Review

FACTORS OF CANCER-RELATED FATIGUE IN PATIENTS WITH MALIGNANT DISEASES

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Summary

Symptoms of fatigue and exhaustion are considered to be the most common complaints in patients with oncological diseases during and after treatment. The manifestations can be on a physical, cognitive and emotional level. At diagnosis, 40% of patients report fatigue, and this percentage increases to 90% during treatment. However, the exact determinants of fatigue are not yet known. This article is a literary review of the problem of cancer-related fatigue – mechanisms, risk factors, and the impact on the lives of those affected. Literary data on the role of subjective well-being in terms of fatigue and emotional responses of patients with oncological diseases are described. A number of contemporary studies of the combined effect of fatigue and pain on the functioning of oncology patients have been discussed. It is concluded that the symptoms of fatigue, exhaustion and pain are considered the most common complaints in patients with oncologic pathology during and after treatment, whose manifestations may be physical, cognitive and emotional. On the other hand, human health satisfaction is one of the most important predictors of life satisfaction, which contributes significantly to the overall well-being of the patients group discussed.
Key words: cancer-related fatigue, pain, subjective well-being

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Introduction

The metaphorical notion of "cancer" is a common term denoting about 100 diseases, which are different in terms of etiology, the course of the disease itself and its treatment [1, 2]. The oncological diseases significantly affect the physical and emotional functioning of the patients and their families [3].

Despite the huge variety of diagnoses, therapeutic methods and the various social, demographic and personal characteristics of those affected, the common experience is related to the "life-threatening nature of cancer" and the

insecurity as to whether and when a person will actually be cured" [4].

In addition, cancer is not just a single event with an undoubted ending but a permanent condition characterized by growing uncertainty, late consequences from the disease itself and from its treatment and, last but not least, serious psychological distress [5].

Over the last decades, with the rise of survival rates as a result of the advance in the treatment of oncological diseases and their early detection, the scientific efforts were focused on analyzing the quality of life and the psychological functioning during the treatment and upon its completion instead focusing solely on the manifestations of the disease [3].

The official statistical data show that in 2013 in Bulgaria, the registered cases of malignant diseases were 3702.4/100 000 cases, of which 432.4 were newly detected. In 2014, the number of the registered cases rose to 3819.0/100 000 cases, as the newly detected ones were 461.9. The data show that the largest relative share within the structure of the cancer morbidity is that of female breast cancer (102.7/100 000), prostate gland cancer (79.9/100 000), lung cancer in males (95.1/100 000) and females (21.4/100 000), colorectal carcinoma in males (41.2/100 000) and females (32.7/100 000), and other localizations [6].

It has been predicted that, in 2025, the incidence of oncological diseases will reach 234.8/100 000 [7]. The estimated and observed 5-year cancer survival in Bulgaria within the period 2000-2005 is 28%, which is far below that in economically developed countries. Bulgarian is at the bottom of the black list of oncological diseases survival [6]. This determines the significance and the social damages that society is currently suffering as a result of the disease.

The aim ot that study was to analyse the main factors of cancer related fatigue and investigate the relationship between cancer-related fatigue, pain, as well as variables associated with subjective well-being and life satisfaction.

Material and Methods

An initial literature review was conducted. Four reference databases were searched (MEDLINE, ELSEVIER – Science Direct, ELSEVIER – SCOPUS, Springer). The initial search resulted in 520 articles. Studies were included if they were published between 1980 and 2017, were written in English or German, and enrolled human adults. The 60 remaining articles were assessed for relevance to the area by visually examining their titles for keywords: cancer-related fatigue, pain, subjective well-being, life satisfaction.

Cancer-related fatigue of patients with oncological diseases

The symptoms of fatigue and exhaustion are thought to be the most common complaints among patients with oncological pathology during treatment and after its completion, and are jointly called cancer-related fatigue [8, 9]. According to the contemporary definition of the National Comprehensive Cancer Network [10, 11], fatigue is a restriction of physical and mental capacity which has occurred as a result of the medical treatment and significantly affects the activity of the patient and, despite the adequate rest and relaxation, it does not decrease. Kuhnt et al. (2010) [12] define fatigue as a multi-dimensional structure with typical symptoms: physical (physical exhaustion, fatigue), mental (sadness, irritability, hopelessness) and cognitive (concentration and memory disorders). Servaes et al. (2002) [13] define fatigue in a way similar to Kuhnt et al. (2010) [12]. According to the authors, mental fatigue is manifested as emotional and cognitive disorders – loss of motivation, reduced energy, lack of initiative, sadness, anxiety, concentration, and thinking and sleep disorders.

Despite the studies conducted for many years, the exact definition of fatigue is still a challenge [14]. As a consensus, the Fatigue Coalition USA suggested applying ICD-10 criteria for defining it (Table 1) [15].

Table 1. Suggested ICD (International Classification of Diseases) - 10 criteria for diagnosing fatigue (Cella, 2001)

A Six (or more) of the following symptoms persist (almost) every day for two weeks during the last month and at least one of the symptoms is fatigue (A1)
A1 Substantial fatigue, lack of energy or increased need of a rest which are not connected with the current changes in the levels of activity.
A2 Complaints of general weakness or heavy limbs.
A3 Reduced concentration or attention.
A4 Reduced motivation or reduced interest in the everyday activities.
A5 Sleeplessness or increased need of sleep.
A6 The sleep is not convalescent and restorative.
A7 Need of great efforts to start certain activities.
A8 Significant emotional reactions (for example, sadness, weakness or irritability).
A9 Inability to complete the tasks owing to fatigue.
A10 Problems with the short-term memory.
A11 Fatigue lasting a few hours after physical exercise.
B These complaints have a clinically significant severity or constitute a limitation for social, professional and other important activities.
C The complaints are related to the oncological disease or result from the therapy of such a disease.
D The symptoms are not the result of psychiatric comorbidity as a major depressive disorder, somatoform disorders or an obsession.

Etiology

During the last years, the studies conducted for many years have started examining the risk factors for the occurrence of fatigue, and especially the fatigue that persists for months or years upon the completion of treatment [16]. The research in this area focuses mainly on the genetic, demographic, medical, behavioral and psychosocial predictors of the emergence of fatigue.

In addition to the factors related to the disease and its treatment, Bower et al. (2000) indicate some psychological factors like personality traits (optimism and anxiety) accompanying the physical symptoms and lifestyle, as a reason for the emergence of fatigue [17]. Regardless of the conducted intensive studies, at present there is no overall theory explaining the reasons for its occurrence [18].

Based on the current understanding, fatigue is regarded as a multi-dimensional structure including somatic, psychological factors, and behavioral aspects [10].

Some of the likely reasons and predisposing primary factors for the occurrence of fatigue might be the production of cytokines as a defence reaction of the body towards the emergence of the tumour, as well as immunological, endocrine, neurological, psychological, hematological (anemia, hypokalemia, hypocalcemia), musculoskeletal factors, and factors related to nutrition (for example, dietary) [19].

Secondary reasons occurring as a result of the oncological disease, for example a defence reaction of the body against the tumour, the tumour therapy and its effect on the patient – sleep disorder, pain, dyspnea and the disease-related emotional stress may lead to depression, anxiety, and social isolation [20, 21].

Spread

The spread of fatigue described in scientific literature ranges from 14% to 99% [10]. Fatigue is the most common symptom in patients with oncological diseases [15, 22, 23] and cancer survivors [24, 25]. During the stage of diagnosing, up to 40% of the patients complain of fatigue and this percentage rises to 90% during the treatment [26]. Most of the patients complain of fatigue throughout the therapy of oncological diseases – 90% of the patients undergoing radiation therapy and 80% of the patients undergoing chemotherapy. Studies have shown that fatigue may occur months or even years after the completion of the treatment in approximately 1/3 of the patients with oncological diseases [27].

During the active treatment, the

aforementioned values of the spread of fatigue range from 30% to 90% [28] upon the completion of the treatment, and one out of three patients suffers from long-term fatigue - 30% [28, 29].

Pain

In addition to fatigue, pain is another of the most common symptoms in patients with oncological diseases. Some studies describe the effect these symptoms have on the physical and psychological functioning, and on the quality of life of patients along the entire trajectory of the disease [30]. Pain is relatively common in patients suffering from oncological diseases, its frequency ranging from 14% to 100% [31]. During the period of diagnosing, about 20-75% of adult patients complain of pain [31]. In patients undergoing active treatment, this percentage rises to 60-70% [32] and in the later stages of the disease, pain is registered in 23-100% of the patients [31]. According to Roenn et al. (2012) pain is related to the malignant disease and may be caused by the disease itself or may be a side effect of the treatment [33]. Persistent and increasing pain is regarded as a sign of progressing and deterioration of the disease [34].

Over the last 20 years, there has been data on the relation between pain and the disorder in the mood of patients with a malignant disease [35]. Ahles et al. (1983) [34] compare patients with oncological diseases with and without a pain. These authors have established higher levels of depression, anxiety, hostility and somatization of the complaints among the patients experiencin pains, compared to those not having pains.

Interesting data have been obtained in the study of Petkova et al. (2011) [3] from patients with oncological diseases. The study aimed to assess anger and depression as well as their effect on the intensity of pain. The authors examined 63 patients: the average age of the examined people was 54.5 (SD=14.6), those married were 87%, and 55% were men. The established average levels of anger among the examined groups of patients with oncological diseases were 31.6 (SD=7.5), and 9.9 (SD=3.6) for depression. The authors included a group of patients having pains but not suffering from any oncological diseases. The data from the comparison between the two groups showed significantly higher levels of anger in the patients feeling pains and having oncological diseases, than the levels of anger in the groups of patients having pains but not suffering from any oncological disease – 31.6 (SD=7.5) and 28.3 (SD=6.4), respectively. These authors established higher risk of intensive pain with the existence of anger predisposition in this study [3].

Rao et al. (2004) conducted another study that examined adult patients with oncological diseases at advanced stage and established the existence of pain in 80% of them [36]. They found that in adult patients with oncological pathology, the symptoms usually overlapped and often included nausea and vomiting, pain, depression, fatigue, sleeplessness, loss of appetite, reduced libido and higher levels of anxiety [36]. Liao et al. (2000) [37] assessed fatigue of people of advanced age and established a statistically significant relation between fatigue and depression, and pain and physical functioning. According to the same authors, the correlation between the symptoms of pain, fatigue and depression should be additionally assessed in patients over 65 years of age [37].

Bernabei et al. (1998) [38] examined 13 625 hospitalized patients over 65 years of age. Of the 4003 patients, 24%, 29% and 38% of these ≥85 years of age, 75-84 years of age and 65-74 years of age, respectively, reported having pains on a daily basis. The age, sex, race, marital status, physical activity, depression and the cognitive status were independently related to the existence of pain [38].

Data obtained from other studies have shown the existence of correlations between pain and fatigue among patients with oncological diseases. Arndt et al. (2005) [39] examined 314 women with mammary gland carcinoma one year after the diagnosis and established a moderate correlation between pain and fatigue ($r=0.68$; $p<0.001$). Ferell et al. (1998) also established a correlation between pain and fatigue ($r=0.69$; $p<0.05$) in patients in different stages of an oncological disease [40].

Interesting data was obtained from a survey of Beck et al. (2005) [41] conducted on 84 women with different localizations of oncological disease and pain. The authors concluded that pain has a significant effect on the severity of fatigue ($F=6.17$; $p<0.001$) and 20% ($R^2=0.20$) of the changes in the severity of fatigue could be explained with the existence of pain.

Permanent pain of patients with oncological diseases may have a significant negative impact on the patients' quality of life and endurance during chemotherapy and radiation therapy. Incomprehensive examination and inadequate treatment of the pain lead to disruption in the functioning of the body, an increased risk of depression and anxiety and, eventually, deterioration of the patients' quality of life [31].

Subjective well-being

The complex biopsychosocial approach of medical servicing requires therapeutic methods aimed at improving the quality of life of the patients, an important element of which is the subjective well-being involving statements and feelings that express the overall subjective evaluation of life satisfaction.

The model of subjective well-being of Diener et al. (1999) [42] places the focus on registering the positive aspects of the experiences of a person and includes an emotional or an emotional-cognitive evaluation component: a comprehensive cognitive and affective evaluation of the past, present and future [42].

Subjective well-being has been determined as a broad, varied category of phenomena, including emotional reactions of people, their satisfaction with different spheres of life, as well as their ideas about life quality in general. In this regard, subjective well-being can be viewed as a broad term including the experiencing of pleasant emotions, happiness, a low level of negative feelings and a high level of life satisfaction [43].

Subjective well-being, life satisfaction among patients with oncological diseases

A cancer diagnosis is considered to be a prototype of a critical event in a person's life [44]. Disrupted well-being is often viewed as a key element, typical of critical life events and its recovery in people in crisis is equal to "successful coping" in most of the studies [45].

McDonough et al. (2014) [44] established that social support may act as a positive predictor of changes in subjective well-being whereas stress is said to be a negative predictor of changes. The same authors indicated data based on a study conducted on 173 women who survived mammary gland carcinoma, at an average age of 55.4 years (SD=10.99). The results obtained from the study showed that the higher levels of social support (β=0.21) predicted improvement of the subjective well-being and lower levels of overall stress (β =-0.59) [46]. Similar results were confirmed by the data obtained in the study of Pinquart et al. (2009) on 163 patients with oncological diseases before the initiation of chemotherapy [46]. The authors stated that social support, self-confidence and, to a lesser extent optimism and purpose in life, correlated with subjective well-being. In a study Olsson et al. (2017) [47] conducted on women with mammary gland carcinoma one month after surgical treatment, life satisfaction was mainly related to social support 3.2 (1.6÷6.3), and $p<0.05$ among married women and the women having a partner 4.2 (2.0÷8.4), and $p<0.05$.

Interesting data were obtained from a study of Bazalinski et al. (2014) [48] of patients with a stoma with colorectal carcinoma after completion of treatment. The authors established a strong positive correlation between education and life satisfaction ($p=0.051$). However, this correlation is statistically insignificant in case of $p<0.05$, while there is a strong positive correlation between self-efficacy and life satisfaction ($p\leq0.001$).

It is known that cancer-related suffering is intensive, personal and has a substantial effect on all aspects of a person's life. In this regard, Ferell at al. (2008) state that the physical symptoms may have a negative effect on the psychological and spiritual well-being of the patients, and it is necessary to assess the personal value and suffering related to disabling symptoms like fatigue [49]. Beutel et al. (2006) [50] emphasized the negative correlation between fatigue and life satisfaction, and the results they obtained for physical, affective and cognitive fatigue were as follows: r=-0.34; r=-0.36; r=-0.26, and $p<0.01$. On the other hand, the high level of subjective well-being (life satisfaction, lack of negative emotions, the presence of optimism and positive emotions) leads to better health and longevity [51].

Conclusions

Fatigue is the most common symptom among patients with oncological diseases [13-15]

and cancer survivors [25]. During the state of diagnosing, up to 40% of the patients complain of fatigue and this percentage rises to 90% in the course of treatment among 90% of the patients undergoing radiation therapy and 80% of the patients undergoing chemotherapy [26]. The high fatigue values during treatment may lower again upon its completion, but compared to the levels of healthy people, even many years after that, the average values of these patients are above the mean [52].

Approximately 1/4 up to 1/3 of the cancer survivors have persistent fatigue lasting up to 10 years after diagnosis, which often causes major disruptions in their functioning and life quality [53].

The complexity of fatigue shows significant individual variability in terms of severity and manifestation. Considering the wide spread and effect of fatigue amongin patients with malignant diseases, the identification of the psychological factors which are largely related to the emergence, severity and sustainability is an important goal. It would allow the early diagnosis of fatigue, identification of vulnerable patients, the development of targeted interventions and guidelines for its control and the improvement of the quality of life and well-being of patients with malignant diseases and cancer survivors. Early diagnosis and targeted treatment of fatigue will contribute to minimizing its effects on the physical and the emotional state of the patients. This, in turn, would help the patients adhere to the treatment, which is an important element for ensuring effectiveness.

Along with fatigue, pain is another common symptom seen in patients with malignant diseases. The results of numerous studies have described the effect that fatigue and pain may have on the physical and mental functioning of the patients and their quality of life during the course of the disease [30]. According to Beck et al. (2005) [41], intensive and prolonged pain is related to high levels of fatigue and has a significant effect on the severity of fatigue ($F=6.17$; $p<0.001$), as 20% ($R^2=0.20$) of the changes in the severity of fatigue can be explained with the existence of pain. Pain, and in particular pain in patients with malignant diseases, is not a purely physical experience since it covers many aspects of human functioning, including physical, psychological and social aspects as well as the mutual influence between them [3]. The psychological factors play an important role in the perception, persistence and aggravation of the pain in case they are not the reasons for it [54].

Life satisfaction and well-being are considered to be predictors of the quality of life as health satisfaction is the most important predictor of life satisfaction and, thus significantly contributes to the overall well-being [55, 56]. Based on the analysis of the literature, we can draw the conclusion that social support predicts ($\beta=0.21$) improvement of subjective well-being and lower levels of overall stress ($\beta=-0.59$) [46]. Life satisfaction in patients with oncological diseases is related primarily to social support 3.2 (1.6÷6.3), and $p<0.05$, marital status 4.2 (2.0÷8.4), and $p<0.05$ [47], education ($p=0.051$), and self-efficacy ($p\leq0.001$) [48]. On the other hand, life satisfaction is vert negatively correlated with chemotherapeutic treatment, [57] the physical ($r=-0.34$), affective ($r=-0.36$) and cognitive ($r=-0.26$; $p<0.01$) aspects of fatigue [50].

The concept of life satisfaction would help us understand in which areas of life the patients with oncological diseases experience an imbalance between their personal goals and current life circumstances.

Therefore, it is important to assess life satisfaction, on the one hand, and the well-being of patients with oncological diseases, on the other hand, because it is obvious that the longer the patient feels satisfied, the higher the level of adaptation and the sense of well-being is, which will ensure the completion of the treatment with a maximum level of adherence and observance of the therapeutic course of the patients.

The psychosocial component upon the occurrence of a malignant disease and during its course is significantly manifested and this circumstance must be taken into consideration. The success of treatment often depends on this psychological condition [58]. In this regard, it is good for the medical staff to maintain hope of the patients as an important part of their treatment.

The most successful approach would be the one that conforms to the individual features of each patient. Scientific studies need to answer a few key questions: Who is exposed to the risk of a tumour-related fatigue and why? What are the mechanisms underlying fatigue during treatment and after its completion? Subsequent

in-depth surveys could give us important conclusions regarding the better understanding, the determination of proper objectives and the effective and complex treatment of fatigue during the various stages of the trajectory of an oncological disease as early as possible and, if appropriate and necessary, the patients need to be referred to mental health specialists [54].

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