

Impact of fatigue on quality of life in oncology patients treated with immunotherapy

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Abstract

Fatigue is one of the most common side effects of immunotherapy, affecting 78-96% of patients. The mechanism is not fully understood, but may relate to the pro-inflammatory state induced by immunotherapy. Compared to chemotherapy, immunotherapy has less impact on quality of life and allows patients to maintain satisfactory quality of life for longer. However, fatigue can still significantly affect patients' physical capabilities and ability to participate in enjoyable activities. Guidelines recommend assessing fatigue and quality of life from diagnosis and throughout treatment. Multiple validated tools exist to measure fatigue objectively. Management approaches include both pharmacological and non-pharmacological methods. Exercise, particularly aerobic and yoga, appears to be one of the most effective non-pharmacological interventions for improving fatigue and quality of life. Overall, while immunotherapy-related fatigue impacts quality of life, it seems to do so to a lesser degree than other cancer treatments. More research is needed on optimal management strategies.

Keywords: fatigue, oncology, immunotherapy, quality of life.

Rezumat

Fatigabilitatea este una dintre cele mai frecvente efecte secundare ale imunoterapiei, afectând 78-96% dintre pacienți. Mecanismul nu este pe deplin înțeles, dar poate fi legat de starea pro-inflamatorie indusă de imunoterapie. Comparativ cu chimioterapia, imunoterapia are un impact negativ mai redus asupra calității vieții și permite pacienților să mențină o calitate satisfăcătoare a vieții pentru mai mult timp. Cu toate acestea, fatigabilitatea poate afecta în continuare în mod semnificativ capacitățile fizice ale pacienților și capacitatea de a participa la activități plăcute. Ghidurile recomandă evaluarea fatigabilității și a calității vieții de la diagnostic și pe parcursul tratamentului. Există mai multe instrumente validate pentru măsurarea obiectivă a fatigabilității. Abordările de gestionare includ metode farmacologice și nefarmacologice. Exercițiile fizice, în special aerobice și yoga, par a fi una dintre cele mai eficiente intervenții nefarmacologice pentru îmbunătățirea fatigabilității și a calității vieții. În general, în timp ce fatigabilitatea legată de imunoterapie afectează calitatea vieții, aceasta pare să o facă într-o măsură mai mică decât alte tratamente pentru cancer. Sunt necesare mai multe cercetări privind strategiile optime de gestionare.

Cuvinte cheie: fatigabilitate, oncologie, imunoterapie, calitatea vieții.

Introduction

In oncology, fatigue is an under-explored symptom. It can be attributed to the neoplasia disease itself and associated comorbidities or oncologic treatments. [1] Regarding the assessment of fatigability, there are several objective tools that can be used but there is no standard. First and foremost, the clinician should give particular importance to the patient's medical history and the factors that might cause fatigue in the absence of oncologic treatment, factors that could be addressed. European and American oncology guidelines recommend assessing the patient for this symptom at diagnosis and at regular intervals during treatment as well as at the end of treatment. [2]

Immunotherapy ranks high among the types of treatments used in oncology in recent years, but despite remarkable results in the management of oncologic disease, it can cause multiple adverse effects some of which are difficult to associate with the treatment and therefore difficult to identify and address therapeutically. [3] The most reported side effect by patient is fatigability. The pathophysiologic mechanism of this side effect is not fully understood, but the pro-inflammatory status given by immunotherapy is hypothesized to play a crucial role,

including also the hormonal changes that may occur and sleep disturbances. [4,5]

The quality of life of patients who complain of fatigability during immunotherapy treatment is affected both in terms of their physical ability to perform daily activities that previously did not require extra effort, but also in terms of psychosocial impact, as patients are unable to care for themselves or participate in collective activities that bring them pleasure. [3]

The therapeutic approach to fatigability includes pharmacological methods such as methylphenidate, dexamethylphenidate, dexamfetamine, modafinil and armodafinil, but their use in clinical practice is limited. Non-pharmacological methods such as aerobic exercise or yoga seem to improve the quality of life of these patients. [2]

Aim of the literature review

To identify the relationship between reported fatigability in cancer patients treated with immunotherapy and the impact on their quality of life.

Research question for the literature review

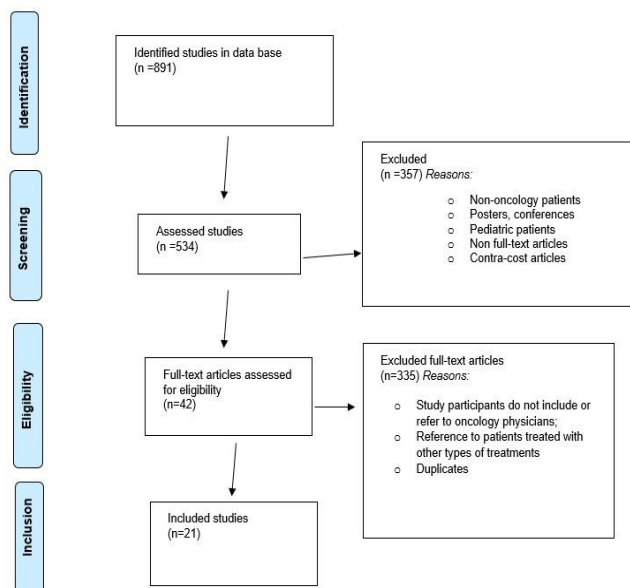
To identify the impact of fatigability on the quality of life of adult patients diagnosed with neoplasms of different localizations undergoing immunotherapy.

Search method

Articles were searched using the PubMed search engine with the following search keywords: "palliative care", "fatigue", "immunotherapy", "cancer", "immune checkpoint inhibitors", "oncology", "quality of life". Only full-text articles were included. Exclusion criteria included articles that included pediatric populations or professionals from other health fields as well as studies that we could not get access to full-text. After selecting the studies, we divided the studies by themes considered relevant to the research.

Review, meta-analysis, questionnaire, retrospective study, scientific articles and therapeutic guidelines were included.

PRISMA flow diagram



1. Table with included studies

Author/Year	Study type	Aim	Results
Boutros et al., 2021	Systematic review Meta-analyses	Compares side effects described by oncology patients with solid tumours of immunotherapy and standard chemotherapy.	Patients treated with immunotherapy retain a longer time to clinical deterioration and maintain a satisfactory quality of life for longer compared to those treated with chemotherapy.
Blaney et al., 2010	Questionnaire	Subjectively describes fatigability in relation to immunotherapy, patients' perspectives on exercise, and barriers and facilitators encountered in approaching exercise. Patients with stage III or IV malignant melanoma undergoing immunotherapy were included.	Patients report decreased fatigue and improved quality of life following exercise.
Cortellini et al., 2019	Multicentre retrospective study	Assess the correlation between early and late fatigability and clinical impact in PD-1 or PDL-1 treated patients in clinical practice.	Early fatigue occurring during immunotherapy seems to be an unfavourable prognostic factor but in order to properly assess its role we need to consider the patient's performance status.
Fabi et al., 2020	Guideline	Description of fatigue management in cancer patients	A correct approach to fatigue in cancer patients
Faury et al., 2020	Systematic Review	Correct methods for reporting the quality of life of cancer patients undergoing immunotherapy	Correct identification of the scales used to assess patients' quality of life
Hall et al., 2019	Systematic Review	To identify subjective complaints and impact on quality of life of cancer patients treated with immunotherapy compared with other oncologic treatments.	Immunotherapy is better tolerated compared to other oncologic treatments in terms of quality of life but conclusions are limited due to the heterogeneity of the evaluated trials. The tools currently used may miss these symptoms with the need for immunotherapy treatment-specific scores.
Henson et al., 2020	Review	methods of assessment and therapeutic methods for four of the most common symptoms of patients with advanced neoplasia: fatigability, pain, nausea and vomiting, and dyspnoea.	Many patients report worsening symptoms as death approaches. If not identified and treated correctly, these symptoms have a negative impact on patients' ability to function socially, quality of life and compliance with treatment. A multidisciplinary palliative approach is needed

			from the time of diagnosis, throughout the course of treatment and after the completion of oncologic treatment.
Hyatt et al., 2019	Original research	Subjective description of the impact of immunotherapy-induced fatigability and patients' perspective on exercise and how it can be performed and also its impact on quality of life.	Patients were willing to exercise during immunotherapy treatment with a high rate of improvement in fatigability. Identifying preferred exercise regimens may be helpful in creating a personalized approach.
Kiss et al., 2022	Original research	Comparison of the incidence of fatigability in patients treated with immunotherapy versus other oncologic therapies.	Although immunotherapy is associated with fatigability, the incidence was higher in patients treated with other types of oncologic treatments.
Larun et al., 2024	Review	To determine the effect of physical exercise compared with other pharmacologic methods in oncologic patients undergoing immunotherapy in combating fatigue, pain, sleep disturbances.	Patients who exercised had a lower degree of fatigability at the end of treatment compared with those who underwent passive treatments. The long-term impact of these types of exercise and the associated risks are unknown.
Montagut-Martínez et al., 2022	Systematic review	Identification of health assessment tools.	There are several instruments to quantify fatigability: Multidimensional Fatigue Symptom Inventory, Fatigue Questionnaire, Fatigue Assessment Questionnaire, Cancer Fatigue Scale and Revised Piper Fatigue Scale, Functional Assessment of Cancer Therapy-Anemia (FACT-An), Functional Assessment of Cancer Therapy-Fatigue (FACT-F), Piper Fatigue Self-Report Scale, Schwartz Cancer Fatigue Scale, Fatigue Symptom Inventory, Profile of Mood States Fatigue/Inertia Subscale, Lee's Visual Analogue Scale for Fatigue.
Naidoo et al., 2015	Review	Identifying the safety profile of monotherapy or combination therapy with anti PDL-1, PD-1 or CTLA-4 agents in neoplasms with different localizations.	It appears that anti PD-1 or PDL-1 agents are less toxic compared to anti CTLA-4 agents with a slightly different safety profile in pneumonitis or immune-induced colitis.
Sidney et al., 2017	Original research	Description of palliative care applied to the cancer patient.	Palliative care focuses on a comprehensive approach to patients in terms of physical, psychological, social, cultural, spiritual and communication aspects. This approach includes techniques to improve the capacity and quality of communication and the ability to make difficult decisions.
Tavio et al., 2002	Review	Addressing fatigue in cancer patients.	The importance of addressing fatigability as a symptom that affects patients both physically and psychosocially increases with the succession of oncologic treatments, and an early approach during oncologic treatment is needed.
Theobald et al., 2004	Original research	Description of the main side effects of immunotherapy in relation to insomnia	Fatigability is most often associated with insomnia and a possible explanation is that the patient feels the need to rest more during free time which leads to insomnia at night.
Tykodi et al., 2018	Original research	Summarizing the results of eight phase II-IV clinical trials in relation to the use of Nivolumab. The evaluation included the impact of adverse effects on patients' physical ability and quality of life.	Results show a lower impact on quality of life of Nivolumab compared to drugs in the comparator arm.
Vilchynska et al., 2016	Article	Evaluation of chronic fatigue syndrome, its aetiology and guidelines used in its management.	Fatigability is a complex syndrome requiring a multidisciplinary approach. In the absence of clear evidence of the effectiveness of pharmacological and non-pharmacological methods with the exception of exercise,

			psychosocial interventions, an individualized and needs-oriented approach is considered appropriate.
Yip et al., 2024	Systematic review	Evaluating the experiences of patients on checkpoint inhibitor treatment in relation to quality of life, clinical efficacy and safety.	The subjective experience of each individual patient is very important and the therapeutic approach must take this into account.
Zarogoulidis et al., 2023	Original research	Evaluation of the incidence of insomnia and fatigue in patients treated with chemotherapy or immunotherapy in lung cancer	Patients treated with chemotherapy reported no improvement in sleep disturbance and fatigability during treatment compared to those treated with immunotherapy. Once a partial or complete response was achieved with immunotherapy, a decrease in fatigability and sleep disturbance was observed
Zhang et al., 2022	Multimodal, sequential exploratory study	Subjective description of symptoms during immunotherapy treatment in patients with bronchopulmonary cancer and assessment of the relationship between described symptomatology and survival	Symptoms such as dyspnoea, fatigability and chest pain were associated with chemo-immunotherapy while xerostomia and blurred vision were associated with immunotherapy. For patients who died within 2 years the most common symptoms were dyspnoea, loss of appetite, taste changes and muscle weakness while for those who survived the most common symptoms were skin rash and chills.
Zhou et al., 2021	Systematic review meta-analysis	Incidence of side effects of any grade in patients treated with PD-1, PDL-1 inhibitors	Comprehensive description of side effects of treatment with PDL-1 or PD-1 inhibitors.

Results presented narratively by themes

a. Definition of fatigability

There is no clear definition of fatigability, it needs to be seen in context. In oncology, fatigability is viewed either as a symptom given by the neoplastic disease itself or as a side effect of the therapies followed by the patient or as a symptom of a concomitant pathology, most often of a psychiatric nature, such as depression or personality disorders. There are two forms of fatigue. The acute form, considered physiological, in which the body is able to balance its energy through rest. As for the chronic form, considered pathological, the patient is unable to regain energy no matter how well rested he is. In the oncological sphere, fatigue is one of the most common complaints of patients; it is estimated that 78% to 96% of patients suffer from fatigue, particularly during treatment. Depending on the type of treatment administered, fatigue occurs in 50-100% of patients and may persist after treatment. Fatigue associated with immunotherapy is characterized by a constellation of symptoms including flu-like symptoms, fever, chills, myalgia, headache and general weakness. [1]

Sleep changes are frequently associated with fatigue in cancer. The relationship between the two symptoms is a complex one and can be explained by the fact that the patient feels the need to rest very often during the day after exerting effort in daily activities and this leads to nocturnal insomnia. Also, the oncologic treatment followed can give daytime sedation and as a consequence nocturnal insomnia occurs. [6,7]

b. Assessment of fatigability in oncologic patients

Criteria for defining cancer-related fatigability according to ICD-10

Symptoms persisting every day or nearly every day for two successive weeks in the last month:

1. Significant fatigue, reduced energy level, or increased need for rest disproportionate to the physical activity performed along with any of the following:
 - a. Generalized muscle weakness or feeling of heavy legs
 - b. Decreased concentration or attention
 - c. Reduced motivation or interest in usual activities
 - d. Insomnia or hypersomnia
 - e. Sleep deprivation
 - f. Difficulty initiating activities
 - g. Increased emotional reactivity
 - h. Difficulty performing daily activities due to fatigue
 - i. Problems with short-term memory
 - j. Persistent fatigue for more than 3h
2. Symptoms affect social, occupational or important activities
3. Anamnesis, clinical and laboratory data demonstrate that these symptoms are related to neoplastic disease or the treatment given
4. The symptoms are not the result of a psychiatric comorbidity, such as depression, delusions or psychosomatic illness. [1]

There are several tools for quantifying fatigue in clinical practice. The most commonly used are the Multidimensional Fatigue Symptom Inventory, Fatigue Questionnaire, Fatigue Assessment Questionnaire, Cancer Fatigue Scale, and Revised Piper Fatigue Scale, Functional Assessment of Cancer Therapy-Anaemia (FACT-An), Functional Assessment of Cancer Therapy-Fatigue (FACT-F), Piper Fatigue Self-Report Scale, Schwartz Cancer Fatigue Scale, Fatigue Symptom Inventory, Profile of Mood States Fatigue/Inertia Subscale, Lee's Visual Analogue Scale for Fatigue. [1,8]

a. Quality of life assessment in oncology patients

An important issue that arises when wishing to assess fatigability and quality of life in oncology patients is that they consider these symptoms as normal in the context of the

pathology and their standards of living change at the time of diagnosis and this can create difficulties in objectively assessing the quality of life of these patients, this term being subjective.[9]

The European oncology guidelines recommend that all patients should be assessed for the presence and severity of fatigability at diagnosis and at regular intervals during treatment. These assessments should be carried out using standardized and validated tests and patients who are diagnosed with fatigability should be thoroughly assessed to identify a possible reversible cause. The diagnosis should include a complete history of symptoms, complete physical and neurologic examination, oncologic disease status at that time, and a minimal panel of laboratory tests. [2]

The inclusion in clinical practice of the assessment of fatigability in oncologic patients, regardless of the treatment used, may help early detection of this side effect, especially in patients who consider it to be normal, and the application of pharmacologic or non-pharmacologic methods to maintain or even improve the quality of life for these patients. [10]

b. The relationship between immunotherapy and fatigability

Immunotherapy has opened a new era in the management of patients diagnosed with neoplasms with different localizations. Although the therapeutic effect of immunotherapy is unquestionable, it comes with a significant suite of adverse effects, some of which are difficult to anticipate and manage.[3] It should not be forgotten, however, that immunotherapy offers a longer time to clinical deterioration compared to conventional chemotherapy.[11] The toxicity profile of immunotherapy is different compared to other cytotoxic and targeted therapies. In general, these side effects are fewer but can be very dangerous and require early and effective management, but studies show that they affect quality of life in a lower percentage compared to classical chemotherapy. [12,13]

One of the most commonly encountered side effects is fatigability; it is thought to be the most common side effect of any grade reported (18.3%) and the most common side effect of grade 3 or more (0.89%). [14] Studies show that patients receiving immunotherapy present a lower impact on quality of life compared to those receiving other types of treatments (chemotherapy or targeted therapies). Also, no correlation has been observed between the type of immunotherapy used (anti-PDL1, anti-PD1, anti-CTLA4) or between the localization of the cancer and the degree of side effect. [10,15]

The exact mechanism by which fatigability occurs in patients treated with immunotherapy is not fully understood but recent studies show that there is no correlation between the dose administered and the degree of side effect.[16] A possible explanation could be the pro-inflammatory status given by the immunotherapy, but other factors such as anaemia or muscle dysfunction are also implicated. [4] Also, some patients may develop immune-induced hypothyroidism or autoimmune anaemia causing symptoms of fatigability.[16]

The effect that immunotherapy-associated fatigue has on patients goes beyond the patient's physical ability and includes the patient's ability to self-care and participate in activities that before diagnosis and treatment provided pleasure and comfort. These should be taken into account when the clinician decides whether or not that patient is eligible for immunotherapy or whether they require interventions to prophylaxis the fatigability that may occur during treatment in order to maintain a satisfactory quality of life. [3,5]

c. Management of fatigability

Management of fatigability includes pharmacologic and nonpharmacologic methods. Regarding non-pharmacologic methods, physical activity is the most popular option. It should be specified that this does not apply to cachectic patients. Moderate exercises are recommended for patients with chronic fatigability and also thought to increase patients' quality of life. [2,17] A systematic literature review evaluated the effect that these exercises have on patients and the results were divided, as some patients reported lack of motivation, dizziness, xerostomia, accentuation of pain syndrome, which led to abandoning these exercises, while others reported feeling more energized and happier following these exercises. [18,19]

Among pharmacologic methods, the most commonly cited are methylphenidate, dextro-methylphenidate, dexamphetamines, modafinil and armodafinil, but their use in clinical practice is limited and more evidence is needed for their inclusion in guidelines. [2]

Current studies could not conclude whether exercise alone or in combination with antidepressant medication reduces fatigability more than medication alone. Also, there is insufficient evidence for improved quality of life or maintenance of long-term effects in these patients. [20]

Meta-analyses and studies have shown a small, but significant impact of aerobic or yoga-type exercise for patients suffering from fatigability, especially in the early stages of the disease. In some patients, due to advanced pathology, treatment or complications, these exercises are difficult or impossible to perform. In these situations, attention should be paid to energy conservation and rest. Psychosocial interventions, including educational or social reintegration programs can be effective. [21]

Discussion and conclusions

The studies included in this review present relevant information about fatigability as a general symptom applied in oncology as well as the impact this has on patients' quality of life. The focus was on immunotherapy-induced fatigability in oncology patients.

Immunotherapy-induced fatigue can be explained by the pro-inflammatory status given by immunotherapy, but also by related conditions. Patients' quality of life is less influenced by immunotherapy compared to chemotherapy. Current guidelines recommend the assessment of patients' fatigue and quality of life at diagnosis, but also during and after treatment. There are several methods of objective assessment of fatigue and quality of life and there is no consensus in their application. The management of this symptom includes pharmacologic and non-pharmacologic methods. Pharmacological methods are not fully studied and there is no clear recommendation in therapeutic guidelines. Non-pharmacological methods seem to be more effective than pharmacological ones and among these, aerobic or yoga exercises are the most preferred by patients.

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