness, burnout, lassitude, malaise, apathy, impatience, and/or inability to perform daily activities. It occurs frequently before the diagnosis of cancer and may persist for a long time after the end of cancer therapy. It is a common problem that occurs regardless of the type of cancer and applied therapeutic procedure. The appearance of this symptom significantly affects the quality of life of patients and often reduces the effectiveness of implemented treatment. The symptom of fatigue occurs among approximately 80% of patients treated with chemotherapy and/or radiotherapy, as well as among more than 75% of patients with metastatic disease. Causes of fatigue include metabolic and immune system disorders as well as increased level of tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ). Recent studies also indicate a significant contribution of other cytokines, especially pro-inflammatory ones, i.e. interleukin-1 (IL-1), interleukin-6 (IL-6), soluble tumour necrosis factor receptor type II (sTNF type II) and C-reactive protein (CRP). A patient reporting fatigue should be properly diagnosed and thoroughly interviewed by doctors. Patients are mostly treated non-pharmacologically (by means of physical exercise and psychotherapy) and pharmacologically (by applying methylphenidate and methylprednisolone). What is also extremely important is proper education of the patient and their closest family/friends on the symptoms, which significantly reduces anxiety and stress. On the other hand therapeutic management hinders the subjectivity of feeling and lack of standardised scales to rate symptoms.

**Key words:** cancer-related fatigue, CRF, mechanism causing CRF, comorbid condition, treatment.

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## The problem of fatigue in patients suffering from neoplastic disease

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Excessive fatigue is a common problem of modern society that exists in almost every population with a different level of intensity. In most cases this symptom is a natural defensive response to physical and mental stress, which is usually released after rest. The significant majority of patients receiving anti-cancer therapies experience fatigue problems; however, this symptom differentiates from fatigue affecting the rest of society [1]. Cancer-related fatigue (CRF) has a significant impact on the social and economic life of people affected by this problem and may last months or even years after termination of the treatment of the underlying disease [1–6]. A favourable response to oncological treatment or its discontinuation does not alleviate CRF [2]. Fatigue is described as weariness, burnout, lassitude, malaise, apathy, impatience and/or inability to perform daily activities [7] and is often the first symptom reported by patients before the diagnosis of cancer is given [7, 8]. The relation between CRF and cancer, and the applied treatment has not been decisively explained. CRF intensifies during anti-cancer treatment and seems to be more intense comparing to fatigue unrelated to cancer [1], to which CFS (chronic fatigue syndrome) may be assigned. Distinctive characteristics include additional symptoms occurring with chronic fatigue syndrome: sore throat, painful and swollen lymph nodes, especially in neck and armpit, muscle and joint pain without inflammation and swelling, and severe or never experienced before headache [9]. Fatigue is also the most durable symptom among oncological patients with active cancer [7]. Patients undergoing intense treatment combined with opioids drugs whose general condition is bad and who have lost over 5% of their body weight within 6 months more often report CRF in its moderate to severe level [9].

### Definition and classification

The National Comprehensive Cancer Network (NCCN), version 01.2014, defines fatigue related to cancer as an alarming, permanent, and subjective feeling of physical, emotional and/or cognitive fatigue or exhaustion related to cancer or its treatment, which is not proportional to the level of exercise and limits the ability to perform daily activities [3, 7, 10–13]. This symptom is not suppressed after taking a rest [2, 4, 14–16] and, in fact, it may be exacerbated by the process of taking a rest [2, 4, 17]. According to NCCN 80% of patients undergoing chemo- and/or radiotherapy experience CRF [3, 18] as well as over 75% of patients with metastatic disease [9].

Experts point out 4 criteria needed for diagnosis to be given:

1. 2-weeks or a longer period of time in the previous month, when the patient experienced in a significant level CRF or limited activity along with additional symptoms related to CRF every day or almost every day;
2. the occurrence of CRF leading to experience anxiety and functional disorders in a significant level;
3. the occurrence of clinical symptoms suggesting that CRF is a result of malignant tumour or therapy that has been applied in this case;

4. CRF not being a result of a patient's mental state that may simultaneously coexist, especially as a result of depression [2].

One of the approaches to the problem of fatigue related to cancer is its classification as central and peripheral. Peripheral CRF occurs within neuromuscular junctions and in muscle tissue, which results in disability of the peripheral nervous system and muscular system to respond to stimulation from the central nervous system (CNS). Mechanisms engaged in peripheral fatigue include the lack of adenosine triphosphate and accumulation of metabolic waste products [4], which leads to the deterioration of physical fitness, as a result of abnormalities in the circulatory system, metabolism system and other physiological activities [2]. Central CRF that develops in the central nervous system occurs as a result of progressive failure to send impulses to mobile neurons [4] and is characterised by failure to focus and maintain attention on tasks and activities that demand motivation [2].

### Pathogenesis of disease

The pathogenesis of CRF is multi-factorial [2, 19] and not entirely known [20]. Researchers have proven the significant role of pro-inflammatory cytokines in the CRF development. The antagonists' level of interleukin-1, a soluble tumour necrosis factor receptor type II (sTNF) and the level of neopterin were significantly higher among patients with breast cancer and fatigue symptoms than among patients without CRF, 5 years after diagnosis. One of the hypotheses assumes that CRF compromises the mutual final transmitting tract for a number of important functional systems, including the central nervous system, immune system, musculoskeletal system, cardiovascular system and respiratory system. Currently, it is suggested that nervous, cardiovascular and immune system that control pro-inflammatory tracts and active factors activating 5-hydroxytryptamine (serotonin) and catecholamine and regulate CNS are engaged in the CRF development. The next hypothesis states that there is a growth possibility of tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) during chemotherapy, which may lead to changes in the daily level of cortisol, round-the clock arrhythmia resulting in sleep disorders and fatigue, increased release of central 5-hydroxytryptophan (5-HT), which is a serotonin precursor, activation of the vagus nerve and decrease in skeletal muscle tension. It is followed by general weakness and changes in skeletal muscle metabolism, which in the case of chronic changes leads to their progressive dystrophy [2]. Recent research on genes coding the process of fatigue have presented the activity increase of pro-inflammatory transcription factors for CRF. Patients with breast cancer and chronic fatigue have shown greater expression of nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells (NF- $\kappa$ B) along with decreased expression of anti-inflammatory genes, regulating synthesis of glucocorticoids among others. Inflammatory processes related to cancer development may cause energy metabolism disorders and suppress muscle contractions. These observations indicate that an increased level of interleukin-6 in plasma and C-reactive protein (CRP) may be related to more intensified level of fatigue among oncological patients in terminal state of disease [7].

Changes within cytokines may be secondary in regard to hypothalamic-pituitary-adrenal axis disorders (HPA) and, as a consequence, may influence cortisol regulation by this system. Nonetheless, deregulation of HPA axis is more rarely observed than changes in immunological environment [21]. Moreover, low level of circulating cortisol is observed among patients experiencing CRF. This hormone causes a number of biological effects which include regulation of blood pressure, cardiovascular system functions, carbohydrate metabolism and immunological functions. Malignant tumour and/or anti-cancer treatment may cause deregulation of the HPA axis, leading to endocrinological changes, which result in fatigue. A greater relation between HPA axis disorders and circadian rhythm of cortisol (than with total level of this hormone in serum) is recognised among patients suffering from cancer. Changes within the HPA axis may be caused by numerous substances related to cancer (IL-1, IL-6, and TNF- $\alpha$ ). Oncological treatment may directly impede this axis (glucocorticoids, radiotherapy, chemotherapy). The function of the HPA axis is to influence the cells' development of the immune system as well as cytokines production, including pro-inflammatory cytokines. On the other hand, cortisol impedes the production of pro-inflammatory cytokines, thus a decrease of cortisol level causes an increase in the level of cytokines. Although a relation between HPA axis disorders and CRF is suggested, co-existing diseases, such as sleep disorders, may also have an impact on this axis. In turn, HPA axis function is to influence cells' development of the immune system as well as production of cytokines, including pro-inflammatory ones. On the other hand cortisol impedes production of pro-inflammatory cytokines, thus decrease of cortisol level leads to increase of cytokines level. Although relation between HPA axis disorders and CRF is suggested, nevertheless, co-existing diseases, such as sleep disorders, may also have an impact on this axis. Next potential process through which malignant tumour may cause fatigue is circadian rhythm disorder. This rhythm is controlled by the biological clock, which is responsible for endogenous and physiological processes. It comprises a 24-hour cycle and is sensitive to environmental factors (i.e. cycle changes: light – darkness) and psychological factors (i.e. stress, anxiety, diseases). Many changes within circadian rhythm have been diagnosed among oncological patients, such as: changes in endocrine system (i.e. secretion of cortisol, melatonin and prolactin), changes in metabolic processes (i.e. body temperature and level of circulating proteins), and changes in immune system (level of circulating leukocytes and neutrophils – production impediment or stimulation). Patients with advanced cancer generally show the greatest changes in circadian rhythm. Researchers suggest a connection between CRF and circadian rhythm through changes in the secretion of cortisol during the day as well as in rest/activity rhythm, which is deregulated among patients experiencing sleep disorders. Causes that may be related to circadian rhythm disorder which is induced by cancer include genetic, psychosocial and environmental factors [4]. Another reason for CRF may be metabolic disorders [2, 22]. Cancer-related fatigue may result from abnormalities in energy production and consumption, which may be used for tumour growth. This is

reflected in mitochondria biogenesis disorders, disturbing the balance between aerobic and anaerobic metabolism. Oxidative phosphorylation is the main energy source for muscle tissue. It has also been observed that tumour cells seem to have an advantage when the level of glucose transforming into lactate is high, which favours glycolysis. This theory may also be associated with abnormal production of adenosine triphosphate during oxidative phosphorylation. Thanks to it, a favourable environment for tumour growth may develop and simultaneously may deprive the organism of the energy needed to maintain correct functioning of the muscular system and neurocognitive processes. Mitochondria are mandatory for energy production which is the basic source of protein synthesis. On the other hand energy production disorders are related to decreased muscle biosynthesis. On the other hand, energy production disorders are related to decreased muscle biosynthesis. Muscle is rich in mitochondria, and any disorders have an impact on cardiac system efficiency. These observations have also been confirmed by noticing that aerobic training as well as strength (anaerobic) training stimulates mitochondria biogenesis. Aerobic exercises are an effective way to treat CRF and may work by affecting many transmitting tracts causing a decrease in the level of pro-inflammatory cytokines in blood plasma, enhancing the reduction of visceral fat and/or increasing tissue sensitivity to insulin and glucose output. Cancer-related fatigue may be also related to abnormal glucose output by muscle tissue, which is necessary for their normal functioning, which causes the growth of fat tissue in insulin resistance [2]. Increased physical activity affects suppression of neoplasia through its favourable influence on hormonal control and stimulation of the immune system [23].

### Symptoms

Patients perceive fatigue as the most worrisome and annoying symptom related to cancer and its treatment [2, 3, 24, 25]. They consider CRF more troublesome than pain, nausea, and vomiting [2, 3, 26–28], which can be controlled by drugs [2, 3, 26]. CRF decreases the quality of life [2, 29] and occurs more often with such malignant tumours as pancreatic and breast cancer, and lymphoma [2]. De Jong *et al.* report that 58–94% of patients with breast cancer experience CRF during treatment and 56–95% after supplemental chemotherapy [2, 30]. Moreover, many patients claim that their energy level never goes back to the state it was in before diagnosis and treatment [2].

Sleep disorders are experienced by most patients during chemotherapy. Hot flashes and pain influence the quality and efficiency of sleep, and contribute to the occurrence of CRF and functioning disorders during the day. Pain influences CRF both directly and indirectly [2] because it is one of the main symptoms occurring during cancer [31]. It is an exhausting symptom for the patient; moreover, it can additionally lead to fatigue due to sleep disorders and can reduce the ability to perform physical activity. The meaning of these observations is crucial because 2/3 of patients experience pain in the terminal stage of cancer [32–34] in moderate to severe intensity [35] and 1/3 in its intermediate stage [33]. Although painkillers often decrease the level of

experienced fatigue, their side effects may intensify fatigue [9]. Problems with sleeping are related to CRF, depression, and a decrease in the quality of life [2]. Fatigue caused by sleep disorders may be displayed by redundant drowsiness during the day [9].

### Cancer-related fatigue and its relation to oncological treatment

Cancer treatment causes a lot of side effects. They mostly affect bone marrow, and the nervous and digestive systems, and may be a significant factor leading to severe CRF, which may result in limiting or terminating treatment of the underlying disease. Oncological surgery may also induce CRF directly after the surgery, although intense fatigue may often be caused by an increased analgesic effect. Dynamic intensification of fatigue is described as the most severe symptom related to accumulation of the ionising radiation dose during radiotherapy or radio-chemotherapy being given at the same time [7]. De Sanctis *et al.* examined 40 women with the early stage of breast cancer, who have been treated by means of surgery and supplemental radiotherapy (50 Gy in 25 fractions, 2 Gy daily) in 2007–2010. These data suggest that undesirable skin reactions in form of greatly advanced erythema caused by radiotherapy may be responsible for biological fatigue mechanisms through the activation of pro-inflammatory cytokines in plasma [36]. Patients suffering from cancer and receiving hormonal therapy by means of aromatase inhibitors often report undesirable symptoms like hot flashes combined with sleep disorders and CRF. Women undergoing chemo- and radiotherapy are more likely to experience CRF as much as 10 years after the termination of treatment, compared to women that undergo only radiotherapy. 74% of men suffering from prostate cancer report some kind of fatigue and 39% of patients report chronic fatigue when treated by means of radio- and hormone therapy [9]. There are many drugs applied to alleviate or control undesirable symptoms of oncological treatment, which can cause CRF. Co-existing diseases and lasting treatment related to them may also contribute to experiencing fatigue, especially among the ageing population; these are hypothyroidism [2, 37], diabetes, and high blood pressure [2].

### Evaluation of cancer-related fatigue and co-existing diseases

One of the significant problems in the evaluation of CRF and confirmation of the diagnosis is the lack of unified scales and guidelines. The main source of information that helps in the diagnosis is reporting of symptoms by the patients, which everybody experiences subjectively, so medical history is not an objective method to diagnose CRF [2]. NCCN and ASCO guidelines for CRF recommend evaluation of the level of fatigue of all patients suffering from cancer during the first appointment, regularly during and after termination of oncological treatment as well as in case of clinical recommendation. NCCN and ASCO recommend a 10-grade scale to evaluate the level of fatigue during preceding 7 days, in which 0 means “no fatigue” and 10 “the most severe fatigue imaginable”. 0–3 total points means

lack to low level of fatigue, moderate level: 4–6 points, and severe: 7–10 points. During the examination and medical history fatigue characteristics should be evaluated and described: the beginning, changeability, duration, inducing factors, and the effect on physical and mental activity [9]. Patients and their families must be provided with information regarding symptoms and general conduct in case of CRF. Medical history and physical examination should be conducted and targeted to diagnose diseases or symptoms contributing to the occurrence of fatigue, such as any drugs taken and their side effects, pain, emotional disorders, anaemia, sleep disorders, malnutrition, co-existing diseases, and alcohol or other substance abuse. Then, the right treatment can be applied [2, 9]. Anaemia may be caused by cancer or oncological treatment. Its frequency depends on diagnosis, severity of disease, duration of cancer, and applied treatment.

The causes of anaemia may include bleeding, haemolysis, nutritional deficiencies, and bone marrow involvement by cancer. Additionally, pro-inflammatory cytokines (TNF- $\alpha$ , IL-1, IL-6 and IFNs) as well as erythropoiesis block lead to a decrease in production of erythrocytes, which in turn contributes to anaemia and fatigue. The function of haemoglobin may be distorted through the change in the transport of ions (potassium, chlorides, and magnesium) that go through the erythrocyte membrane as a response to tumour or applied treatment. The survival period of erythrocytes is shortened in cancer-related anaemia, and the magnesium level in erythrocyte may play an important role in causing chronic fatigue. Although the way in which anaemia or haemoglobin disorders influence CRF has not been completely recognised, organ impairment is suggested due to hypoxia [4]. Mental illnesses may also cause fatigue and be presented through this symptom. Depression and anxiety are two most common mental disorders co-existing with CRF. Patients suffering from depression and fatigue also report greater impairment of physical activity than patients reporting the same level of fatigue, but occurring as a single symptom; therefore, mood disorders are not to be disregarded among patients with CRF. Lack of appetite, gastrointestinal adverse events, weight loss, and low levels of albumin contribute to malnutrition and are displayed by fatigue [9]. Cachexia includes the loss of fat tissue as well as skeletal muscle tissue leading to anorexia, weight loss, fatigue, functional disorders, and shortening of survival period. Sleep disorders may be caused by several of the mechanisms described above, including HPA axis disorders and circadian rhythm disorders, as well as changes in serotonin metabolism and cytokine expression [4].

### Treatment

Treatment should be directed individually towards each patient and targeted at reducing anxiety, decreasing fatigue severity and the effect on conducting regular, everyday activities [2, 9]. There are many drugs and non-pharmacological measures currently being researched that help alleviate the symptom of fatigue related to cancer. Non-pharmacological interventions include increased physical activity [2, 9, 38, 39] and psychosocial therapy [2, 9, 39], which can be applied as a separate method of treatment in the case of benign CRF that does not affect the quality of life of pa-

tients [40]. Research results show that physical exercises are advantageous in conquering CRF, both during and after oncological treatment [2, 9, 21, 41, 42]. Nonetheless, there is no research regarding the type of the most effective exercises and workouts as well as their intensity, frequency, and duration. A workout program should be planned for each patient individually starting at a low intensity, considering the patient's general state and physical condition. Psychosocial therapies bringing advantages in the case of CRF occurrence include cognitive behavioural therapy [2, 9, 21, 43], education/counselling, and supporting/expressive therapy [2, 9, 21]. Massages and relaxation therapy also have a positive impact on CRF, especially because currently there is no medicine directly used for its treatment. NCCN advises treatment of diseases as well as disorders co-existing with cancer and related to CRF [2, 9]. There are two substances named that may be helpful: methylphenidate [9, 44] and methylprednisolone. Methylphenidate is a stimulating drug (serotonin-specific and non-adrenaline reuptake inhibitors) applied in the initial dose 2.5–5 mg, once or twice a day, gradually increasing the dose with the evaluation of reaction to treatment and side effects (anxiety, sleep disorders, lack of appetite). On the other hand, methylprednisolone (anti-inflammatory and immunosuppressive glucocorticoid) applied in dose of 16 mg twice a day among patients suffering from advanced cancer has a significant influence on decreasing fatigue, and increasing appetite and mood. Glucocorticoids may unfortunately cause sleep and mood disorders, as well as lead to a decrease in muscle strength, when applied for a long period of time, which may increase fatigue [9]. It has also been proven that fatigue intensity may be reduced among patients suffering from anaemia undertaking chemotherapy after erythropoietin (glycoprotein hormone polypeptide stimulating various phases of erythropoiesis) has been applied [3].

### Conclusions

Fatigue related to cancer is a very common problem affecting patients suffering from cancer. Taking into consideration multicentre observations, CRF is currently recognised too rarely, diagnosed and treated in clinical and ambulatory conditions. It permanently affects the quality of life of patients. They become too tired to be able to fully participate in every-day activities, which decreases the patients' mood and self-esteem. This symptom is reported by patients and should not be disregarded by the patient nor medical staff. Treatment of diseases contributing to fatigue occurrence related to cancer is a very crucial element of complex oncological treatment. Although the number of examinations, awareness, and knowledge regarding CRF has increased recently, there is still no coherent definition, grading scale, targeted conduct, or successful treatment.

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