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Fatigue among patients with brain tumors

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Practice points

- Cancer-related fatigue is extremely common among patients with malignant gliomas and considered one of the most distressing symptoms in this population.
- Fatigue is a subjective experience that should be systematically assessed using patient self-reports at regular visits during and following treatment.
- The most important risk factor for fatigue among patients with brain tumors appears to be poor performance status.
- More research is needed to understand the pathophysiology of fatigue in this population.
- Fatigue has found to be a strong independent prognostic factor for survival among patients with recurrent high grade glioma (incremental prognostic value beyond performance status).
- No clear evidence-based guidelines exist regarding the use of pharmacologic agents in management of fatigue for patients with brain tumors. There is some evidence regarding the role of stimulants for patients with severe fatigue but further research in this area is needed.
- Exercise, which is the well-supported level 1 evidence to mitigate fatigue among patients with solid tumors, has not been subjected to rigorous randomized trials in this setting.

Fatigue is a ubiquitous and an extremely distressing symptom among patients with brain tumors (BT), particularly those with high-grade gliomas. The pathophysiology of cancer-related fatigue (CRF) in the context of patients with BT is multifactorial and complex, involving biological, behavioral, medical and social factors. The etiology of CRF in the general oncology population is pointing to the role of inflammatory cytokines as a key factor in the genesis of CRF, but this research is currently limited in the setting of BT. CRF should be screened, assessed and managed according to clinical practice guidelines. Fatigue has recently emerged as a strong, independent prognostic factor for survival that provides incremental prognostic value to the traditional markers of prognosis in recurrent high-grade gliomas. Therefore, strategies to treat fatigue warrant investigation, not only to improve the QOL of a group of patients with often limited life expectancy, but also possibly to optimize survival.

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KEYWORDS

• brain tumor • cancer-related fatigue • fatigue

Background

Malignant brain tumors (BT) are devastating illnesses that not only carry a dismal prognosis, but can profoundly affect one's function and quality of life. An estimated 23,180 primary malignant BT are expected to be diagnosed in the USA in 2015 [1]. Primary malignant BT includes all tumors of the brain, CNS, pituitary glands and olfactory tumors of the nasal cavity. Treatment of BT often includes partial or full surgical resection, chemotherapy, and/or radiation therapy [2]. Overall, the 5-year survival rate in the USA following diagnosis of BT is 34.2% [3]. The 5-year survival rates for the most common histologic subtypes, anaplastic astrocytoma and glioblastoma, are only 27 and 5%, respectively [1].

Prognosis varies on a number of factors including age, histology and molecular markers, location of the tumor and completeness of the resection [4]. Increasingly issues related to health behavior, functional status and patient-reported outcomes are noted to have significant implications on prognosis [3].

Quality of life (QOL) is an important area of clinical neuro-oncology and encompasses the multidimensional wellbeing of a person [5]. Patient-reported outcomes, including measures of QOL such as fatigue and other symptoms, are routinely used as secondary outcome measures in clinical trials and are increasingly used to help predict patient outcomes, including potentially survival. As in many other solid tumors, fatigue is frequently reported as the most common and distressing symptoms in BT patients throughout the disease trajectory, particularly patients facing high-grade gliomas [6–8].

Cancer-related fatigue (CRF) is defined as “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” [9]. CRF differs substantially from so-called ‘healthy’ or ‘normal’ fatigue as it tends to be more severe, more distressing and less likely to be relieved by rest. Researchers have reported that greater than 80% of patients with BT experience fatigue during therapy [10]. The incidence of CRF may approach 89–94% among patients with recurrent malignant gliomas, when measured using validated and reliable instruments for this population [8]. Among patients with low-grade glioma, 39% reported fatigue up to 8 years after completion of therapy [11].

Fatigue has even been rated as being more troublesome than other symptoms, such as pain or nausea and vomiting, which can generally be managed by medications [12]. CRF can also have profound psychosocial, and economic impacts [13]. Despite the importance of fatigue in quality of life among patients with malignancy, it is well established that fatigue has been under-reported, underdiagnosed and undertreated [14].

QOL is a prognostic factor for survival among patients with other solid tumors [15]. QOL is frequently impaired in BT patients, due to a multitude of factors including motor impairments, insomnia, communication deficits and existential concerns [16]. In BT patients, unlike other solid tumors, QOL measures do not add to the prediction of survival beyond traditional measures of prognosis which include age, tumor grade and histology, number of prior progressions and performance status [17,18]. However, fatigue, when measured independently is emerging as a significant, independent prognostic factor for survival in high-grade glioma [6,19–20]. Therefore, understanding CRF in the context of brain tumors is not only critical for optimization of quality of life among patients with an extremely limited lifespan, but it may have implications for survival as well.

The primary purpose of this review is to demonstrate the current state of the literature on BT and fatigue. This was accomplished by reviewing all relevant publications through PubMed using a combination of the keywords ‘brain tumor’, ‘fatigue’, ‘cancer-related fatigue’ and the associated MESH terms through 1 August 2015. We will discuss the implications of fatigue among patients with brain tumors, review potential etiologies and hypotheses on the pathophysiologic mechanisms of fatigue, highlight available assessment tools and examine treatment strategies that involve both pharmacologic and nonpharmacologic interventions. The vast majority of research evaluating CRF has occurred among patients with breast cancer and other cancer patients. Therefore, the discussion that follows is extrapolated from studies evaluating patients without brain tumors, although evidence in the BT population is cited whenever possible.

Pathophysiology

The pathophysiology underlying CRF, like other cancer symptoms, is complex and not completely understood. Fatigue is rarely an

isolated symptom among patients with cancer. Other common symptoms in the BT setting, such as pain, emotional distress, sleep disturbances, deconditioning, depression and anorexia can play an important role in the genesis of fatigue [21]. Indeed, a study evaluating issues related to quality of life in patients with BT found inter-related symptoms of depression, fatigue, emotional distress and existential distress, which affected 50% of the patients in this sample [22]. Treatment of BT (i.e., radiation therapy and chemotherapy) and other concomitant medication, such as corticosteroids and anticonvulsants, often cause additional symptoms that limit functional status and overall QOL [10,23]. A variety of demographic, medical, psychosocial, behavioral and biologic factors may influence the genesis of CRF in patients with BT (Figure 1).

One recent study evaluated risk factors for fatigue severity among patients with primary BT. Armstrong *et al.* found that among 201 BT patients, those who were women, had active disease, or poor performance status were at increased risk for moderate-to-severe fatigue [2]. Performance status was the strongest predictor of CRF: patients with low performance status (KPS) were almost six-times more likely to report moderate-to-severe fatigue [2]. As expected, other symptoms including, pain, distress, sleep dysfunction and physical weakness were also associated with fatigue [2].

Accumulating evidence highlights the role of inflammatory processes in the genesis of CRF [24,25]. Investigators have proposed that tumors and treatments used to eliminate them activate the proinflammatory cytokine network, leading to symptoms of fatigue via cytokine signaling in the CNS [26]. In addition, the inflammatory response can persist for months or years after treatment is completed, which correlates to persistent levels of fatigue even after active treatment has ended [27]. It is important to emphasize that factors other than cancer and its treatment can influence inflammatory activity including psychological, behavioral and biological factors [24]. This may explain why all these variables may ultimately play a role in the expression of CRF. More research is needed to evaluate the role of these inflammatory cytokines and the biologic mechanisms of symptoms including fatigue in the brain tumor setting [28]. Table 1 outlines key articles involving the emerging role of inflammation in cancer-related fatigue and their results in a variety of cancer types, including BT.

Assessment of cancer-related fatigue among patients with brain tumors

Ultimately, fatigue is a symptom that is a subjective experience. Therefore, validated, reliable, assessment tools are paramount in appropriately and systematically assessing this challenging clinical problem. Since fatigue is commonly associated with other cancer symptoms, a multisymptom assessment tool is often helpful to identify fatigue. Some of these global multi-symptom assessments can help identify other associated and contributing symptoms such as poor sleep, poor appetite or depression. These tools include the Edmonton Symptom and Assessment System, MD Anderson Symptom Inventory or Rotterdam Symptom Checklist. More specific tools for fatigue can look at function and what parts of quality of life are affected including the following (Table 2):

- A verbal rating scale (VRS), visual analog scale (VAS) and numerical rating scale (NRS) (as is used in the Edmonton Symptom Assessment System) of the linear analog scale are commonly used and recommended by the National Comprehensive Cancer Network as the first phase of screening every patient for the presence of fatigue [9]. For example, on a 0–10 numeric scale (zero = no fatigue and 10 = worst fatigue imaginable), mild fatigue is indicated as a score of 1–3, moderate fatigue is 4–6 and severe fatigue is 7–10. This may be the most pragmatic tool used in a busy clinical setting.
- Brief Fatigue Inventory. This is a short, easy to use, validated in mixed cancer types and includes questions about general activity, relationships and overall QOL [38,39].
- Functional Assessment of Cancer Therapy – Fatigue Scale. This uses a 5-point Likert scale and has been validated with patients with various cancer types. It includes a 13-item fatigue subscale, which is reasonable in length [40,41].
- Multidimensional Fatigue Inventory [42,43]. This has been validated in mixed cancer types and has a short form that is reasonable in length.

Treatment of cancer-related fatigue

A number of nonpharmacologic and pharmacologic measures can be used to try to mitigate fatigue among patients with BT. Most of the

Figure 1. Demographic, medical, psychosocial, behavioral and biologic factors may influence the genesis of cancer-related fatigue in patients with brain tumors.

recommendations that follow are based on expert panel recommendations or based on evidence for other cancer types.

Noncancer comorbidities such as cardiac, pulmonary and renal dysfunction may contribute substantially to fatigue in the patient with cancer and needs careful assessment. Review of current medications is essential. Many medications used in the BT setting can contribute to the worsening of fatigue, including anti-epileptics, opiate analgesics, anti-psychotics, anti-emetics and muscle relaxants. Reducing the dosage, changing the timing or eliminating these medications entirely if possible can be helpful [9,49]. Moreover, it is important to determine if related and treatable symptoms or conditions are present. Chronic pain and fatigue often present together and optimization of analgesic medications may be useful. Depression can often be associated with fatigue and is a common complication in patients with BT [50]. The evidence for the use of anti-depressant agents in the setting of depression in cancer has been mixed [51–53] and high-quality randomized trials of antidepressant treatment efficacy are lacking in the setting of BT. A Cochrane review of two double-blinded placebo-controlled studies failed to show any benefit with the use of paroxetine for CRF,

although it may be beneficial for depression [54].

Sleep disturbances are a neglected problem in oncology and can be a significant factor related to CRF [55]. Reducing or eliminating medications that can cause insomnia and restlessness, such as corticosteroids, may be useful. Nonpharmacologic strategies can be valuable, and randomized trials have supported cognitive-behavioral therapy and mindfulness-based stress reduction programs for patients with cancer [56,57]. However, the efficacy of pharmacologic therapies in reducing both insomnia and CRF is lacking in BT and other solid tumors.

Psychotherapy such as cognitive-behavioral therapy (CBT) to alter the way people behave and cope with fatigue and stress may be beneficial [58]. CBT can be delivered in a group or individual setting and has found to be effective [59]. Psychoeducational and lifestyle management interventions, such as energy conservation and activity management (ECAM), have been studied in multiple randomized controlled trials demonstrating a positive effect on fatigue outcomes [60]. The largest, multisite randomized clinical trial evaluating ECAM for patients with cancer established a significant reduction in CRF for the participants receiving the experimental intervention in comparison to the control group [61]. Although

Table 1. The role of inflammation in cancer-related fatigue.

Study (year)	Cancer type	Key findings	Ref.
Bower <i>et al.</i> (2002)	Breast	Circulating markers of inflammation stimulated cytokine production in participants with persistent fatigue	[29]
Bower <i>et al.</i> (2011).	Breast	Elevated sTNF-RII was found to be associated with persistent fatigue, especially in those who underwent chemotherapy	[30]
Alexander <i>et al.</i> (2009)	Breast	Participants with elevated levels of CRP, suggestive of low-grade inflammation, met the criteria for cancer-related fatigue syndrome	[31]
Orre <i>et al.</i> (2009)	Testicular	Patients 5–20 years post-treatment with persistent fatigue had higher levels of IL-1RA and CRP	[32]
Dantzer <i>et al.</i> (2008)	Review	Comprehensive review pertaining to systemic inflammation and illness	[25]
Carmichael <i>et al.</i> (2006)	Mouse study	Increases in proinflammatory cytokines caused mice to have a decreased exercise tolerance and to fatigue more quickly	[33]
Bower <i>et al.</i> (2005)	Breast	Dysregulation of the HPA axis with flattened fluctuation of cortisol is present in those with CRF	[34]
Sephton <i>et al.</i> (2000)	Breast	Low natural killer cell activity is associated with flattened fluctuation of cortisol	[35]
Monk <i>et al.</i> (2006)	Breast	Patients who received a TNF- α decoy receptor with a docetaxel (known to cause fatigue), were able to receive more docetaxel and experienced less fatigue	[36]
Armstrong <i>et al.</i> (2010)	All primary brain tumors	There is a relationship between fatigue and other concurrent symptoms, such as: pain, distress, drowsiness and weakness. Symptom clusters such as this may share a biologic mechanism such as cytokine administration or production	[2]
Mantovani <i>et al.</i> (2010)	All solid tumors	COX-2 inhibitor use improved cancer cachexia, circulating cytokines and fatigue	[37]

the inclusion criteria included individuals undergoing chemotherapy, radiation and status post surgical intervention, they did not include individuals with brain tumors [61].

The evidence is limited to support complementary therapies such as qigong, hypnosis, music therapy, Reiki/therapeutic touch and massage as treatments for general CRF. Several recent randomized trials have demonstrated that yoga was effective in reducing CRF, although most of these trials were conducted in women with breast cancer [62,63]. A recent meta-analysis of seven acupuncture studies concluded that while acupuncture may show promise, only two out of seven had significant reductions in fatigue [64,65].

Exercise and physical activity continue to demonstrate the strongest evidence (level 1 evidence) on the reduction of CRF among all nonpharmacological interventions [60,66,67]. Although the largest meta-analysis to date included a few studies involving patients with solid brain tumors, limited research continues to exist on the correlation between exercise and CRF for patients with brain tumors [68,69]. Multiple evidence-based exercise and activity guidelines have been established and continue to emerge for specific cancer populations, however only two case studies exploring the effects of exercise and potential guidelines for this patient population have been recently published [60,66,70,71].

There are a number of pharmacologic interventions which may be effective in the treatment of fatigue in the cancer setting. Neurostimulants, in particular methylphenidate, have also been studied in multiple placebo-controlled trials in general cancer patients with mixed results [72,73]. In the brain tumor population, there have been several uncontrolled studies of neurostimulants with encouraging results on fatigue [74–77]. However, placebo-controlled studies on the use of neurostimulants in primary brain tumor patients specifically has also yielded mixed results including studies during radiation treatment [78]. A study of armodafinil in primary brain tumor patients undergoing radiation therapy found no overall significant effect on CRF. However, when the subgroup of patients who had higher levels of fatigue at baseline was analyzed, significant improvements were found [79]. However, this study was not powered to detect differences in subgroups, which was a limitation. A study of modafinil found no significant differences in fatigue of primary brain tumor patients [80]. Another study of methylphenidate and modafinil found improvements in fatigue; however, those improvements were not statistically significant [75].

A number of strategies have been used to try to reduce inflammation in hopes of treating general cancer fatigue. Studies of anti-inflammatory agent studies in general cancer patients, such as

Table 2. Tools for assessing cancer-related fatigue.

Study (year)	Cancer type (n)	Assessment tool(s)	Key findings	Ref.
Mendoza <i>et al.</i> (1999)	All types (305)	Brief Fatigue Inventory (BFI)	The BFI is a reliable measure for assessing fatigue severity	[38]
Mystakidou <i>et al.</i> (2008)	Incurable cancer (102)	BFI-Greek	The BFI is a valid research tool for assessing CRF in Greek cancer patients	[39]
Stone <i>et al.</i> (2000)	Outpatients with cancer (576)	Functional Assessment of Cancer Therapy- Fatigue (FACT-F) [Investigator designed]	Fatigue was reported as 'Somewhat' or 'very much' in 58% of patients. Fatigue affected patients significantly more than any other reported symptom. Fatigue was reported to be not well managed by 33% of patients with the symptom; the most common advice for fatigue was 'rest and relaxation'	[40]
Yellen <i>et al.</i> (1997)	Fourteen anemic oncology patients and five oncology experts	Development of the FACT-F and FACT-anemia	The FACT-F and FACT-Anemia are useful measures of quality of life in cancer treatment. The Fatigue Subscale may be used as a very brief, but reliable and valid measure of fatigue	[41]
Lin <i>et al.</i> (2009)	Not cancer- chronically unwell patients (783)	Multidimensional Fatigue Inventory (MFI-20)	The MFI-20 is a valuable tool for assessing fatigue in chronically unwell and well populations. The MFI-20 could also serve as a diagnostic tool in fatiguing illnesses	[43]
Huang <i>et al.</i> (2010)	Breast cancer survivors, during/after endocrine therapy (371)	11-point visual analog scale	60% had experienced or were experiencing fatigue during endocrine therapy	[44]
Spratt and Sakae (2012)	Oropharyngeal carcinoma, undergoing radiation therapy (87)	12-point visual analog scale	The average fatigue score at the time of completion of therapy up to 1 year post-RT was significantly worse than baseline	[45]
Okuyama <i>et al.</i> (2000)	All types (307)	Cancer Fatigue Scale	CFS is a brief (15 item), valid and feasible measure of fatigue for cancer patients	[46]
Stein <i>et al.</i> (1998)	Breast cancer (in treatment) (275)	Multidimensional Fatigue Symptom Inventory (MFSI)	The 83-item MFSI was designed to assess global, somatic, affective, cognitive and behavioral symptoms of fatigue. This inventory may be useful in identifying patterns of fatigue	[47]
Alexander <i>et al.</i> (2009)	Breast cancer survivors (200)	Bidimensional Fatigue Scale and FACT-F	The BFS and FACT-F can be used to identify breast cancer survivors at higher risk of clinically significant ongoing fatigue Neither scale can be used as a diagnostic instrument for cancer-related fatigue	[48]

nonsteroidal anti-inflammatory drugs, have had conflicting results [36,37]. The use of erythropoietic stimulants has been studied in multiple trials and the evidence suggests that these agents do reduce fatigue in general cancer patients with hemoglobin less than 10 g/dl. The evidence is more limited in milder anemia [81–84].

Discussion

Fatigue has recently emerged as a strong, independent prognostic factor for survival that provides incremental prognostic value to the traditional markers of prognosis in recurrent high-grade gliomas [6,19–20]. Therefore, strategies to treat fatigue warrant investigation, not only to improve the QOL of a group of patients with

often limited life expectancy, but also possibly to optimize survival. Exercise has been recognized to reduce CRF in large meta-analysis including patients with various cancer types during or following treatment [85,86]. Interestingly, exercise behavior has recently been shown to be a strong independent predictor of survival that provides incremental prognostic value to KPS, as well as traditional markers of prognosis in patients with malignant recurrent glioma [87]. Although the mechanisms underlying this observation are not crystallized, increasing evidence has pointed to capacity of exercise to modulate inflammatory cytokines, products of oxidations and metabolic factors that may alter the tumor microenvironment [88].

Roberts *et al.* recently published a retrospective study evaluating the impact of in-patient rehabilitation on function and survival among patients with newly diagnosed glioblastoma [89]. Outcomes were compared between 100 patients (mean KPS 70) who underwent in-patient rehabilitation to 312 patients (mean KPS 80) who did not undergo rehabilitation, presumably because they had higher functional status and did not require in-patient rehabilitation. As expected, significant gains were made among those in function and mobility among those patients who went through rehabilitation. Interestingly, after adjusting for factors known to be associated with survival (age, extent of resection, KPS score), there was no statistical difference in the length of survival between patients who did and did not undergo rehabilitation, although presumably the group requiring in-patient rehabilitation had a greater burden of disease and/or symptomatology, which may imply a poorer survival prognosis. The authors hypothesized that improving mobility through rehabilitation provides the opportunity for enhanced exercise behavior which may improve survival. Clearly, there is a tremendous opportunity for further research to understand the mechanisms of CRF and the role of exercise behavior among patients with BT and create tailored interventions to improve quality of life in this vulnerable cohort of patients.

Conclusion & future perspective

Fatigue is a ubiquitous and an extremely distressing symptom among patients with BT, particularly those with high-grade gliomas. The pathophysiology of CRF in the context of patients with BT is multifactorial and complex, involving

biological, behavioral, medical and social factors. Fatigue is rarely an isolated symptom and most commonly occurs with other symptoms in the setting of brain tumors, including weakness, pain, anemia, sleep disturbances and depression, in symptom clusters. Therefore, patients should be screened for multiple symptoms that may vary according to their clinical circumstances. The etiology of CRF in the general oncology population is pointing to the role of inflammatory cytokines as a key factor in the genesis of CRF, but this research is currently limited in the setting of BT. No clear evidence-based guidelines exist regarding the use of pharmacologic agents in management of fatigue for patients with brain tumors. There is some evidence regarding the role of stimulants for patients with severe fatigue but further research in this area is needed. Exercise, which is the well-supported level 1 evidence to mitigate fatigue among patients with solid tumors, has not been subjected to rigorous randomized trials in this setting. Regardless of the pathophysiology, CRF should be screened, assessed and managed according to clinical practice guidelines and using validated tools that are available [9,49].

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