Cancer-related fatigue: a review

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Summary

Cancer-related fatigue is the most prevalent cancer symptom, reported in 50%-90% of patients and severely impacts quality of life and functional capacity. The condition remains underreported and often goes untreated. Guidelines suggest screening for fatigue at the initial visit, when the diagnosis of advanced disease is made, and at each chemotherapy session, as well as the identification of treatable contributing factors such as anemia, hypothyroidism, depression and sleep disorders. Brief assessment tools such as the Brief Fatigue Inventory or the Visual Analog Scale may be appropriate in the initial scoring of fatigue severity, but the initial approach to treatment usually requires a more comprehensive assessment, education, and the determination of an individualized treatment plan. Patients with moderate or severe fatigue may benefit from both pharmacological and non-pharmacological interventions, whereas mild fatigue that does not interfere with quality of life can be treated with non-pharmacological measures alone. Non-pharmacological measures that have shown to be promising include cognitive-behavioral interventions such as energy conservation and activity management (ECAM), exercise and perhaps sleep therapy. Many other modalities may be beneficial and can be used on an individual basis, but there is insufficient evidence to promote any single treatment. Pharmacological therapies that have shown to be promising include the psycho-stimulants methylphenidate and dexmethylphenidate, modafinil (in severely fatigued patients only), and erythropoietin-stimulating agents in patients with chemotherapy-associated anemia and hemoglobin levels < 10 g/dL. Recently, our group reported impressive results with the use of the dry extract of Guarana (*Paullinia cupana*), with no significant side effects and at low cost, for the treatment of physical and mental cancer-related fatigue.

Keywords: Guarana (Homeopathy); fatigue; chemotherapy, adjuvant; neoplasms.

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Introduction

Cancer-related fatigue (CRF) is a common and treatable symptom that severely affects numerous aspects of the cancer patient's quality of life[1]. Patients report fatigue as one of the most important and stressful symptoms related to cancer and its treatment[2]. This symptom is a strong and independent predictor of the decrease in patients' personal satisfaction and quality of life[3]. Although the current recommendations suggest a customary investigation for CRF[4], this symptom remains underreported and generally does not receive adequate treatment for several reasons[2], which will be discussed in this review.

The estimated prevalence varies widely, reflecting a diversity of populations in which the symptom has been studied. Similarly, studies have assessed the subjective nature of such condition and the several methods employed in its diagnosis. Around 50% to 90% of cancer patients experience fatigue in general[5-9], with the latter figure representing patients submitted to anti-cancer treatment such as chemotherapy (CT) and radiotherapy (RT)[7]. Fatigue can be a symptom that persists for months to years in this population after CT; in one study, a third of the patients that had been cured from cancer still experienced fatigue five years after the end of treatment[10] and in another study, fatigue was referred by 60% of patients with Hodgkin's disease that had been disease-free for five years.

According to the recommendations of the National Comprehensive Cancer Network (NCCN), cancer-related fatigue is defined as a persistent symptom, a subjective feeling of physical, emotional or cognitive tiredness or exhaustion related to cancer or its treatment that is not proportional to the recently performed activity, and which can interfere with the usual patient's functional capacity[4].

The pathogenesis of cancer-related fatigue has not been thoroughly described and several mechanisms can contribute to its development[11]. Among the described mechanisms are the effects of cancer and its treatment on the central nervous system, muscle energetic metabolism, sleep, circadian rhythm[12], inflammatory and stress mediators[13], immune system activation[14,15], hormonal alterations related the effects on hypothalamus-pituitary axis, early menopause[16], or androgen-deprivation in men[11-22].

CRF is very common in patients submitted to RT[23] and in a large number of patients receiving biological modifiers, such as Interferon and Interleukin 2[24]. Modifiable and reversible causes that can collaborate to the development of fatigue, such as hypothyroidism[25,26], depression and anemia[27] must be always investigated and treated.

Diagnosis and approach of cancer-related fatigue

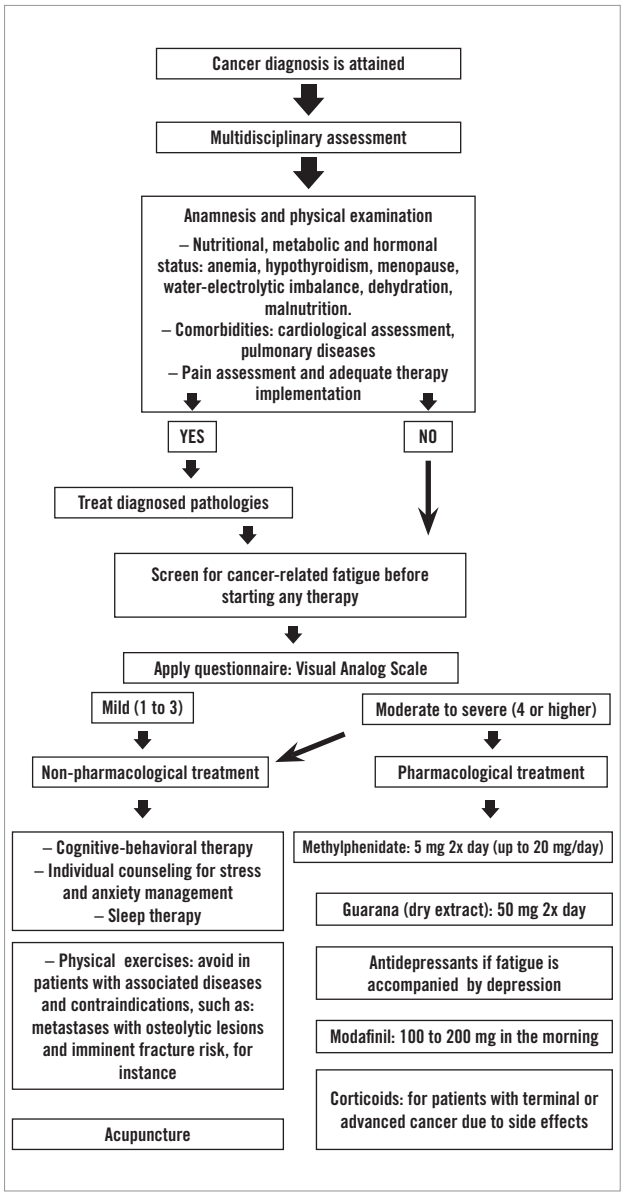
The NCCN currently suggests that all patients with cancer must be investigated for cancer-related fatigue during the initial consultation, when the diagnosis of advanced disease is attained and at each visit for CT administration. Although the established guidelines are clear, there are impediments related to the diagnosis of fatigue and the patients' reports on symptoms related to their routine that can be significantly altered. Physicians sometimes have insufficient knowledge on fatigue and its treatment or can underestimate its impact on patient quality of life, whereas patients might consider fatigue symptoms as a an inevitable consequence of cancer treatment, among the several other side effects to which they are submitted when start treatment with certain medications.

The patient's major objective of attaining cure or remission of the disease can corroborate the fear of reporting symptoms and receiving a less aggressive treatment that can result in a lower chance of cure. Side and adverse effects become a bridge through which the expected clinical improvement are achieved, whereas important symptoms, such as fatigue, end up unreported and untreated[6,28,29].

Several instruments used in the investigation and approach of cancer-related fatigue management have already been validated, but none of them is a sole diagnostic modality. The diagnosis can be achieved through a combination of clinical history and physical examination, relevant laboratory assessment, information obtained from family members or caregivers that are part of the patient's daily life and the use of standardized measures to assess fatigue (Figure 1). The simplest (fastest and easiest) among these measures are the Visual Analog Scale (VAS) and the Brief Fatigue Inventory (BFI)[4,16,30]. The FACIT-F (The Functional Assessment of Cancer Therapy Instrument)[31] and MFSI-SF (Multidimensional Fatigue Symptom Inventory-Short Form)[32] questionnaires have been validated in several languages; however, there are some other questionnaires that are not so detailed and therefore, not so often employed in clinical research.

The diagnosis of cancer-related fatigue is usually achieved after the exclusion of reversible or treatable causes of fatigue, such as hypothyroidism, anemia, sleep disorders, pain, emotional stress, menopause, medication adverse effects, electrolytic disorders or pathologies, such as heart failure, myopathies and pulmonary fibrosis, for instance[33,34]. Once these potential contributing factors are evaluated, the patients must be investigated through a brief and self-explanatory questionnaire such as the VAS or the BFI[34]. Patients with moderate or severe fatigue can benefit from an association of pharmacological and non-pharmacological treatments, whereas those with mild fatigue, which does not interfere with their quality of life, can receive non-pharmacological treatment only[4]. The follow-up of disease severity and impact on quality of life, as well as patient's functionality must be carried out often. CRF evaluation and classification must be the first step in the clinical interpretation of cancer patients, so that an adequate treatment strategy can be implemented.

Figure 1 – Algorithm for diagnosis and treatment of cancer-related fatigue.



CRF evaluation and classification should be the first step in the clinical assessment of cancer patients for the implementation of an appropriate treatment strategy. Reassessment regarding the patient's treatment progress can be carried out through the questionnaires used for CRF screening and thus, a behavior pattern of the fatigue is established, providing differentiated treatment options for different patients with different types of tumors and distinct disease stages and treatment. Patients with mild fatigue can start non-pharmacological therapies and be reassessed during treatment. In case of persistent fatigue or worsening of the initial condition, combined therapy is indicated. The combined therapy is also indicated for patients diagnosed with moderate or severe fatigue at the diagnosis.

Non-pharmacological treatment

The initial approach of CRF requires a comprehensive view and understanding by patients of their own symptoms, which normally requires the establishment of individualized treatment. Expectations regarding treatment must be clear and agreed so that there are no frustrations or promises of improvement bigger than what the treatment can offer, which will guarantee the success of the therapy instituted for each patient[34].

Most patients with fatigue will benefit from a non-pharmacological treatment. A review of 77 randomized controlled studies involving non-pharmacological treatment for CRF showed benefits obtained with the following measures: cognitive-behavioral therapy, exercises, hypnosis, relaxation and psychoeducation for fatigue[35]. The most relevant and effective non-pharmacological treatments to date will be described next.

Exercises

According to the most recent recommendations, the most effective measure against CRF is the regular practice of physical exercises. However, only a minority of patients are advised on how to implement an exercise routine that is effective and adequate for daily life. Studies on physical exercises in patients with fatigue consistently showed their benefits in fighting fatigue, improving quality of life and functional capacity, reducing stress and improving several other symptoms[36-50]. Regular physical exercises increase functional capacity and thus, decrease the necessary effort to perform activities of daily living (ADL)[51]. The type of exercise is not as important as the simple fact of performing a physical activity[37,52]. Allowing the patient the possibility of choosing the best exercise that can be adapted to his or her routine, and to give the information and incentive to accomplish these activities turn out to be essential to attain excellent results[50]. A recent meta-analysis that assessed behavioral interventions and physical exercises for CRF evaluated 56 studies and found statistically significant benefits with both interventions[53].

Cognitive-behavioral therapy

Many patients with CRF can benefit from some type of psychological intervention and a number of modalities have been studied in several different populations. Interventions such as group therapy[54,55], individual counseling[56], stress reduction with relaxation training[57-60], formal cognitive-behavioral therapy[61-64], education for fatigue management[65], and support therapies[66] have shown promising results.

In a systematic review of 27 studies, the data demonstrated that interventions focused specifically on fatigue are more effective than nonspecific interventions[67]. For instance, the Strategy of Energy Conservation and Activity Management (ECAM) was studied in 396 patients with

cancer and fatigue. The patients were randomly distributed to receive advice on diet and nutrition or ECAM, in addition to the monitoring of several activities and levels of fatigue attributed to these activities. A small benefit was observed in the treatment of CRF in the group treated with ECAM[68].

Sleep disorders

Difficulty to sleep is a frequent problem for cancer patients, which might be directly related to the pathology, the consequences of treatment[69], or the emotional stress caused by the treatment. Benefits have been demonstrated with sleep hygiene therapy, which is simply a compilation of practices that try to introduce different habits before bedtime into the life of patients and are related to the improvement in functional capacity to perform ADL, sleep quality parameters[69], and fatigue improvement in randomized controlled clinical trials[70]. However, an important randomized study with 219 patients with breast cancer did not show any benefits regarding individualized sleep quality improvement therapy in comparison to controls when the CRF was assessed in these patients[71]. Therefore, it is clear that behavioral interventions improve sleep quality; however, the impact of these therapies on the treatment of CRF is yet to be clarified.

Alternative and complementary medicine

The possible benefits of alternative treatments for CRF have yet to be elucidated. Two clinical studies have suggested the benefits of acupuncture in the treatment of fatigue. In the first study, 37 patients with persistent fatigue were treated with 6 to 8 sessions of acupuncture, after which they demonstrated a statistically significant improvement at the BFI, when compared with their baseline assessments. In another study, 47 patients with fatigue were randomized and received acupuncture, acupressure or sham acupuncture. A significant benefit was found to be favorable to acupuncture when compared to acupressure and sham acupuncture[72].

Pharmacological treatment

Patients with moderate to severe CRF can benefit from pharmacological treatments together with non-pharmacological treatments, especially if quality of life or the daily activities are impaired as a direct consequence of these symptoms[73].

Methylphenidate/dexmethylphenidate

Psychostimulants have shown to be a promising option that will be part of a multimodal therapy for the treatment of CRF. Several small studies have suggested that methylphenidate improves fatigue[74-77]. Additional benefits of this medication have been reported regarding the following symptoms: anxiety, appetite, nausea, pain and drowsiness[74]; moreover, cognitive and functional capacity improvement was observed in studies with 12 patients with melanoma[76] and 30 patients with brain tumors[78].

Randomized clinical studies have been carried out with this medication. A small double-blind crossover study suggested that methylphenidate would potentiate the analgesic effects of narcotics used by the patients and would decrease the drowsiness caused by these medications[79]. However, negative results were found in a randomized study with 112 patients that had fatigue and cancer and received methylphenidate or placebo for 7 days. A nurse contacted the patients daily by telephone until day 8 and on each day, fatigue was measured through the FACIF-F (primary outcome). After this period, the patients could choose to receive four additional weeks of methylphenidate. A significant benefit in the treatment of fatigue was observed in both groups, the one that received placebo and the one that received methylphenidate, with no difference between the groups. When compared with the patients that received placebo, a significant number of those that received methylphenidate for eight days did not choose to receive this medication after this period, as they could have chosen to do, if they had perceived symptom improvement during the time when they were receiving the medication. This study recalls the therapeutic power of the placebo effect and the role of non-pharmacological interventions, such as telephone calls made by a nurse and the comfort that simple and effective measures can have as therapeutic action against fatigue[80].

Dexmethylphenidate was assessed in a randomized controlled double-blind phase II study that consisted of assessment of 154 patients with fatigue that received at least four cycles of CT for treatment of breast and ovarian cancer, predominantly. A significant improvement in CRF was observed in the arm that received treatment when compared to the placebo group; however, there were more adverse effects and medication withdrawal in the group that received dexmethylphenidate[81]. A meta-analysis evaluating both studies mentioned above, however, concluded that methylphenidate or dexmethylphenidate was more effective than placebo for the treatment of CRF[82].

Modafinil: Benefits have been observed regarding the action of modafinil on the central nervous system of patients with CRF in a randomized, placebo-controlled study with 642 patients published as an abstract. Patients reported fatigue through a scale that scored the level of fatigue between 1 and 10. Although there was a significant difference between the two study arms in favor of modafinil, the improvement was much more significant in patients that had severe fatigue at baseline[83]. Two non-randomized pilot studies suggested a possible benefit of modafinil in the treatment of CRF[84,85].

Erythropoietin-stimulating agents

Many patients with cancer develop anemia as a consequence of the malignity, treatment or even the comorbidities that they previously presented. Anemia is one of the main reversible causes of CRF[27]. When the patient has anemia, an investigation on the possible causes must be carried out to evaluate the presence of iron, B12 or folate deficiency, hemorrhage or hemolysis. In the absence of a cause that can explain the anemia or if it persists after the treatment of the underlying cause, erythropoietin-stimulating agents (ESAs) and blood transfusions must be considered. Recommendations regarding the use of ESAs were published by the American Society of Oncology (ASCO) and the American Society of Hematology (ASH) in 2002 and updated in 2007[86].

The use of epoetin and darbepoetin for anemia treatment associated with CT that is "close to or below 10 g/dL" is recommended to increase hemoglobin levels and decrease the number of transfusions. It has been described that blood transfusions are a therapeutic option in several clinical situations. Among the information mentioned by the recommendations is a meta-analysis, which showed that the highest evidence of benefit regarding quality of life and lowest need for blood transfusions is found in the group that received basal epoetin and hemoglobin ≤ 10 g/dL[87]. According to a systematic review, there was no statistically significant difference between the use of epoetin and darbopoetin[88]. Iron deficiency diagnosis and treatment are recommended, when detected[86].

A concern regarding the use of ESAs lies in the increased risk of thromboembolic events when these medication are used, which is supported by a meta-analysis available at the Cochrane database of 2006[89]. In spite of the lower quality of the studies included in this database, according to an Update Committee, caution is recommended when using ESAs in patients considered to be high-risk for the development of thromboembolic events, especially regarding patients with multiple myeloma treated with thalidomide or lenalidomide[86].

Additional concerns have arisen, as two clinical placebo-controlled phase II studies published in 2003, among others published after that, showed that there is evidence related to higher mortality and less local regional progression-free time in patients treated with ESAs. More than 50% of the trials were carried out in patients that were not receiving CT, in most of which a hemoglobin level > 12 mg/dL was the objective and patients with hemoglobin levels > 10 mg/dL before the clinical approach were not excluded. Although this information made the US Food and Drug Administration (FDA) add a restriction warning to the prescription of epoetin and darbepoetin in March 2007, the aforementioned Update Committee found it difficult to interpret and apply the recommendations to clinical practice. The NCCN recommendations say that the use of ESAs must be avoided in patients with anemia non-related to CT and that these drugs must be sued only in patients with hemoglobin levels < 10 mg/dL, aiming at a level that does not exceed 12 mg/dL[73,86]. The same group mentions that there is enough evidence to justify the use of ESAs in patients with anemia associated with a low risk of myelodiaplasia[86].

Guarana (*Paullinia cupana*)

Guarana (*Paullinia cupana*) is a plant native to the Amazon basin, cultivated in Brazil and Venezuela, of which energetic and tonic properties have been known by the Maues natives, in Amazonas and also in Bahia. They used it before battles and during long walks to increase resistance to thirst, heat and fatigue. It has been used as an "alternative" medicine for several diseases such as headaches, indigestion, kidney dysfunction, muscle pain, menstrual cramps, depression and fatigue; it has been recently tested in a non-oncologic population and showed to be beneficial regarding the cognitive performance and mood improvement, being well-tolerated at a dose of 75 mg[90].

The energetic and tonic properties of Guarana are due mainly to the methylxanthines present in its seeds, predominantly caffeine (trimethylxanthine). Caffeine, at the usually consumed doses, acts by blocking the action of endogenous adenosine in its receptors, A1 and A2A. Adenosine is a neurotransmitter or neuromodulator that causes sedation by inhibiting the release of several neurotransmitters, such as norepinephrine, dopamine, acetylcholine, glutamate and GABA[91]. Caffeine, theobromine and theophylline are called methylxanthines and are part of a group of compounds sometimes classified as true alkaloids (purine alkaloids), characterized by their anti-inflammatory activity.

In two studies carried out by our group, the dry extract of Guarana administered at a dose of 75 mg once a day, to patients undergoing RT and 50 mg twice a day, to patients undergoing CT for the treatment of breast cancer, showed a positive and significant result in the treatment of mental and physical fatigue in these patients. Therefore, Guarana has shown to be a promising option, with no side effects and affordable to our population[92].

Other pharmacological agents

Several other pharmacological treatments have been studied for the treatment of CRF. The use of corticoids has resulted in a decrease in depression levels and analgesic consumption, as well as an increase in appetite and daily activities as shown in a small clinical, randomized placebo-controlled trial with 14 days of oral methylprednisolone in patients with end-stage cancer[93]. However, larger studies involving the prolonged use of corticoids in other populations have not been carried out to date. Donepezil was studied in a randomized trial that did not show any

benefit when compared to placebo in patients that had CRF[94]. Studies have not yet demonstrated any significant benefit of using dextroamphetamine[95], multivitamins[96] or antidepressants[97,98] in the treatment of fatigue. In a meta-analysis that evaluated the use of corticoids and paroxetine, neither of the two substances showed a better result than the placebo group in the treatment of CRF[82].

Combined approach in the treatment of cancer related fatigue

Patients can benefit from a multimodal approach consisting of several treatment strategies and the most prominent example of this perspective carried out in practice is the Cancer-related Fatigue Clinic established in 1998 by M. D. Anderson Cancer Center. This clinic aims at improving patients' quality of life through fatigue decrease. The project's objective is to integrate the physical assessment of fatigue to the development of a treatment plan that includes pharmacological and non-pharmacological measures, as well as providing education aiming at family and caregiver comprehension regarding the behavior of patients that have fatigue. Recently, the results of these interventions carried out between 1998 and 2005 have been published. Before the initial assessment, the patients were submitted to laboratory evaluation that included electrolytes, red blood cells and thyroid hormones. The patients also answered a group of questionnaires that evaluated fatigue. At the initial consultation, the doctors defined and individualized the treatment plan. The treatment modalities could include the treatment of reversible causes of fatigue or comorbidities; recommendations and discussions on fatigue, including the possibility of access to literature related to the theme, among other non-pharmacological and pharmacological measures offered as treatment modalities. Fatigue was assessed using the BFI as severe (score of 7-10) or non-severe (0-6), being subsequently subdivided in moderate (4-6) and mild (0-3). The primary objective was to reduce the fatigue score according to the implemented measures to reach such level of symptom improvement. The most commonly implemented measures were ECAM (98.5%), sleep hygiene (97%), physical exercises (95%), relaxation techniques (27%), use of antidepressants (27%), analgesics (25%), stimulants (22%), anxiolytics (17%) and nutritional counseling (10%)[34].

Of more than 260 patients, 47% initially reported severe fatigue, 42% reported moderate and 10% mild fatigue. Only 54% of the patients returned for a second scheduled consultation, and therefore, a loss of follow-up might have affected the results. Among the patients that were followed at a second visit, 59% achieved a decrease in fatigue of a least one category of the scores measured by the BFI. The generalization of results to other populations is uncertain, as many patients had requested a previous consultation at this clinic with the objective of treating their fatigue; most of the patients were Caucasians females, who were motivated to treat their symptoms. The most common malignant diseases found in these patients were breast cancer and hematological diseases[34].

The algorithm shown in Figure 1 illustrates the approach used in patients with CRF.

Final considerations

CRF is one of the most prevalent symptoms in cancer patients, being reported by 50% to 90% of all patients and severely affecting quality of life, in addition to decreasing the daily functional capacity of patients. Fatigue symptoms remain underreported and are not adequately treated. The current recommendations indicate the investigation of fatigue at the patient's initial consultation, when a diagnosis of advanced disease is achieved and at each visit for CT administration, as well as the identification of treatable causes and factors that contribute to the manifestation of this symptom.

Standardized questionnaires must be used, such as the BFI and the VAS, as they are appropriate for the initial classification of fatigue. However, the initial approach of this symptom requires more than applying a questionnaire. A broad approach must be carried out with general recommendations on fatigue, in addition to the establishment of an individualized therapeutic approach plan. Patients with moderate or severe fatigue can benefit from both pharmacological and non-pharmacological measures, whereas those with mild fatigue that does not affect quality of life can be treated with non-pharmacological measures as the only therapeutic approach.

The non-pharmacological treatment shows to be promising with measures such as cognitive-behavioral therapies (ECAM), physical exercises and maybe sleep therapies. Other treatment modalities can be beneficial and used as individualized management; however, there scarce evidence to affirm that symptom improvement can be achieved with other therapy types.

The pharmacological treatment has shown promising results that include the use of psycho-stimulants such as methylphenidate and dexmethylphenidate, modanafil (in patients with severe fatigue) and erythropoietin-stimulating agents in patients with CT-related anemia and hemoglobin < 10 mg/dL. Additionally, corticoids can be prescribed to patients with terminal disease and severe fatigue.

As there is no consensus regarding the cost-benefit of investing in clinical practice specialized only in CRF, a better treatment can be offered through a multimodal and multidisciplinary approach in a clinical practice that is attentive to symptom improvement or worsening in these patients, with professionals that are aware of CRF patients' symptoms. Each case must be individually evaluated and initially classified according to a scale of fatigue, anamnesis and physical examination, considering the patient's

limitations and comorbidities and to what extent these symptoms are related to cancer and its treatment or if they were already present throughout the life of these patients due to other pathologies or activities developed by them. The fatigue will be present not only due to the disease, but also due to treatment given to the patient, which can cause or aggravate the fatigue that had manifested previously. The limitations of each patient must be reassessed and discussed, so that the best treatment can be determined according to the patient's perspective on the disease and the evolution of the pathology and its treatment.

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