Comprehensive Psychoneuroendocrinology 8 (2021) 100099

Contents lists available at ScienceDirect

Comprehensive Psychoneuroendocrinology

journal homepage: www.sciencedirect.com/journal/comprehensive-psychoneuroendocrinology

Associations of meaning of illness with psychosocial, clinical, and immunological characteristics in patients with Leptomeningeal metastasis☆

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ARTICLE INFO

Keywords:
Leptomeningeal metastasis
Meaning of illness
Quality of life
Depression
Symptoms
Cytokine

ABSTRACT

Background: Leptomeningeal metastasis (LM) creates symptoms related to both the disease within the nervous system and treatment toxicities. Biologic processes, such as inflammation and behavioral processes, such as the meaning ascribed to illness (Meaning of Illness: MoI), can impact physical and psychosocial symptoms. The aim of this study was to understand the relationships among MoI, physical and psychosocial symptoms, and inflammation in patients with LM.

Methods: Thirty enrolled participants completed the MD Anderson Symptom Inventory-Brain Tumor with spine experimental symptoms added. Meaning of illness, quality of life (QoL), and depression were captured by validated instruments. Interleukin (IL)-6 and tumor necrosis factor (TNF)-α in serum and cerebrospinal fluid (CSF) were measured by ELISA. Correlations were performed to assess relationships among the variables.

Results: Participants were primarily white (73%), female (63%). Median age was 54 years (34–83). Breast (50%) and lung (20%) were most common diagnosis. Higher MoI scores were associated with better QoL ($p < .01$) and fewer depressive symptoms ($p < .01$). All CSF samples contained IL-6 and all but one sample had elevated IL-6. Higher levels of IL-6 in the CSF were associated with greater symptom burden ($p < .01$) and interference of symptoms in daily life ($p = .02$) but not MoI.

Conclusions: MoI was associated with QoL and depression. High levels of IL-6 in the CSF were associated with more severe symptoms. This study provides the groundwork for future research, including interventional studies to improve QoL in patients with LM.

1. Introduction

Leptomeningeal metastasis (LM) is a late complication of advanced cancer resulting from spread of the cancer to the leptomeninges, subarachnoid space, and cerebrospinal fluid (CSF). It may be related, in part, to the inability of many systemic chemotherapeutic agents to cross the blood-brain-CSF barrier, thus creating a sanctuary site within the CNS for malignant cells [1]. Survival is generally less than 6 months [2, 3], though longer survival has been reported in some patients [4]. The disease trajectory is one of persistent neurologic decline. Breast cancer, melanoma, and non-small cell lung cancer are the most involved primary cancers [5,6]. However, all patients with solid and hematologic malignancies are at risk.

Patients with LM have a unique symptom burden that includes the effects of cumulative treatment toxicity, the consequences of advanced cancer, and neurologic symptoms related to the location of the disease

☆ This work was supported by: The American Cancer Society Doctoral Degree Scholarship in Cancer Nursing [DSCN-11-280-01-SCN]; to JGW; and the Elizabeth W. Quinn Research Award 2014, 2015: to JGW.

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https://doi.org/10.1016/j.cpnec.2021.100099
Received 8 June 2021; Received in revised form 13 October 2021; Accepted 17 November 2021
Available online 19 November 2021

within the craniospinal axis [6,7]. Therapy is not standardized but typically includes radiation, systemic and/or intrathecal chemotherapy [2,3]. Each modality contributes to potentially severe and cumulative neurotoxicity that, combined with symptoms from underlying disease and previous treatments, can increase symptom burden and severely diminish quality of life (QoL). Research designed to understand the physical and psychosocial symptoms in patients with LM has been limited. Given the unique aspects of this late complication of systemic cancer, efforts to better understand symptoms in LM patients are warranted.

The link between the psychosocial characteristics of cancer patients and their symptoms is well documented. One psychosocial characteristic that is related to symptoms in cancer patients is the meaning of illness (MoI), which refers to the individual's perception of an illness experience and the significance of the illness for the self [8]. There is evidence that QoL, symptom burden, and depression are associated with MoI in patients with cancer [9]. MoI was characterized by Lipowski [10] as the positive or negative ascription of meaning to an illness experience (Table 1). Ascriptions of positive meaning, such as seeing the illness as a challenge or as adding value to one's life, are associated with improved symptom tolerance [11,12], less depression [13], and better QoL [14] in patients with cancer. Negative ascriptions of meaning are associated with poorer QoL [15].

Furthermore, investigating the role of inflammation in both physical and behavioral symptoms is relevant to LM patients. Presence of inflammatory cytokines in the brain, particularly interleukin (IL)-6 and tumor necrosis factor (TNF)-α, likely mediates sickness behaviors such as fatigue and depression [16–18]. Elevated levels of IL-6 in the CSF has been associated with suicide attempts [17]. This is relevant for patients with advanced cancer because suicide-related deaths are of significant concern [19] and highlight the need to understand potential links between elevation of cytokine levels in the CSF with behavioral and clinical characteristics that often co-occur with cancer.

There is evidence for associations between MoI, psychosocial and clinical symptoms. However, it is unknown whether these associations are present in patients with LM. Therefore, our objectives for this study were to explore the relationships of MoI with symptom burden, depression, and QoL; to describe participants' self -reports of positive and negative ascriptions of MoI; to describe associations between levels of inflammatory cytokines (IL-6 and TNF-α) in the CSF with MoI, symptom burden, depression, and QoL; to describe correlations between CSF and serum cytokine (IL-6 and TNF-α) levels; and to explore whether adding spine-related items from the MD Anderson Symptom Inventory (MDASI)-Spine (SP) [20] to the MDASI-Brain Tumor (BT) [21] could enhance our understanding of symptom burden in LM patients.

Table 1
Categories of meaning of illness.

Category	Description
1. Illness as challenge *Positive*	Tends to motivate healthy coping strategies. Illness is viewed as other life events that create demands and must be managed.
2. Illness as enemy *Negative*	Tends to anxiety, fear, and anger. There may be hostility and denial or passive surrender to disease.
3. Illness as punishment *Negative*	Tends to anxiety, depression, and anger, especially if punishment is viewed as unjust.
4. Illness as weakness *Negative*	Illness is a sign of failure and shame. May lead to denial or concealment of illness.
5. Illness as relief *Negative*	Allows the avoidance of demands, responsibilities, or personal crises. May tend toward malingering and hypochondria.
6. Illness as strategy *Negative*	Used to gain attention and concern of others.
7. Illness as irreparable loss *Negative*	Tends to depression, anger, and resistance to rehabilitation, and possible suicide.
8. Illness as value *Positive*	Belief that illness may enhance spirituality and awareness of the beauty and value of life

Note: Taken from Lipowski [10].

2. Material and methods

This study was conducted at The University of Texas MD Anderson Cancer Center in collaboration with The University of Texas Health Science Center at Houston Cizik School of Nursing. Approval for conducting the study was received from both Institutional Review Boards.

2.1. Patients

Patients with non-hematological malignancies stemming from primary CNS and systemic cancers, who had been diagnosed with LM were identified and consecutively screened for eligibility by a medical record review. Eligibility criteria included age of at least 18 years old; able to speak, read, and write English; and had a diagnosis of LM from a solid tumor based on CSF cytological or radiographic evidence. Patients with cognitive deficits precluding informed consent or self-report based on chart review or the opinion of the primary oncology team were excluded. The sample size was based on the primary objective of measuring associations between MoI as measured by the Constructed Meaning Scale (CMS) and symptom burden as measured by the MDASI-BT. As there were no prior data to estimate the correlation between MoI and MDASI-BT scores, we used nQuery Advisor 7.0 to evaluate the power of a sample size of 30 to detect a difference in the correlation coefficient between MoI and MDASI-BT. A sample size of 30 had 71% power to detect a difference of 0.45 between MoI and MDASI-BT using a two-sided hypothesis test with a significance level of 0.05.

2.2. Instruments

All surveys were administered to patients by trained research staff. In the case of those undergoing CSF analysis, the surveys were administered prior to withdrawal of CSF.

2.2.1. Constructed Meaning Scale

The CMS was developed to measure meaning in the context of a life-threatening illness [8]. It has been validated in patients with advanced cancer [22]. To explore MoI in LM patients, researchers operated on the assumption that the illness experience would include both physical and psychosocial experiences of the patient, regardless of whether the symptoms were directly caused by LM.

2.2.2. MD Anderson Symptom Inventory-Brain Tumor

The MDASI-BT was developed and validated specifically for measuring symptom burden in patients with primary brain tumors [23]. It has also been validated for measurement of symptom burden in patients with brain metastases [21].

As patients with LM may have a disease involving the brain and/or the spine, we added five additional items to the MDASI-BT that were taken directly from the MDASI-SP, an instrument developed and validated for use in patients with tumors involving the spine [20]. The five items unique to the MDASI-SP included: (1) radiating spine pain at its worst; (2) numbness or tingling in the neck, trunk, arms, legs, or crotch at its worst; (3) weakness in the arms and/or legs at its worst; (4) loss of control of bowel and/or bladder at its worst; and (5) sexual function at its worst, each rated on a 0-to-10 scale. Hereafter, we refer to the MDASI-BT with the added spine-related items as the modified MDASI-BT.

2.2.3. Functional Assessment of Cancer Therapy-general (FACT-G)

The FACT-G (Version 4) is a validated self-report instrument that uses a set of subscales to measure physical, social/family, emotional, and functional well-being from the patient's perspective [24]. The FACT-G has been used to evaluate QoL in patients with primary CNS and

other solid tumors [25–27].

2.2.4. Center for Epidemiologic Studies depression scale-revised (CESD-R)

The CESD-R is is designed to measure depression [28] and has been validated in patients with advanced cancer [29].

2.3. Demographic and clinical characteristics

Demographic data regarding age, gender, ethnicity, educational level, and marital status were captured. Additional clinical characteristics collected included information about prior medical history, history of depression, primary tumor, sites of metastasis, location of LM lesions (brain, spine, or both), the status of LM disease (newly diagnosed or on active treatment), Karnofsky Performance Score (KPS), and concurrent medications.

2.4. Cytokine analysis

CSF and blood serum were analyzed for IL-6 and TNF-α using an ELISA cytokine analysis kit from R&D Systems. This kit has been validated for serum and plasma and was used according to the manufacturer's instructions. Approximately 10 mL of blood was collected for the analysis. CSF was collected via an intraventricular reservoir immediately prior to intrathecal treatment. Samples were collected once at time of enrollment regardless of the time of day. CSF and serum samples were centrifuged, aliquoted, and frozen at −80 °C until batch analysis was performed.

2.5. Statistical analysis

All analyses were performed in SAS 9.3 (SAS Institute Inc., Cary, NC, USA) or R statistical software (R Core Team, 2020, version 3.63). Data were summarized using descriptive statistics, including means and standard deviations. Medians and ranges were reported for numeric variables; frequencies and proportions were reported for categorical variables. The reliability of each instrument, including the MDASI-BT and the modified MDASI-BT, was estimated using Cronbach's alpha. Histograms and quantile-quantile plots, as well as the Shapiro-Wilk and Kolmogorov-Smirnov tests, were applied to check the normality of the data. For normally distributed data, the Pearson correlation coefficient was calculated to assess the strength of the correlation between variables. For non-normally distributed data, the Spearman rank correlation coefficient was used to measure the relationship between the two variables. A linear regression was used to model the relation between the CMS and individual symptoms on the modified MDASI-BT. The relation between the CMS and the life interference subscale was addressed separately. Correlations between serum and CSF cytokine levels were analyzed, and a linear regression model was applied to estimate the relationship between the two variables. Scores of the unmodified MDASI-BT, modified MDASI-BT, MDASI-Life interference questions alone, and spine related items alone from the MDASI-Sp were summarized and the Analysis of the Variance model was applied to estimate the difference between the average scores.

3. Results

3.1. Sample

We screened 47 patients from March to September 2016, enrolling 30 patients to one of two groups: (1) newly diagnosed patients with LM and (2) patients on active treatment for LM. There were 15 patients in each group. We excluded fourteen patients for reasons including: unable to speak, read, and write English (n = 4), severe cognitive deficits (n = 4), physician decision (n = 2), under 18 years old (n = 1), and logistical reasons (n = 3). Three patients declined to participate.

Table 2 provides a demographic summary of the study cohort. The included patients were mostly white (73%), married (83%), and female (63%). The age range for the entire cohort was 34–83 years (median 54 years).

Table 2
Demographic characteristics of 30 included patients.

Variable		No. of patients (%)
Biological Sex	Male	11 (37)
	Female	19 (63)
Education	High school	8 (27)
	Some college	7 (23)
	Bachelor's degree	5 (17)
	Graduate degree	10 (33)
Ethnicity	Asian-Pacific Islander	1 (3)
	Asian-Indian	2 (7)
	White	22 (73)
	Latino	5 (17)
Marital Status	Married	25 (83)
	Divorced	2 (7)
	Single	2 (7)
	Widowed	1 (3)
Employed	No	23 (77)
	Yes	7 (23)
Age, y	Median (Min, Max)	53.5 (34, 83)
	Mean ± SD	52.2 ± 11.9

Table 3 provides a summary of the patients' clinical characteristics. The most common primary tumors were breast (50%) and lung (20%) tumors, followed by melanoma and glioblastoma (10% each). As a group, primary brain tumors comprised 19% of the primary tumors in the sample. Thirty percent (n = 9) of participants had no active sites of metastasis other than the leptomeninges. The most common site of metastasis was the brain (23%), and 40% of the patients had metastasis to the brain plus other sites. LM was most commonly detected in the brain only (53%), followed by both the brain and the spinal cord (27%). Twenty-seven percent of patients were receiving no treatment for LM and 27% were receiving intrathecal chemotherapy alone.

Sixty-four percent of patients (n = 10) who were on active treatment for LM (n = 15) were not on active treatment directed at the primary tumor. Treatments for LM included IT chemotherapy alone (n = 5), IT

Table 3
Clinical characteristics of 30 included patients.

Variable		No. of patients (%)
History of depression	No	23 (77)
	Yes	7 (23)
Primary tumor	Breast	15 (50)
	Lung	6 (20)
	Melanoma	3 (10)
	Glioblastoma	3 (10)
	Medulloblastoma	1 (3)
	Grade III astrocytoma	1 (3)
	Ependymoma	1 (3)
[a]Sites of metastasis	None	9 (30)
	Brain	7 (23)
	Brain plus other sites	12 (40)
	Bone	1 (3)
	Lung	1 (3)
Location of LM	Brain	16 (53)
	Spine	6 (20)
	Both	8 (27)
KPS	40	1 (3)
	50	3 (10)
	60	1 (3)
	70	6 (20)
	80	5 (17)
	90	10 (33)
	100	4 (13)
Drug treatment	Steroid	19 (63)
	Anticonvulsant	13 (43)
	Analgesic	23 (77)
	Antidepressant	7 (23)

[a] Other than leptomeningies

trastuzumab alone (n = 1), systemic chemotherapy alone (n = 7), combined radiation and systemic chemotherapy (n = 1) and combined IT chemotherapy and IT trastuzumab (n = 1). KPS scores ranged from 40 to 100 (median, 80).

3.2. Objective one: associations between MoI and symptom burden, QoL, and depression

3.2.1. Modified MDASI-BT

There were no significant correlations between MoI and symptom burden (r = −0.34, p = .12) as measured by the modified MDASI-BT or life interference subscale (r = −0.28, p = .26). Analysis of associations between individual symptoms on the MDASI-BT and the additional spine related items with MoI did not reveal any significant correlations.

Symptom analysis revealed 29 patients (97%) endorsed symptoms on the MDASI-BT, meaning that a score of at least 1 was assigned. Twenty-five patients (83%) endorsed spine related symptoms. Twenty-six patients (87%) reported that symptoms interfered with their lives. The median number of symptoms reported on the MDASI-BT per patient was 14 (range = 0–22). A median of 3 spine related items were endorsed (range = 0–5). On the Life Interference subscale a median of 5 items were endorsed (range = 0–6).

3.2.2. FACT-G

Total scores on the FACT-G ranged from 39 to 103 ($\bar{x}$ = 74.97, n = 30), indicating wide variability in reporting of QoL. Seven participants declined to answer the item regarding satisfaction with sex life, so the missing scores for this item were excluded from the total score. Higher ascription of MoI was significantly associated with better QoL (r = 0.63, P < .01).

3.2.3. CESD-R

The total scores ranged from 0 to 36 ($\bar{x}$ = 12.31, n = 29). Higher ascription of MoI was significantly associated with less depression (r = −0.55, p < .01). A score of 16 indicates subthreshold depressive symptoms (The Center for Epidemiologic Studies). Seven patients (23%) scored 16 or above on the CESD-R. Of these, none endorsed suicidal ideation.

3.3. Objective two: describing MoI in LM

3.3.1. Constructed Meaning Scale

Scores ranged from 18 to 41 ($\bar{x}$ = 30, SD = 5.8). The median (25th, 75th percentile) score was 30 (27.0, 34.8). Thirty-three percent (n = 10) of patients agreed that their illness had a negative effect on the things that they valued most about themselves. Forty-three percent (n = 13) of patients agreed that they felt they were making a complete recovery from their illness. Fifty-seven percent of patients (n = 17) rejected the notion that they would never recover from their illness; this response was not related to whether a patient was newly diagnosed or on active treatment for LM (p = .79).

3.4. Objective three and four: association between CSF and serum cytokines with MoI, symptom burden, QoL and depression. Correlation between serum and CSF cytokines

CSF was collected on 20 participants for cytokine analysis. Reasons CSF was not collected included physician preference (6), patient transitioning to hospice (1), no CSF collection planned at time of data collection (2) and symptoms precluding CSF collection (1). Serum for cytokine analysis was collected on 24 participants. Reasons for not collecting serum included participant declined (2), unsuccessful phlebotomy (3), and participant was transitioning to hospice (1).

Table 4 summarizes findings. Serum IL-6 level was not significantly associated with any of the MoI, QoL, depression or symptom burden. Interleukin-6 was detected in all samples of CSF and was elevated in all but 1 patient. There was a significant positive association between CSF IL-6 level and both the modified MDASI-BT score (p = .01) and the interference subscale score (p = .02).

Table 4
Correlations between cerebrospinal fluid IL-6 levels and biobehavioral assessment scores.

Instrument	*r*	*p*-value
Modified MDASI-BT (mean score-all items)	.56	.0107*
Modified MDASI-BT (mean score-interference subscale)	.51	.0209*
CMS (total score)	−.38	.1008
FACT-G (total score)	−.49	.0869
CESD-R (total score)	.34	.1516

*Significant.
Abbreviations: MDASI-BT: MD Anderson Symptom Inventory-Brain Tumor; CMS: Constructed Meaning Scale; FACT-G: Functional Assessment of Cancer Therapy-General; CESD-R: Center for Epidemiologic Studies Depression Scale-Revised.

Normal ranges of plasma IL-6 and TNF-α are 0–5 pg/ml and 0–22 pg/ml respectively [30]. Normal ranges of CSF IL-6 and TNF- α are 0–1 pg/ml and 0–2 pg/ml respectively [30]. In the global sample analysis, IL-6 levels were higher in CSF than in serum. The median (25th, 75th percentile) scores were 5.45 pg/ml (1 pg/ml, 21.8 pg/ml) in CSF and 1.0 pg/ml (0.1 pg/ml, 5.7 pg/ml) in serum, though the difference did not reach statistical significance. However, there was a wide variation in the difference between CSF IL-6 and serum IL-6 in individual patients. Two patients exhibited CSF IL-6 levels >20 pg/ml over serum levels. There were no significant correlations between TNF-α levels and MoI, QoL, depression, or symptom burden. Nor was there a significant correlation between CSF and serum IL-6 or TNF-α.

4. Discussion

The illness experience of patients with LM is unique in that patients often have multifocal neurologic symptoms in addition to symptoms from the primary tumor and toxicities from previous and current treatments. Therefore, while there is increasing interest in finding effective treatment for LM, a corresponding drive to better understand and manage symptoms is needed. To our knowledge, this is the first study investigating MoI in patients with LM and investigating associations between MoI and clinical, psychosocial, and inflammatory characteristics.

The primary aim of this study was to investigate associations between MoI and symptom burden in patients with LM. Our patients were highly symptomatic with over one-half endorsing multiple symptoms despite frequent use of analgesics, antiepileptics, and steroids. Other researchers have found that the number of symptoms correlate with MoI [31]. Our analysis looked at associations between MoI and symptom severity and individual symptoms, such as pain [9,32]. We found no significant associations between MoI and overall symptom burden or with individual symptoms which differs from earlier studies. For example Barkwell [32], found that patients who ascribed a positive meaning, “challenge,” to their illness reported less pain. It is possible that the small sample size was not adequate to capture these associations. Therefore, continuing this investigation with a larger sample size may be warranted.

In this study, we found that a higher level of MoI was associated with higher QoL. This finding is congruent with those of other studies [15,33,34] giving support to the idea that developing interventions aimed at helping patients ascribe positive meaning to their illness has the potential to improve QoL. This is a significant finding for patients with LM in that poor QoL may be a catalyst in choosing to abandon therapy and likely contributes to depression.

Another key finding in this study was the association of higher levels of MoI with lower levels of depression. Other researchers have found similar associations [33,35]. Recognizing this association is vital to

assessing depression and designing and applying effective, meaning-centered interventions for depression in cancer patients and for designing new clinical trials, including interventional studies, to further develop our understanding of this relationship.

Our next objective was to describe MoI in patients with LM. One-third of patients indicated that their illness negatively affected their sense of self-value. This is concerning because degradation of self-value affects the patient's ability to maintain a sense of wholeness [36], suggesting that a breakdown in self-value may lead to depression and diminished QoL.

Interestingly, 10 patients (33%) indicated that they disagreed with the item on the CMS that they would "never recover from illness," and 7 patients (23%) strongly disagreed. Thus, despite the poor prognosis of patients with LM, over half of the participants rejected the idea that they could not recover. This finding did not differ between those who were newly diagnosed with LM and those who were undergoing active treatment for LM, indicating that holding firm to this belief is common throughout the disease trajectory and despite worsening neurologic status.

One explanation of this finding may be Fife's [8] description of modifying one's original construct of meaning as a response to illness. It is possible that the high percentage of patients who rejected the notion that they would "never recover from illness" reflects this process. Furthermore, Schoen and Nicholas [37] posited that higher levels of positive meaning among patients with cancer may reflect a tendency to escalate meaning in response to the challenge of having cancer. This would correspond with Lipowski's [10] notion of "challenge" as a positive category of meaning. Further investigation of this phenomena would deepen our understanding of MoI in patients with advanced cancers, potentially leading to meaning centered interventions that could greatly benefit patients in managing depression and improving QoL.

To our knowledge, this is the first reported study examining relationships between MoI and inflammatory markers within the serum and CSF. Higher levels of CSF IL-6 levels were associated with greater symptom burden. This may be due to pro-inflammatory activity of IL-6 in the CNS and warrants further study.

It was particularly surprising that there was no correlation between high levels of serum or CSF IL-6 and TNF-α with higher scores on the CESD-R because these PICs have been found in other studies to correlate with major depressive disorder and suicidal ideation [17,18]. It is possible that aggressive symptom management, including the use of antidepressant therapy, modulated the levels of depression in our cohort. Small cohort size and missing data may also have contributed to the lack of positive associations between depression and serum or CSF IL-6 and TNF-α levels. It will be important in future studies to include potential effects of concurrent medications on mood and levels of inflammatory markers within the serum and CSF.

All but one of our participants had elevated levels of CSF IL-6. This observation of higher CSF cytokine levels in the setting of LM supports the idea of CNS production of IL-6, possibly in response to or by malignant cells, thus worsening symptom burden in LM patients. Investigation into the origin of CSF cytokines and their role in symptom burden may enhance our understanding of this finding.

Because symptoms may occur anywhere in the central or peripheral nervous system in LM, we added five spine-related items to the MDASI-BT to assess whether this helped to capture the distinctive symptom burden of LM patients. Although we did not find a significant difference between the MDASI-BT and the modified MDASI-BT, deeper analysis revealed a great deal of information about symptom burden in patients with LM. There was not a single cardinal symptom, however, symptom burden was high with over one-half of patients endorsing multiple symptoms and life interference from those symptoms. Our study quantitatively recognizes the severity and multiplicity of symptoms in this population and will provide a foundation for developing interventions to monitor and address distressing symptoms.

Eighty-three percent of patients endorsed spine related symptoms and the median number of spine related symptoms endorsed was 3/5. Furthermore, responses to the spine-related questions on the modified version revealed a wide range of severity, with some responses indicating very severe symptoms, evidence supporting the need for future studies investigating the benefit of the modified MDASI-BT as a measure of symptom burden in LM patients.

There were limitations to our study. Many patients were undergoing aggressive symptom management with antiepileptic drugs, analgesics, antidepressants, and steroids. Patients with adequate symptom control may be less likely to ascribe a negative MoI [38], which may explain the lack of association between symptom burden and MoI in this study. Conversely, some medications such as steroids or antiepileptic drugs may adversely affect mood, potentially mediating negative changes in MoI. Future studies investigating possible relationships between the medications used to manage symptoms and MoI would add to understanding the relationship between MoI and symptoms.

There was a small sample size and uneven gender distribution. There were only 11 male participants, reflecting the predominance of breast cancer as the most common solid tumor leading to LM [5,39]. It is possible that some of our findings are related to gender. Still, the unequal gender distribution would make this difficult to interpret. In addition, since half of the study sample consisted of patients with newly diagnosed LM, it may be that the sample was biased toward patients with a lower symptom burden since an increase in symptoms is expected as the disease progresses. Furthermore, the cross-sectional design did not allow us to investigate changes in the study variables over time.

As the study enrollment progressed, it became obvious that dividing patients into simple groups of newly diagnosed and actively treated was complicated by the fact that some patients who were considered newly diagnosed had undergone radiation to the CNS and that, once the blood-brain-CSF barrier is disrupted by radiation or metastasis, even treatments not aimed at treating LM could potentially penetrate this barrier, thus blurring the distinction between those who were newly diagnosed and those on active treatment aimed at LM. Collecting data on prior treatments, and perhaps grouping patients in a way that would better account for prior treatments, would be important in future studies.

Other limitations include the heterogeneous types of solid tumors represented in this cohort, variability in the time since diagnosis, and variation in the behavioral measures used in the studies cited, all of which may limit our finding's generalizability.

Finally, we did not collect cytokine samples in a manner that enabled accounting for potential diurnal changes in cytokine levels as this proved to be logistically challenging. Therefore, some of the variation in cytokine levels between patients may be partially explained by diurnal variability. The study was cross-sectional and sought to accommodate the patients' schedules for regular CSF and serum sampling. Future studies should focus on collecting samples considering diurnal cycles.

5. Conclusion

Many patients rise to the challenge of having cancer, ascribing a more positive meaning to their disease, even in the face of a grim prognosis. There is evidence that the meaning that patients ascribe to serious illnesses such as LM affects their perceptions of symptom frequency and severity, their QoL, and their experiences of depression. Our findings revealed that patients who report better MoI also have better QoL and fewer depressive symptoms, indicating that a meaning-centered intervention could benefit LM patients. Aggressive control of symptoms, including symptoms of depression, may lead to better MoI in patients with LM. Including markers of systemic and CNS inflammation in future studies would deepen our understanding of the impact of inflammation on symptom burden, depression, and QoL in patients with LM.

Authorship

Experimental Design: JGW, BJO, TSA, MRG, RC, GLW, CRA, YY, CF.
Implementation: JGW, BJO, CH.
Data Analysis: YY, CRA, JW, CH.
Data Interpretation: JGW, BJO, TSA, RC, MRG, GLW.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The experimental work for this study was completed while Dr. Terri S. Armstrong was employed as a Professor of Nursing at the University of Texas Health Science Center Cizik School of Nursing.

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